Does Vitamin D Affect Risk of Developing Autoimmune Disease?: A Systematic Review

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Objectives: We evaluated the epidemiologic evidence that vitamin D may be related to human autoimmune disease risk.

Methods: PubMed, limited to English from inception through April 2010, was searched using keywords: "vitamin D," "autoimmune," and autoimmune disease names. We summarized in vitro, animal, and genetic association studies of vitamin D in autoimmune disease pathogenesis. We sorted epidemiologic studies by design and disease and performed a systematic review of (a) cross-sectional data concerning vitamin D level and autoimmune disease; (b) interventional data on vitamin D supplementation in autoimmune diseases; and (c) prospective data linking vitamin D level or intake to autoimmune disease risk.

Results: Vitamin D has effects on innate and acquired immune systems, and vitamin D receptor polymorphisms have been associated with various autoimmune diseases. In experimental animal models, vitamin D supplementation can prevent or forestall autoimmune disease. Of 1446 studies identified and screened, 76 studies that examined vitamin D levels in autoimmune disease patients, particularly with active disease, and compared with controls. Nineteen observational or interventional studies assessed the effect of vitamin D supplementation as therapy for various autoimmune diseases (excluding psoriasis and vitiligo) with a range of study approaches and results. The few prospective human studies performed conflict as to whether vitamin D level or intake is associated with autoimmune disease risk. No interventional trials have investigated whether vitamin D affects human autoimmune disease risk.

Conclusions: Cross-sectional data point to a potential role of vitamin D in autoimmune disease prevention, but prospective interventional evidence in humans is still lacking.

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The cause of the breakdown in immune tolerance that allows for the development of immunity to self-targets in autoimmune diseases such as rheumatoid arthritis (RA), inflammatory bowel disease, and multiple sclerosis (MS) is unknown. It is hypothesized that environmental exposures, including factors that stimulate endogenous inflammation, trigger the development of autoimmunity in genetically susceptible individuals (1). Autoimmune diseases cluster within families and within individuals, with many individuals developing more than 1 autoimmune disease (2-4). Polymorphisms in several genes have been associated with increased susceptibility to multiple autoimmune diseases (2,5-8). Autoimmune diseases also share epidemiologic risk factors such as cigarette smoking and crystalline silica exposure (9,10). Many autoimmune diseases are characterized by

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activation of the adaptive immune system with associated innate immune cell activation leading to inappropriately elevated levels of widespread systemic inflammation, in particular, tumor necrosis factor-α (TNFα) and interleukins-1 and -6 (IL-1 and IL-6), potent cytokines produced by macrophages and monocytes among other cell types.

The Autoimmune Diseases Coordinating Committee of the National Institutes of Health estimated that 23.5 million Americans were affected by 1 or more autoimmune diseases in 2005 (11). This number appears to be growing and is almost certainly an underestimate (12). For unknown reasons, most autoimmune diseases are more common among women than men, although this is less true after menopause (13). Together, autoimmune diseases are the third leading cause of morbidity in the industrialized world and a leading cause of mortality among women (14,15). With the exception of celiac sprue and pernicious anemia, there are no current means for the prevention or cure of most autoimmune diseases. Treatment of autoimmunity often consists of corticosteroids, immunosuppressive agents, and biologic agents that target TNF and other inflammatory cytokines. The 2005 National Institutes of Health report estimated that the annual direct and indirect costs of autoimmune diseases in the U.S. far exceed $100 billion annually (11).

Vitamin D, obtained from diet, supplements, or conversion of 7-dehydrocholesterol in the skin by ultraviolet-B radiation, is hydroxylated in the liver to 25-hydroxyvitamin D [25(OH)D], the major circulating vitamin D metabolite (16,17), which is further synthesized by 1α-hydroxylase to the active form, 1,25-dihydroxyvitamin D [1,25$(OH)_2$D]. Current dietary recommendations are geared only to prevent quite low vitamin D levels. Circulating 1,25$(OH)_2$D has a very short half-life and is tightly regulated by parathyroid hormone. Fibroblast growth factor 23, which is produced in osteoblasts, is also important in regulating 1,25$(OH)_2$ production in the kidney (18). "Normal" levels for 25(OH)D at most laboratories are >20 ng/mL. However, at 25(OH)D levels below 30 ng/mL, parathyroid hormone secretion is increased, suggesting that the current "normal" levels for vitamin D are inadequate (19-21). Vitamin D deficiency using the current standard for serum 25(OH)D level is relatively common. In 1 study, over 50% of inpatients at Massachusetts General Hospital had low 25(OH)D levels (22).

Vitamin D is an inexpensive and relatively safe nutritional supplement, widely held to have anti-inflammatory and immunomodulating effects. The purported health benefits of this inexpensive and available dietary supplement have received enormous attention in both the medical literature and the popular press (23-26). It has been widely hypothesized that vitamin D deficiency acts as an environmental trigger for the induction of autoimmunity, and that high-dose vitamin D supplementation could be preventive (27-34), yet the scientific evidence appears to conflict. The Agency for Healthcare Research and Quality recently performed a systematic review entitled, "Vitamin D and Calcium: A Systematic Review of Health Outcomes," published in August 2009 (35). The report investigated the published literature regarding serum 25(OH)D or 1,25$(OH)_2$D concentrations and multiple disease outcomes, including autoimmune diseases. The review did not include studies investigating sunlight exposure as a source of vitamin D intake nor did it include studies in which dietary intake of vitamin D was assessed without measurement of serum levels, as nutrient composition tables for vitamin D were thought to be inadequate. The report also excluded cross-sectional and retrospective case-control studies where the measure of exposure occurred after or concurrent with the outcome. After these exclusions, no studies were identified that addressed the relationship between vitamin D and incident autoimmune disease. We sought to perform an extensive systematic review of the published literature to evaluate the strength of all types of evidence linking vitamin D intake to the risk of incident autoimmune diseases.

METHODS

We searched the PubMed database from inception through April 2010 restricted to English language and human studies with the following search terms "vitamin D AND"; "autoimmune disease"; "autoimmunity"; "rheumatoid arthritis"; "spondylitis"; "spondyloarthropathy"; "psoriatic arthritis"; "systemic lupus erythematosis"; "scleroderma"; "systemic sclerosis"; "myositis"; "dermatomyositis"; "polymyositis"; "vasculitis"; "polymyalgia rheumatica"; "type 1 diabetes"; "multiple sclerosis"; "autoimmune thyroiditis"; "Graves"; "Hashimoto's"; "inflammatory bowel disease"; "Crohn's disease"; "ulcerative colitis"; "vitiligo"; "autoimmune hepatitis"; "Behcet's"; "uveitis"; "Addison's." We excluded review articles, case reports, and studies primarily related to bone metabolism or osteoporosis (unless they included relevant data on vitamin D and autoimmune disease risk). Studies on the topical and parenteral treatment of psoriasis and vitiligo with vitamin D analogs were beyond the scope of this review and treatment with vitamin D-related compounds has been extensively reviewed in a systematic manner (eg (36)). In addition, primary biliary cirrhosis and celiac disease were not included in the PubMed search since loss of fat-soluble vitamins is common in these diseases and vitamin D deficiency is highly prevalent in cirrhotics (37). We also conducted hand searches of reference lists to add to our list of articles.

We aimed to address the following questions: (1) What are the cross-sectional data linking vitamin D to autoimmune disease?; (2) What are the prospective data linking vitamin D to the risk of future autoimmune disease?; and (3) What are the interventional data concerning dietary and/or supplemental vitamin D and risk of autoimmune disease? We carefully reviewed the abstracts of the studies identified and selected those relevant to our questions to

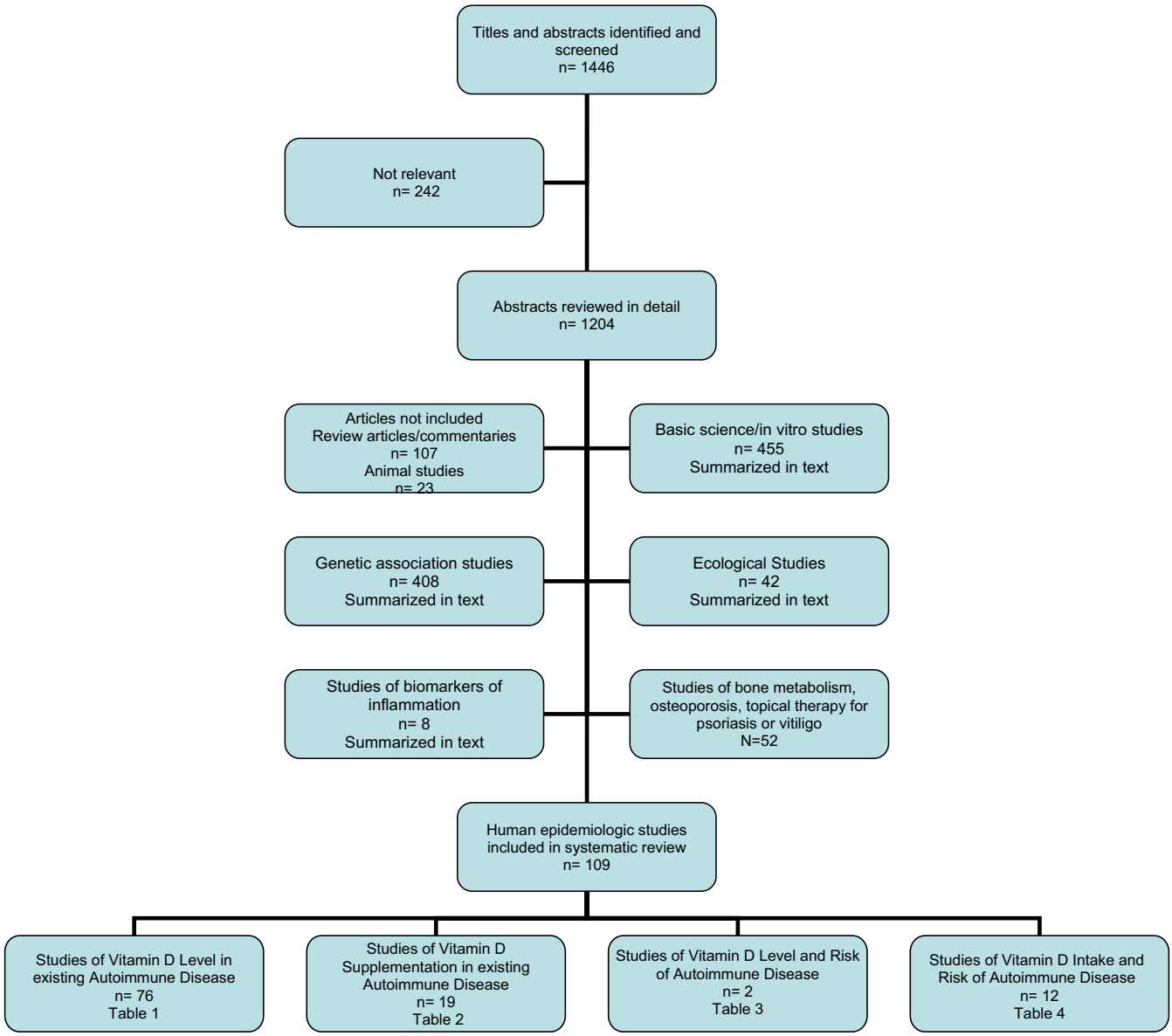

Figure 1 Flow diagram of literature search strategy and review. (Color version of figure is available online.)

perform a systematic review of the strengths and weaknesses of this literature. We included and qualitatively summarized background basic science studies, both in vitro and in animal models, genetic studies, studies of vitamin D's effects on biomarkers of systemic inflammation, as well as ecologic/geographic epidemiologic studies of the incidence or prevalence of autoimmune diseases according to latitude (potentially related to vitamin D from UV light).

To explore the potential for publication bias among studies of vitamin D intake and risk of developing autoimmune disease, a funnel plot was created for these studies by plotting the risk estimates (odds ratios or relative risks) of developing an autoimmune disease in each study (*x*-axis) against the number of autoimmune cases in each study (*y*-axis). (A pattern resembling a symmetrical inverted funnel is generally interpreted as showing no significant publication bias, whereas the absence of studies in the lower sections of an inverted funnel, where small studies would lie, implies the presence of publication bias (38).)

RESULTS

We identified 1446 potentially relevant studies through our literature search and sorted and reviewed them as in Figure 1. Two hundred forty-two were immediately excluded as irrelevant to this review, leaving 1204 that were reviewed in further detail. Basic science and in vitro studies, genetic studies, ecological studies, and studies of biomarkers of inflammation were reviewed and summarized in the text. The human epidemiologic studies were sorted into epidemiologic studies of vitamin D levels in existing autoimmune disease (See the supplemental Table 1), studies and

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Table 2 Studies and Trials of Vitamin D Supplementation in Existing Autoimmune Disease

Autoimmune Disease	Population	Study Design	Subjects	Controls
Rheumatoid arthritis	Yugoslavia	Open-label trial	19 RA on DMARDs	—
Rheumatoid arthritis	Sweden	Double-blind trial	25 RA treated	24 RA placebo
Psoriatic arthritis	Hungary	Open-label trial	10 PsoA	9 PsoA placebo
Psoriatic arthritis	North America	Open-label study	10 PsoA	—
Systemic lupus erythematosus	Spain	Open-label; observational	60 SLE	20 SLE
Scleroderma	Holland	Randomized, double-blind, placebo controlled trial	7 scleroderma, 20 morphea	—
Scleroderma	Macedonia	Open-label trial	3 morphea	—
Scleroderma	Holland	Open-label trial	7 pediatric linear scleroderma	—
Scleroderma	Holland	Open-label trial	3 generalized morphea	—
Scleroderma	France	Open-label trial	11 scleroderma p	—
Type I diabetes mellitus	China	Randomized controlled trial	17 latent autoimmune diabetes (LADA)	18 LADA
Type I diabetes mellitus	Italy	Randomized controlled trial	34 recent-onset T1D Receiving calcitriol plus insulin	33 recent-onset T1D receiving nicotinamide plus insulin
Multiple sclerosis	Canada	Randomized controlled trial	25 MS	24 MS
Multiple sclerosis	North America	Observational study	40 MS on either low-dose cholecalciferol or high-dose ergocalciferol	9 MS without vitamin D
Multiple sclerosis	Canada	Open-label trial	12 MS patients in an active phase	—

Table 2 Continued

Vitamin D Analog	Follow-up Period/ Duration of Study	Results	Year	Reference
Oral alpha-calcidiol (2 μg/d)	3 mo	Clinical improvement in the majority of 89%	1999	Andjelkovic et al (182)
Oral calciferol (100,000 IU/d)	1 yr	67% objective and subjective improvement; lower sedimentation rates and higher hemoglobin levels	1973	Brohult et al (181)
Oral alphacalcidol (0.25 μg twice/d)	6 mo	$P = 0.048$ for disease activity at 6 mo	2009	Gaal et al (183)
Oral 1,25(OH) D	6 mo	$P < 0.01$ for tender joint count	1990	Huckins et al (184)
2 μg/d various doses cholecalciferol or calcidiol liquid	2 yr	$P = 0.87$ and $P = 0.63$ for disease activity and damage indices; $P = 0.001$ for fatigue based on a visual analogue scale. No effect on SLE activity	2010	Ruiz-Irastorza et al (185)
Oral calcitriol 0.75 μg/d for 6 mo plus 1.25 μg/d for 3 mo	9 mo with 6 mo follow-up	No significant difference between placebo and calcitriol with regards to skin score	2000	Hulshof et al, (190)
Oral calcitriol 0.5 to 0.75 μg/d	4 to 6 mo with 6 mo follow-up	Significant clinical improvement with regards to joint mobility, skin flexibility, skin induration	1999	Caca-Biljanovska et al (188)
Oral calcitriol 0.25 to 0.75 μg/d per dose-escalating protocol	3 to 10.5 mo	5 of 7 patients with good to excellent improvement of skin lesions	1999	Elst et al (189)
Oral calcitriol 0.5 to 0.75 μg/d	3 to 7 mo	Improved mobility of joints and increased skin extensibility	1994	Hulshof et al (187)
Oral calcitriol at a mean dose of 1.75 μg/d	6 mo to 3 yr	Significant improvement of clinical findings	1993	Humbert et al (186)
1 alpha-OH D3 0.5 μg/d (± Insulin)	1 yr	$P < 0.01$; 70% vs 22% maintained fasting C-peptide 1 alpha-OH D3 plus insulin therapy can preserve beta-cell function in patients with LADA	2009	Li et al PMID 19488999 (191)
Calcitriol 0.25 μg on alternate days	1 yr	$P < 0.03$ for reduction in insulin requirement at 3 and 6 mo but not 9 and 12 mo Calcitriol has a modest effect on residual beta-cell function and only temporarily reduces the amount of insulin required	2006	Pitocco et al (192)
Up to 40,000 IU/d over 28 weeks, then 10,000 IU/d for 12 wk	52 wk (Phase I/II dose-escalation trial)	$P = 0.09$ for annualized relapse rate (0.26 vs 0.45) Treatment group patients appeared to have fewer relapse events, although not statistically significant	2010	Burton et al (195)
Cholecalciferol (<800 IU/d) or ergocalciferol (50,000 IU/d) for 7 to 10 days then weekly or biweekly doses	4 to 12 mo	$P = 0.01$ for 25(OH) D increase in patients switching from low- to high-dose supplementation; effect on relapse rate not studied	2009	Hiremath et al (165)
Daily calcium + increasing doses of vitamin D3 (from 28,000 to 280,000 IU/wk)	28 wk	$P = 0.03$ for decreased number of gadolinium-enhancing lesions per patient Vitamin D did not affect disease progression or activity but the number of gadolinium-enhancing lesions per patient decreased	2007	Kimball et al (194)

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Table 2 Continued

Autoimmune Disease	Population	Study Design	Subjects	Controls
Multiple sclerosis	North America	Open-label trial	15 cases of relapsing-remitting MS	—
Multiple sclerosis	Israel	Open-label trial	5 relapsing-remitting MS	—
Multiple sclerosis	U.S.	Observational	16 MS	—
Inflammatory bowel disease	Eastern Europe	Open-label trial	17 Crohn's taking 1,25(OH)2 D	19 Crohn's taking 25(OH) D

DMARDs, disease-modifying anti-rheumatic drugs; PsOA, psoriatic arthritis; T1D, type 1 diabetes; LADA, latent autoimmune diabetes.

trials of vitamin D supplementation in existing autoimmune disease (Table 2), epidemiologic studies of vitamin D level, and risk of autoimmune disease (Table 3) and epidemiologic studies of vitamin D intake and risk of autoimmune disease (Table 4). We reviewed the evidence in each of the studies in these tables in detail and summarized it in the text.

Basic Science: In Vitro and In Vivo Studies

Through binding to the vitamin D receptor (VDR), the lipid-soluble active $1,25(OH)_2D$ regulates an array of genes, many involved in inflammation and acquired and innate immune responses (27,39-42). VDRs are found at high levels on dendritic cells, T and B lymphocytes, and macrophages. The function of these cells is profoundly affected by binding of activated $1,25(OH)_2D$ (43-47). The 1α-hydroxylase that converts 25(OH)D to its active form is expressed in the kidney, in activated macrophages, dendritic cells, and other tissues (29,48,49). This form of the enzyme, unlike that in the kidney, is not regulated by parathyroid hormone, but rather inducible by factors including interferon-γ and is downregulated with dendritic cell maturation (50). The expression of VDRs on resting CD4+ T cells increases 5-fold with T-cell activation (51). $1,25(OH)_2D$ inhibits the expression of IL-2, an important growth factor for T lymphocytes, and suppresses the secretion of Th1 cytokines IL-12, interferon-γ, and TNF, while increasing IL-4, IL-5, and IL-10, leading to the development of a Th2-skewed T-cell population (52-58). The addition of $1,25(OH)_2D$ to CD4+ T cells also inhibits the expression of IL-6, a cofactor stimulating Th17 cells, important in the development of autoimmunity (59,60). When added to systemic lupus erythematosus (SLE)-patient derived B cells in vitro, $1,25(OH)_2D$ inhibits autoantibody production (61).

In vitro, $1,25(OH)_2D$ inhibits the differentiation of monocytes into dendritic cells and blocks the stimulatory effects that T cells have on them (58,62,63). Instead, $1,25(OH)_2D$ promotes monocyte differentiation into macrophages, prevents them from releasing inflammatory

Table 3 Epidemiologic Studies of Vitamin D Level and Risk of Developing an Autoimmune Disease

Autoimmune Disease	Population	Study Design	Subjects	Controls
Rheumatoid arthritis	Holland	Case-control	79 subjects who donated blood and later developed RA. Samples from 3 time points: 1, 2, and 5 yr before symptoms	79 controls matched for age, sex, and time of sample donation
Multiple sclerosis	North America	Case-control	257 military recruits with banked blood who later developed MS	514 controls matched for age, sex, race/ethnicity, and dates of blood collection

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Table 2 Continued

Vitamin D Analog	Follow-up Period/ Duration of Study	Results	Year	Reference
Oral calcitriol 2.5 μg/d	48 wk	33% at baseline vs 29% at both 24 and 48 wk (for gadolinium-enhancing lesions). On-study exacerbation rate (27%) was less than baseline	2005	Wingerchuk et al (219)
Alphacalcidol 1.5 μg/d	6 mo	3 patients stable, 1 improved, 1 relapsed	2003	Achiron et al (220)
Calcium, magnesium, and vitamin D as cod liver oil cod liver oil at the rate of 5000 i.u./d	1 to 2 yr	Fewer exacerbations than expected historically $P < 0.01$	1986	Goldberg et al (193)
Supplemental (1,25 OH vs 25(OH) D)	12 mo	$P < 0.05$ (for disease activity) 1,25(OH)2 D has a more prominent beneficial effect on disease activity compared with 25(OH) D	2009	Miheller et al (196)

cytokines and chemokines (64), and reduces their capacity to present antigens to lymphocytes by decreasing MHC-II molecule cell surface expression (39,65). $1,25(OH)_2D$-VDR transcriptional signaling also exerts anti-inflammatory effects through the downregulation of the prostaglandin pathway and cyclooxygenase-2 (66) and tolerizing effects through capacity to convert CD4 T cells into IL-10-secreting T regulatory cells, suppressing the proliferation of responder T cells (67). 1,25(OH)2D interacts with VDRs on osteoblasts, stimulating expression of the receptor activator of nuclear factor kB ligand (27). Immature dendritic cells that have differentiated from monocytes in the presence of $1,25(OH)_2D$ respond poorly to inflammatory chemokines that regulate dendritic cell maturation and migration to lymph nodes (45). Experimental data show that 25(OH)D can inhibit pro-inflammatory cytokines such as IL-6 and TNF-α, decrease serum levels of C-reactive peptide (CRP), and upregulate production of the anti-inflammatory cytokine IL-10 (44). $1,25(OH)_2D$ downregulates dendritic cell production of IL-12 and augments IL-10, important in the development of T regulatory (Treg) cells (27,58). As dendritic cells are central to the maintenance of both protective immunity and self-tolerance (68,69), vitamin D's influence on their maturation and function could have consequences on autoimmune disease risk and/or progression. However, as the pathogenesis of autoimmune disease itself is still unclear, many of the pathways implicated suggest a potential role of vitamin D insufficiency in disease progression, but it is not clear to what role in the triggering of autoimmune disease vitamin D intake or deficiency play.

In vivo, supplementation with $1,25(OH)_2D$ forestalls the development of inflammatory arthritis, autoimmune encephalomyelitis (a model for MS), type I diabetes, and autoimmune thyroiditis in experimental animal models (70-74). Treatment with a low calcemic vitamin D analog had a prophylactic as well as therapeutic effect on a murine model of Th1-like colitis (75). Administration of $1,25(OH)_2D$ or its analogs to nonobese diabetic mice modulates the expression of chemokines and cytokines and prevents diabetes (76). Vitamin D receptor knock-

Table 3 Continued

Hormone Studied	Confounders Considered	Results	Year	Reference
25(OH) D	Age, sex, time sample donation	No association between vitamin D level and preclinical RA (1, 2, 5, and more yr before symptoms)	2006	Nielen et al (197)
25(OH) D	Age, sex, race/ethnicity, and dates of blood collection	OR 0.59, 95% CI 0.36 to 0.97, for the risk of MS among whites Inverse relation is particularly strong before age 20. No association among blacks and Hispanics	2006	Munger et al (198)

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Table 4 Epidemiologic Studies of Vitamin D Intake and Risk of Developing Autoimmune Disease

Autoimmune Disease	Population	Study Design	Subjects	Controls	Vitamin D Intake
Rheumatoid arthritis	North America (Nurses' Health Study)	Prospective cohort	722 who developed RA	186,389	Dietary and supplement intake
Rheumatoid arthritis	North America (Iowa Women's Health Study)	Prospective cohort	152 who developed RA	29,386	Diet and supplement intake
Systemic lupus erythematosus	North America (Nurses' Health Study)	Prospective cohort	190 who developed SLE	186,389	Diet and supplement intake
Type I diabetes mellitus	Finland (Diabetes Prediction and Prevention Study)	Birth cohort	165 children who developed 3 times per day or advanced beta-cell autoimmunity	3723 infants	Maternal vitamin D intake and at 1 and 3 mo post partum
Type I diabetes mellitus	Italy	Case-control	83 T1D ages 0 to 14	166 age- and sex-matched, same region	Vitamin D administration during lactation as baby (recall)
Type I diabetes mellitus	Sweden	Cohort-retrospective and prospective	8.7% at 1 yr and 8.9% at 2.5 yr + for glutamic acid decarboxylase or islet antigen-2 autoantibodies	18,886 infants	Questionnaire: vitamin D supplementation during pregnancy, at 1 yr and 2.5 yr
Type I diabetes mellitus	North America (Diabetes Autoimmunity Study in the Young)	High-risk cohort	16 children who developed islet-cell autoimmunity	206 children without islet-cell autoimmunity	Maternal dietary and supplemental vitamin D intake during pregnancy—recalled after birth
Type I diabetes mellitus	Norway	Case-control	545 cases (children mean age 10.9)	1668 controls population (children mean age 9.3)	Questionnaire: vitamin D supplement use during pregnancy and the first year of life (recalled)
Type I diabetes mellitus	Finland	Birth cohort	81 developed T1D	10366 newborns	Vitamin D supplementation during first year of life

Table 4 Continued

Follow-up Period/ Duration of Study	Confounders Considered	Results	Year	Reference
Up to 22 yr	Age, all women, race, age at menarche, oral contraceptive use, parity, duration of breastfeeding, menopausal status, postmenopausal hormone use, cigarette smoking, latitude of residence at age 15 (North, Middle or South U.S.), physical activity, body mass index	No association; highest quintile intake RR 1.0 (95%CI 0.8, 1.3)	2008	Costenbader et al (200)
11 yr	Age, all women, all postmenopausal	Higher intake at baseline associated with lower risk up to 11 yr later: RR 0.67 (95%CI 0.44,1.00)	2004	Merlino et al (199)
Up to 22 yr	Age, all women, race, age at menarche, oral contraceptive use, parity, duration of breastfeeding, menopausal status, postmenopausal hormone use, cigarette smoking, latitude of residence at age 15 (north, middle, or south U.S.), physical activity, body mass index	No association; highest quintile intake RR 1.4 (95%CI 0.8, 2.3)	2008	Costenbader et al (200)
Mean of 4.3 yr	Familial diabetes and genetic risk factors for T1D, sex, gestational age, maternal age, maternal education, delivery hospital, route of delivery, number of earlier deliveries, and smoking during pregnancy	Maternal intake of vitamin D from food RR 1.25 (95%CI 0.80,1.95), and from supplements RR 1.05 (95%CI 0.95 to 1.16) for risk of advanced beta cell autoimmunity/type 1 diabetes in offspring	2010	Marjamaki et al (208)
Recall as adults	Medical history of severe infections nor history of surgical operations	OR 0.31 (95% CI 0.11, 0.8) for vitamin D administration during lactation and risk type 1 DM	2007	Tenconi et al (202)
2.5 yr	Familial type 1 diabetes, maternal education, maternal age, delivery type, weight increase from birth, breast-feeding duration, introduction of cow's-milk protein, fish intake	OR 0.71 (95% CI 0.52 to 0.96) for reduced islet-cell autoimmunity at 1 yr, but OR 1.25 (95%CI 0.91, 1.73) at 2.5 yr. Surrogate measure for type 1 diabetes used.	2007	Brekke et al (221)
Average 4 yr	HLA genotype, family history of type 1 diabetes, presence of GDM, and ethnicity	HR 0.37 (95% CI 0.17 to 0.78) for increased maternal vitamin D intake and risk for islet-cell autoimmunity. Surrogate measure for type 1 diabetes used.	2003	Fronczak et al (207)
	Maternal use of cod liver oil during pregnancy, child's use of cod liver oil during the first year of life, duration of exclusive breastfeeding, child's age at introduction of solid foods, maternal education, maternal smoking during pregnancy, maternal age at delivery, child's number of siblings, type 1 diabetes among child's siblings or parents, and the child's age and sex	OR 0.98 (95% CI 0.73, 1.31) for maternal use of vitamin D $\geq$5 times/wk vs none during pregnancy and OR 0.97 (0.73, 1.29) for vitamin D use $\geq$5 times/wk during first year of life	2003	Stene et al (203)
31 yr	Sex, maternal parity, gestational and maternal age, maternal education, social status, birth weight, and growth rate in infancy and suspected rickets	RR 0.12 (95% CI 0.03 to 0.51) for regular vs no supplementation	2001	Hypponen et al (206)

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Table 4 Continued

Autoimmune Disease	Population	Study Design	Subjects	Controls	Vitamin D Intake
Type I diabetes mellitus	Norway	Case-control	78 cases	980 controls	Questionnaire: Maternal vitamin D intake during pregnancy (recall)
Type I diabetes mellitus	Europe (7 centers)	Case-control	820 cases	2335 controls—population-based, age-group matched	Questionnaire or interview: recalled infancy vitamin D intake
Multiple sclerosis	North America (Nurses' Health Study)	Prospective cohort study	173 MS cases	92,253 women	Dietary and supplemental vitamin D

out mice develop severe diarrhea, rectal bleeding, and marked body weight loss, leading to death in 2 weeks. Thus, vitamin D deficiency is thought to compromise the mucosal barrier and increase susceptibility to mucosal damage and potentially the risk of inflammatory bowel disease (77).

Evidence in Humans: Associations of Vitamin D with Circulating Biomarkers of Systemic Inflammation

Cross-sectional studies in healthy and ill populations suggest potential favorable effects of vitamin D—as measured by circulating 25(OH)D, sun exposure, or dietary or supplement intake—on inflammatory biomarkers (78-80). Inverse associations between serum vitamin D levels and serum CRP concentrations have been found in patients with diabetes mellitus, atherosclerotic vascular disease, inflammatory polyarthritis, and prolonged chronic illness (35,81,82). Increased TGF-β serum levels were observed when vitamin D was given for a 6-month period to 16 subjects with MS (83). TNF-α, interferon-γ, and IL-13 levels, however, did not change after supplementation. In a trial involving 200 overweight subjects enrolled in a weight loss program, participants were randomized to vitamin D (83 μg/d) or placebo in a double-blind manner for 12 months and serum TNF-α levels did decrease more in the vitamin D group than in the placebo group marker (10.2% compared with 3.2% decrease; $P = 0.049$) (84). In a recent interventional study, 324 adults were assigned to 20,000 IU of vitamin D per week, 40,000 IU vitamin D per week, or placebo. Multiple cytokines, including IL-2, -4, -5, -10, -12, -13, -17, intercellular adhesion molecule-1, interferon-γ, monocyte chemotactic protein-1, and high CRP, were measured at the start and end of 1 year. No significant differences in changes levels of any of these cytokines was detected, nor was there any indication of a polarization of the T cells toward a Th2 dominant type (85).

Ecologic Associations Implicating Vitamin D in Autoimmune Disease

Evidence comes from ecologic observations that several autoimmune diseases, including inflammatory bowel disease, MS, type I diabetes, and RA, are more prevalent at northern latitudes where sun exposure is reduced (86-92). The strongest ecologic evidence linking vitamin D with autoimmune disease risk is for MS (93). An increased prevalence of MS at northern, compared with southern, latitudes has long been observed and a strong inverse correlation of MS incidence with UV light exposure is also seen (91,94). MS has also been associated with birth during the winter compared with other seasons of the year and it is hypothesized that this could reflect low maternal vitamin D during pregnancy (95). Last, seasonal variation in MS relapses detected by magnetic resonance imaging has been observed, with increased flares occurring during the winter compared with summer months (96).

Genetic Polymorphisms in Vitamin D Pathway Genes Associated with Autoimmune Diseases

Polymorphisms in the VDR gene have been associated with increased risk of multiple autoimmune diseases, including Hashimoto's thyroiditis, inflammatory bowel disease, Graves' disease, RA, SLE, primary biliary cirrhosis, autoimmune hepatitis, Addison's disease, vitiligo, celiac disease, and type I diabetes, as well as MS in humans (97-112). A vitamin D response element is found in the promoter region of the HLA DRB1*1501 allele, an allele strongly associated with MS susceptibility pathogenesis in Caucasians (112). However, not all of the polymorphisms associated with autoimmune diseases in past studies have known functional consequences and the strengths of the associations vary. Moreover, not all of these associations have been replicated.

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Table 4 Continued

Follow-up Period/ Duration of Study	Confounders Considered	Results	Year	Reference
—	Age, sex, breastfeeding and maternal education	OR 1.27 (95% CI 0.70, 2.31) for vitamin D supplementation in first year life	2000	Stene et al (204)
—	Age, birth weight, duration of breast feeding, maternal age, and study center	OR 0.67 (95% CI 0.53, 0.86) for vitamin D supplementation in infancy	1999	EURODIAB Substudy 2 study group (222)
Up to 20 years	Age, all women, smoking, and latitude at birth	RR 0.67 (95% CI 0.40,1.12); *P* trend 0.006; for highest quintile	2004	Munger et al (201)

Cross-Sectional Studies of Vitamin D in Existing Autoimmune Diseases (Table 1)

Circulating 25(OH)D, reflecting all sources of vitamin D exposure with a half-life of 2 to 3 weeks, has been used in epidemiologic studies as a comprehensive and stable indicator of vitamin D status (17,113). Some studies have assessed 1,25(OH)2D levels, but as the half-life of 1,25(OH)D is only 4 hours and this metabolite is dependent on fluctuating calcium need, these results are harder to interpret (113). Studies of vitamin D levels comparing populations with and without existent autoimmune diseases have been conducted around the world and with somewhat conflicting results. In RA, for example, 2 past studies revealed lower levels of 25(OH)D in RA patients than in healthy matched controls (114,115), but 5 studies did not find such a difference (116-120). Patel and colleagues found a strong inverse association between baseline levels of serum 25(OH)D in patients with newly diagnosed early inflammatory polyarthritis (45% of whom were classified as having RA at 1 year) and baseline disease activity, as assessed by tender joint counts, RA disease activity scores (DAS28), and health assessment questionnaires scores (121). For each 10 ng/mL increase in 25(OH)D, they found a decrease in the DAS28 of 0.3 and in the C-reactive peptide level of approximately 25%. At 1 year, only significant inverse association between higher baseline vitamin D levels had lower health assessment questionnaires scores. In a large group of individuals at increased risk for RA, however, plasma 25(OH)D concentrations were not associated with the presence of RA-related autoantibodies (122).

In SLE, at least 6 case-control studies have now demonstrated a lower level of 25(OH)D in SLE cases than in matched controls (118,123-127). Several studies have found that lower levels of vitamin D correlate with more active SLE (125,126,128-131), but several others have not confirmed this (118,123,132-134). One study showed that the 25(OH)D level was lower in hydroxychloroquine users than nonusers and hydroxychloroquine is known to inhibit the synthesis of vitamin D (135). A case-control study from Hungary reported lower 25(OH)D levels in individuals with undifferentiated connective tissue disease (before starting medications) than controls in summer and winter seasons and demonstrated that levels were lower in those with more active manifestations and among the 35 who developed into a diagnosed connective tissue disease within 2.3 years of follow-up (136). A study involving 113 children with SLE, juvenile RA, or juvenile dermatomyositis did not find an abnormal prevalence of 25(OH)D or 1,25(OH)D deficiency, although the study's primary goal was to assess osteocalcin levels (134).

There have been 4 case-control studies comparing 25(OH)D and 1,25(OH)D levels in patients with ankylosing spondylitis to healthy controls. A study of 100 AS patients and 58 controls in Turkey found that 25(OH)D levels were lower in patients than controls (137), but an earlier study of 38 AS patients and 52 controls in Germany had not detected a significant difference (138). Two studies by Lange and coworkers have found that 1,25(OH)D levels are lower in ankylosing spondylitis patients and negatively correlated with disease activity, thought possibly related to the high prevalence of osteoporosis seen in this disease (139,140). Seventy-six ankylosing spondylitis patients had significantly lower 25(OH) levels than did 120 psoriatic arthritis patients, and a significant negative correlation between C-reactive peptide levels and 25(OH)D levels was reported in the combined cohort of these patients in a study by Teichmann and coworkers (141).

We found 8 past studies addressing vitamin D levels in patients with scleroderma. Of the 5 case-control studies, 2 demonstrated lower 25(OH)D levels in patients with scleroderma than controls (142,143), and 3 did not (144-146). In 2 case-only analyses, it was found that 25(OH)D levels were, not surprisingly, lower in those with more severe underlying scleroderma, more longstanding disease, more disease activity, more pulmonary hypertension, and lower diffusing lung capacity (147,148).

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In type I diabetes mellitus, there have been at least 9 studies documenting lower 25(OH)D levels in established or new-onset type I diabetes patients, compared with matched controls (149-157), and only 1 published study that did not confirm this (158). It has also been shown that 25(OH)D levels are lower in individuals with poorly controlled type I diabetes (159), ketoacidosis (160,161), incipient nephropathy, or tubulointerstitial damage (150,157).

In MS as well, there have now been several studies reporting that 25(OH)D levels are lower in cases with MS than in healthy controls (162-168), and 2 that have not (169,170). Lower vitamin D levels have been found in MS patients especially during the summer, compared with winter months (171), in those with progressive as opposed to relapsing-remitting forms of the disease (172), and associated with increased disability in MS (163,166), and clinical activity and risk of relapse (162,167,168,172).

Two case-control studies have reported lower 25(OH)D levels in patients with Crohn's disease compared with controls (173,174), and 3 of 4 studies have found that levels are lower in those with active inflammatory bowel disease (173-176). The only study of the association between vitamin D level and thyroid autoimmunity was conducted in India where a large group of over 600 healthy individuals were screened for antithyroid antibodies. A weak but significant inverse correlation was found between vitamin D level and titer of antithyroid peroxidase autoantibodies (177). One cross-sectional case-only study of 25(OH)D levels in patients with vitiligo reported apparently low levels, without controlling for season (178). We found no epidemiologic studies of vitamin D levels in existing pernicious anemia, vasculitis, adult inflammatory myositis, polymylagia rheumatica, Addison's disease, uveitis, or Behcet's disease.

In sum, many, but not all, case-control studies, circulating levels of 25(OH)D and occasionally $1,25(OH)_2D$ have been found to be lower in subjects with various autoimmune diseases than in matched healthy controls. The evidence pointing to lower vitamin D levels in existing disease is not equally strong for all autoimmune diseases and some diseases have yet to be studied. The differences between the many similar studies of a specific disease may relate to their different sizes and the heterogeneity in their statistical power, as well as to adjustment for confounding factors. Taken together, it is also apparent from these studies that ethnic origin (179), season of the year (180), and disability (163,166) have strong effects on circulating vitamin D levels and it is not clear that all of these cross-sectional studies controlled for these important confounders. Additionally, disease activity and disability, glucocorticoid use (132), serum creatinine (132), microalbuminuria (157), ketoacidosis (160,161), and use of hydroxychloroquine (135) influence circulating vitamin D levels. Hydroxychloroquine prescribed in several autoimmune diseases may inhibit the conversion of 25(OH)D to $1,25(OH)_2D$ (135). Thus, while interesting, the major limitation of these cross-sectional studies is that reverse causation is very likely. Low vitamin D level may be the consequence, not the cause, of active autoimmune disease.

Vitamin D Supplementation and Effects on Existing Disease Activity (Table 2)

Several small open-label studies and interventional trials have tested the effects of supplementation with vitamin D, or its analogs, on the activity of established autoimmune diseases. In a double-blind trial conducted in 1973, oral calciferol (100,000 IU/d) for 1 year was administered to 25 subjects who were compared with 24 subjects who received a placebo. The intervention group had improved hand strength, decreased morning stiffness, and need for analgesics/anti-inflammatory medications and decreased erythrocyte sedimentation rate (181). In a more recent study, high-dose 1-alpha(OH)D3 (alphacalcidiol) reduced pain and CRP levels in 19 RA subjects in a 3-month open-label trial (182).

Two small open-label studies of 6 months each have shown some promise for oral alphacalcidol (0.25 μg twice/d) and 1,25(OH)D in reducing disease activity and tender joint counts in psoriatic arthritis (183,184). In an open-label observational study of 60 SLE patients in Spain who took vitamin D3 supplementation for 2 years, significant improvement was seen in subject fatigue, as measured by a visual analog scale, but not SLE disease activity measures (185). An ongoing National Institutes of Health sponsored trial is investigating vitamin D supplementation on disease activity and interferon-related cytokine activation ("the interferon signature") in SLE.

Five small trials have now studied the effects of oral calcidiol supplementation on scleroderma, morphea, or linear scleroderma (186-190). While earlier open-label studies had shown some benefit, in particular for morphea, the most recent randomized trial found that calcitriol was not more effective than placebo in patients with morphea, and the scleroderma group in that trial ($n = 7$) was too small to any draw conclusions (190). On the other hand, randomized trials in Italy and China have now shown that vitamin D supplementation in individuals with latent autoimmune diabetes (autoantibodies highly associated with the development of type 1 diabetes) can forestall the development of type 1 diabetes, although it only temporarily reduces the amount of insulin required (191,192).

We found 5 small studies or trials of vitamin D supplementation for MS. Fewer exacerbations of disease were seen among 16 MS patients given calcium, magnesium and vitamin D supplements for 1-2 years in an open-label study in 1986 (193). In another open-label study of calcium and escalating doses of vitamin D supplementation in 12 MS patients, there did not appear to be an effect on disease progression or activity but the number of gadolinium-enhancing lesions per patient appeared decreased af-

ter just 12 weeks (194). In the largest randomized controlled trial yet, 25 MS subjects were randomized to doses of up to 40,000 IU/d over 28 weeks, followed by 10,000 IU/d for 12 weeks over 52 weeks, and 24 MS subjects were randomized to placebo. While the treatment group appeared to have fewer relapse events, the difference was not statistically significant ($P = 0.09$) possibly due to insufficient statistical power (195). Thus far, the studies have been small and inconclusive and larger scale trials are called for.

Last, 1 open-label trial in Eastern Europe has compared the effects of supplementation with 25(OH)D to those of 1,25(OH)D for Crohn's disease and found that 1,25D supplementation was associated with a significantly greater decrease in disease activity (assessed by Crohn's Disease Activity Index) (196).

Studies to date have mainly been small and mostly open-label and include a range of vitamin D preparations, doses, and durations. However, it appears that vitamin D may have an adjunctive role in amelioration of RA, MS, type I diabetes, and perhaps SLE and Crohn's disease. This evidence addresses the question of whether vitamin D has an effect on established disease, but not on the risk of developing an autoimmune disease de novo.

Epidemiologic Studies of Vitamin D Level and Risk of Developing Autoimmune Disease (Table 3)

In the hierarchy of epidemiologic studies, stronger data for association with susceptibility are afforded by prospective studies. Additionally, prospective studies are able to address the potential role of vitamin D in the pathogenesis of autoimmune disease. The relation between vitamin D serum or plasma level—measured by circulating 25(OH)D—and the incidence of autoimmune diseases have been examined in only 2 prospective observational epidemiologic studies of RA and MS, but not in other autoimmune diseases. Serum 25(OH)D level was not related to future RA risk in a Dutch case-control study examining blood bank samples from 79 individuals who developed RA compared with 79 healthy controls, matched on age, sex, and time of blood donation (197). To address the question on MS, Munger and colleagues used banked blood samples from Department of Defense military recruits, 257 of whom later developed MS. Higher serum levels of 25(OH)D were associated with a significantly lower risk of incident MS, but only among whites, not blacks nor Hispanics, and the effect was most pronounced for individuals under age 20 (198).

Epidemiologic Studies of Vitamin D Intake and Risk of Developing Autoimmune Disease (Table 4)

Prospective epidemiologic data on vitamin D intake and the risk of developing autoimmune diseases have been systematically reviewed and summarized in Table 4. The diseases that have been studied include RA, SLE, type 1 diabetes mellitus, and MS. For RA risk, the data have been somewhat conflicting. In the Iowa Women's Health Study, higher baseline vitamin D intake was associated with decreased risk of subsequent RA (199). In the Nurses' Health Study, a prospective cohort study involving over 180,000 women with multiple dietary assessments over 20 years, intake of vitamin D was not related to risk of developing either SLE or RA (200). However, in the same cohort, an inverse relationship was discovered between higher intake of vitamin D from supplements, but not overall dietary intake and lower risk of incident MS up to 20 years later (201).

Several observational studies have addressed the association between maternal vitamin D intake in pregnancy, lactation, or intake in infancy and early childhood and the risk of developing type 1 diabetes. A meta-analysis of 4 case-control studies (202-204) was performed in 2008 (205) (omitted from Table 4 due to redundancy). Pooled data from the case-control studies showed that the risk of type 1 diabetes was significantly reduced in infants who were supplemented with vitamin D compared with those who were not supplemented (pooled odds ratio 0.71, 95% CI 0.60 to 0.84). One large birth cohort study prospectively assessed vitamin D supplementation during the first year of life (as part of a ricket's prevention study) and confirmed cases of type 1 diabetes in the children up to 31 years later. They found a strongly protective effect of regular vitamin D supplementation in the first year of life: RR 0.12 (95% CI 0.03-0.510) (206).

Surrogate markers for the development of type 1 diabetes, glutamic acid decarboxylase, or islet antigen-2 autoantibodies, which are highly associated with type 1 diabetes risk, have been used in a few prospective studies. Two birth cohorts of infants at high genetic risk of type 1 diabetes have investigated relationships between maternal intake of vitamin D during pregnancy and the development of this islet cell autoimmunity. A high maternal dietary intake of vitamin D in foods, but not supplements, assessed after pregnancy by questionnaire, was associated with increased risk of islet cell autoantibodies among the children followed for an average of 4 years in an American birth cohort (207). A larger prospective birth cohort in Finland has reported no association between maternal vitamin D intake (also assessed postpartum by questionnaire) and risk of type 1 diabetes or islet cell autoantibodies in their high genetic risk offspring, followed up to 4.3 years, however (208).

Our funnel plot for the studies examining the relationship of vitamin D dietary intake and the risk of the 4 autoimmune diseases that have been studied is shown in Figure 2. Given the dearth of studies, we have included studies of all 4 autoimmune diseases with substantial heterogeneity in design, exposure assessment, and timing in relation to onset of disease/autoantibodies and outcomes. The plot appears slightly asymmetric, displaying potential publication bias with few small nonprotective studies.

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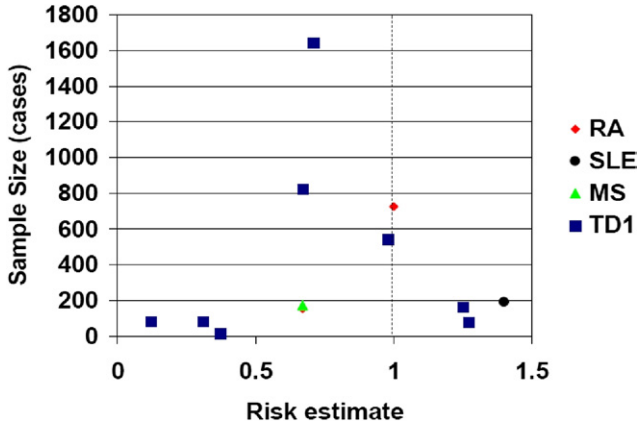

Figure 2 Funnel plot of the risk estimates (odds ratios or relative risks) of developing autoimmune disease associated with vitamin D intake (supplementation vs none or highest vs lowest level of intake). Risk estimates below 1.0 indicate a protective effect. Sample size of the study refers to the number of autoimmune disease cases in each study. The appearance of an inverted funnel, where small studies of positive and negative studies have been published, argues against a potential publication bias. (Color version of figure is available online.)

However, given the small number of studies, no conclusions can be drawn.

Potential Causes of Conflicting Results

While the development of an autoimmune response to self-antigens underlies all of these diseases, it is likely that vitamin D is not uniformly involved in the pathogenesis of each and every autoimmune disease and is more important in the etiology of some versus others among them. It is clear that not all autoimmune diseases have been equally studied and for most there is a dearth of evidence addressing the potential effects of vitamin D on autoimmune disease susceptibility. Past case-control studies may have been biased by subject recall; cohort studies may have been underpowered for small effects, and potential confounders such as socioeconomic status may not have been consistently well addressed. Prospective observational studies that rely on dietary intake are hampered by subjects' ability to accurately recall food intake and by inadequate means of assessing vitamin D content of all foods. The inconsistency in epidemiologic data regarding vitamin D intake and risk of autoimmune disease has led to some debate and may result in part from the fact that oral vitamin D intakes in many of the studied populations were too low to produce significant effects, as well as limited within population variability in intakes. The difference between high and low oral intakes in observational studies is generally only 300 to 400 IU/d. Given that a vitamin D_3 intake of 1 μg [40 IU] increases circulating 25(OH)D by ~1 nmol/L (209), such an increment would be expected to raise 25(OH)D by $\leq$10 nmol/L.

Misclassification of vitamin D status due to incomplete or single exposure assessments could also contribute to null or inconsistent findings. The critical window for vitamin D intake or level to affect risk of developing an autoimmune disease is not known and may vary according to disease: maternal intake during pregnancy, early life intake, and intake during different phases of adulthood may not be equally relevant to different diseases. Possible health benefits of vitamin D may be offset by other components in dairy products, which are main dietary sources of vitamin D. Disentangling independent effects of vitamin D and calcium on risk of autoimmune disease in observational studies is difficult due to their high correlation in countries—including the U.S.—where milk is fortified with vitamin D. The use of vitamin D supplements in a trial setting would eliminate this problem.

CONCLUSIONS

Understanding of the pluripotent immunomodulating and anti-inflammatory effects of vitamin D is advancing. Despite the in vitro and animal evidence for vitamin D's potential to decrease systemic inflammation and prevent autoimmune disease in humans, there remains insufficient human data to firmly support the hypothesis that vitamin D intake is related to the risk of developing autoimmune disease. Data from laboratory studies and cross-sectional and observational epidemiologic investigations suggest a potential protective effect for vitamin D in autoimmune disease susceptibility.

The human epidemiologic and interventional evidence, however, is weak. Despite the multitude of cross-sectional and case-control studies that demonstrate lower levels of vitamin D among individuals with autoimmune diseases than healthy controls, these studies are not able to address causality. Reverse causality, that the disease process of an autoimmune disease, even in early disease, could lower circulating vitamin D concentration is a likely possibility in these studies. Prospective epidemiologic data on vitamin D status and whether intake level has any effect on the incidence of autoimmune diseases are limited or conflicting. There have been no large randomized trials of high-dose vitamin D supplements for the primary prevention of autoimmune diseases in a general population.

Confirming or refuting that elevated dietary vitamin D intake reduces systemic inflammation and/or the risk of incident autoimmune disease is critical, as no prophylactic therapy currently exists for these diseases. The growing enthusiasm for vitamin D supplementation, however, underscores the need for timely and rigorous testing of this hypothesis before use becomes so prevalent as to render it impossible. To understand the effects of moderate- to high-dose vitamin D supplementation, a high-quality, double-blind randomized controlled trial with a large sample size and long duration and designed specifically to include an assessment of these outcomes in a general population is necessary.

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TABLE 1. SUPPLEMENTARY DATA

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.semarthrit.2010.07.009.

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Table 1 Epidemiologic Studies of Vitamin D Levels in Existing Autoimmune Diseases

Autoimmune Disease	Geographic	Study Design	Subjects	Controls
Rheumatoid arthritis	Turkey	Case-control	65 RA	40 healthy controls
Rheumatoid arthritis	North America	Case-only	266 early RA	—
Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis	Israel	Case-control	85 RA, 22 psoriatic arthritis, 14 AS	—
Rheumatoid arthritis	North America	Case-control (nested in high-risk cohort)	76 RA autoantibody positive, asymptomatic "at-risk" subjects	154 RA autoantibody negative "at risk" controls
Rheumatoid arthritis	Italy, Estonia	Case-control	64 female Estonian RA, 53 female Italian RA	30 Estonian, 35 Italian age- and sex-matched
Inflammatory polyarthritis	Great Britain	Case-only	183 consecutive inflammatory polyarthritis <6 mo	—
Rheumatoid arthritis	Germany	Case-only	96 RA	—
Rheumatoid arthritis	Denmark	Case-control	29 RA, 21 SLE, 12 OA	72 healthy controls
Rheumatoid arthritis	Finland	Case-only	143 female RA patients	—
Rheumatoid arthritis	Denmark	Case-control	102 RA	38 healthy subjects
Rheumatoid arthritis	Great Britain	Case-control	30 RA	30 OA
Rheumatoid arthritis	Great Britain	Case-control	30 RA	30 OA
Ankylosing spondylitis and psoriatic arthritis	Germany	Case-only	76 AS, 120 PsoA	—
Ankylosing spondylitis	Turkey	Case-control	100 AS	58 healthy controls
Ankylosing spondylitis	Germany	Case-control	58 AS	58 matched healthy controls
Ankylosing spondylitis	Germany	Case-control	70 AS	45 matched healthy controls
Ankylosing spondylitis	Austria	Case-only	73 AS	—

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Table 1 Continued

Hormones Studied	Association	Results	Year	Reference
25(OH) D	No	$P = 0.94$ No difference in RA subjects vs healthy controls, but significant decrease in subgroup with highest disease activity	2010	Turhahoglu et al (116)
25(OH) D	No	No multivariate associations of 25(OH) D with any disease measures with the exception of borderline association with rheumatoid factor positivity at enrollment ($P = 0.05$) No significant associations with disease activity after multivariate analysis	2010	Craig et al (117)
25(OH) D and PTH	No	Association between vitamin D level and ethnic origin but not disease activity (among other factors)	2009	Braun-Moscovici et al (210)
25(OH) D	No	No association of autoantibody status and vitamin D level in individuals at high risk RA.	2009	Feser et al (122)
25(OH) D	Yes	Inverse correlation between levels and DAS28 scores among Italian patients in summer ($r = -0.57$, $P < 0.0001$) and Estonian patients in winter ($r = -0.40$, $P < 0.05$)	2007	Cutolo et al (211)
25(OH)D, 1,25(OH)2 D	Yes	Significant inverse relationship between 25(OH)D level at baseline and tender joint count, DAS28, CRP, and HAQ, and between baseline 1,25(OH)(2)D and HAQ	2007	Patel et al (121)
25(OH) D and PTH	Yes	$P < 0.001$ (with glucocorticoids), $P < 0.01$ (without glucocorticoids) Inverse correlation between vitamin D level and disease activity	1998	Oelzner et al (212)
1,25(OH)2 D and 25(OH) D	No	No difference in vitamin D levels compared to controls	1995	Muller et al (118)
1,25(OH)2 D 25(OH)D	Yes	63% of patients had levels below normal limit during summer	1993	Kroger et al (213)
25(OH) D; 24,25(OH) D; 25,26-OH D; 1,25(OH)2 D	Yes	$P < 0.01$ to 0.001 (for 25(OH) D) 25(OH) D levels lower than in controls and significant inverse relation between level and functional class	1987	Als et al (115)
1,25(OH)2 D	No	No difference between RA and OA and 1,25(OH)2 D levels did not correlate either with articular index or with sedimentation rate	1982	Bird et al (119)
25(OH) D	No	No significant correlations between 25(OH) D and duration of arthritis or articular index	1980	Bird et al (120)
25(OH) D; 1,25(OH)2 D	Yes	$P < 0.0005$ for negative correlation between CRP and 25-OH D when combining AS and PsoA; $P < 0.0005$ for 25-OH level in PsoA vs AS	2009	Teichmann et al (141)
25(OH) D and PTH	No	$P < 0.05$ for 25(OH) D lower in cases than controls	2010	Mermerci Baskan et al (137)
25(OH) D; 1,25(OH)2 D; PTH	Yes	$P < 0.05$ for negative correlation between 1,25(OH)2 D and disease activity and TNF-alpha	2005	Lange et al (140)
25(OH) D; 1,25(OH)2 D; PTH	Yes	$P < 0.01$ for negative correlation between 1,25(OH)2 D and disease activity	2001	Lange et al (139)
25(OH) D and PTH	—	18% with 25(OH) D < 8 ng/mL, 73% with 25(OH) D less than 20 ng/mL	2001	Falkenbach et al (214)

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Table 1 Continued

Autoimmune Disease	Geographic	Study Design	Subjects	Controls
Ankylosing spondylitis	Germany	Case-only	14 AS at entry and 15 mo later	—
Ankylosing spondylitis	Germany	Case-control	38 AS	52 controls
Systemic lupus erythematosus	Poland	Case-control	45 SLE	49 controls
Systemic lupus erythematosus	Europe and Israel	Case-only	378 SLE	—
Systemic lupus erythematosus	South Korea	Case-control	104 SLE	49 controls
Systemic lupus erythematosus	North America	Case-only	198 SLE	—
Systemic Lupus Erythematosus	Canada	Case -only	124 female SLE	—
Systemic lupus erythematosus	Saudi Arabia	Case-control	165 SLE	214 volunteers
Systemic lupus erythematosus	North America	Case-only	181 SLE	—
Systemic lupus erythematosus	North America	Case-only	38 pediatric SLE	207 healthy controls
Systemic lupus erythematosus	Brazil	Case-control	36 SLE	26 controls
Systemic lupus erythematosus	Spain	Case-only	92 SLE	—
Systemic lupus erythematosus	U.S.	Case-only	37 SLE	—
Systemic lupus erythematosus	Canada	Case-only	25 SLE	—
Systemic lupus erythematosus	Denmark	Case-control	21 SLE, 29 RA, 12 OA	72 healthy controls
Systemic lupus erythematosus and dermatomyositis and juvenile RA	North America	Case-only	17 pediatric SLE, 13 juvenile dermatomyositis, 83 JRA	—
Undifferentiated connective tissue disease	Hungary	Case-only	161 UCTD	59 controls
Scleroderma	Italy	Case-only	108 scleroderma	—
Scleroderma	Brazil	Case-control	10 juvenile scleroderma	10 matched controls
Scleroderma	Italy	Case-control	60 Scleroderma	60 controls

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Table 1 Continued

Hormones Studied	Association	Results	Year	Reference
25(OH) D; 1,25(OH)2 D and PTH	No	Vitamin D levels did not differ significantly between baseline and follow-up in AS patients	1997	Lee et al (215)
1,25(OH)2 D and PTH	No	No significant difference	1993	Franck et al (138)
25(OH) D	Yes	Lower 25(OH) D in cases than controls $P = 0.0005$, and antibodies to 1,25 (OH) D detected in 4 pts (8.9%, NS).	2010	Bogaczewicz et al (127)
25(OH) D	Yes	$R = -0.12$, $P = 0.018$ for vitamin D levels and disease activity scores Negative correlation between 25(OH) D levels and disease activity in SLE patients	2010	Amital et al (129)
25(OH) D	Yes	$P = 0.03$ for vitamin D insufficiency in SLE compared to controls, but did not correlate with SLE disease activity	2010	Kim et al (123)
25(OH) D	Yes	$R = -0.234$, $P = 0.002$ for inverse correlation of vitamin D with disease activity	2010	Ben-Zvi et al (128)
25(OH) D and 1,25(OH)2 D	No	No significant association between low vitamin D levels and disease activity; 25(OH) D levels associated with season, glucocorticoid exposure, and serum creatinine	2010	Toloza et al (132)
25(OH) D	Yes	$P < 0.0001$ for vitamin D deficiency in SLE vs controls	2009	Damanhouri (124)
25(OH) D	Yes	$P = 0.018$ for negative correlation between low 25(OH) D and SLE disease activity index (adjusted for age, season, and white race)	2009	Wu et al (130)
25(OH) D; 1,25(OH)2 D; iPTH	Yes	$P = 0.01$ for low 25(OH) D low level and disease activity index scores	2009	Wright et al (125)
25(OH) D; 1,25(OH)2 D; PTH	Yes	$R = -0.65$; $P < 0.001$ for 25(OH) D level and negative correlation with disease activity index	2009	Borba et al (126)
25(OH) D	No	$P = 0.08$ for fatigue and vitamin D deficiency; no significant association with disease activity	2008	Ruiz-Irastorza et al (133)
25(OH)D	Yes	65% < 80 nmol/L and 20% <47.7 nmol/L. Above normal level correlated with low disease activity, but also with significantly higher dsDNA antibodies.	2008	Thudi et al (131)
25(OH) D; 1,25(OH)2 D; PTH	No	1,25-OH lower in SLE patients using hydroxychloroquine compared to nonusers	2001	Huisman et al (135)
1,25(OH)2 D and 25(OH) D	Yes	$P = 0.0008$ for decreased 25(OH) levels in SLE vs controls; no correlation with anti-DNA antibodies, sedimentation rate, or blood counts	1995	Muller et al (118)
25(OH) D; 1,25(OH)2 D; PTH	No	No significant differences between active and inactive stages of pediatric SLE with regards to vitamin D levels	1990	Reed et al (134)
25(OH) D	Yes	25(OH) D significantly lower than in controls in summer and winter. Significant associations of low 25(OH) D with active manifestations and with evolution to diagnosed connective tissue disease within 2.3 yr	2008	Zold et al (136)
25(OH) D	Yes	Vitamin D deficiency is associated with more severe disease $P = 0.026$ for longer disease duration, $P = 0.014$ for lower diffusing lung capacity, $P = 0.037$ for higher pulmonary artery pressure	2010	Caramaschi et al (147)
25(OH) D, iPTH	Yes	$P = 0.04$ for lower vitamin D levels compared with controls	2010	Shinjo et al (143)
25(OH) D	Yes	$P < 0.001$ for lower vitamin D levels compared with controls, but No associations with disease features or skin score	2009	Calzolari et al (142)

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Table 1 Continued

Autoimmune Disease	Geographic	Study Design	Subjects	Controls
Scleroderma	France and Italy	Case-only	90 scleroderma	—
Scleroderma	Israel	Case-only	60 scleroderma	—
Scleroderma	North America	Case-control	8 scleroderma	8 matched healthy controls
Scleroderma	Holland	Case-control	20 scleroderma	—
Scleroderma	Holland	Case-control	25 scleroderma	92 controls
Type I diabetes mellitus	India	Case-control	50 children within 1 wk of diagnosis of T1D	50 healthy children
Type I diabetes mellitus	North America	Case-control	46 new-onset T1D, 110 established T1D	153 control subjects 106 first-degree relatives
Type I diabetes mellitus	Great Britain	Case-control	40 T1D, 40 T2D	41 nondiabetic controls
Type I diabetes mellitus	North America	Case-only	128 Pediatric T1D	—
Type I diabetes mellitus	Qatar	Case-control	170 pediatric T1D	170 healthy controls
Type I diabetes mellitus	Australia	Case-only	64 pediatric new-onset T1D	—
Type I diabetes mellitus	Australia	Case-control	47 pediatric T1D	94 healthy controls
Type I diabetes mellitus	Sweden	Case-control	459 T1Dat diagnosis, 138 8 yr later	208 matched controls
Type I diabetes mellitus	North America	Case-control	50 T1D	63 T2D
Type I diabetes mellitus	Italy	Case-control	46 T1D	24 healthy controls
Type I diabetes mellitus	Germany	Case-control	49 new-onset T1D	42 healthy controls
Type I diabetes mellitus	Mexico	Case-only	22 T1D	—
Type I diabetes mellitus	Norway	Case-control	46 pubertal T1D	191 healthy controls
Type I diabetes mellitus	Denmark	Case-only	74 T1D	—
Multiple sclerosis	Holland	Case-control	36 MS	20 healthy controls

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Table 1 Continued

Hormones Studied	Association	Results	Year	Reference
25(OH) D and iPTH	Yes	$R = -0.17$ ($P = 0.04$) for negative correlation between low vitamin D and disease activity score	2009	Vacca et al (148)
25(OH) D, PTH	—	46% of scleroderma patients are vitamin D deficient	2008	Braun-Moscovici et al (179)
25(OH) D; 1,25(OH)2 D	No	Similar levels in cases and controls	1991	Matsuoka et al (144)
25(OH) D; 1,25(OH)2 D; 24 to 25(OH) D	No	Normal 25(OH) D and 24,25(OH) D levels in scleroderma; lower 1,25(OH)2 D in a subgroup with calcinosis	1985	Serup et al (145)
1,25(OH)2 D	No	$P < 0.001$ for higher 1,25(OH)2 D in scleroderma compared to controls	1984	Serup et al (146)
25(OH) D	Yes	$P < 0.009$ for lower vitamin D in new-onset diabetics	2009	Borkar et al (149)
25(OH) D	No	$P = 0.87$ No significant associations of reduced vitamin D level and T1D	2009	Bierschenk et al (158)
1,25(OH)2 D, PTH, Erythropoietin	Yes	$P = 0.001$ for median vitamin D level in cases vs controls Tubulointerstitial damage associated with low 1,25(OH)2 D	2009	Singh et al (150)
25(OH) D	—	61% Vitamin D insufficient; 15% Vitamin D deficient	2009	Svoren et al (216)
25(OH) D, PTH	Yes	$P = 0.009$ for mean vitamin D level; 28.8% vs 17.1% severe vitamin D deficiency	2008, 2009	Bener et al (151,217)
25(OH) D	—	$P = 0.001$ (for associate acidosis); low vitamin D in 42% with acidosis vs 5.6% without acidosis Acidosis may alter vitamin D metabolism or low vitamin D may contribute to presenting with ketoacidosis	2009	Huynh et al (160)
25(OH) D, 1,25(OH)2 D	Yes	$P = 0.002$ for 25(OH) D deficiency	2007	Greer et al (152)
25(OH) D	Yes	$P < 0.0001$ for vitamin D level at diagnosis; $P = 0.04$ for vitamin D level 8 yr later	2006	Littorin et al (155)
25(OH) D	No	$P = 0.01$ for lower 25-OH-D levels in T2D vs T1D (adjusted for body mass index and age)	2006	Di Cesar et al (156)
25(OH) D; 1,25(OH)2 D; PTH	Yes	$P < 0.01$ for vitamin D levels Lower vitamin D level in incipient nephropathy/microalbuminuria	1999	Verrotti et al (157)
25(OH) D; 1,25(OH)2 D	Yes	$P < 0.01$ for 1,25(OH)2 D at onset of T1D	1991	Baumgartl et al (153)
25(OH) D	Yes	$P < 0.001$ for low 25(OH) D in poorly controlled T1D	1990	Arreola et al PMID 2103709 (159)
25(OH) D; 1,25(OH)2 D; 24,25(OH) D	Yes	$P < 0.05$ for 1,25(OH)2 D Relative decrease in 1,25(OH)2 D and increased 24,25(OH) D levels in T1D at puberty	1985	Rodland et al (154)
25(OH) D; 1,25(OH)2 D; 24,25(OH) D	—	$P < 0.02$ for 1,25-OH level during ketoacidosis; $P < 0.01$ for 25(OH) D in T1D groups with diabetic nephropathy	1983	Storm et al (161)
25(OH) D	—	$R = -0.359$, $P = 0.048$ 25(OH) D negative correlation with IgG index in MS	2010	Vogt et al (162)

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Table 1 Continued

Autoimmune Disease	Geographic	Study Design	Subjects	Controls
Multiple sclerosis	Norway	Case-control	36 MS	38 other neurologic diseases
Multiple sclerosis	North America	Case-control	173 MS + 9 transverse myelitis	16 other neurologic diseases
Multiple sclerosis	Argentina	Case-control	132 MS- various forms	60 healthy controls
Multiple sclerosis	Holland	Case-control	103 MS	110 healthy controls
Multiple sclerosis	Finland	Case-control	23 MS	23 healthy controls
Multiple sclerosis	Great Britain	Case-control twin study	40 monozygotic and 59 dizygotic twins with MS	40 monozygotic and 59 dizygotic twins without MS
Multiple sclerosis	Holland	Case-control	267 MS	—
Multiple sclerosis	Ireland	Case-control	29 MS	22 age- and sex-matched controls
Multiple sclerosis	Australia	Case-control	136 MS	272 controls
Multiple sclerosis	Finland	Case-control	40 MS	40 controls
Multiple sclerosis	Germany	Case-control	53 MS	415 controls
Hashimoto's thyroiditis	India	Case-only	642 healthy individuals	—
Crohn's disease	India	Case-control	34 Crohn's	34 irritable bowel syndrome controls
Crohn's disease and ulcerative colitis	America	Case-only	130 young Crohn's and UC	—
Crohn's disease	Japan	Case-control	33 Crohn's	15 healthy controls
Crohn's disease	Great Britain	Case-only	40 Crohn's	—
Vitiligo	Great Britain	Case-only	45 Vitiligo	—

DAS28, Disease Activity Score 28 joint assessment; HAQ, Health Assessment Questionnaire; PsOA, psoriatic arthritis; T1D, type 1 diabetes; T2D, type 2 diabetes; UC, ulcerative colitis.

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Table 1 Continued

Hormones Studied	Association	Results	Year	Reference
Serum and cerebrospinal fluid 25(OH) D	Yes	$P = 0.0012$ and 0.041 for cerebrospinal fluid-to-vitamin D serum ratio (lower in MS compared with other neurological diseases)	2010	Holmoy et al (164)
25(OH) D	—	84% of all patients had insufficient levels Large numbers of patients with MS and transverse myelitis are deficient in vitamin D		Hiremath et al (165)
1,25(OH)2 D, 25(OH) D	Yes	$P < 0.00001$ for 25(OH) D and 1,25(OH)2 D levels (lower in relapsing-remitting MS during exacerbation compared with remission)	2009	Correale et al (167)
1,25(OH)2 D, 25(OH) D	Yes	Among women: for every 10 nmol/L increase in serum 25(OH) D level the odds of MS decreased 19% (OR = 0.81; 95% CI 0.69 to 0.95) for dose-dependent decreased odds of MS among women); $r = -0.29$; $P = 0.02$ for negative correlation between disability status and 25(OH) D levels in women only	2009	Kragt et al (166)
25(OH) D and iPTH every 3 mo for 1 yr	Yes	$P = 0.012$ for inverse relationship between serum vitamin D level and MS clinical activity	2008	Soilu-Hanninen et al (218)
25(OH) D	No	No association with having MS ($P = 0.4$)	2008	Orton et al (170)
25(OH) D, 1,25(OH)2 D	Yes	$P = 0.043$ for high 25(OH) D and chance of remaining relapse-free	2008	Smolders et al (172)
25(OH) D; 1,25(OH)2 D; PTH	No	No differences between cases and controls	2007	Barnes et al (169)
25(OH) D	Yes	OR = 3.07 (95% CI 1.37 to 6.90) for disability and vitamin D insufficiency	2007	van der Mei et al (163)
25(OH) D	Yes	$P = 0.03$ for lower vitamin D level during relapse vs remission	2005	Soilu-Hanninen et al (171)
25(OH) D	Yes	$R2 = 0.8491$ for vitamin D level; $R2 = 0.7931$ for brain lesions (2-fitted, third-order polynomial curves corresponding closely when 25(OH) D data lagged 2 mo) Inverse correlation of gadolinium-enhancing lesions on MRI and vitamin D levels following seasonal fluctuations	2000	Embry et al (168)
25(OH) D	-	$r = 0.08$, $P = 0.04$ For vitamin D level inverse correlation with antithyroid antibodies	2009	Goswami et al (177)
25(OH) D	Yes	Correlation coefficient −0.484, significance $P < 0.004$ Lower vitamin D levels in Crohn's disease and association with severe disease activity	2009	Joseph et al (173)
25(OH) D, iPTH	No	$P = 0.97$ in multiple regression for vitamin D level and disease activity	2006	Pappa et al (176)
25(OH) D, iPTH	Yes	$P = 0.04$ for vitamin D and disease activity in logistic regression	2004	Tajika et al (174)
25(OH) D, 24,25(OH) D, $1,25(OH)_2$ D, PTH	Yes	$P < 0.05$ for low 25(OH) D levels in active disease	1985	Harries et al (175)
25(OH) D	Yes	55.6% were insufficient (<30 ng/mL), and 13.3% were very low (<15 ng/mL).	2007	Silverberg et al (178)