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REVIEW

Prediction models and questionnaires developed to predict vitamin D status in adults: a systematic review

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Abstract

A systematic review of prediction models/questionnaires developed to identify people with deficient/insufficient vitamin D status shows the potential of self-reported information to estimate vitamin D status. The objective is to identify and compare existing screening tools, developed to identify vitamin D deficiency or insufficiency in adults. A systematic search of literature was conducted using MEDLINE, Scopus, Web of Science and CINAHL databases. Risk of bias and applicability concerns were assessed by quality assessment of diagnostic accuracy studies (QUADAS-2). Data were extracted on socio-demographic, anthropometric, risk factors, serum 25 hydroxyvitamin D [25(OH)D] levels, statistical methods and predictive ability. A total of 12 studies were considered for inclusion for this systematic review after screening of 4851 abstracts and 15 full-text articles. Ten of twelve studies developed prediction models and 2 studies developed questionnaires. The majority of studies had low risk of bias and applicability as assessed by QUADAS-2. All studies included only self-reported predictors of vitamin D status in their final models and development of scores. Sunlight exposure and related factors were important significant contributors to the predictive ability of the models and/or questionnaires. Sensitivity and specificity of the prediction models or questionnaires ranged from 55 to 91% and 35 to 84%, respectively. Six out of twelve studies converted final models to scores associated with vitamin D status. There was no evidence that any of these existing tools have been translated into clinical practice. The prediction models or questionnaires identified in this systematic review were moderately sensitive and specific for identifying people with vitamin D deficiency or insufficiency. The substantial contribution of sunlight exposure to the prediction of vitamin D status highlights the importance of including this information when developing vitamin D screening tools.

Keywords Adults · Prediction · Questionnaire · Screening · Vitamin D

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Introduction

The role of vitamin D for musculoskeletal and non-skeletal health [1] has been recognized since the discovery by McCollum and colleagues in 1922 that rickets can be cured by vitamin D supplementation [2]. Vitamin D deficiency is a serious global public health issue [3]. Vitamin D deficiency is frequent across all age groups [4] and, paradoxically, has higher prevalence in sun-drenched countries such as Pakistan and Italy [5, 6], and countries where food fortification with vitamin D has been in practise for a number of years such as the USA or Canada [5, 7, 8]. The increasing recognition of vitamin D in musculoskeletal health has resulted in an increased uptake of people being tested for vitamin D, which, in turn, imposes a significant cost burden on the healthcare system. In Australia, there was an average increase of 59% per year for biochemical vitamin D testing [serum 25 hydroxyvitamin D, 25(OH)D)] between 2000 and 2010 [9, 10]. However, vitamin D testing may have been prescribed more frequently than required (42.9% had >1 test between 2006 and 2010 in Australia) [9, 10]. Similar trends of increased vitamin D testing have been reported in France [11], the UK [12], the USA [13] and Canada [14].

Blood tests play an important role in diagnosis and management of various health conditions; however, unnecessary blood testing is not beneficial [15]. There is a lack of available data demonstrating the clinical utility of screening serum 25(OH)D [10], data on cost-effectiveness of vitamin D screening is conflicting. According to the French National Authority for Health, the cost of vitamin D testing per year is more than the cost of 1 year of supplementation [11]. Australian, Canadian and French governments have recently restricted vitamin D testing benefits to those with symptoms of vitamin D deficiency, such as individuals with osteoporosis, osteomalacia, hyperparathyroidism, hypo- and hypercalcemia, in order to reduce this economic burden [16–18].

There is no current, low-cost, quick and simple alternative to blood tests available to determine a person's vitamin D status. Therefore, there has been increased attention directed towards the development of vitamin D screening tools that use self-reported data to estimate vitamin D status in order to minimize health care costs attributable to vitamin D testing. Previous research has identified numerous socio-demographic and lifestyle factors associated with vitamin D deficiency [19–23] which could be used to develop prediction models and questionnaires that predict vitamin D deficiency or insufficiency. The aims of this review are to identify existing vitamin D screening tools, including prediction models or questionnaires, developed to identify adults aged 18 years and over with vitamin D deficiency or insufficiency. Furthermore, we aimed to identify and compare self-reported socio-demographic, anthropometric and/or lifestyle risk factors associated with vitamin D deficiency/insufficiency that have been utilized in these prediction models and questionnaires.

Methods

This systematic review adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for Diagnostic Test Accuracy (DTA) studies [24] and is registered in PROSPERO, the International Prospective Register of Systematic Reviews (CRD42019125867).

Eligibility criteria

Any studies published between January 2008 and October 2019 that developed models or questionnaires (index test) to predict vitamin D status as determined by serum 25(OH)D levels (reference standard) in adults aged 18 years or older (with or without vitamin D deficiency and/or insufficiency), and used socio-demographic, anthropometric and/or lifestyle risk factors associated with vitamin D deficiency/insufficiency, were eligible for inclusion. Studies were excluded if they were (i) conference abstracts, (ii) studies on children or pregnant women, (iii) studies that used geriatric assessment tools to predict vitamin D status or (iv) not published in English. Tools that were developed by pharmaceutical companies but not published in a peer-reviewed journal were also excluded.

Index test

The index test considered for this systematic review was a questionnaire or a predictive model used to identify vitamin D status based on combinations of self-reported risk factors such as age, sex, body mass index (BMI), smoking status, alcohol intake, physical activity, sun seeking habits, use of sunscreens, season of blood draw, medications and vitamin D and calcium supplements.

Reference standard

Serum 25 hydroxyvitamin D [25(OH)D] level is the best measure of vitamin D status [25]. 1,25(OH)D3 is the biologically active form of vitamin D but its circulating half-life is shorter than 25(OH)D and is generally normal or elevated because of secondary hyperparathyroidism [25]. Serum 25(OH)D levels measured by the commonly used assays such as protein binding assay, radioimmunoassay (RIA), chemiluminescent immunoassays (CLIA) and high-performance liquid chromatography - tandem mass spectrometry (HPLC/MS-MS) [26] were considered as reference standard for this systematic review.

Search strategy and identification of studies

A comprehensive electronic search of the literature was conducted using MEDLINE, Scopus, Web of Science and CINAHL databases using Medical Subject Headings (MeSH) terms and key words including "Vitamin D" and

"Screening tools", with limiting terms being "Age" and "Animal". (Table- S1). From the initial yield, one reviewer (GN) screened all titles, abstracts and full texts against the pre-determined eligibility criteria. A second reviewer (JT) cross-checked 2% of the excluded articles and 100% of all articles identified as being eligible for inclusion. Any disagreements were resolved by the involvement of third reviewer (SLB-O).

Data extraction

Data extraction was performed independently by one reviewer (GN) and cross-checked for accuracy by a second reviewer (JT). Any discrepancies were resolved by a third independent reviewer (SLB-O). Data extracted from the included studies included sample size, country in which the study was conducted, age, sex (proportion of women), mean 25(OH)D levels (reference standard) and cut-points to define vitamin D status, risk factors used in each study, exclusion criteria, statistical methods used and tool presentation (conversion of final model into scores). Data regarding the predictive ability of models and questionnaires were also extracted, including sensitivity, specificity and/or area under the curve (AUC).

Risk of bias and applicability

The methodological quality of each study was assessed independently by two reviewers (GN and KL). After initial assessment, the two reviewers discussed any discrepancies and where agreement could not be gained, the disagreements were resolved by a third reviewer (SLB-O). To assess the quality of studies in terms of risk of bias and applicability, the Quality Assessment tool for Diagnostic Accuracy of Studies tool version 2 (QUADAS-2) was used [27]. The QUADAS-2 tool enables the assessment of primary diagnostic accuracy studies and involves 4 domains of patient selection, index test, reference standard, flow and timing [27]. However, given that one signalling question included in the QUADAS-2 tool was not relevant to this systematic review, it was excluded from the two domains of patient selection (Did the study avoid inappropriate exclusions?) and index test (Were the index test results interpreted without knowledge of the results of the reference standard?). It is suggested that signalling questions can be modified or removed according to the type of systematic review [27].

Results

Study selection

A total yield of 9183 records were ascertained from the electronic search strategy and 2 articles identified through manual search. Following the exclusion of duplicate records, 4851 potentially eligible studies were cross-referenced against the pre-determined eligibility criteria. After screening all abstracts, 4836 articles were excluded, leaving a total of 17 (2 articles identified manually) potentially eligible records for full-text screening. The main reason for the exclusion of papers based on abstracts was that they had not developed a prediction model or questionnaire. The final selection of eligible articles included 12 studies for qualitative synthesis [28–39]. Figure 1 presents the flow diagram of the systematic identification of potentially eligible studies.

Study characteristics

Ten of the twelve studies developed prediction models using a variety of factors associated with vitamin D status, while two studies developed a questionnaire [30, 32]. Combined, the included studies encompassed a total of 17,088 participants (69% women) aged 18–84 years. The majority of studies included both sexes, ranging from 41.1% [28] to 68.6% [33] of women, while two studies included only women [35, 36]. The studies were performed in a range of countries, including the United States of America (USA) ($n = 3$) [29, 30, 35], France ($n = 2$) [28, 31], The Netherlands ($n = 2$) [36, 37], and one each in Japan [32], China [33], Brazil [34], Australia [38] and Italy [39]. The characteristics of included studies are presented in Table 1.

Serum 25 hydroxyvitamin D [25(OH)D] levels and vitamin D status

The most commonly used vitamin D assay was chemiluminescent assay (CLIA), and two studies [32, 33] used liquid chromatography–tandem mass spectrophotometry (LC-MS/MS) assay for measuring serum 25 (OH)D levels. Across the studies, mean serum 25(OH)D levels ranged from 42 nmol/L [38] to 71 nmol/L [29]: nine of the twelve studies used different cut-points to define vitamin D status, while two studies investigated the continuum of serum 25(OH)D levels [29, 36]. Six studies [28, 31, 33, 34, 37, 38] considered <50 nmol/L of vitamin D as 'insufficient' and three studies considered the same cut off as 'deficient' [30, 32, 35].

Risk factors considered in the development of prediction models and questionnaires

Risk factors considered in the development of prediction models or questionnaires varied across studies and are presented in Table 2. Overall, risk factors included were sociodemographic, lifestyle factors, sunlight exposure and related factors, season or month of blood drawn, self-reported health status and medical conditions, clinical and biochemical assessments, vitamin D and calcium intake (dietary or supplemental) and use of medications (type and number).

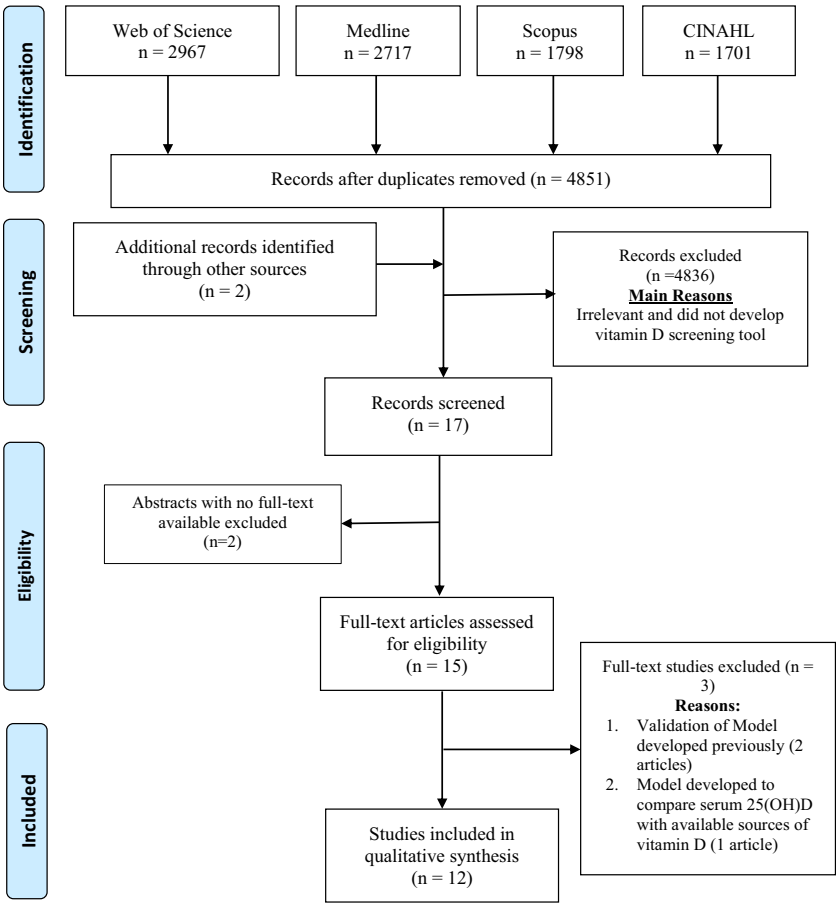

Fig. 1 Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram for identification and screening of studies

Socio-demographic and anthropometric factors

All studies included age and sex (except for women only studies [$n = 2$]) in the development of prediction model or questionnaire. Eleven of twelve studies included BMI, four studies included ethnicity [29, 30, 34, 38] and two studies included education level [36, 37].

Lifestyle factors

The most commonly assessed lifestyle factors were physical activity, smoking status and alcohol intake. All three factors were included in five [29, 32, 34, 37, 38] of the twelve studies, three studies included either only physical activity [31], physical activity and smoking status [33] or alcohol intake and smoking status [36].

Sunlight exposure

Sunlight exposure was included in five of the studies and recorded as either time spent in sunlight (minutes/day) [30, 32, 33, 39] or as usual sun exposure (none, moderate or high) [31]. Other factors included relating to sunlight exposure were exposure to ultraviolet B (UVB) radiation [29, 32, 33, 38], tanning ability of skin [29, 30, 32, 38], use of sunscreen [30, 32, 35] and skin tone [31, 38].

Health status and medical conditions

Self-reported health status was included in two studies [37, 38]. Falls were recorded in four studies as history of falls [28, 34, 36] or total number of falls [40]. In addition to this, fear of falling and history of vertebral fractures were used in model development in one study [28]. Other medical conditions were also considered but specific to each study except for mobility and functional limitations [28, 36, 37] recorded in three studies.

Vitamin D and calcium intake

Seven and five studies reported vitamin D [29, 30, 32, 33, 35, 36, 38] and calcium [28, 32, 36, 37, 39] intake, respectively, and were recorded either as dietary source [29, 30, 32, 33, 35, 36, 38] and/or supplements [29, 30, 33, 36, 38].

Use of medications and other supplements

Studies varied in the type of medications used by the participants to develop prediction models or questionnaires. One

Table 1 Characteristics of the studies included for review, presented in alphabetical order based on the first author

Author, year	Population and region (years of study)	Age (years) mean ± SD and/or range (years)	Sample size (% women)	Mean 25(OH)D levels nmol/L ± SD (assay)	25(OH)D cut-points, unless indicated as continuous values	Number of risk factors considered for inclusion in the tool/ questionnaire	Exclusion criteria
Annweiler et al. 2015 [28]	Community-dwelling older adults, Lyon, France (2009–2012)	70.2 ± 4.8	1924 (41.1%)	42.6 ± 22.6 (RIA)	≤ 75 nmol/L hypovitaminosis D; ≤ 50 nmol/L (insufficient); ≤ 25 nmol/L (severely deficient)	23	Institutionalized, unable to understand and speak French, acute medical illness in past month, dementia, unable to walk 6 m or taking vitamin D supplements
Bertrand et al. 2012 [29]	Female nurses: (NHS 1989–1990 and NHS II 1996–1999) and male health professionals (HPFS 1993–1994), USA	NHS: 30–55; NHS II: 25–42; HPFS: 40–75	NHS: 2079 (100%); NHS II: 1497 (100%); HPSF: 911 (0%)	NHS: 71.1 ± 27; NHS II: 65.6 ± 24.4; HPFS: 64.6 ± 24.9 (RIA or CLIA)	Continuous values	18	–
Bolek-Berquist et al. 2009 [30]	Young adult volunteers, Wisconsin, USA (2004)	24 ± 4	184 (53%)	62.4 ± 27.4 (CLIA)	< 40 nmol/L (deficient)	15	Medical conditions affecting vitamin D and calcium metabolism, eating disorders, skin diseases, using oral corticosteroids, anticonvulsants, insulin or bisphosphonates
Deschasaux et al. 2016 [31]	Adults from SU.VI.Max (1994–2007) and NutriNet-Sante (2009), France	SU.VI.Max: 53; NutriNet-Sante: 47‡	SU.VI.MAX: 1557 (46.5%); NutriNet-Sante: 781 (56.8%)	SU.VI.MAX: 50.4 ± 25.9; NutriNet-Sante: 60.1 ± 29.2 (CLIA)	≤ 50 nmol/L (insufficient)	7	Taking vitamin D supplements, presence of epilepsy and renal failure
Kuwabara et al. 2019 [32]	Adults, Kinki, Japan (2017–2018)	19–70	Development sample: 434 (54.3%); Validation sample: 215 (64.2%)	47.7 (36.7–61.1) $	<50 nmol/L (deficient)	17	People with liver disease, CKD, IBD, cancer, diabetes, and osteoporosis and taking vitamin D supplements
Lee et al. 2016 [33]	Joint (knee or hip) arthroplasty patients, Hong Kong, China (2011–2014)	67 ± 9	227 (69.6%)*	51 (42–63) ¥ (LC-MS/MS)	< 12.5 nmol/L (severely deficient); 12.5–29 nmol/L (moderately deficient); 30–49 nmol/L (mildly deficient); 50–220 nmol/L (sufficient)	12	Pre-existing comorbidities, use of anticonvulsants, glucocorticoids or antiretroviral
Lopes et al. 2014 [34]	Community-dwelling older adults, Sao-Pãulo, Brazil (2005–2007)	Development sample: 72.9 ± 4.9; Validation sample: 72.3 ± 4.4	Development sample: 750 (58.8%); Validation sample: 158 (62%)	48.4 ± 23.2 (RIA)	≤ 50 nmol/L (insufficient)	21	History of cancer, primary hyperthyroidism, chronic kidney disease and using

Table 1 (continued)

Author, year	**Population and region (years of study)**	**Age (years) mean ± SD and/or range (years)**	**Sample size (% women)**	**Mean 25(OH)D levels nmol/L ± SD (assay)**	**25(OH)D cut-points, unless indicated as continuous values**	**Number of risk factors considered for inclusion in the tool/ questionnaire**	**Exclusion criteria**
							bisphosphonates, taking vitamin D supplements
Lukaszuk et al. 2012 [35]	Women, Illinois, USA (2010)	34.0 ± 10.0 (20–50)	54 (100%)	59.4 ± 26.4 (CLIA)	< 50 nmol/L (deficient); 50–74.9 nmol/L (insufficient); ≥ 75 nmol/L (sufficient)	17	Men, ethnicity other than Caucasian, BMI <18 and 25–29.9 kg/m^2, pregnant, haemophilic, hepatic or renal disease, and taking vitamin D supplements >1500 IU/day
Merlijn et al. 2018 [36]	Older women, Noord-Holland, Netherland (2010–2013)	Development sample: 73.5 ± 6.1; Validation sample: 73.1 ± 6	Development sample: 2689 (100%), Validation sample: 856 (100%)	51.8 ± 20.5 (CLIA)	<30 nmol/L, <40 nmol/L, <50 nmol/L, <60 nmol/L	17	Ethnicity (Black, Arabic and Asian), living in residential care, or taking vitamin D supplements
Sohl et al. 2014 [37]	Older adults, Netherlands (1995–1996)	76.0 ± 6.7	1509 (52%)	53.2 ± 24.0 (Competitive binding protein assay)	<30 nmol/L (deficient; <50 nmol/L (insufficient)	26	–
Tran et al. 2013 [38]	Older adults, Four Eastern States (NSW, VIC, QLD, TAS), Australia (2010–2011)	60–84	643 (47%)	42.0 ± 14.0 (CLIA)	<25 nmol/L (deficient); <50 nmol/L (insufficient)	15	Taking vitamin D supplements >400 IU/day, history of kidney stones, hyperparathyroidism, osteomalacia, osteoporosis or sarcoidosis
Vignali et al. 2017 [39]	Adults, Pescopagano, Italy (2010–2011)	48.2 ± 17.9	620 (62%)	59.9 ± 29.2 (RIA)	Continuous values and following cut-points: <25 nmol/L; 25–49.9 nmol/L; 50–77.9 nmol/L; >75 nmol/L	7	Taking vitamin D supplements, medications affecting vitamin D metabolism, or individuals with kidney and liver disorders

‡ Median age; *Number of women written in text and table of the original publication are different; $ - Median and interquartile range; ¥ - Median and range

Abbreviations: *BMI* body mass index, *CKD* chronic kidney disease, *CLIA* chemiluminescence immunoassay, *HPFS* Health Professionals Follow-up Study, *IBD* inflammatory bowel disease, *IU* International Units, *LC-MS/MS* liquid chromatography–tandem mass spectrophotometry, *NHS* Nurses' Health Study, *NHS II* Nurses' Health Study II, *NutriNet-Santé* web-based nutrition-and-health-focused cohort, *NSW* New South Wales, *QLD* Queensland, *RIA* radioimmunoassay, *SD* standard deviations, *SU.VI.MAX* Supplémentation en Vitamines et Minéraux Antioxidants cohort, *TAS* Tasmania, *USA* United States of America, *VIC* Victoria

Table 2 Risk factors for vitamin D deficiency and insufficiency that were considered for inclusion in the development of prediction models and questionnaires

Author, year	Socio-demographic and anthropometric factors	Lifestyle factors	Sun exposure and related factors	Self-reported health status and medical conditions	Clinical and/or biochemical assessments	Vitamin D and calcium intake	Medication and/or other supplements (non-calcium or vitamin D)
Annweiler et al. 2015 [28]	Age, sex, BMI (continuous), EPICES score	Living alone, use of walking aid	–	Cognitive disorders, history of falls and vertebral fractures, fear of falling, polymorbidity, wearing glasses	TUG test, hand grip strength, lower limb proprioception, visual activity, sad mood	Calcium: Supplements	Medications: Psychoactive drugs, anti-osteoporotic drugs, bisphosphonates, strontium, number of medicines taken daily
Bertrand et al. 2012 [29]	Age, **BMI (categorical)**, **ethnicity**, hair colour, geographic region	**Physical activity (METs per week)**, **alcohol intake,** smoking status,	Season of blood drawn, **exposure to ambient UVB radiation**, susceptibility to burn, ability to tan, number of lifetime sunburns	Menopausal status, age at first birth	–	Vitamin D: **Dietary and supplement**	Medications: **Postmenopausal hormone use**
Bolek-Berquist et al. 2009 [30]	Age, sex, ethnicity	–	Season of blood drawn, time spent in sunlight during past week, **received suntan in past 12 months**, use of sunscreen, **use of tanning booth**	Diarrhoea, chronic intestinal disorders (Crohn's disease, ulcerative colitis, coeliac disease)	–	Vitamin D: Dose (IU/d), supplements alone or with calcium, **milk intake**, cod liver or fish oil	Other supplements: Multivitamins
Deschasaux et al. 2016 [31]	Age, **sex, BMI (continuous)**, **latitude**	**Physical activity (low, <1 h/day, ≥1 h/day)**	Month of blood drawn, **sun exposure** (low, moderate or high), skin tone (Fitzpatrick classification)	–	–	–	–
Kuwabara et al. 2019 [32]	**Age**, **sex**, BMI (categorical)	**Physical activity (>twice/week, once per week, 1to 2 times a month, never)**, alcohol intake, smoking status, FDSK	**Season of blood drawn**, **Suntan + use of sunscreen**, **sun exposure in last 3 months**, time spent in sunlight during past week (minutes/day), time spent outdoor regularly, time spent out door in holidays, use of sunscreen on arms and legs, paying attention to UV exposure	–	–	**Vitamin D: Vitamin D rich fish intake** Calcium: dietary	–
Lee et al. 2016 [33]	Age, sex, BMI (continuous)	Physical activity (none, <0.5 h/week, 0.5–1 h/week, >1 h/week), smoking status	Season of blood drawn, **time spent in sunlight during past week**, **exposure to ambient UVB radiation**	–	**Osteoarthritis index using questionnaire**	Vitamin D: **Milk intake (>1 cup/day; yes/no)**, supplements, fish oil	Other supplements: Multivitamins
Lopes et al. 2014 [34]	Age, **sex**, BMI (continuous), ethnicity	Physical activity (low/high), alcohol intake, smoking status	**Season of blood drawn**	Falls in past 12 months, **diabetes**, hypertension, osteoporosis,	Phosphorous levels, alkaline phosphates, **iPTH**, eGFR, glycemia, BMD T-scores (femoral, total hip and lumbar spine), calcium levels	–	–
Lukaszuk et al. 2012 [35]	Age, **BMI (normal and obese)**	–	**Use of sunscreen**	Fall (Autumn) - winter depression	– –	Vitamin D: **Dairy consumption**	Medications: Taking one or more medications

Table 2 (continued)

Author, year	Socio-demographic and anthropometric factors	Lifestyle factors	Sun exposure and related factors	Self-reported health status and medical conditions	Clinical and/or biochemical assessments	Vitamin D and calcium intake	Medication and/or other supplements (non-calcium or vitamin D)
Merlijn et al. 2018 [36]	**Age, BMI (categorical)**, education level	Alcohol intake, **smoking status**, **use of walking aid**	Month of blood drawn, **time spent outdoor in summer**, time spent outdoor in winter	Falls in past 12 months, impaired mobility		Vitamin D: **Supplements (either prescribed or unprescribed)**, fatty fish 2 times per week, daily use of margarine Calcium: **Supplements**	Medications: Use of ≥6 medications; Other supplements: **Multivitamins**
Sohl et al. 2014 [37]	**Age, sex†, BMI† (continuous)**, education level, **partner status†**, degree of urbanization (% of people living in city)	Physical activity as **bicycle (yes/no), gardening (yes/no)** sporting (yes/no), walking (yes/no) **alcohol intake, smoking status,**	**Season of blood drawn**	Self-reported health status, **presence of appetite (yes/no)†**, depressive mood (yes/no), anxiety, functional limitations (walking, **using transport***, climbing stairs), pain while walking, memory complains	MMSE: remember date (yes/no), **remember year (yes/no)***	–	Medications: **Use (yes/no)** Other supplements: **Vitamin use**
Tran et al. 2013 [38]	**Age**, sex, **BMI (continuous)**, ethnicity, Australian state (QLD, NSW, VIC, TAS), residential location (metro or regional)	**Physical activity (METs per week)**, alcohol intake, smoking status	**Time spent outdoor (often, sometimes, seldom)**, skin tone (tanning and burning ability), **exposure to ambient UVB radiation**	**Self-reported health status**, history of chronic disease (cancer, diabetes, and/or cardiovascular disease)	–	**Vitamin D intake (IU/day)**	–
Vignali et al. 2017 [39]	Age, sex, BMI (continuous)	–	Month of blood drawn, **time spent in sunlight(minutes/day), beach holiday (yes/no), time spent outdoor (often, sometimes, seldom)**	–	–	–	–

Abbreviations: *25(OH)D* 25 hydroxyvitamin D, *BMD* bone mineral density, *BMI* body mass index, *eGFR* estimated glomerular filtration rate, *EPICES* Evaluation of Deprivation and Inequalities in Health Examination Centres, *FDSK* food diversity score Kyoto, *iPTH* intact parathyroid hormone, *METs* metabolic equivalent of task, *MMSE* mini-mental state examination, *NSW* New South Wales, *QLD* Queensland, *TAS* Tasmania, *TUG* timed up and go, *UV* ultraviolet, *VIC* Victoria

Bold—risk factors significantly associated with vitamin D status in final prediction model, Underline—indicates the risk factors adjusted for within multivariable models

† Indicates predictors significantly associated with <50 nmol/L, * indicates predictors significantly associated with <30 nmol/L

study included medications commonly used for bone formation or prevention of bone loss [28], and another study included postmenopausal hormone use [29] for the development of a prediction model. Three studies reported number of medications used per day [28, 35, 36] as a predictor and four out of twelve studies considered use of multivitamins as a predictor of vitamin D status [30, 33, 36, 37].

Risk of bias and applicability

After assessing the quality of studies using the QUADAS-2, the initial agreement between the assessors (GN and KL) was 77%, and after discussion, 94% agreement was reached. The remaining 6% discrepancies were resolved by consultation with a third reviewer (SLB-O). Overall, 7 of 12 studies were considered as having a low risk of bias for patient selection, 10 studies for index test, 11 for reference standard and 9 for flow and timing (Supplementary Fig. 1). In terms of applicability, 9 (patient selection and index test) and 11 (reference standard) studies were considered as having a low concern.

Predictive ability

All the studies in their final models and development of scores included only self-reported predictors of vitamin D status except for studies where ambient UVB exposure was considered. Self-reported risk factors that significantly contributed to predictive ability of models and questionnaires (Table 2) to determine vitamin D status were older age [36–38], sex (woman) [31, 34, 37], higher BMI [29, 31, 35–38], partner status [37], non-Caucasian [29], low physical activity [29, 31, 32, 37, 38], being a smoker [36, 37] and alcohol user [29, 37]. Among sunlight exposure and related factors, significant predictors of vitamin D status were time spent in sunlight or outdoors [31–33, 36, 38, 39], tanning in past 12 months [30], use of tanning booths [30] and winter season [32, 34, 37]. Self-reported health status [38] (poor), having diabetes [34] and poor appetite [37] along with dietary [29, 30, 32, 33, 35] or supplemental [29, 36, 38] intake of vitamin D, use of calcium supplements [36] and multivitamins [36, 37] were also significant contributors in the predictive ability of the prediction models and questionnaires. Ambient UVB exposure [29, 33, 38] also significantly contributed to the predictive ability of the prediction models but is the only factor which is not self-reported. Use of sunscreen in one study was significantly associated with vitamin D status.

Statistical methods used to develop the prediction models and to test the ability of questionnaires, approaches used to test model performance and internal and external validation are presented in Table 3. Eight out of the twelve studies had performed external validation of the model; however, considerable variation existed between the methods employed. For instance, only one study [31] used data from different cohorts for external validation, whereas seven studies split their own dataset into one sample each for development and validation. False negative results were only reported by Annweiler and colleagues [28] and based on three different thresholds of 34 for ≤75 nmol/L, 166 for ≤50 nmol/L and 184 for ≤25 nmol/L ($n = 1924$). The proportion of false negative results in the development sample was 8.4%; however, this increased to 14.3% in the validation sample for lowest threshold of ≤25 nmol/L. The coefficient of determination (R^2) represents the amount of variation in serum 25(OH)D explained by models and was reported in three studies [29, 33, 38]. Two studies reported Nagelkerke's R^2, used for categorical outcomes. The developed models account for 14–56% of the variation in serum 25(OH)D levels (Table 3). Only two studies [33, 39] reported the contribution of individual risk factors to the predictive ability. In the model developed by Lee et al. [33], UVB exposure accounted for 42% of the variation in serum 25(OH)D levels. The contribution of other factors was, respectively, sunlight exposure 18%, milk intake 13%, age 8% and BMI and use of vitamin D supplements 7%. The questionnaire developed by Vignali and colleagues [39] was based on factors related to sunlight exposure and month of investigation, time spent in sunlight and beach holidays. Percentage of variation explained by each factor in a model was 28, 13.5 and 6.4%, respectively in the prediction of vitamin D status.

Predictive ability was reported as sensitivity, specificity and/or area under the curve (Table 3). The highest sensitivity of 98% (AUC = 0.93) and 87% (AUC = 0.86) was observed for the model developed by Annweiler and colleagues [28] to identify people with <75 nmol/L and < 50 nmol/L, respectively. Specificity of the models was 80% and 70% for <75 nmol/L and < 50 nmol/L, respectively. The model developed by Merlijn and colleagues [36] used multiple cut-points of vitamin D and AUC ranged from 0.77 to 0.73 for <30, <40, <50 and < 60 nmol/L. Tran and colleagues [38] also developed models with two cut-points of serum 25(OH)D < 25 nmol/L and < 50 nmol/L for Australian older adults. The performance of the model was highest for predicting <25 nmol/L (AUC = 0.8) in comparison to <50 nmol/L and higher in comparison to Annweiler's model for <25 nmol/L (AUC = 0.38). The lowest sensitivity observed was 55.9% to identify people with <50 nmol/L with specificity of 72.3% [34]. Six studies [29, 31, 32, 34, 36, 37] converted their final prediction model into scores; however, one out of those six did not provide details of their developed scores [29].

Discussion

To our knowledge, this is the first systematic review to explore existing prediction models and questionnaires developed specifically to predict vitamin D status in adults. Of the

Table 3 Statistical methods used to develop the prediction models and for testing questionnaires

Author, year	Statistical methods	Model performance and internal validation	External validation	TP, FP, TN and FN	R^2	Predictive ability	Outcome	Conversion of final model into score
Annweiler et al. 2015 [28]	Univariate logistic regression models. Then, a non-linear models of feed forward (ANN) for the identification of hypovitaminosis D.	Sensitivity, specificity, PPV and NPV, AUC and stratified cross validation	Sensitivity, specificity, PPV, NPV, AUC and stratified cross validation	For ≤25 nmol/L TP = 341 FP = 153 TN = 1246 FN = 184	–	For <25 nmol/L Sensitivity = 64.9% Specificity = 89.0%	Clinical diagnostic tool for identification of older adults with hypovitaminosis D	No
				For ≤50 nmol/L TP = 1122 FP = 190 TN = 446 FN = 166	–	For <50 nmol/L Sensitivity = 87.1% Specificity = 70.1%		
				For ≤75 nmol/L TP = 1695 FP = 38 TN = 157 FN = 34	–	For <75 nmol/L Sensitivity = 98.0% Specificity = 80.5%		
Bertrand et al. 2012 [29]	Series of univariate linear regression models for selection of predictors followed by multivariable linear regression model. Predicted score was calculated using regression coefficient of each variable.	Spearman correlation coefficient for agreement between predictive and observed 25(OH)D levels	Spearman correlation coefficient to assess agreement between predictive scores and actual serum 25(OH)D levels and cross classification of participants by quintiles of predicted score and actual serum 25(OH)D levels	–	NHS: 33% NHS II: 25% HPFS: 28%	NHS = 59.8%, NHS II = 66.5% HPFS = 61.4% correctly classified in the same quintile of actual serum 25(OH)D levels as continuous	Prediction model to determine vitamin D status	Yes
Bolek-Berquist et al. 2009 [30]	Univariate and multivariable logistic regression models.	Sensitivity and Specificity	–	–	–	For <40 nmol/L Sensitivity = 79% Specificity = 78%	Questionnaire to identify young people at low and high risk of vitamin D deficiency	No
Deschasaux et al. 2016 [31]	Multivariable unconditional logistic regression model. Scores computed using odds ratio rounded to closed 0.5 and adding up for individual participant. High score reflected high risk of vitamin D insufficiency. Sensitivity and specificity also computed.	Sensitivity, specificity, TP, FP, PPV and NPV	Sensitivity, specificity, TP, FP, PPV and NPV	For ≤20 nmol/L at score ≥ 7: TP = 595 FP = 250 TN = – FN = – in development sample TP = 194 FP = 159 TN = – FN = – in validation sample	–	For <50 nmol/L Sensitivity = 67% Specificity = 63%	Vitamin D insufficiency prediction score	Yes

Table 3 (continued)

Author, year	Statistical methods	Model performance and internal validation	External validation	TP, FP, TN and FN	R^2	Predictive ability	Outcome	Conversion of final model into score
Kuwabara et al. 2019 [32]	Multivariate logistic regression with stepwise backward selection method. B coefficient of significant predictors were multiplied by 8 to convert into integral number. The sum of these scores were used to determine the risk of vitamin D deficiency.	AUC, sensitivity, specificity, PPV, NPV	AUC, sensitivity, specificity, PPV, NPV	–	–	For <50 nmol/L AUC = 0.75 Sensitivity = 61% Specificity = 79%	Vitamin D deficiency questionnaire	Yes
Lee et al. 2016 [33]	Univariate and multivariate firth logistic regression models.	ROC curve and Hosmer-Lemeshow goodness of fit test.	–	–	14%	for <29 nmol/L Sensitivity = 68% Specificity = 69%	Screening test for moderate to severe vitamin D deficiency	No
Lopes et al. 2014 [34]	Multivariable logistic regression model. Index risk of vitamin D deficiency was computed using odds ratios	AUC, sensitivity, specificity	AUC, sensitivity and specificity	–	–	For <50 nmol/L Sensitivity = 55.9% Specificity = 72.3%	Prediction model for vitamin D insufficiency	Yes
Lukaszuk et al. 2012 [35]	Multivariable logistic regression	–	–	–	–	92% were correctly identified for 50–74.9 nmol/L*	Vitamin D status screening tool	No
Merlijn et al. 2018 [36]	Multivariable logistic regression model with backward selection method. Regression coefficients were multiplied by 10 and divided by 3 to compute risk scores.	AUC, sensitivity, specificity, PPV and NPV	Model was validated in an external sample and AUC was calculated	– – – –	21%¥ for <30 nmol/L 25%¥ for <40 nmol/L 24%¥ for <50 nmol/L 18%¥ for <60 nmol/L	For <30 nmol/L AUC = 0.77 For <40 nmol/L AUC = 0.76 For <50 nmol/L AUC = 0.75 For <60 nmol/L AUC = 0.73	Prediction model for vitamin D insufficiency	Yes
Sohl et al. 2014 [37]	Logistic regression model with backward selection method. Regression coefficients in the model were divided by the smallest regression coefficient to compute risk scores.	Hosmer-Lemeshow goodness of fit test, sensitivity, specificity, PPV and NPV	Model was validated in an external sample and AUC was calculated	– –	31%¥ 28%¥	For <30 nmol/L AUC = 0.80 Sensitivity = 61% Specificity = 84% For <50 nmol/L AUC = 0.71 Sensitivity = 61% Specificity = 82%	Prediction model for vitamin D deficiency	Yes
Tran et al. 2013 [38]	Multivariable linear regression model using backward stepwise regression method to find out independent predictors. Further analysis was performed using univariate and multivariable logistic regression models.	ROC curve, Hosmer-Lemeshow goodness of fit, boot strapping, sensitivity, specificity, PPV and NPV	–	– –	21%	For <25 nmol/L AUC = 0.82 Sensitivity = 74% Specificity = 73% at predicted probability ≥0.1 For <50 nmol/L AUC = 0.73	Prediction model for vitamin D deficiency	No

Table 3 (continued)

Author, year	Statistical methods	Model performance and internal validation	External validation	TP, FP, TN and FN	R^2	Predictive ability	Outcome	Conversion of final model into score
Vignali et al. 2017 [39]	Univariate and multivariable linear regression models.	BIC, R^2, cross validated correlation coefficient	Cross validated correlation coefficient between observed and predicted serum (25(OH)D	–	55.7%	For <25 nmol/L Predictive ability = 90.2%* For 25–49.9 nmol/L Predictive ability = 95.8%* For 50–74.9 nmol/L Predictive ability = 91.3%* For >75 nmol/L Predictive ability = 85.9%*	Algorithm developed using questionnaire	No

Abbreviations: *ANN* artificial neural network, *AUC* area under the curve, *BIC* Bayesian information criterion, *FN* false negative, *FP* false positive, *NPV* negative predictive value, *PPV* positive predictive value, *ROC* receiver operating characteristic, *TN* true negative, *TP* true positive

*Reviewed study did not report sensitivity and specificity; ¥ Nagelkerke's R^2

welve studies systematically identified as eligible for inclusion in this review, all were heterogenous in terms of defining cut-points for vitamin D deficiency or insufficiency and risk factors used to develop tools for prediction of vitamin D status of adults. Increasing age, female sex, low physical activity, limited sunlight exposure and low vitamin D intake (dietary or supplemental) were consistently associated with vitamin D deficiency and significantly contributed to the predictive ability of the models. Study populations were mainly Caucasian, and the predictive ability of these instruments cannot be generalized to non-Caucasians. This may also explain why skin tone did not contribute significantly to predictive ability. Most of the studies excluded medical conditions that affect vitamin D metabolism. Overall, the predictive ability of the models or questionnaires was moderate for determining vitamin D deficiency or insufficiency, although some reported >80% sensitivity. Above all, none of these prediction models and questionnaires were translated and implemented into clinical practice or for use by community-dwelling people by themselves. Development of a tool that considers important self-reported risk factors for vitamin D deficiency in a simple way may be more practical for achieving this outcome.

Age, sex, BMI and ethnicity have been previously identified as independent predictors of vitamin D deficiency and insufficiency [41–44], and these risk factors were commonly assessed in all studies, except for ethnicity. Omission of ethnicity from the prediction models is problematic as there is increasing evidence to suggest particularly high prevalence of vitamin D deficiency [7, 45–47] in South Asians [20, 48–50], sub-Saharan Africans [43] and African Americans [44]. The causes of deficiency in these population groups could be darker skin tone, latitude, cultural habits, and low intake of vitamin D and calcium [51]. This suggests ethnic background is an important consideration in determining risk for vitamin D deficiency or insufficiency. Inclusion of ethnicity in self-reported vitamin D screening tools could improve their precision and provide more opportunity to test and compare tools internationally.

Lack of physical activity, smoking and increased alcohol intake are well-recognized lifestyle factors associated with vitamin D deficiency. Alcohol intake and smoking status were measured differently across studies. Smoking was categorized as either current smoker (yes/no) [34, 36, 37] or never, ex- or current smoker [33, 38]. Lifestyle factors used in studies were self-reported, although some studies converted self-reported physical activity data into metabolic equivalent of task (METs hours) per week. An increasing body of evidence suggest that physical inactivity is associated with vitamin D deficiency or insufficiency [42, 52, 53]. Although reporting physical activity as MET hours per week is a widely used method [54], it requires specific questionnaires and calculations to determine physical activity levels. A simple approach of asking the amount of time spent walking or exercising during the

last week may be easy to collect and answer by community-dwelling adults. Development of a predictive tool should incorporate physical activity in a simplified way so that no further calculations or conversions are required. For instance, Deschasaux and colleagues [31] measured physical activity level by asking whether individuals achieved <1 h/day or ≥ 1 h/day, and this simple question significantly contributed to the predictive ability of the scores.

Exposure to sunlight is an important source of vitamin D synthesis in skin [4], hence a significant predictor of vitamin D status. Time spent in sunlight is positively associated with vitamin D status but only three studies considered this factor in the development of a tool. Merlijn and colleagues [36] used time spent outdoors in winter and summer; however, it is unclear if that accounts for exposure to sunlight. Exposing arms for 6–7 min during summer or 7–40 min in winter is beneficial to maintaining sufficient vitamin D levels in moderately fair-skinned people [55]. Therefore, incorporating time spent in sunlight might improve the sensitivity and specificity of a tool in identifying people with or without vitamin D deficiency or insufficiency. It is also important to consider use of sunscreen and clothing style in a self-employed screening tool as these are important sun protection factors that prevent vitamin D synthesis in skin. None of the studies reviewed had included clothing style in the development of the screening tool, despite variation in clothing differing between religions and thus playing an important role in determining vitamin D status [56–59].

As exposure to UVB (wavelength, 290–315 nm) is needed for cutaneous synthesis of vitamin D [55, 60] and the amount of UVB reaching the earth in summer and winter is associated with vitamin D status [61], UVB exposure determined by latitude, altitude and cloud cover [29, 33, 38] significantly contributed to the predictive ability of the models. However, using a complex measurement in prediction tools is not practicable. Skin tone is another factor that influences cutaneous synthesis of vitamin D [61]. People with dark skin tone have less capacity for the cutaneous synthesis of vitamin D due to high melanin content as compared to fair-skinned people [62]. Hence, skin tone is an important predictor of vitamin D status but was used only in two studies [31, 38]. As the included studies mainly involved Caucasian people, it is perhaps not surprising that skin tone was not a significant predictor.

The effect of season on serum levels of vitamin D is well known; in particular, serum 25(OH)D levels are low in winter as compared to summer [63, 64]. However, three studies [31, 36, 39] considered month of blood drawn instead of season as a predictor of vitamin D status. For future work in this field, we suggest the use of season of blood collection, rather than the month, for enhancing the reliability of a prediction tool: furthermore, the use of season would enhance the applicability of the test for use in all countries.

There has been a little consideration towards the interaction between medications and vitamin D, as evidence suggests that there are certain drugs that disrupt vitamin D metabolism and function [65, 66] such as antiepileptics and antiretroviral drugs. Despite these known interactions between medications and vitamin D, it is difficult for older adults to recall the names of medications they are using. Only one study [28] required participants to recall specific drugs, whereas three studies [28, 35, 36] alternatively included the number of medications used per day as predictor of vitamin D status. It is possibly more feasible for community-dwelling adults to answer a simple question about number of drugs taken in order to account for effects of polypharmacy on vitamin D status.

Studies included in this systematic review were mainly focused on identifying people with vitamin D deficiency or insufficiency, rather than those with sufficient vitamin D levels. Importantly, the predictability of low serum 25(OH)D (for instance cut-points of <25 nmol/l or < 30 nmol/l) is of great importance as these low levels should be avoided in any case. The majority of included studies excluded people with existing medical conditions that may affect vitamin D status and some studies excluded people taking vitamin D supplements. There appears to be no benefits of supplementing people with sufficient vitamin D levels [67]. Thus, it is important to identify people with and without vitamin D deficiency and insufficiency. However, we highlight that the majority of studies reviewed did not report the ability of tools to identify false negatives.

The presentation of a vitamin D screening tool is important; it must be user-friendly and provide immediate feedback on vitamin D status based on composite scores. Tools developed for clinicians will assist decision-making about recommending blood tests or prescribing supplements. Five studies included in this systematic review calculated scores associated with risk factors and a composite score to determine vitamin D status. For instance, Deschasaux et al. [31] and Lopes et al. [34] computed a score for each risk factor and the highest score was associated with increased risk of vitamin D insufficiency.

Although few studies included in this review utilized clinical assessments [28, 33] and biochemical measures [34] for development of the vitamin D screening tool, these measures were subsequently excluded from the final prediction models. The final prediction models reported in the above studies focused on self-reported information. Only two studies reported the contribution of individual risk factor in the predictive ability of the model. It is crucial to determine the contribution of each risk factor in the predictive ability of model to test and improve the existing models by selecting predictors that highly influence vitamin D status. These predictive models and questionnaires highlighted the potential of using self-reported risk factors to develop vitamin D screening tools so that people can easily determine their vitamin D status.

The PRISMA-DTA guidelines were used to structure the systematic review. We applied the QUADAS-2 tool, recommend by Cochrane to assess the risk of bias and applicability

of diagnostic accuracy studies. Limitations of this systematic review are excluding non-English studies.

In conclusion, the prediction models or questionnaires identified as part of this systematic review were moderately sensitive and specific to identify people with vitamin D deficiency or insufficiency. Only two of the twelve studies reported the contribution of each risk factor to the predictive ability of the final model. The highest contribution of sunlight exposure to the prediction of vitamin D levels highlights the importance of this information for inclusion in the development of vitamin D screening tools in future. While a blood test may remain the best way to measure serum 25(OH)D status, having the results regarding vitamin D status from a reliable, self-reported screening tool may negate the need for a blood test, and indeed could help clinicians to make informed decisions regarding the need for supplementation to manage vitamin D deficiency. Future work should also consider the intake of vitamin D supplements, and medical conditions that may affect vitamin D status, in order to discriminate between those with or without vitamin D insufficiency. Similarly, the inclusion of clothing style, related to cultural and/or religious practices and/or ethnicity, may improve the precision of a self-reported vitamin D tool. A self-administered prediction tool may be beneficial for community-dwelling adults to understand their risk of vitamin D deficiency or insufficiency with immediacy of feedback about vitamin D health status, ease of administration and low cost.

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Compliance with ethical standards

Conflict of interest Ghazala Naureen, Kerrie M Sanders, Lucy Busija, David Scott, Karen Lim, Jason Talevski, Catherine Connaughton and Sharon L. Brennan-Olsen declare that they have no conflict of interest.

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