

Vitamin deficiencies in pediatric eosinophilic esophagitis: A systematic review

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Abstract

Background: Nutritional deficiencies are seen in patients with food allergy. Low vitamin D levels have been found in patients with atopic conditions. Eosinophilic esophagitis (EoE) is a chronic immune antigen-mediated disease found to be highly associated in patients with atopic disease and treated with dietary elimination with recommendations to utilize a dietician to prevent nutritional deficiencies. Nonetheless, the relationship between EoE and vitamin deficiency remains unclear. We aimed to systematically review the evidence to support a possible association between vitamin deficiency and eosinophilic esophagitis.

Methods: Electronic searches were performed with keywords relating to EoE and vitamins among pediatric patients in MEDLINE, EMBASE, and The Cochrane Library. Summary estimates were calculated. Citations were reviewed against pre-defined criteria. (Inclusion: human subjects, aged 0-18, with eosinophilic esophagitis. Exclusion: adults over 18 years, non-English papers).

Results: The search yielded 1707 studies. Five of these studies with a total of 137 pediatric patients were included in the systematic review. Outcome measures were assessed at different points in EoE treatment across studies. The single common outcome measure across all included studies was vitamin D. Reported prevalence of low vitamin D varied in these studies (0%-52%). Vitamin D levels of children with EoE both pre- and post-intervention were low.

Conclusions: There is limited published literature on vitamin deficiencies associated with EoE both pre- and post-intervention. The limited data on vitamin D suggest that insufficiency or deficiency may be present in these patients, but it remains unclear whether deficiency is caused by diet. More prospective, well-defined studies, in addition to routine reporting on dietary intake and nutritional status, are needed to make any conclusions or recommendations for screening.

KEYWORDS

adolescent, child, eosinophilic esophagitis, vitamin D, vitamins

1 | BACKGROUND

Eosinophilic esophagitis is a chronic immune antigen-mediated disease characterized by isolated esophageal eosinophilia with symptoms of esophageal dysfunction.¹⁻³ It has been shown to be highly associated with other atopic conditions including food allergy.⁴

Nutritional deficiencies have been seen in patients with food allergy. The elimination of the main food allergens including cow's milk, egg, nuts, soy, wheat, fish, and shellfish that supply essential nutrients can be causal, and guidelines recommend nutritional counseling to ensure sufficient intake.^{5,6} We also know that children with EoE may present with feeding difficulties, aversive feeding, and subsequent FTT.² However, screening for vitamin deficiencies is not part of the current algorithm at the time of EoE diagnosis. In addition, one treatment for EoE is a food elimination diet and this itself might lead to nutritional deficiencies, but how much literature there is to support this for EoE remains unclear. Nonetheless, the American Academy of Allergy, Asthma & Immunology recommends that anyone treated with dietary elimination work with a nutritionist or dietitian to prevent nutritional deficiencies.⁷

There is also literature demonstrating an association between vitamin D, food allergy, and the immune system.⁸ Low vitamin D levels have been found in other atopic conditions such as asthma and atopic dermatitis as well. It would therefore be suggestive that there might be an association with low vitamin D and EoE.

The aim of this study was to evaluate, assess, and quantify the prevalence of vitamin deficiencies among pediatric patients with eosinophilic esophagitis both pre- and post-treatment by conducting a systematic review of the literature on the relationship.

2 | METHODS

This study was constructed using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.⁹ Accordingly, a protocol was registered in PROSPERO, an international prospective register of systematic reviews (Registration #: 124417; URL: https://www.crd.york.ac.uk/PROSPERO/record_email.php).

2.1 | Search strategy

Comprehensive literature searches investigating the prevalence of vitamin deficiencies among pediatric patients with eosinophilic esophagitis were developed and performed by a medical librarian [KM], upon consultation with the PI [AS].

The initial search was run on November 30, 2018, via Ovid MEDLINE® ALL (In-Process & Other Non-Indexed Citations and Ovid MEDLINE® 1946 to November 30, 2018). Follow-up searches via The Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Methodology Register, Technology Assessments (HTA)) and Ovid

Key Messages

Eosinophilic esophagitis is a chronic immune antigen mediated disease found to be highly associated in patients with atopic disease and treated with dietary elimination. Current recommendations suggest that all patients should have a multidisciplinary team approach including a dietitian to prevent nutritional deficiencies. However the data to support this recommendation is unclear or lacking. We attempted to review the literature to find evidence of nutritional deficiencies associated with EoE itself or related to the therapy of EoE.

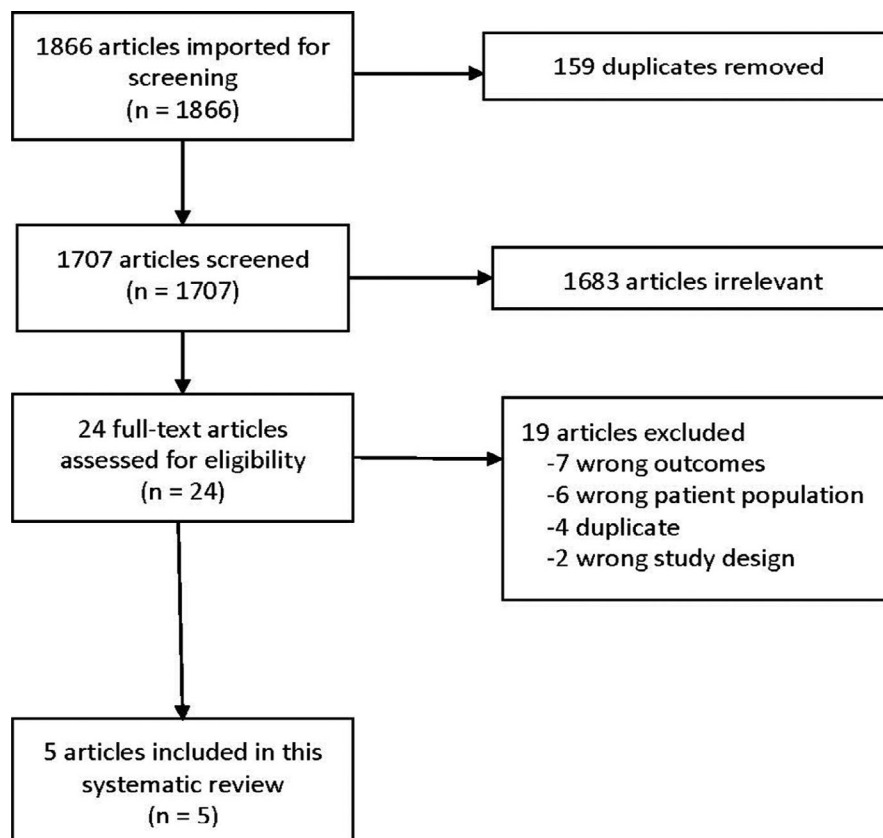
EMBASE (1974 to 2018, December 3) were run on December 3, 2018. Search terms in each database included all subject headings and/or keywords associated with: Eosinophilic Esophagitis, Esophagitis, Elimination Diet, Vitamins, Ascorbic Acid, Vitamin A, Vitamin B Complex, Choline, Folic Acid, Niacin, Riboflavin, Thiamine, Vitamin B 12, Vitamin B 6, Vitamin D, Vitamin E, Vitamin K, Ascorbic Acid Deficiency, Scurvy, Vitamin A Deficiency, Vitamin B Deficiency, Choline Deficiency, Folic Acid Deficiency, Pellagra, Riboflavin Deficiency, Thiamine Deficiency, Vitamin B 12 Deficiency, Vitamin B 6 Deficiency, Vitamin D Deficiency, Rickets, Vitamin E Deficiency, and Vitamin K Deficiency. Search terms were joined using Boolean operators OR and AND, as appropriate. There were no language, publication date, or study-type restrictions implemented. In accordance with the Institute of Medicine's Committee on Standards for Systematic Reviews standard 3.2.1, gray literature sources were searched and screened to address potential biased reporting of published research results.¹⁰ The full Ovid MEDLINE search strategy is available in Appendix S1.

2.2 | Study selection

After excluding duplicates, two researchers independently [AS and AF] screened the title and abstracts of 1631 citations using Covidence,¹¹ a systematic review screening tool. Any discrepancies were resolved by consensus. All citations were reviewed against pre-defined inclusion/exclusion criteria. (Inclusion: human subjects, aged 0-18, with eosinophilic esophagitis. Exclusion: adults over 18 years, non-English papers).

Full-text review followed the initial title and abstract screening phase. Studies were selected for inclusion using the same process utilized during title and abstract screening. Upon completion of full-text review, all searches were re-run on July 19, 2019, returning an additional 76 citations after de-duplication. Using the same evaluation strategy detailed above, 2 additional full-text articles were screened; however, none meet established inclusion criteria. In total, data were extracted from 5 included studies. See the full PRISMA flow diagram for an outline of the overall screening process (Figure 1).

FIGURE 1 Flowchart for the process of identifying studies that were included and excluded from the systematic review



All included studies were assessed for quality using the Black and Downs checklist for measuring study quality.¹² This checklist consists of 27 questions designed to evaluate both randomized and non-randomized studies for overall quality of reporting, and for internal and external validity. Quality levels were assigned to each included study, using the categories proposed by Hooper, Jutai, Strong, and Russell-Minda (2008): excellent (Black and Downs score ≥ 26), good (20-25), fair (15-19), and poor (≤ 14).¹³ The scoring methodology of the checklist is structured so that only randomized controlled trials can receive a score of 26 or greater. Each author [AS, AF, KM] scored included studies individually, with quality levels assigned only after consensus was reached (Table 1).

3 | RESULTS

In total, our search yielded 1707 studies to be screened, 1683 were excluded, and 24 were identified as meeting criteria for full-text screening (Figure 1). Of these, 19 were excluded for incorrect outcomes, patient population, study design, or duplication. The remaining 5 studies were included in the systematic review (Table 1).¹⁴⁻¹⁸

Of the 5 studies, 3 were abstracts (2 poster presentations from conference proceedings; 1 case report) and 2 were full-text articles. Overall, 137 pediatric patients were in the included studies. Additional study characteristics and outcome data are presented in Table 1. The single common outcome measure across all studies was serum vitamin D, specifically as serum 25-hydroxyvitamin D (25(OH)D) in 4 of 5

studies. The case report did not specify how vitamin D level was assessed. Reported prevalence of low vitamin D varied in these studies (0%-52%) excluding the case report. Degree of insufficiency was not specified in all studies. Single studies also measured calcium excretion, ferritin, pre-albumin, and PTH.^{15,18} Outcome measures were assessed at different points in EoE treatment across studies.

3.1 | Pre-EoE treatment

Two studies measured vitamin D status prior to treatment for EoE.^{14,17} In one study of 35 children, those with EoE were found to have lower vitamin D levels than those without EoE, though without statistical significance ($P = .8$).¹⁴ A questionnaire was used to assess vitamin D intake and sunlight exposure, but the results were not included in the available abstract. A case report of a boy on a restricted diet for reported food intolerances prior to EoE diagnosis was found to have low vitamin D. The authors associated this with his restricted diet but details were not provided. Neither study assessed vitamin D level post-treatment.

3.2 | Post-EoE treatment

One abstract assessed bone markers in 14 children with EoE who had completed the full six-food elimination diet (SFED) and were in the process of food reintroduction at time of analysis.¹⁵ Data on timing of reintroductions and length of elimination phase were not

TABLE 1 Study characteristics and outcome data of studies included in the systematic review

First author, publication year	Population	Study period	N	Design	Outcome indicator	Results	Prevalence of below normal vitamin D level	Quality ^a
Waterhouse, 2011	0-18 y	-	35	Abstract, prospective	25(OH)D	Non-significant but overall lower 25(OH)D levels in EE with GERD compared to controls (quantifiable data unavailable)	Not specified	Poor
Linglart, 2015	1.4-13.6 y	-	14	Abstract, convenience retrospective	25(OH)D Urinary calcium excretion Urinary D-pyridinolines	1. Vitamin D was below normal range in half of patients 2. Urinary calcium excretion and urinary D-pyridinolines indicated abnormally high bone resorption/turnover (above normal in most patients)	50%	Poor
Slack, 2015	Adults and Children	2010-2014	35 adults, 34 children	Prospective	25(OH)D	Median Vit D 28.9 Insufficient levels more common with higher age and BMI No associations between Vit D and median eos, peak eos, or milk elimination	52% total (20% deficient, 32% insufficient)	Fair
George, 2017	Children	-	1	Abstract, case report	-	Vitamin D deficiency (100%)	100%	Poor
Mehta, 2018	1-7 y	2012-2015	53	Prospective	Serum ferritin, pre-albumin, PTH, 25(OH)D 3-d food diary for intake	Normal mean ferritin, pre-albumin, PTH, and vitamin D levels. Adequate carbohydrate, protein, fat, calorie, and micronutrient intake with the exception of low vitamin D intake in GERD and low vitamin D and calcium intake in EoE children	0%	Poor

^aDowns and Black scoring of quality assessment: 26-28 (excellent), 20-25 (good), 15-19 (fair), and ≤14 (poor).¹²

reported. Pre-treatment analysis was not conducted for comparison. 25(OH)D levels were below normal range in 50% of subjects, and this was associated with elevated urinary calcium excretion and D-pyridinolines suggesting high bone resorption.¹⁵

3.3 | Unclear, both, or during EoE treatment

Two studies did not specify timing of vitamin D measurement in relation to timing of or participation in EoE treatment.^{16,18} Slack et al found vitamin D insufficiency overall was more common in adults (median 25.5 years) and those with higher BMI (median 25.2 kg/m²),¹⁶ while vitamin D sufficiency was more common in younger participants (median 16.2 years) and lower BMI (median 19.8 kg/m²).¹⁶ Combined results showed that there was no significant difference in peak or median esophageal eosinophil counts or total or specific IgE in those with sufficient vitamin D level versus those with insufficient vitamin D level. Similarly, there was no difference in vitamin D level between participants eliminating cow's milk and participants consuming cow's milk.

Mehta et al assessed dietary intake of vitamin D and included only children ages 1-7 years old.¹⁸ Thirty-eight percent of participants were currently on some form of elimination diet. Of the 62% of children with EoE who completed food diaries, intake of vitamin D and calcium was insufficient, while total calories, protein, carbohydrates, fat, and iron were sufficient. Nutrient intake was compared to daily recommended intake (DRI) levels for age. Laboratory assessment of ferritin, pre-albumin, PTH, and vitamin D was sufficient. Both intake and laboratory values for those on an elimination diets were not significantly different than those not on elimination diets, apart from higher PTH in the diet group.¹⁸

4 | DISCUSSION

Vitamin D deficiency (<20 ng/mL or <50 nmol/L) is reported to be prevalent in 42% of adults and 15% of children.¹⁹⁻²¹ There are several reasons to suspect that patients with EoE may have higher prevalence of vitamin D deficiency than the general population. Children with EoE can present with a variety of complaints including difficulty feeding and feeding refusal in young infants, toddlers, and young children.²² As a result, they may present with weight loss and failure to thrive with subsequent nutrient deficiencies at the time of diagnosis.² Vitamin D has been shown to be associated with food allergy and immune system.⁸ There are data to suggest that low blood vitamin D level is a risk factor for food allergy.²³ Since EoE is triggered by allergens, this could suggest that low vitamin D could be a risk factor for the development of EoE as well. In the data we reviewed, the 2 prospective studies differ in the reported prevalence of low vitamin D, one reporting a higher prevalence than the general population, and the retrospective data similarly suggest a higher prevalence of lower vitamin D in EoE.

Elimination diets are a mainstay in treatment for EoE with cow's milk being a common trigger of EoE, especially in children.^{2,24,25} There are published data associating rickets as the result of severe vitamin D deficiency in children with cow's milk allergy; therefore, a prolonged elimination diet would raise concern for this adverse event.^{26,27} Nonetheless, we cannot draw any conclusions from this review to indicate that patients on elimination diets for EoE have higher risks of rickets or complications from vitamin D deficiency and this needs to be explored further.

Due to the differing designs, poor quality, and limited number of studies, caution should be used when interpreting the data. Our review indicates that there are limited published data investigating vitamin deficiency associated with EoE, more specifically vitamin D, and most of which is poor quality. From the data available, there are insufficient data to calculate a prevalence of vitamin D deficiency in children with EoE or to conclude that it is greater than the general population. Furthermore, we cannot draw conclusions on whether this may be related to diet or disease. High-quality prospective studies are needed to determine the true prevalence of vitamin D deficiency in EoE patients, and more routine reporting on dietary intake and nutritional status is needed to make any conclusions or recommendations for screening in these patients or need for supplementation.

CONFLICT OF INTEREST

The authors have no conflicts to disclose related to this manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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Appendix A: Ovid MEDLINE Search

1. ESOPHAGITIS/
2. Eosinophilic Esophagitis/
3. (Esophagitis or Esophagitides or Eosinophilic Esophagitides or Eosinophilic Chronic Esophagitides or Eosinophilic Chronic Esophagitis or eosinophilic oesophagitis or caustic esophagitis or caustic oesophagitis or esophagus inflammation or oesophagitis).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
4. Elimination Diet*.mp.
5. 1 or 2 or 3 or 4
6. Vitamins/
7. Ascorbic Acid/
8. Vitamin A/
9. Vitamin B Complex/
10. CHOLINE/
11. Folic Acid/
12. NIACIN/
13. RIBOFLAVIN/
14. THIAMINE/
15. Vitamin B 12/
16. Vitamin B 6/
17. Vitamin D/
18. Vitamin E/
19. Vitamin E/
20. Vitamin K/
21. Ascorbic Acid Deficiency/
22. SCURVY/
23. Vitamin A Deficiency/
24. Vitamin B Deficiency/
25. Choline Deficiency/
26. Folic Acid Deficiency/
27. PELLAGRA/
28. Riboflavin Deficiency/
29. Thiamine Deficiency/
30. Vitamin B 12 Deficiency/
31. Vitamin B 6 Deficiency/
32. Vitamin D Deficiency/
33. RICKETS/
34. Vitamin E Deficiency/
35. Vitamin K Deficiency/
36. Vitamin*.mp.
37. (L-Ascorbic Acid or Hybrin or Magnorbin or Sodium Ascorbate or Ferrous Ascorbate or Magnesium Ascorbate or Magnesium di-L-Ascorbate or Magnesium di L Ascorbate or Magnesium Ascorbicum or ascorbic acid* or acidum ascorbicum or acidylina or adenex or afj c

or agrumina or allercorb or allicorb or antiscorbutic vitamin or arcavit c or arcavite c or arkovital c or ascelat or ascofar or ascomed or asconvita or ascor or ascorbate or ascorbate sodium or ascorbic acid potassium salt or ascorbicap or ascorbicin or ascorbico or ascorbin or ascorbina or ascorbinic acid or ascorbit or ascorbite or ascorbitol or ascorbivit or ascorbivite or ascorbone or ascorbutina or ascorbyl or ascorbyn or ascorcee or ascorgil or ascorin or ascormin or ascorteal or ascorval or ascorvel or ascorvit or ascorvite or ascorvitina or askorbin or austrovit c or austrovite c or bentavit c or bentavite c or c crivit or c ine or c level or c lisa or c long or c monovit or c monovite or c prana or c rivitin or c rivitine or c sol or c tamin or c tamine or c tonic or c tron or c vescent or c vicotrat or c vicotrate or c vimin or c vimine or c vit or c vita or c vital or c vitam or c vite or c-vimin or c-will or cantan or cantaxin or catavin c or ce arom or ce limo or ce major or ce quin or ce quine or ce vi sol or ce vita or ce vitan or ce-vi-sol or cebetate or cebicure or cebion or cebione or cecap or cecon or cecon drops or cecon solution or cecone or cecorbin or cecorbine or cecorbyl or cecorbyle or cecrisina or cedon or cedone or cedoxon or cedoxone or cee-500 or ceevifil or cegiolan or celaskon or celaskone or celin or celine or cenetone or cenol or cenolate or cequinyll or cereon or cergona or cescorbat or cetamican or cetamid or cetamin knoll australia or cetamine or cetamine knoll australia or cetebe or ceterapion or ceterapione or cetrinets or cevalin or cevaline or cevatine or cevex or cevibram or cevigal or cevigen or cevigol or cevilat or cevimin or cevimine or cevisol or cevit or cevita or cevitic acid or cevitamin or cevitanic acid or cevitaminum kolin or cevitan or cevite or cevitec or cevitol or cewin or chewcee or chivibit c or ci drol or ciamin or ciamina ormo or ciargin or cofilina or cipca or cisir or cital or citamino or cith or citoascorbina or citoxyl or citran or citravite or citritabs or citrovitamina or civigor or civitin or civitine or co biagini or concemin or cortalex or d ascorbic acid or d xyloascorbic acid or dagrascorbin or dagravit c or dancimin c or davitamom c or dayvital or delo c or difvitamin c or dumovit c or dumovite c or e ascorbic acid or e xyloascorbic acid or erftamin c or erftamine c or esuron or esurvite or esurvite or flavettes or godabion c or gregovite c or hiee or hybrin or ido c or ikacee or inovitan c or irocevit or irocevite or jarexin or jarexine or lacivit or lacivite or laroscorbine or leder c or leder-c or lemascorb or levo ascorbate or levo ascorbic acid or limcee or limo ce or liqui cee or myascorbin or natrasorb or novo ascorbic or nybadol or paa 500 or parkovit c or pharascorbine or pharatomvit c or pharatomvite c or planavit c or planavite c or plivit c or plivite c or potassium ascorbate or pro-c or proscorbin or proscorbine or redoxon or redoxon c or redoxon forte or ribena or scorbacid or scorbacide or scorbettes or scorbex or scorbin c or scorbital or scorbimine or scottavit c or scottavite c or secorbate or sevalin or sigmavit c or sigmavite c or sodascorbate or sodium ascorbate or sodium l ascorbate or sweetcee or synum c or take-c or tanvimil-c or testascorbic or ucemine c or upsa c or upsa-c or vi ci sin or vi dom c or vi-c 500 or vicef or vicelat or vicietrin or vici monico or viciman or vicin or vicitina or vicon or viforcit or viforcite or viscorin or viscorine or vita-cedol orange or vitac or vitace or vitacee or vitaci or vitacimin or vitacimine or vitacin or vitacine or vitamin C or vitamin c 1 or vitaplex c or vitapric or vitapur c or vitasan c or vitascorbin or vitascorbine or vitascorbol or vitascorbol 500 or vitelix c or vitocee or vorange or wandervit c or wandervite c or witamina c or xitix or xon-ce or xyloascorbic acid).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

Appendix A: Ovid MEDLINE Search

38. (Aquasol A or Retinol or All-Trans-Retinol or All Trans Retinol or 11-cis-Retinol or retinol or a 313 or a mulsal or a mulsin or a mulsine or a sol or a vi pel or a vit or a vitadit or a vitamin or a vitan or a-fil or a313 or acon or acrisina or acrisine or actifral a or adatone or afoxin or afoxine or afillina or afilline or agiolan or alcovit a or alfa monovite or alfa sir or alfaergin or alfaergine or alfamin or alfamine or alfamonovit or alfasir or alfasole or alfasterolo or alfatar or alfavena or alfavene or alfavitina or alfavitine or alfene or alphalin or alphaline or alphasterol or amulsal or amulsin or amulsine or amulvit or anatola or anatole or anavit or anti infective vitamin or antixerophthalmic vitamin or aoral or apexol or apostavit or arcavit A or asol or asteril or atav or aterapion or avibon or avibon theraplix or avimin or avimine or avipel or avipur or avit or avitabiol or avitadit or avital or avitaminum kolin or avitan or avitana or avitane or avite or avitil or avitina or avitol or avogina or avogine or avoleum or axerodina or axerodine or axerol or axerophthol or axerophthylum or bentavit a or bentavite a or bio tan or biosterol or biotan or chivibit a or cytobiase or dagravit a or davitamon a or difvitamin a or dohyfral a or elageno a or endo a or envit a or epiteliol or evitol zambeletti or fletase or gadeol or gadol or halivitan or halivitane or homagenets aoral or hydrosol or ido a or idratene or inovitan a or lord factor or meditalfa or mulsal a or multamine or nio a let or oleovit a or oleovitamin a or ophthalamine or panvita or plivit a or prepalin or prepaline or preparato a or primavit or quotivit or retinol alcohol or retinyl alcohol or ro a vit or super a or testavol or ucemine a or vaconex or vafol or veroftal or vi alpha or vi dom a or viadenin or vialpha or viatate or vidoma or vitadone or vitadral or vitalen a or vitalfa or vitama or vitamin A or vitamin a alcohol or vitamin a1 or vitaplex a or vitapur a or vitasan a or vitavel a or vitpex or vogan or vogan neu or wandervit a or Xerophthol).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

39. (Vidine or Pteroylglutamic Acid or Pteroylglutamic Acids or Folic Acid or Folic Acids or Folvite or Folacin or Folate or Choline or alpha choline or amonita or b cholin or beta cholin or beta choline or bilineurine or biocholine or biocolina or bursine or cholin or fagine or hepacholine or laevocholine or levocholine or lipotril or luridine or n choline or sincaline or urocholine or folic acid* or acfol or acide folique ccd or acido folico or apo-folic or filicine or folacin or folart or folate or folate sodium or foldine or foliamin or folic acid dha or folicet or folicid or folina or folinsyre or folitab or folium acid or folivit or folsan or folverlan or folvite or gravi-fol or ingafol or lactobacillus casei factor or lafol or lexpec or megafol or neocepri or nsc 3073 or pteroylglutamic acid tablets or pteroyl glutamate or pteroyl l glutamic acid or pteroyl monoglutamate or pteroylglutamate or pteroylglutamic acid or pteroylmonoglutamate or pteroylmonoglutamic acid or rubiefol or sodium folate or vifolin).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

40. (B complex or dagravit b complex or fortaplex or milgamma or nevramin or Neurobion).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

41. (nicotinic acid* or acido nicotnico or acidum nicotnicum or akotin or apelagrin or apo-nicotinic acid or beta pyridine carboxylic acid or bionic or davitamon pp or direktan or direktane

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or efacin or efasin or enduracin or enduracin or naotin or natinat or niac or niacin or niacine or niacor or niaspan or niaspan or nicacid or nicangin or nico span or nico tamin or nico zef or nicobid or nicocap or nicocidin or nicocrisina or nicodan or nicodane or nicolar or niconacid or niconacide or nicoseptin wirkstoff or nicosode or nicospan or nicosyl or nicotabs or nicotamin or nicotene or nicotin acid or nicotinat or nicotinate or nicotinate sodium or nicotinese or nicotinic acid natriumsalt or nicotinic acid sodium or nicotinipca or nicotyl or nicovasen or nicyl or nikacid or nipellan or novoniacin or nyacine or nyclin or pellagramin or pellagramine or pellagrin or pellagrine or pelonin or pelonine or pepevit or peviton or pp factor or pyridine 3 carbonic acid or pyridine 3 or carbonic acid natriumsalt or pyridine 3 carboxylic acid or pyridine beta carboxylic acid or slo niacin or sodium nicotinate or vasotherm or vitaplex n or wampocap or wampopap or riboflavin or beflavin or beflavine or flavaxin or hyrye or lactoflavin or lactoflavine or ovoflavin or pabriflan or riboflavine or ribovel).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

42. (thamine or aneurin or aneurine or benerva or beneuran or beneurin or betabion or betalin s or betaxin or bethiamin elixir or bevitine or bewon or biamine or biden elixir or metabolin or pabiamine or sheramin elixir or thiamin or thiaminium chloride hydrochloride or vibex).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

43. (Nico-400 or Nico 400 or Nico400 or Nicobid or Nicocap or Nicolar or Nicotinate or Wampocap or Enduracin or Induracin or Lithium Nicotinate or Riboflavin or Thiamin or Aneurin or Thiamine or nicotinic acid* or acido nicotinico or acidum nicotinicum or akotin or apelagrin or apo-nicotinic acid or beta pyridine carboxylic acid or bionic or davitamon pp or direktan or direktane or efacin or efasin or enduracin or enduracin or naotin or natinat or niac or niacin or niacine or niacor or niaspan or niaspan or nicacid or nicangin or nico span or nico tamin or nico zef or nicobid or nicocap or nicocidin or nicocrisina or nicodan or nicodane or nicolar or niconacid or niconacide or nicoseptin wirkstoff or nicosode or nicospan or nicosyl or nicotabs or nicotamin or nicotene or nicotin acid or nicotinat or nicotinate or nicotinate sodium or nicotinese or nicotinipca or nicotyl or nicovasen or nicyl or nikacid or nipellan or novoniacin or nyacine or nyclin or pellagramin or pellagramine or pellagrin or pellagrine or pelonin or pelonine or pepevit or peviton or pp factor or pyridine 3 carbonic acid or pyridine 3 or carbonic acid natriumsalt or pyridine 3 carboxylic acid or pyridine beta carboxylic acid or slo niacin or sodium nicotinate or vasotherm or vitaplex n or wampocap or wampopap or riboflavin or beflavin or beflavine or flavaxin or hyrye or lactoflavin or lactoflavine or ovoflavin or pabriflan or riboflavine or ribovel).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

44. (Cyanocobalamin or Cobalamins or Cobalamin or Eritron or cyanocobalamin or acravit b12 or almeret or anacobin or anacobine or antipernicin or antipernicine or apavit b12 or aquocobinamide cyanide or arcored or b docin or bagovit b12 or bedoc or bedoce or bedodec or bedodeka or bedoxyl or bedoz or bedozane or bedumil or behepan or behepane or beniform or benol or bentavit b12 or berubi or berubigen or berubigene or berubin or berubine or

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betalily 12 or betalin 12 or betaline 12 or betamine b12 or beterapion 12 or betolvex or bevatine or bevatine 12 or bevidoral or bevidox or bevitex or bex or bexii or bexitab or bimil or biocres or biopar or bitevan or bivetan or byladoce or cabadon m or calomist or catavin or catavine or clarentin 12 or clarentine 12 or cn cobalamin or cn cobalamine or cobadoce forte or cobal-1000 or cobalamide or cobalin or cobaline or coballamine or cobalmed or cobaltron or cobaltrone or cobamin or cobamine or cobastab or cobavite or cobeminum or cobione or cobolin-m or cobrumin or cobrumine or cohemin or cohemine or covit or creliverol-12 or cresiro or cresirol or crodabion b12 or crystal b-12 or crystamin or crystamine or crystimin 1000 or crystwel or cyanacobalamin or cyanaton or cyanatone or cyancobalamin or cyano cobalamin or cyano cobalamine or cyanobalamin or cyanocobal or cyanocobalamine or cyanocobalomin or cycobemin or cycobemine or cycobeminet or cyclamin or cyclamine or cycoplex or cyomin or cyredin or cytacone or cytagon or cytamen or cytamene or cytaton or cytatone or cytobex or cytobion or cytobione or davitamon b12 or depo-cobolin or dicibin or dicopac or distivit or dobetin or dobetine or doce oral or docecrisina or docemine or doceoral or docibin or docibine or docigram or docivit or dodecabee or dodecavite or dodevitina or dodex or douzoral b12 or dozefull or ducobee or dumovit b12 or duodebex or duodecibin or duodecibine or embiol or emobione or endoglobin or erftamin 12 or erftamine 12 or eritrone or eritrosir or eritrovit b12 or eruhaemon or erycytol or erythrotin or erythrotine or examen or examene or extrinsic factor or fermin or fresmin or godabione b12 or griseovit or grisevit or grisovit or hematolamin or hemo b doze or hemoergene or hemomin or hemomine or hemosalus b12 or hepagon or hepagone or hepavis or hepavit or hepcovite or heptenyl 12 or hypovitaminosis b12 or ido b12 or intrinase or intrindon or intrinolone or kaybovite or la-12 or lactobacillus lactis dorner factor or lagavit b12 or lifaton b12 or livonal schering or lld factor or macrabin or mavena B12 or megabione or megalovel or mepharnbin or mepharubine or milbedoce or millevit or nascobal or nascobal or navagron or navagrone or neurobaltina or neurobaltine or neuroforte-r or norivite-12 or normocytin or osfavit b12 or palvite or parentosol b12 or pernaevit or pernical or pernicipur or pernipuvon or pernorol or pharmatovit b12 or pinkamin or pinkamine or plecyamin or plecyamine or poyamin or poyamine or rametine or rectocenga or recytomin or recytomine or redamin or redamine or redisol or regividerm or reticulogen or reticulogene or rhodacryst or robelvit or rojamin or rotamin or rotamine or rubavit or rubentin or rubentine or rubesol or rubion or rubione or rubivitan or rubivite or rubramin or rubramin pc or rubranova or rubrine or rubripca or rubrocitol or rubrovit or rubyvan or rubyvit or ruvite or sytobex or transcyanacobalamin or twel be or twelbe or tweltone or twelve oral or twelveoral or ucemine b12 or vi-twel or vibalt or vibecon or vibecone or vibicon or vibicone or vibisone or vicapan n or viemin 12 or virubra or vitabee 12 or vitadom or vitamina b12-ecar or vitapur b 12 or vitarubin).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

45. (Pyridoxine or pyridoxal or Pyridoxamine or adermine or adermine hydrochloride or becilan or beesix or benadon or bexivit or bonadon n or bonasanit or campoviton 6 or esa b or gravidox or hexa betalin or hexa-betalin or hexabetalin or hexabione hydrochloride or hexavibex or hexavibex steri-vials or hexermin or hexobion or hexobion 100 or pabroxin or piridoxin or piridoxine or pyridipca or pyridosine or pyridoxin or pyridoxine hydrochloride or pyridoxinium chloride or pyridoxol or pyrivel or pyroxin or uvimag b6 or viderma).mp. [mp=title, abstract,

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original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

46. (Tocopherol or alpha tocopherol acetate or alpha tocopherol glycolate or alpha tocopherol palmitate or alpha tocopherolphosphate or alpha tocopheryl acetate or alpha tocopheryl acetic acid or alpha-tocopherol or alpha-tocopherol acetate or aquasol e or austrovit e or covitol or covitol 1360 or covitol 400c or covitol f 1000 or covitol f1000 or d a tocopherol or d alpha tocopherol or d alpha tocopherol succinate or d alphetocopheryllacetate or d vitamin e or dagravit e or dalfatol or davitamon e or dermorelle or detulin or dextro alpha tocopherol or dextro vitamin e or dl alpha tocopherol or dumovit e or e ferol or e perle or e perte or e recordati or e toplex or e vicotrat or e vimin or e vita or e viterbin or ecoferol or efer or eferol or enoulant forte or ephynal or eplonat or eprolin or epsilan m or epsylan m or erevit or esol or esorb or eterapion or eviabit or evigen or eviol or evion or evit or evitol or godabion e or gonavit or hanobak or ido e or juvela or juvele or levo alpha tocopherol or livingpherol or mixed tocopherols concentrate or mulsal e or natopherol or optovit e or phytoferol or pletocol or socopherol or spondyvit or toco 500 or tocoferolo bioglan or tocomine or tocopherex or tocopherol acetate or tocopherol gumpro or tocopheryl acetate or tocophrine or tocovigor or tocovital or toferol or topherol or vi dom e or vi e caps or vi ea or vi etal or vibolex e or vidom e or viea or vietal or viprimol or vita e gelucaps or viteolin or viteoline or wandervit e).mp.

[mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

47. (Avitaminosis or Vitamin Deficienc* or Ascorbic Acid Deficienc* or Vitamin C Deficienc* or Scurvy or Scurvies or Hypoascorbemia or Hypoascorbemias or Scorbutus or Vitamin A Deficienc* or Vitamin B Deficienc* or Choline Deficienc* or Folic Acid Deficienc* or Hyperhomocysteinemia* or Pellagra* or Riboflavin Deficienc* or Thiamine Deficienc* or Vitamin B12 Deficienc* or Vitamin B 6 Deficienc* or B6 Vitamin Deficienc* or Vitamin B6 Deficienc* or Pyridoxine Deficienc* or Vitamin D Deficienc* or Ricket* or Rachitis or Rachitides or Vitamin E Deficienc* or Vitamin K Deficienc*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

48. 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47

49. 5 and 48