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Review Article

The association between vitamin D concentration and pain: a systematic review and meta-analysis

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Abstract

Objective: Pain-related conditions, such as chronic widespread pain and fibromyalgia, are major burdens for individuals and the health system. Evidence from previous research on the association between circulating 25-hydroxyvitamin D (25(OH)D) concentrations and pain is conflicting. Thus, we aimed to determine if there is an association between mean 25(OH)D concentration (primary aim), or proportion of hypovitaminosis D (secondary aim), and pain conditions in observational studies.
Design: Published observational research on 25(OH)D concentration and pain-related conditions was systematically searched for in electronic sources (MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials) and a random-effects meta-analysis was conducted on included studies.
Results: Eighty-one observational studies with a total of 50 834 participants were identified. Compared with controls, mean 25(OH)D concentration was significantly lower in patients with arthritis (mean difference (MD): −12·34 nmol/l; $P<0·001$), muscle pain (MD: −8·97 nmol/l; $P=0·003$) and chronic widespread pain (MD: −7·77 nmol/l; $P<0·001$), but not in patients with headache or migraine (MD: −2·53 nmol/l; $P=0·06$). The odds of vitamin D deficiency was increased for arthritis, muscle pain and chronic widespread pain, but not for headache or migraine, compared with controls. Sensitivity analyses revealed similar results.
Conclusions: A significantly lower 25(OH)D concentration was observed in patients with arthritis, muscle pain and chronic widespread pain, compared with those without. These results suggest that low 25(OH)D concentrations may be associated with pain conditions.

Keywords
Vitamin D
Pain
Systematic review
Meta-analysis
Observational studies

Pain is defined by the International Association for the Study of Pain as 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage'[1]. Pain, and conditions with pain as a prominent symptom, including chronic widespread pain, musculoskeletal pain (e.g. lower-back pain), arthritis and headache, are the most common reason for primary care and medical consultations[2–4]. The prevalence of chronic pain ranges from 8 to 60 % and over, depending on the population studied[5]. Recent reviews of painful conditions have reported that the prevalence of fibromyalgia varies from 2 to 8 % in the general population[6]; while the global prevalence of lower-back pain is 9·4 %[7], of rheumatoid arthritis is 0·24 %[8] and of current migraine is more than 10 % in adults[4]. Painful conditions can seriously influence quality of life, lead to work disability, and result in major economic burdens for both individuals and the health system[2,4,5,8–12].

Vitamin D comprises a group of fat-soluble secosteroids[13] and the receptor of vitamin D has been identified in muscle tissue[14]. Although the optimal level of serum 25-hydroxyvitamin D (25(OH)D) is a topic of ongoing research, vitamin D deficiency is typically defined as 25(OH)D < 50 nmol/l[15]. Vitamin D deficiency is very common in both developed[16] and developing countries[17]. There is increasing evidence from observational studies that vitamin D deficiency is associated with a wide range of acute and chronic diseases[18], including diseases with pain as a prominent symptom[19]. Previous research has provided inconsistent findings on the association between vitamin D status and pain. A meta-analysis of seven observational studies with 2420 statin-treated patients found that 25(OH)D levels were lower in those with myalgia than in those without[20]. However, it used a fixed-effects model, not justified by the high heterogeneity of the results ($I^2=94$ %), which when

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repeated with a random-effects model was no longer significant (mean difference (MD): −3·52; 95 % CI −8·55, 1·51 ng/ml; $P = 0·17$). Another meta-analysis of twelve observational studies with 1854 participants reported inconsistent results, with significantly increased odds of vitamin D deficiency associated with chronic widespread pain, but no difference in mean 25(OH)D levels between people with and without chronic widespread pain[21]. Moreover, these previous meta-analyses have not reported the association between 25(OH)D concentration and other pain-related conditions, such as arthritis and headache. In addition, recent reviews of randomized controlled trials have reported inconsistent conclusions about whether vitamin D supplementation improves chronic pain, with two being qualitative reviews[22,23] and only one using quantitative methods[24].

Given the limited evidence and inconsistent conclusions from previous reviews and meta-analyses, which for observational studies only searched up to September 2014[20,21], we conducted an updated meta-analysis of all observational studies reporting data on 25(OH)D levels and pain, including studies of non-statin users and participants with different pain conditions, to determine if there is an association between these two variables.

Methods

Search strategy

Two trained researchers (Z.W., Z.M.) independently searched MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (up to April 2017) using the following key words: Vitamin D, Vitamin D2, Vitamin D3, Cholecalciferol, Ergocalciferol, 25-hydroxyvitamin D, Pain, Myalgia, Myopathy, Myalgic, Headache, Migraine, Arthritis and Sciatica, for original publications pertinent to vitamin D levels and pain (search strategy listed in the online supplementary material, Supplement 1). In addition, we manually searched the reference lists of eligible articles and previous reviews for additional studies.

Aims

Two aims were predefined in the meta-analysis. The primary aim was the difference in mean circulating 25(OH)D concentration (nmol/l) between participants with and without pain-related conditions. The secondary aim was the difference in proportions of hypovitaminosis D in the participants with and without painful conditions. For the latter, we used the original definition of hypovitaminosis D from each paper (eight studies with a threshold of 75 nmol/l; thirty-four studies with 50 nmol/l; two studies with 25 nmol/l; six studies with other definitions, which were 20 nmol/l, 30 nmol/l, 37·5 nmol/l, 80 nmol/l and 100 nmol/l).

Eligibility criteria

We included observational studies in the current meta-analysis if the study: (i) was a cohort, case–control or cross-sectional study; (ii) enrolled adult participants (≥18 years old); (iii) described specific information on pain, such as a pain definition or category; and (iv) reported the 25(OH)D level and/or the proportion of hypovitaminosis D in participants with and without pain. There was no language or ethnicity restriction. In addition, the studies which selected controls with pain conditions were excluded.

Data extraction

Reviewers (Z.W., Z.M.) independently identified the included articles by screening title, abstract and full text (κ coefficient = 0·73), and the main data were extracted based on a standardized data collection form developed for the study. Any inconsistencies were resolved by consensus and discussion.

Quality assessment of individual studies

The quality of each included study was assessed using the Newcastle–Ottawa scale[25]. Specifically, there were five items for cross-sectional studies, and eight items for cohort and case–control studies. We used the same score to categorize the quality of studies as reported previously[26]: 5 as very good, 4 as good, 3 as satisfactory and 0–2 as unsatisfactory in cross-sectional studies; similarly, 7–8 as very good, 5–6 as good, 4 as satisfactory and 0–3 as unsatisfactory in case–control or cohort studies.

Synthesis and analysis

Mean and SD of serum 25(OH)D levels, and number of participants with and without pain, were collected for the continuous exposure measurement. All 25(OH)D levels were transformed to nmol/l in the meta-analysis. Digitizer software (GetData Graph Digitizer version 2.26; www.getdata-graph-digitizer.com/) was used to extract the data from graphs, and Wan *et al.*'s[27] methods were used to estimate the mean and SD by reported median and range, or median and interquartile range. Sample size and the proportion with hypovitaminosis D were collected for the dichotomous exposure measurement.

Weighted MD and 95 % CI were calculated for continuous exposure, and OR and 95 % CI were calculated for dichotomous exposure, to allow the combining of different study designs in the synthesis analysis. Heterogeneity was measured using Cochran's Q test and the I^2 statistic ($I^2 > 50\%$ denotes large or extreme heterogeneity). Random-effects models were used in the meta-analysis[28]. Predefined analyses were performed to detect the relationship of 25(OH)D with pain by different painful conditions (arthritis, muscle pain, chronic widespread pain, and headache or migraine), type of study design, statin user and different cut-off points of vitamin D deficiency (25 nmol/l, 50 nmol/l and 75 nmol/l). Interactions were tested between different subgroups using a standard method[29]. In addition, we also conducted meta-regression to examine other sources of heterogeneity (e.g. year, sample size, mean age, female proportion, type

of study). Sensitivity analyses were also conducted by individually excluding each study in turn, and by collectively excluding low-quality studies or those that used other definitions of vitamin D deficiency (as listed above). We generated funnel plots for visual assessment of publication bias, as well as performed the Egger test[30]. All tests were two-tailed and $P \leq 0{\cdot}05$ was considered statistically significant. We conducted the meta-analysis using the Stata statistical software package version 13.1 and Review Manager software (Revman version 5.2).

Results

Included studies

A total of 2340 unique articles were identified by searching the three electronic databases and by applying snowballing techniques. After reviewing titles and abstracts, 2155 publications were excluded. The full texts of the remaining 185 studies were assessed for their eligibility and a further 107 were excluded because they did not meet the eligibility criteria (see Supplement 1). The remaining seventy-eight publications, which reported eighty-one observational studies with data on vitamin D concentration and pain, were included in the current meta-analysis (Fig. 1).

The eighty-one observational studies involved nineteen cross-sectional studies[31–48], fifty-six case–control studies[49–102] and six cohort studies[103–108]. Together, these studies included 50 834 participants, 21 723 of whom were reported as pain subjects, with a median mean age of 49·4 (median SD 10·3) years and median female proportion of 80·5 % (range: 0–100 %); and 29 111 participants who were community- or hospital-based controls without pain-related conditions, with a median mean age of 50·0 (median SD 10·3) years and median female proportion of 78·4 % (range: 0–100 %). The pain conditions or symptoms reported in these studies included arthritis, muscle pain, chronic widespread pain, and headache or migraine. Characteristics of included studies are shown in Table 1.

Quality assessment in included studies

According to the Newcastle–Ottawa scale, sixty-two of the eighty-one observational studies were very good or

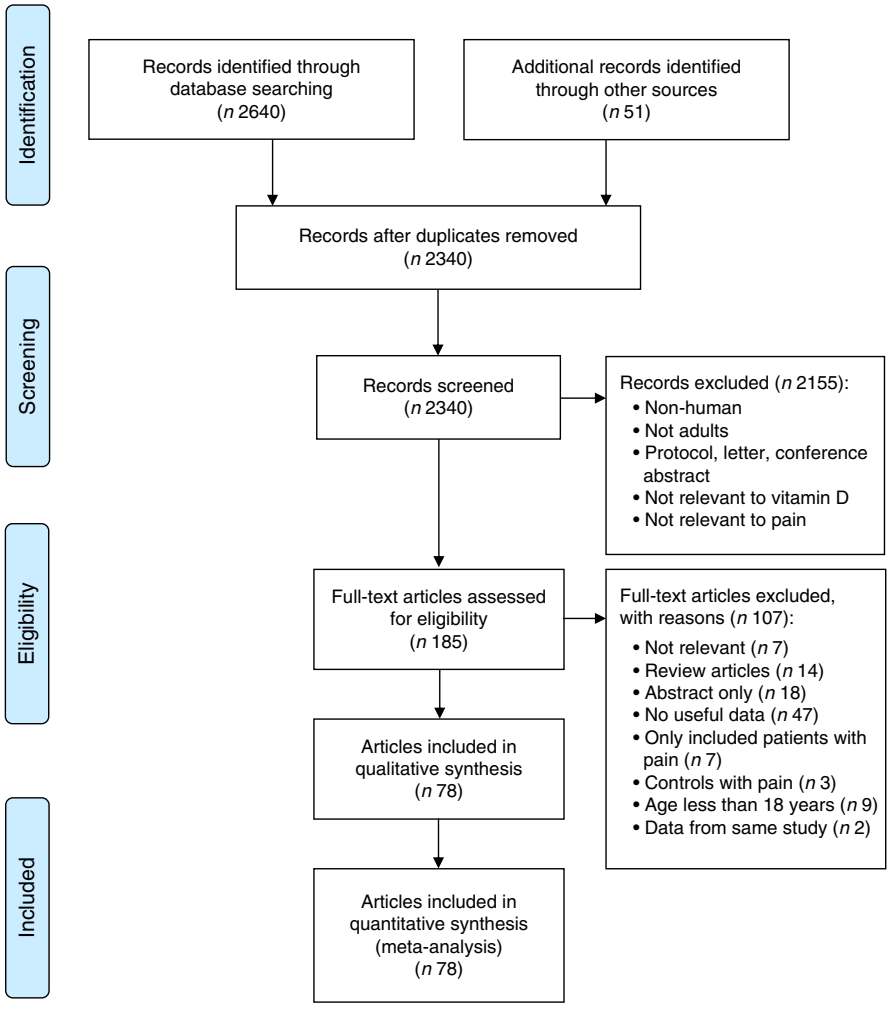

Fig. 1 (colour online) PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) diagram of study selection

Table 1 Characteristics of studies included in the current meta-analysis on the association between vitamin D concentration and pain

				No. of subjects			Age (years)				Female				
				Total	With pain	Without pain	With pain		Without pain		With pain		Without pain		
Study	Country	Population	Pain measurement	*n*	*n*	*n*	Mean or median	SD or IQR or range	Mean or median	SD or IQR or range	*n*	%	*n*	%	Type of study
Cross-sectional studies															
Macfarlane *et al.* (2005)[31]	UK	Females aged 18–36 years	Widespread pain	109	8	101		NA		NA	8	100·0	101	100·0	Community-based
Duell *et al.* (2008)[32]	USA	Hyperlipidaemia patients with statin therapy	Statin-related myalgia	99	38	61	59·3	10·4	58·4	12·3	26	68·4	30	49·2	Hospital-based
Hicks *et al.* (2008)[33]	Italy	People living in the Chianti geographic area	Pain at lower extremities and back	958	420	538		NA		NA	302	71·9	227	42·2	Community-based
Ahmed *et al.* (2009)[34]	USA	Hyperlipidaemia outpatients with statin therapy	Statin-related myalgia	621	128	493	60	11	58	12	76	59·4	219	44·4	Hospital-based
Golan *et al.* (2009)[35]	Israel	Patients with haemodialysis	Chronic pain	100	51	49	64·0	12·5	65·0	15·2	32	62·7	23	46·9	Hospital-based
Linde *et al.* (2010)[36]	USA	Patients with statin therapy	Statin-related myalgia	64	39	25	59·5	10	59·3	13·8	18	46·2	9	36·0	Hospital-based
McBeth *et al.* (2010)[37]	European	Males aged 40–79 years	CWP and other pain	3075	1813	1262		NA		NA	0	0·0	0	0·0	Community-based
Backes *et al.* (2011)[38]	USA	Patients with statin therapy	Statin-related myalgia	129	57	72	62·4	10·5	58·3	13	31	54·4	28	38·9	Hospital-based
Kjaergaard *et al.* (2012)[39]*	Norway	Smokers aged 30–87 years	Headache	2339	907	1432	52·1	10·8	57·1	11·6	606	66·8	686	47·9	Community-based
Kjaergaard *et al.* (2012)[39]*	Norway	Non-smokers aged 30–87 years	Headache	9275	3154	6121	53·7	12·1	59·8	12·5	2006	63·6	2820	46·1	Community-based
Riphagen *et al.* (2012)[40]	Netherlands	Outpatients with statin therapy	Statin-related myalgia	75	22	53		NA		NA		NA		NA	Hospital based
e Silva *et al.*[41]	Twenty-three countries	Postmenopausal women aged 60–85 years	Back pain	9276	6284	2992		NA		NA	6284	100·0	2992	100·0	Community-based
Eisen *et al.* (2014)[42]	Israel	Clinics patients with statin therapy	Statin-related myalgia	272	106	166	66·3	10·2	69·3	10·0	57	53·8	113	68·1	Hospital-based
Madani *et al.* (2014)[43]	Iran	Female nurses	Non-specific MSK pain	200	178	22		NA		NA	178	100·0	22	100·0	Community-based
Alipour *et al.* (2015)[44]	Iran	Adults aged >60 years and without cancer, depression, osteoarthritis, RA	Chronic pain	857	666	191	69·4	7·3	68·7	7·4		NA		NA	Community-based
Hirani *et al.* (2015) [45]	Australia	Male aged ≥70 years	Chronic pain	1616	480	1136		NA		NA	0	0·0	0	0·0	Community-based
Morioka *et al.* (2015)[46]	USA	Adults aged >40 years (NHANES)	MSK pain	5247	1429	3818		NA		NA		NA		NA	Community-based
Tasoglu *et al.* (2015)[47]	Turkey	Male patients with statin therapy	Statin-related myalgia	40	17	23	49·1	7·9	50·6	9·0	0	0·0	0	0·0	Hospital-based
Virtanen *et al.* (2017)[48]	Finland	Middle-aged males	Headache	2601	250	2351		NA		NA	0	0·0	0	0·0	Community-based
Case–control studies															
Pietschmann *et al.* (1989)[49]	Austria	Patients with RA and healthy controls	RA	59	29	30	53†	45–59	52†	42–68	21	72·4	20	66·7	Hospital-based
Muller *et al.* (1995)[50]	Denmark	Patients with RA or osteoarthritis and healthy controls	RA or osteoarthritis	113	41	72		NA		45–65‖	29	70·7	36	50	Hospital-based
Al-Allaf *et al.* (2003)[51]	UK	Premenopausal women with FM and age- & sex-matched controls	FM	77	40	37	42·5	3·6	42·5	4·3	40	100·0	37	100·0	Hospital-based
Benson *et al.* (2006)[52]	Australia	Patients with muscle pain and age- & sex-matched controls	Muscle pain	16	8	8	47·6	16·1	44·4	12·2	7	87·5	7	87·5	Hospital-based
Cutolo *et al.* (2006)[53]*	Italy	Female patients with RA and age- & sex-matched healthy controls	RA	88	53	35	58·5	8·0	59·9	5·3	53	100·0	35	100·0	Hospital-based

Table 1 *Continued*

Study	Country	Population	Pain measurement	No. of subjects			Age (years)				Female				Type of study
				Total	With pain	Without pain	With pain		Without pain		With pain		Without pain		
				n	*n*	*n*	Mean or median	SD or IQR or range	Mean or median	SD or IQR or range	*n*	%	*n*	%	
Cutolo *et al.* (2006)[53]*	Estonia	Female patients with RA and age- & sex-matched healthy controls	RA	94	64	30	56·3	18·4	51·1	20·8	64	100·0	30	100·0	Hospital-based
Lotfi *et al.* (2007)[54]	Egypt	Female patients with LBP and age- & sex-matched health controls	Chronic LBP	80	60	20	32·8	7·1	33·6	8·6	60	100·0	20	100·0	Hospital-based
Tandeter *et al.* (2009)[55]	Israel	Premenopausal women with FM and age- & sex-matched women	FM	150	68	82	43·8	7·6	40·4	9·9	68	100·0	82	100·0	Hospital-based
de Rezende Pena *et al.* (2010)[56]	Brazil	Female patients with FM and age- & sex-matched controls	FM	179	87	92	44·9	8·6	32·0	10·5	87	100·0	92	100·0	Hospital-based
Heidari *et al.* (2010)[57]	Iran	Outpatients with non-specific skeletal pain and controls	Non-specific skeletal pain	478	276	202	44·3	15	46·4	14·2	NA		NA		Hospital-based
Turhanoglu *et al.* (2011)[58]	Turkey	Patients with RA and healthy controls	RA	105	65	40	46·3	11·9	44·8	10·6	NA		NA		Hospital-based
Attar (2012)[59]	Saudi Arabia	Patients with RA and age- & sex-matched healthy controls	RA	200	100	100	47	13	47	15	90	90·0	89	89·0	Hospital-based
Baykal *et al.* (2012)[60]	Turkey	Patients with RA and age- & sex-matched healthy controls	RA	100	55	45	45‡	28–68		NA	40	72·7	33	73·3	Hospital-based
Dong *et al.* (2012)[61]	China	Female patients with RA and healthy controls	RA	130	72	58	59·5	5·3	58·8	5·1	72	100·0	58	100·0	Hospital-based
Heidari *et al.* (2012)[62]	Iran	Patients with inflammatory arthritis (RA and UIA) and controls	Inflammatory arthritis (RA and UIA)	386	147	239	47·1	14·9	49·4	14·5	NA		NA		Hospital-based
Kostoglou-Athanassiou *et al.* (2012)[63]	Greece	Patients with RA and age- & sex-matched controls	RA	88	44	44	NA		NA		NA		NA		Hospital-based
Al-Jarallah *et al.* (2013)[64]	Kuwait	Rheumatology/rehabilitation clinics patients with MSK pain and age- & sex-matched healthy controls	MSK pain	206	124	82	41·7	13·9	43·7	7·4	118	95·2	79	96·3	Hospital-based
Atwa *et al.* (2013)[65]	Saudi Arabia	Patients with RA and age-matched healthy controls	RA	95	55	40	45·6	12·4	45·0	8·0	43	78·2	20	50·0	Hospital-based
Azali *et al.* (2013)[66]	Sweden	Patients with IIM and sex- & month of blood sample-matched healthy controls	IIM	439	149	290	56§	18–72	41§	18–70	97	65·1	192	66·2	Hospital-based
Olama *et al.* (2013)[67]	Egypt	Female patients with FM and age- & sex-matched healthy controls	FM	100	50	50	32·3	9·4	33·1	9·7	50	100·0	50	100·0	Hospital-based
Orgaz-Molina *et al.* (2013)[68]	Spain	Psoriasis patients with arthritis and age- & sex-matched psoriasis without arthritis	Arthritis	122	61	61	44·9	10·9	45·6	11·7	28	45·9	28	45·9	Hospital-based
Rkain *et al.* (2013)[69]	Morocco	Postmenopausal women with chronic LBP and age-, sex- & BMI-matched healthy controls	Chronic LBP	149	105	44	56·5	5·6	56·8	7·4	105	100·0	44	100·0	Hospital-based
Yazmalar *et al.* (2013)[70]	Turkey	Patients with RA or osteoarthritis and healthy controls	RA or osteoarthritis	215	145	70	47·0	9·1	41·4	4·2	99	68·3	26	37·1	Hospital-based
Baykara *et al.* (2014)[71]	Turkey	Patients with chronic non-specific LBP and heathy controls	Chronic non-specific LBP	90	60	30	30·6	7·8	31·0	6·7	37	61·7	19	63·3	Hospital-based
Celikbilek *et al.* (2014)[72]	Turkey	Patients with migraine and age- & sex-matched healthy people	Migraine	101	52	49	35·9	9·1	34·2	10·2	48	92·3	42	85·7	Hospital-based
Chen *et al.* (2014)[73]	China	Patients with RA and age- & sex-matched healthy controls	RA	220	110	110	59·5	11·4	56·9	10·5	75	68·2	71	64·5	Hospital-based
Cote *et al.* (2014)[74]	USA	Patients with RA and age- & sex-matched non-RA controls	RA	1611	270	1341	NA		NA		225	83·3	1125	83·9	Community-based

Table 1 *Continued*

Study	Country	Population	Pain measurement	No. of subjects			Age (years)				Female				Type of study
				Total	With pain	Without pain	With pain		Without pain		With pain		Without pain		
				n	*n*	*n*	Mean or median	SD or IQR or range	Mean or median	SD or IQR or range	*n*	%	*n*	%	
Heidari *et al.* (2014)[75]	Iran	Patients with unexplained arthralgia and controls	Arthralgia	453	167	286	38	13·3	42·6	14·4	135	80·8	221	77·3	Hospital-based
Hiraki *et al.* (2014)[76]*	USA	Female patients with RA and age-, sex-, date of blood draw- & hormonal factors-matched controls from NHS	RA	477	120	357	56·0	7·1	56·0	7·1	120	100·0	357	100·0	Community-based
Hiraki *et al.* (2014)[76]*	USA	Female patients with RA and age-, sex-, date of blood draw- & hormonal factors-matched controls from NHSII	RA	179	46	133	44·4	4·4	44·5	5·3	46	100·0	133	100·0	Community-based
Hong *et al.* (2014)[77]	China	Patients with RA and age- & sex-matched healthy controls	RA	210	130	80	54	14	54	13	95	73·1	57	71·3	Hospital-based
Mateos *et al.* (2014)[78]	Spain	Female patients with FM and age-, sex- & enrolled year-matched healthy controls	FM	410	205	205	51·5	9·6	51·3	9·9	205	100·0	205	100·0	Hospital-based
Sezgin Ozcan *et al.* (2014)[79]	Turkey	Female patients with FM and age- & sex-matched healthy controls	FM	90	60	30	41·9	9·8	38·8	12·7	60	100·0	30	100·0	Hospital-based
Sharma *et al.* (2014)[80]	India	Patients with RA and age- & sex-matched healthy controls	RA	160	80	80	40·98	12·53	42·64	12·67	NA		NA		Hospital-based
Zandifar *et al.* (2014)[81]	Iran	Patients with migraine and age- & sex-matched healthy controls	Migraine	215	105	110	33·6	9·9	32·5	9·5	80	76·2	89	80·9	Hospital-based
Brance *et al.* (2015)[82]	Argentina	Female patients with RA and age-, sex- & BMI-matched healthy controls	RA	75	34	41	52·2	11·1	54·8	10·9	34	100·0	41	100·0	Hospital-based
Cen *et al.* (2015)[83]	China	Patients with RA and normal controls	RA	166	116	50	50·1	10·9	48·1	10·3	93	80·2	40	80·0	Hospital-based
Gullo *et al.* (2015)[84]	Italy	Patients with RA and age- & sex-matched controls	RA	68	27	41	47·5	12·5	46·4	4·1	19	70·4	28	68·3	Hospital-based
Lodh *et al.* (2015)[85]	India	Patients with chronic LBP and controls	Chronic LBP	400	200	200	46·2	15·7	NA		146	73	NA		Hospital-based
Matsumoto *et al.* (2015)[86]	Japan	Outpatients with RA and age- & sex-matched controls	RA	367	181	186	61†	51–69	60†	51–66	151	83·4	155	83·3	Hospital-based
Park *et al.* (2015)[87]	South Korea	Patients with EIA and age- & sex-matched healthy controls	EIA	202	101	101	56·5	12·2	56·6	12·1	86	85·1	86	85·1	Hospital-based
Petho *et al.* (2015)[88]	Hungary	Male patients with psoriasis arthritis and age- & sex-matched healthy controls	Psoriatic arthritis	106	53	53	54·7‡	31–84	54·7‡	31–84	0	0·0	0	0·0	Hospital-based
Yagiz *et al.* (2015)[89]	Turkey	Patients with RA and healthy controls	RA	154	92	62	49·6	13·9	43·9	8·0	83	90·2	35	56·5	Hospital-based
Askari *et al.* (2016)[90]	Iran	Patients with keen osteoarthritis and sex-matched healthy controls	Osteoarthritis	393	131	262	52·0	8·0	55·0	9·0	107	81·7	214	81·7	Hospital-based
Elbassiony *et al.* (2016)[91]	Egypt	Consecutive patients with RA and age- & sex-matched healthy controls	RA	300	150	150	44·2	11·6	46·4	12·9	97	64·7	97	64·7	Hospital-based
Gamal *et al.* (2016)[92]	Egypt	Patients with RA and age- & sex-matched healthy controls	RA	80	55	25	42·2	10·6	41·2	15·8	47	85·5	20	80·0	Hospital-based
Gheita *et al.* (2016)[93]	Egypt	Patients with RA and age- & sex-matched healthy controls	RA	125	63	62	41·6	9·7	39·7	9·8	49	77·8	49	79·0	Hospital-based
Kasapoğlu Aksoy *et al.* (2017)[94]	Turkey	Patients with FM and age- & sex-matched healthy controls	FM	100	53	47	46·4	9·8	44·4	7·6	51	96·2	41	87·2	Hospital-based
Liao *et al.* (2016)[95]	China	Female patients with RA and healthy controls	RA	114	82	32	54·0	14·0	53·0	14·0	82	100·0	32	100·0	Hospital-based
Maafi *et al.* (2016)[96]	Iran	Female patients with FM and healthy controls	FM	142	74	68	38·0	9·8	32·6	10·1	74	100·0	68	100·0	Hospital-based
Okyay *et al.* (2016)[97]	Turkey	Female patients with FM and healthy controls	FM	159	79	80	37·0	9·0	35·8	10·7	79	100·0	80	100·0	Hospital-based
Thorneby *et al.* (2016)[98]	Sweden	Patients with chronic LBP and age- & sex-matched controls	Chronic LBP	88	44	44	55·0	16·0	55·0	15·0	26	59·1	26	59·1	Community-based

Table 1 *Continued*

Study	Country	Population	Pain measurement	No. of subjects			Age (years)				Female				Type of study
				Total	With pain	Without pain	With pain		Without pain		With pain		Without pain		
				n	*n*	*n*	Mean or median	SD or IQR or range	Mean or median	SD or IQR or range	*n*	%	*n*	%	
Wang *et al.* (2016)[99]	China	Patients with RA and age- & sex-matched healthy controls	RA	214	154	60	53·5	12·4	51·4	10·3	88	57·1	35	58·3	Hospital-based
Yildirim *et al.* (2016)[100]	Turkey	Patients with FM and age- & sex-matched healthy controls	FM	198	99	99	49·4	9·2	50·8	8·8	80	80·8	77	77·8	Hospital-based
Brennan-Speranzaa *et al.* (2017)[101]	Australia	Patients with keen osteoarthritis and age-matched controls	Osteoarthritis	29	19	10	66·1	5·2	64·7	7·6	10	52·6	7	70·0	Hospital-based
Wong *et al.* (2017)[102]	Malaysia	Female patients with RA and age-matched healthy controls	RA	106	77	29	54·1	6·9	52·6	5·4	77	100·0	29	100·0	Hospital-based
Cohort studies															
Laroche *et al.* (2014)[103]	France	Early-stage breast cancer and no pain at the start of AI treatment	Joint pain, diffuse pain, neuropathic pain and mixed pain	134	77	57	61	7	62·4	7·2	77	100·0	57	100·0	Hospital-based
Mergenhagen *et al.* (2014)[104]	USA	Patients with statin therapy	Statin-related myalgia	450	50	400	65·5‡	43–91	68·9‡	39–96	5	10·0	16	4·0	Hospital-based
Shantha *et al.* (2014)[105]	USA	Patients with statin therapy	Statin-related myalgia	1160	276	884	63·5	10·1	61·8	13·9	92	33·3	349	39·5	Community-based
Singer *et al.* (2014)[106]	USA	Postmenopausal women with non-metastatic, hormone receptor-positive breast cancer, prescribed adjuvant AI therapy	MSK symptoms	52	28	24	59·8‡	44–76	61·5‡	45–76	28	100·0	24	100·0	Hospital-based
Ovesjo *et al.* (2016)[107]	Sweden	Patients with statin therapy	Myopathy	127	16	111	65§	39–86	65§	32–86	12	75·0	55	49·5	Hospital-based
Calza *et al.* (2017)[108]	Italy	HIV patients with statin therapy	Myalgia	487	42	445	58·6	19·6	52·5	20·2	7	16·7	83	18·7	Hospital-based

IQR, interquartile range; RA, rheumatoid arthritis; NHANES, National Health and Nutrition Examination Survey; FM, fibromyalgia; LBP, lower-back pain; UIA, undifferentiated inflammatory arthritis; MSK, musculoskeletal; IIM, idiopathic inflammatory myopathies; NHS, Nurses' Health Study; NHSII, Nurses' Health Study II; EIA, early inflammatory arthritis; AI, aromatase inhibitor; CWP, chronic widespread pain; NA, not available.
*One publication reported two studies.
†Median and IQR.
‡Mean and range.
§Median and range.
‖Original article reported age range only.

Table 2 Association between 25-hydroxyvitamin D concentration and painful conditions

Category	Subgroup	No. of included studies	No. of participants		Effect estimate		*P* value	Test of subgroup differences, *P* value
			With pain	Without pain	MD	95 % CI		
Pain conditions	Arthritis	33	3018	3925	−12·34	−17·97, −6·71	<0·001	0·004
	Muscle pain	22	1723	3784	−8·97	−14·92, −3·02	0·003	
	Chronic widespread pain	13	4085	3306	−7·77	−11·97, −3·57	<0·001	
	Headache or migraine	5	4468	10 063	−2·53	−5·13, 0·07	0·06	
Study design	Cross-sectional	15	7906	13 457	−3·10	−4·98, −1·21	0·001	<0·001
	Case–control	53	4976	5757	−11·09	−15·25, −6·93	<0·001	
	Cohort	5	412	1864	−23·55	−30·68, −16·41	<0·001	
Statin use	Yes	11	791	2733	−11·15	−20·49, −1·80	0·02	0·85
	No	62	12 503	18 345	−10·17	−13·17, −7·17	<0·001	

MD, mean difference.

good quality[33–35,37,39–43,45,48,49,51,54–57,59,60,62,64–70,72–74,76–82,84,86–100,102–108], sixteen were satisfactory[31,44,46,47,50,52,53,58,61,63,71,75,83,85,101] and the remaining three were unsatisfactory[32,36,38]. Specifically, the quality for cross-sectional studies was good for twelve, satisfactory for four and unsatisfactory for three; for case–control studies, nine were very good, thirty-five were good and twelve were satisfactory; and for cohort studies, three were very good and three good. For the unsatisfactory studies, most of them did not have enough information to evaluate the representativeness for the target population. In addition, all the pain-related outcome measurements were based on questionnaire or self-report, and only a few of them validated the pain measurements. The quality assessment scores are shown in Supplement 2, Supplemental Table 1 (see online supplementary material).

Pooled results

Vitamin D concentration and pain

For the primary aim, seventy-three studies, containing 13 294 participants with pain and 21 078 without pain conditions, reported serum 25(OH)D levels[32,34–40,42–45,47–50,52–75,77–102,104–108]. Two publications reported the vitamin D concentration and pain conditions on different subgroups (smokers and non-smokers[39] or Italian and Estonian[53]), which are reported separately as four different studies in the current meta-analysis (Supplement 2, Supplemental Table 2).

Compared with controls, mean 25(OH)D concentration was significantly lower in patients with arthritis (MD = −12·34 nmol/l; $P < 0·001$), muscle pain (MD = −8·97 nmol/l; $P = 0·003$) and chronic widespread pain (MD = −7·77 nmol/l; $P < 0·001$), but not in patients with headache or migraine (MD = −2·53 nmol/l; $P = 0·06$; Table 2). These mean differences by disease condition were significantly different ($P = 0·004$). Because of this interaction, forest plots are shown by pain condition rather than for all conditions combined (Fig. 2). Additionally, among age- and sex-matched case–control studies, similar lower vitamin D levels also were observed in patients with arthritis (MD = −12·03 nmol/l; $P < 0·001$) and muscle pain (MD = −11·49 nmol/l, $P < 0·01$).

In addition, interaction tests were conducted by type of study design and statin use (Table 2; Supplement 2, Supplemental Figs 1 and 2). There was a significant interaction between the three types of study design ($P < 0·001$). For each study design, pain patients had significantly lower 25(OH)D concentration compared with those without pain, but the effect was strongest in cohort studies (MD = −23·55 nmol/l; $P < 0·001$), moderate in case–control studies (MD = −11·09 nmol/l; $P < 0·001$) and weakest in cross-sectional studies (MD = −3·10 nmol/l; $P = 0·001$). However, there was no interaction between studies of statin users and non-statin users (interaction test $P = 0·85$).

To investigate the impact of other covariables (year, sample size, mean age, female proportion, ratio of participants with and without pain, type of study) on the study-level estimate of the MD in 25(OH)D concentration, we performed random-effects meta-regression analyses. We did not observe any significant association for the above covariables and MD in 25(OH)D levels in both the univariate and multivariate meta-regression analyses (Supplement 2, Supplemental Table 3).

Vitamin D deficiency and pain

For the secondary aim, fifty studies reported the proportion of vitamin D deficiency among 14 027 patients with pain conditions and 14 357 without[31–34,36–38,41–43,46,51,52,54–57,59,61,62,65–69,74–77,79–83,87–89,91–99,103,106,107]. One publication[76] reported results from two studies which are included separately in the current meta-analysis (Supplement 2, Supplementary Table 4). To maintain consistency with the primary aim analyses (Table 2), the secondary aim of vitamin D deficiency was also analysed by pain condition, study design, statin use and cut-off point for vitamin D deficiency (Table 3 and Fig. 3). The odds of vitamin D deficiency was increased for arthritis, muscle

Subgroup/study ID	With pain Mean	SD	Total	Without pain Mean	SD	Total	Weight (%)	MD (95 % CI) IV, random
Arthritis								
Pietschmann (1989)	27·35	19·66	29	37·5	21·39	30	1·3	−10·15 (−20·63, 0·33)
Muller (1995)	65·91	35·8	41	64·06	26·44	72	1·2	1·85 (−10·70, 14·40)
Cutolo 1 (2006)	58·9	39·31	53	54·5	32·54	35	1·1	4·40 (−10·71, 19·51)
Cutolo 2 (2006)	35·1	15·2	64	43·3	14·24	30	1·5	−8·20 (−14·51, −1·89)
Turhanoglu (2011)	104·87	60·08	65	105·72	38·06	40	1·0	−0·85 (−19·62, 17·92)
Attar (2012)	32·3	14·4	100	31·4	16·4	100	1·5	0·90 (−3·38, 5·18)
Baykal (2012)	30·45	19·47	55	48·17	21·96	45	1·4	−17·72 (−25·94, −9·50)
Dong (2012)	55·91	12·98	72	95·85	17·22	58	1·5	−39·94 (−45·29, −34·59)
Heidari (2012)	84·47	87·11	147	82·87	71·39	239	1·0	1·60 (−15·14, 18·34)
Kostoglou-Athanassiou (2012)	38·09	17·72	44	64·4	26·49	44	1·4	−26·31 (−35·73, −16·89)
Atwa (2013)	38·56	16·02	65	61·28	11·21	40	1·5	−22·72 (−28·20, −17·24)
Orgaz-Molina (2013)	84·91	31·13	61	75·83	24·66	61	1·3	9·08 (−0·89, 19·05)
Yazmalar (2013)	72·38	63·65	145	74·43	47·9	70	1·1	−2·05 (−17·32, 13·22)
Chen (2014)	35·62	17·27	110	52·04	16·35	110	1·5	−16·42 (−21·13, −11·71)
Cote (2014)	76·54	31·63	270	77·38	29·64	1341	1·5	−0·84 (−4·93, 3·25)
Heidari (2014)	52·17	71·88	167	74·88	75·63	286	1·2	−22·71 (−36·70, −8·72)
Hong (2014)	43·12	15·59	130	57·97	15·95	80	1·5	−14·85 (−19·25, −10·45)
Sharma (2014)	43	26·85	80	55·97	35·07	80	1·4	−12·97 (−22·65, −3·29)
Brance (2015)	50·92	13·1	34	65·64	30·37	41	1·3	−14·72 (−25·01, −4·43)
Cen (2015)	35·99	12·59	116	54·35	8·2	50	1·6	−18·36 (−21·59, −15·13)
Gullo (2015)	57·41	18·97	27	79·12	12·98	41	1·4	−21·71 (−29·89, −13·53)
Matsumoto (2015)	42·18	9·4	176	48·92	11·81	186	1·6	−6·74 (−8·93, −4·55)
Park (2015)	37·77	17·646	101	42·52	22·15	101	1·5	−4·75 (−10·27, 0·77)
Petho (2015)	51·9	21·8	53	67·2	29·37	53	1·3	−15·30 (−25·15, −5·45)
Yagiz (2015)	35·47	19·97	92	33·52	14·45	62	1·5	1·95 (−3·49, 7·39)
Askari (2016)	20·22	8·24	131	72·88	24·46	262	1·6	−52·66 (−55·94, −49·38)
Elbassiony (2016)	54·91	22·96	150	71·64	23·96	150	1·5	−16·73 (−22·04, −11·42)
Gamal (2016)	48·7	13·5	55	49·1	20·3	25	1·4	−0·40 (−9·12, 8·32)
Gheita (2016)	57·66	31·7	63	81·37	32·7	62	1·3	−23·71 (−35·00, −12·42)
Liao (2016)	32·95	16·72	82	66·39	13·23	32	1·5	−33·44 (−39·28, −27·60)
Wang (2016)	48·67	20·47	154	57·91	16·72	60	1·5	−9·24 (−14·56, −3·92)
Brennan-Sperenzaa (2017)	72·8	19·62	19	76·5	17·71	10	1·2	−3·70 (−17·78, 10·38)
Wong (2017)	43·3	23·1	77	41	17·9	29	1·4	2·30 (−6·01, 10·61)
Subtotal (95 % CI)			**3018**			**3925**	**45·6**	**−12·34 (−17·97, −6·71)**
Heterogeneity: $\tau^2 = 250·33$; $\chi^2 = 940·79$, df = 32 ($P < 0·00001$); $I^2 = 97\%$)								
Test for overall effect: $Z = 4·29$ ($P < 0·0001$)								
Muscle pain								
Benson (2006)	40·88	3·52	8	58·25	15·9	8	1·3	−17·37 (−28·65, −6·09)
Duell (2008)	51·17	24·96	38	75·13	31·2	61	1·3	−23·96 (−35·11, −12·81)
Ahmed (2009)	71·39	32·95	128	85·36	34·44	493	1·5	−13·97 (−20·44, −7·50)
Tandeter (2009)	54·29	25·46	68	48·5	19·49	82	1·4	5·79 (−1·59, 13·17)
de Rezende Pena (2010)	93·62	46·87	87	95·42	40·39	92	1·2	−1·80 (−14·65, 11·05)
Linde (2010)	70·39	28·95	39	60·65	26·21	25	1·2	9·74 (−3·98, 23·46)
Backes (2011)	53·41	24·21	57	54·41	30·2	72	1·4	−1·00 (−10·39, 8·39)
Rlphagen (2012)	45·34	20·58	22	41·1	13·31	53	1·4	4·24 (−5·08, 13·56)
Azali (2013)	63·75	29·96	149	88	31·16	290	1·5	−24·25 (−30·25, −18·25)
Olama (2013)	37·69	15·23	50	46·92	13·48	50	1·5	−9·23 (−14·87, −3·59)
Eisen (2014)	47·8	10·2	108	50·4	15	166	1·6	−2·60 (−5·60, 0·40)
Mateos (2014)	57·41	23·71	205	60·15	23·96	205	1·5	−2·74 (−7·35, 1·87)
Mergenhagen (2014)	65·4	22·46	50	90·36	29·45	400	1·5	−24·96 (−31·82, −18·10)
Sezgin Ozcan (2014)	41·68	23·71	60	53.91	14·73	30	1·4	−12·23 (−20·22, −4·24)
Shantha (2014)	55·66	17·72	276	84·36	11·23	884	1·6	−28·70 (−30·92, −26·48)
Tasoglu (2015)	86·88	27·88	17	79·62	27·41	23	1·0	7·24 (−10·04, 24·52)
Kasapoğlu Aksoy (2017)	55·66	32·2	53	65·64	38·44	47	1·2	−9·98 (−23·98, 4·02)
Maafi (2016)	42·93	33·7	74	24·71	16·22	68	1·4	18·22 (9·63, 26·81)
Okyay (2016)	32·45	20·97	79	40·19	23·46	80	1·5	−7·74 (−14·65, −0·83)
Ovesjo (2016)	50	16	16	60	21·07	111	1·4	−10·00 (−18·77, −1·23)
Yildirim (2016)	39·19	17·97	99	51·42	15.23	99	1·5	−12·23 (−16·87, −7·59)
Calza (2017)	48·42	23·98	42	80·12	37·19	445	1·4	−31·70 (−39·73, −23·67)
Subtotal (95 % CI)			**1723**			**3784**	**30·5**	**−8·97 (−14·92, −3·02)**
Heterogeneity: $\tau^2 = 182·10$; $\chi^2 = 422·43$, df = 21 ($P < 0·00001$); $I^2 = 95\%$								
Test for overall effect: $Z = 2·96$ ($P = 0·003$)								

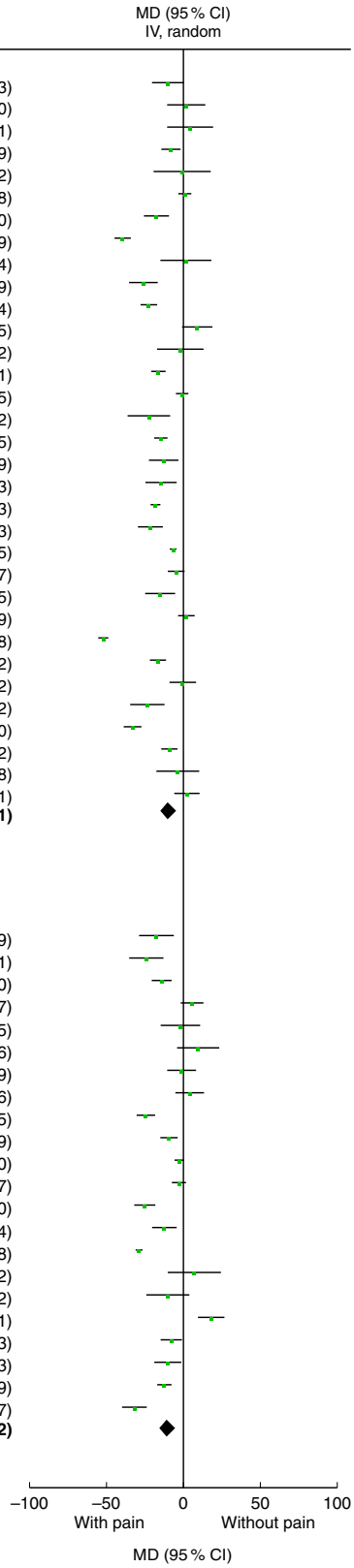

Fig. 2 (colour online) Meta-analysis of the difference in mean serum vitamin D concentration (nmol/l) between participants with and without pain-related conditions. The study-specific mean difference (MD) and 95 % CI are represented by the square and horizontal line, respectively; the centre of the diamond represents the pooled MD and its width represents the pooled 95 % CI. IV denotes inverse variance; random denotes random-effects model

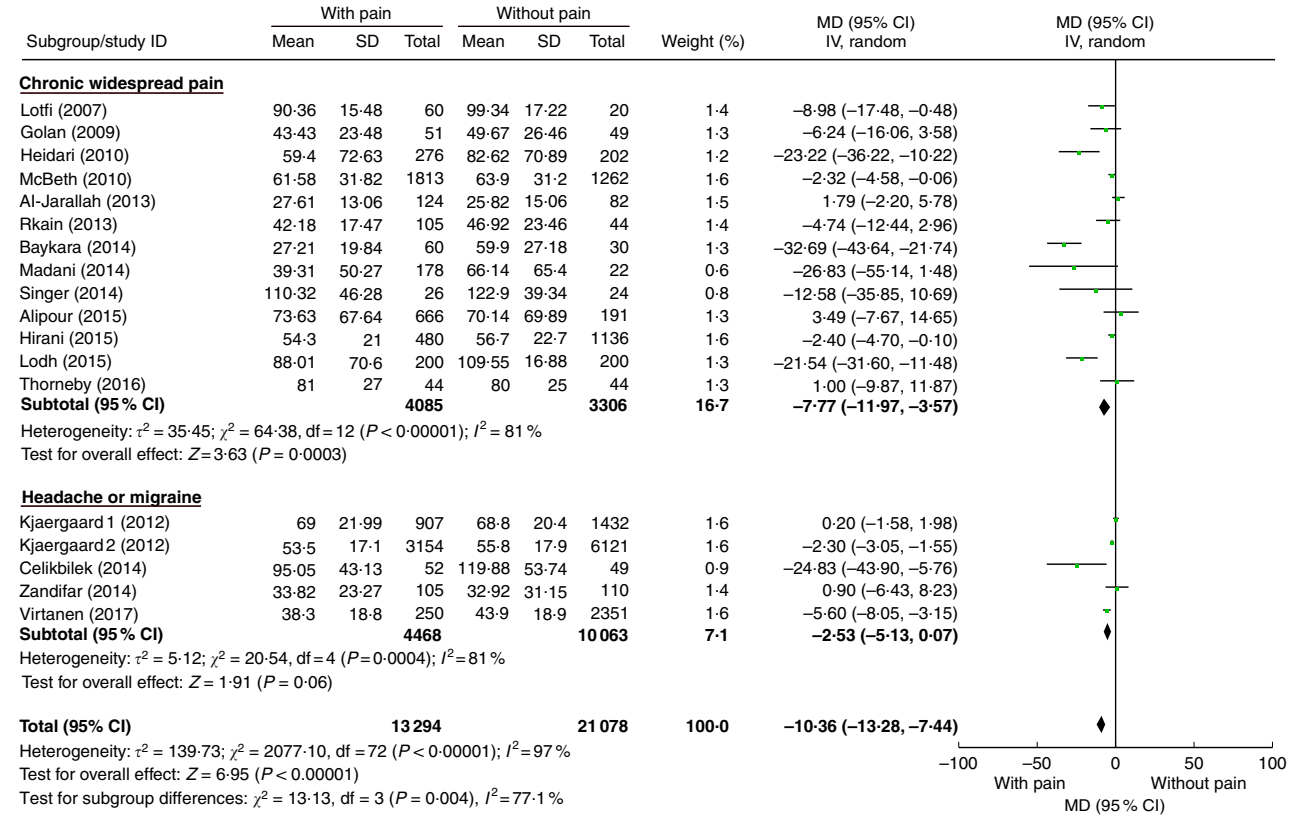

Fig. 2 *continued*

pain and chronic widespread pain, but not for headache or migraine; and also increased for each of the study designs (cross-sectional, case–control and cohort) and for statin users and non-users separately (Supplement 2, Supplemental Figs 3 and 4). There was a significant interaction associated with the 25(OH)D cut-off point ($P = 0·06$), with studies that used cut-offs below 50 or 75 nmol/l reporting significantly increased odds of vitamin D deficiency in patients with pain, but not at a very low cut-off of <25 nmol/l, although there were only two studies in the latter group (Table 3; Supplement 2, Supplemental Fig. 5). Meta-regression analyses did not find any other covariables that were significantly associated with the log(OR) of vitamin D deficiency (Supplement 2, Supplemental Table 5).

Sensitivity analysis and publication bias

For the primary and secondary aims, sensitivity analyses found similar summary measures to those shown in Figs 2 and 3 when studies were individually excluded (see Supplement 2, Supplemental Tables 6 and 7). In addition, after excluding studies with poor quality, we observed similarly lower 25(OH)D levels in arthritis, muscle pain and chronic widespread pain patients than in their controls (see Supplement 2, Supplemental Table 6). There was no convincing evidence of publication bias from funnel plots (Supplement 2, Supplemental Figs 6 and 7), nor from the Egger's test for the primary and secondary aims (25(OH)D concentration: P values for publication bias were 0·49, 0·10, 0·17 and 0·66 for arthritis, muscle pain, chronic widespread pain, and headache or migraine conditions, respectively; while for the proportion of vitamin D deficiency: P values were 0·13, 0·64 and 0·06 for arthritis, muscle pain and chronic widespread pain conditions, respectively).

Discussion

Our results show lower mean 25(OH)D concentration among patients with widespread chronic pain, muscle pain and arthritis than among their controls (Fig. 2). This result was consistent with the increased odds of hypovitaminosis D associated with these three conditions (Fig. 3). In addition, our study found that the weighted MD in 25(OH)D concentration between patients with pain and control groups is large (arthritis: 12·34 nmol/l or 20% difference; muscle pain: 8·97 nmol/l or 14% difference; chronic widespread pain: 7·77 nmol/l or 11·7% difference) compared with disease-related differences in previous studies, such as those which have reported a 3 nmol/l (5%)[109] and a 7 nmol/l (11%) difference[110] between diabetes cases and controls. Overall, these results suggest that low vitamin D status may be associated with the development of painful conditions, with the overall

Table 3 Association between hypovitaminosis D and painful conditions

Category	Subgroup	No. of included studies	No. of participants		Effect estimate			Test of subgroup differences, *P* value
			With pain	Without pain	OR	95 % CI	*P* value	
Pain conditions	Arthritis	21	2148	3411	2·17	1·56, 3·00	<0·001	0·06
	Muscle pain	16	1052	1712	2·03	1·24, 3·33	0·005	
	Chronic widespread pain	12	10 722	9124	1·51	1·24, 1·85	<0·001	
	Headache or migraine	1	105	110	0·89	0·45, 1·76	0·73	
Study design	Cross-sectional	11	10 500	9550	1·42	1·17, 1·73	<0·001	0·07
	Case–control	36	3406	4615	2·08	1·59, 2·73	<0·001	
	Cohort	3	121	192	2·32	0·76, 7·10	0·14	
Statin use	Yes	7	659	1539	1·88	1·15, 3·10	0·01	0·94
	No	44	13 368	12 818	1·92	1·58, 2·33	<0·001	
Cut-off point (nmol/l)	25	2	428	639	1·26	0·93, 1·72	0·13	0·06
	50	34	9398	7573	2·08	1·59, 2·71	<0·001	
	75	8	1999	4142	1·64	1·04, 2·57	0·03	

quality of the evidence being rated as moderate according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria[111] because of the high heterogeneity, although there was no evidence of publication bias, the quality of studies was good and the association was strong (Supplement 2, Supplemental Tables 8 and 9).

Our findings are consistent with previous meta-analyses which found significantly lower 25(OH)D levels in patients on statin therapy with myalgia compared with those without[20] and a positive association between hypovitaminosis D and chronic widespread pain[21]. However, by including a further sixty-two studies in our meta-analysis (three studies that were included in the previous meta-analysis were excluded because of controls with pain conditions or no available data), we have extended previous meta-analyses to show that 25(OH)D levels are also lower in patients with pain not caused by statin therapy – for both the 25(OH)D concentration and hypovitaminosis D aims (Tables 2 and 3). The evidence for the primary aim from the five cohort studies[104–108], which shows that low vitamin D levels at baseline predicted increased incidence of pain-related conditions (Table 2), supports a possible causal association. In addition, in analyses based on painful conditions, lower mean 25(OH)D levels were found in patients with arthritis, muscle pain and chronic widespread pain (compared with those without pain) for both primary and secondary aims, but not in patients with headache or migraine (Table 2). The latter finding could be due to chance because of the small number of studies (three cross-sectional comparisons from two publications, and two case–control studies) and further research is required to clarify this.

The strengths of the current meta-analysis include: (i) two aims that were predefined at the start of the study; (ii) a search of three electronic databases (MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials), which reduces the possibility of missing relevant articles; (iii) assessment for publication bias by both funnel plots and Egger's test; (iv) inclusion of broader pain conditions, particularly studies of patients with pain who were not on statins; and (v) evaluation of the quality of included studies by the Newcastle–Ottawa scale.

Nevertheless, there are several limitations of the current meta-analysis. Most of the included studies were case–control or cross-sectional in design, which could have resulted in reverse causation between pain and lower vitamin D levels. Some studies reported medians, and not means and SD, and information may have been lost in the transfer process. In addition, the included studies lack or have limited adjustment for potential confounders, so the unadjusted association must be interpreted with caution as the spurious associations can be result from potential confounders.

Of major importance is the high heterogeneity observed in the meta-analysis. We tried to identify the sources of this using subgroup, meta-regression and sensitivity analyses, but it remained even when analysing studies by type of pain condition or study design. The high heterogeneity could partly be due to the higher heterogeneity often seen in meta-analyses of observational studies where there is variable control of confounding, compared with randomized controlled trials where effects from standard interventions congregate more closely; and also due to the relatively large number of studies (up to thirty-three) included in the pooled analyses which increases the opportunity for heterogeneity. In our view, this does not lessen the validity of our findings as the results of individual studies almost all go in the same direction (Supplement 2, Supplemental Figs 1 and 2). Further, we used a random-effects model which allows for between-study variation of effect in its calculations.

In addition, the definition of pain varied in each individual publication, so that combining them may also have contributed to the heterogeneity of our results. Therefore, more objective outcome measurements, such as consumption of analgesics as reported in previous studies which have found increased opioid use in people with

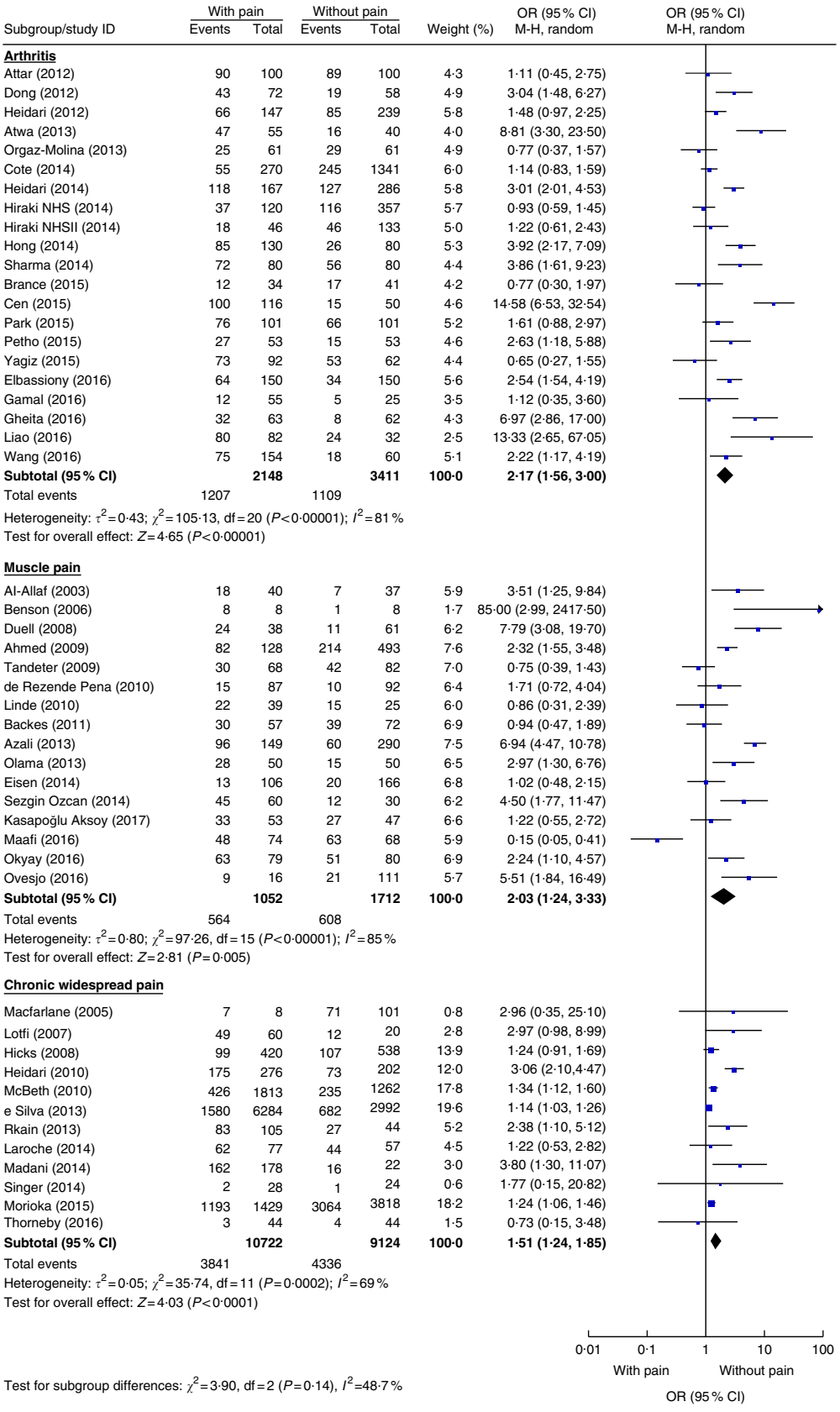

Fig. 3 (colour online) Meta-analysis of the difference in the proportion of vitamin D deficiency between participants with and without pain-related conditions. The study-specific OR and 95 % CI are represented by the square and horizontal line, respectively; the centre of the diamond represents the pooled OR and its width represents the pooled 95 % CI. M-H denotes Mantel–Haenszel; random denotes random-effects model

vitamin D deficiency[46,112], or use of validated questionnaires to assess pain severity and function[113], would help to clarify the association between vitamin D levels and pain in future studies.

Conclusion

In conclusion, our meta-analysis of eighty-one observational studies suggests that low vitamin D concentration is associated with arthritis, muscle pain and chronic widespread pain. Further well-designed randomized controlled trials should be conducted to confirm the relationship between vitamin D levels and painful conditions.

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Supplementary material

To view supplementary material for this article, please visit https://doi.org/10.1017/S1368980018000551

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