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Quick and Easy Screening for Vitamin D Insufficiency in Adults

A Scoring System to Be Implemented in Daily Clinical Practice

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Abstract: Vitamin D is essential regarding several health outcomes. Prevention of insufficiency (25-hydroxyvitamin D concentration ≤20 ng/mL) generally entails blood testing and/or supplementation, strategies that should target at-risk individuals because blood testing is costly, and unwarranted supplementation could result in vitamin D overload with unknown long-term consequences.

Our objective was to develop a simple score (Vitamin D Insufficiency Prediction score, VDIP) for identifying adults at risk of vitamin D insufficiency.

Subjects were 1557 non–vitamin D-supplemented middle-aged adults from the SU.VI.MAX cohort. Scoring points corresponded to the rounded odds ratio for each individual-level characteristic associated with vitamin D insufficiency in a multivariable logistic regression model. Receiver operating characteristic curve (area under curve), sensitivity, specificity, and positive and negative predictive values were computed. External validation was performed in an independent cohort (NutriNet-Santé, N = 781).

For female sex, overweight, low physical activity, winter season, moderate sun exposure, and very fair or dark skin 1.5 points were attributed; 2 points for latitude ≥48°N and spring season; 2.5 points for obesity and late winter; 3 points for low sun exposure. Points were then summed up for each participant. The VDIP score had an AUC = 0.70 ± 0.01 (validation: 0.67 ± 0.02). With a score of 7 or more, 70% of the participants were vitamin D-insufficient (80% in those with a score ≥9), sensitivity/specificity were 0.67/0.63, and positive and negative predictive values were 0.70/0.59.

The VDIP score performed well in identifying middle-aged adults at risk of vitamin D insufficiency (score ≥7, moderate risk; score≥9, high risk), using only simple individual-level characteristics easily assessable in day-to-day clinical practice. Implementation of this simple and costless score could thus obviate unwarranted supplementation and/or blood testing.

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Abbreviations: 25OHD = 25-hydroxyvitamin D, AUC = area under the ROC curve, BMI = body mass index, NPV = negative predictive value, PPV = positive predictive value, ROC = receiver operating characteristic, SNP = single nucleotide polymorphism, SU.VI.MAX = Supplémentation en VItamines et Minéraux AntioXydants, VDIP = vitamin d insufficiency prediction.

INTRODUCTION

Vitamin D seems to be the subject of remarkable research interest, as shown by the 30,000+ hits on Pubmed regarding publications from the last decade. This prohormone is provided by an endogenous synthesis triggered by UVB exposure and, to a much lesser extent, by a limited number of dietary sources or supplements. Vitamin D is converted first to 25-hydroxyvitamin D (25OHD), its main circulating form, and then to 1,25-dihydroxyvitamin D, its biologically active form.[1,2] It is particularly known for its involvement in calcium homeostasis and thus its importance for bone health. However, evidence has emerged regarding the role of vitamin D in a myriad of physiological processes unrelated to calcium metabolism, such as immunity, insulin secretion, neurological function, cardiovascular function, and cell regulation. Hence, vitamin D could conceivably play a central role in the prevention of several inflammatory and chronic diseases, underscoring the importance of maintaining an adequate vitamin D status.[1–3]

Vitamin D insufficiency (blood 25OHD concentration ≤20 ng/mL[4]) is common in adults worldwide with a prevalence around 60% in western Europe and 36% in the US.[3] In France,[5] this prevalence was 42.5% in 2006. It is therefore essential to identify individuals at risk in order to provide appropriate treatment options.

Prevention and treatment of vitamin D insufficiency generally involves vitamin D blood testing and/or supplementation.

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Existing recommendations have pointed out that both measures should target at-risk individuals.[6,7] Indeed, vitamin D testing is certainly not cost-efficient in the general population[6–9] and unwarranted vitamin D supplementation could lead to overload in some individuals who are not vitamin D deficient, which itself has unknown long-term consequences.[10]

In a previous study,[11] we tested a wide range of sociodemographic, lifestyle, anthropometric, and genetic factors in association with plasma 25OHD concentration and were thus able to identify determinants of vitamin D insufficiency. Such knowledge could serve as a basis for the implementation of strategies to identify individuals at high risk for vitamin D insufficiency.

Here, our objectives were (1) to develop a simple score that could be used in daily clinical practice for the detection of middle-aged adults at risk of vitamin D insufficiency and (2) to validate this score in an unrelated sample of adults.

SUBJECTS AND METHODS

Study Population

For the development of the Vitamin D Insufficiency Prediction (VDIP) score, we used data from the Supplémentation en Vitamines et Minéraux Antioxydants cohort, a population-based, double-blind, placebo-controlled, primary prevention randomized trial (SU.VI.MAX, 1994–2007, www.clinicaltrials.gov, NCT00272428), initially designed to assess the effect of a 7.5-year daily antioxidant supplementation on the incidence of cardiovascular diseases and cancer.[12] The study was approved by the Ethics Committee for Studies with Human Subjects at the Paris-Cochin Hospital (CCPPRB no.1706) and the ''Commission Nationale de l'Informatique et des Libertés'' (CNIL no.334641). A total of 13,017 participants were enrolled in 1994 to 1995. All of them provided written informed consent. Participants were advised not to take any dietary supplementation during the study period. Next, a nested case-control study was set up to investigate the association between vitamin D status and cancer risk, including all cases of first incident cancer diagnosed between 1994 and 2007. Two cancer-free controls per case were randomly selected and matched on sex, age, intervention group, and season of blood draw. The present analysis is based exclusively on the subsample of controls (n = 1850) from this nested case-control study.

For the validation of the VDIP score, we used data from the NutriNet-Santé cohort (approved: IRB Inserm n°0000388FWA00005831 and CNIL n°908450/n°909216), a large, ongoing, Web-based nutrition-and-health-focused cohort launched in France in 2009 and open to volunteers aged 18+ with Internet access.[13] Electronic informed consent was obtained from each participant (EudraCT no. 2013-000929-31). Of the 158,429 volunteers enrolled to date, 19,600 have provided fasting blood samples. From that pool, a random sample of 860 individuals was selected for plasma 25OHD concentration assessment.

Both studies were conducted according to the Declaration of Helsinki guidelines.

Baseline Data Collection

At enrollment (1994–1995), SU.VI.MAX participants were invited to complete self-administered questionnaires on sociodemographics, health/risk behaviors and lifestyle (smoking, medication use, physical activity, etc.) and health status. Subjects self-evaluated their usual level of physical activity as follows: irregular, <1 h/d walking equivalent or ≥1 h/d walking equivalent. Height and weight were measured during a baseline clinical examination by study medical staff. A 35 mL venous blood sample was collected at baseline in vacutainer tubes from participants who had been fasting for ≥12 h. All blood draws occurred between October and May. Blood samples were centrifuged immediately after blood draw. Plasma aliquots (preserved in sodium heparin) and buffy-coat fractions were stored frozen in liquid nitrogen at the central biobank.

In turn, in order to be included in the NutriNet-Santé study, participants fill an initial set of sociodemographic, lifestyle, health, anthropometrics, and physical activity questionnaires. Height and weight were self-reported, following the standardized measurement guidelines provided to the participants. Usual level of physical activity is assessed via the web version of the ''International Physical Activity Questionnaire'' (IPAQ)[14] and coded as low, moderate, or high, following the IPAQ guidelines.[15] Among volunteers who had accepted the clinic visit, a 43 mL fasting (≥6 h) blood sample was collected using a vacutainer system. Tubes were fractioned in aliquots containing lithium-heparin and were stored at −80°C at the central biobank.

In both the cohorts, the latitude of each administrative center (corresponding to the place of residence) was retrieved. Next, usual sun exposure and Fitzpatrick skin phototype were obtained through a sun exposure/sun safety questionnaire, which was previously described in details.[16–19] This questionnaire was specifically developed in the context of the SU.VI.MAX study and was used again in the NutriNet-Santé study. Participants were asked to provide an estimation of their usual sun exposure (high, moderate, low, none) and to describe their skin reaction to a first sun exposure without protection, using Fitzpatrick classification.

Assessment of Plasma 25OHD Concentration and Genotyping

In both the cohorts, concentrations of total 25OHD were measured in baseline plasma samples using the same laboratory. Measurement relied on Roche Cobas electrochemoluminescent immunoassay (Roche Diagnostics, Meylan, France), based on the principle of competitive binding, as previously reported.[11,20] The intra-assay coefficient of variation was 4.5% and the inter-assay coefficient of variation was 6.6%.

Finally, SU.VI.MAX subjects were genotyped for 2 single nucleotide polymorphisms (SNPs) of the *GC* gene (rs4588 and rs7041, both coding for the vitamin D-binding protein) which have been associated with vitamin D status in previous studies, including in the SU.VI.MAX cohort.[11] As previously reported in details,[11] genetic polymorphisms were assessed by allelic discrimination using fluorogenic probes and the 5' nuclease (TaqMan) assay (Applied Biosystems, Foster City, CA).

Statistical Analysis

From the 1850 SU.VI.MAX participants with available plasma vitamin D concentration data, the following exclusions were made prior to analysis: taking medication containing vitamin D (n = 12), presence of epilepsy or renal failure (n = 5) and age <45 years (n = 275), leaving 1557 participants for analyses (see the flow chart in Supplemental Digital Content 1, http://links.lww.com/MD/A691). Participants aged <45 years were excluded because of the differential age at inclusion between men (45 years) and women (35 years) in the initial SU.VI.MAX trial.

For the development of the VDIP score, a multivariable unconditional logistic regression model was fit using the SU.VI.MAX data to model the risk of vitamin D insufficiency

TABLE 1. Associations between Vitamin D Insufficiency and Individual Factors, from Unconditional Logistic Regression Models*, SU.VI.MAX cohort, France, and NutriNet-Santé cohort, France

	SU.VI.MAX N = 1557				NutriNet-Santé N = 781			
	≤20 vs >20 ng/mL†				≤20 vs >20 ng/mL†			
	n	OR	95% CI	*P*	n	OR	95% CI	*P*
Sex				<0.0001‡				0.4‡
Male	833	1			337	1		
Female	724	1.81	1.43, 2.29		444	0.88	0.62, 1.24	
BMI, kg/m^2				0.007‡				0.0009‡
<18.5	27	1.86	0.77, 4.48		24	0.27	0.08, 0.96	
≥18.5–<25	889	1			529	1		
≥25–<30	537	1.34	1.04, 1.71		182	1.58	1.07, 2.32	
≥30	104	1.99	1.23, 3.22		46	2.72	1.37, 5.39	
Physical activity				<0.0001				0.3‡
Irregular-Low	364	1.74	1.31, 2.32		170	1.33	0.86, 2.06	
<1h/d walking equivalent-Moderate	438	1.43	1.10, 1.85		291	1.08	0.74, 1.58	
≥1h/d walking equivalent-High	755	1			182	1		
Missing	/	/			*46*	*0.76*	*0.42, 1.36*	
Latitude§				<0.0001				0.0001
Quartile 1	394	1			218	1		
Quartile 2	416	1.07	0.78, 1.48		190	1.16	0.75, 1.82	
Quartile 3	355	1.79	1.29, 2.48		171	1.41	0.86, 2.29	
Quartile 4	392	2.00	1.45, 2.77		202	2.44	1.57, 3.82	
Month of blood draw				<0.0001‡				0.001‡
October–November	265	1			129	1		
December–January	520	1.56	1.11, 2.18		217	1.91	1.10, 3.34	
February–March	604	2.68	1.96, 3.69		341	2.91	1.70, 4.99	
April–May	168	2.21	1.42, 3.46		94	2.03	1.04, 3.98	
Usual sun exposure				<0.0001				0.06‡
None-Low	458	3.01	2.02, 4.50		83	2.21	0.98, 4.98	
Moderate	931	1.51	1.06, 2.16		380	1.45	0.73, 2.88	
High	168	1			54	1		
Missing	/	/			*264*	*1.04*	*0.50, 2.17*	
Fitzpatrick phototype‖				0.06				0.003‡
I	62	1.41	0.74, 2.67		34	1.11	0.48, 2.58	
II	335	1.39	0.97, 1.97		166	1.70	1.03, 2.80	
III	877	1.21	0.91, 1.62		286	1.12	0.71, 1.76	
IV	283	1			149	1		
V	/	/			38	5.40	2.32, 12.6	
VI	/	/			25	1.24	0.49, 3.17	
Missing	/	/			*83*	*1.56*	*0.80, 3.03*	

BMI = body mass index.

* Multivariable unconditional logistic regression models were adjusted for age (<40 y/40–44y/45–49 y/50–54 y/55–65 y) and included all the individual factors presented in the table (sex, body mass index, physical activity, latitude, month of blood draw, usual sun exposure, and Fitzpatrick phototype).

† Number of subjects with 25OHD concentration ≤20 ng/mL/>20 ng/mL in SU.VI.MAX: 888/669 and in NutriNet-Santé: 319/462.

‡ P nontrend.

§ Cut offs for quartiles of latitude were 45.34/48/48.48 in SU.VI.MAX and 43.37/45.46/48.52 in NutriNet-Santé.

‖ I: always burns easily, never tans; II: burns easily, tans minimally; III: burns moderately, tans gradually; IV: burns minimally, tans well; V: burns rarely, tans profusely; VI: never burns, deep pigmentation.

(plasma concentration ≤20 ng/mL). The model was age-adjusted and included sex, body mass index, physical activity, residential latitude, month of blood draw, self-estimated usual sun exposure, and Fitzpatrick skin phototype. To build the VDIP score, points were assigned to each characteristic associated with vitamin D insufficiency using the odds ratio (OR) value rounded to the closest 0.5 to facilitate computation. Attributed points were then summed up for each participant. A higher score thus reflected higher risk of vitamin D insufficiency. Sensitivity analyses were performed following the introduction of dietary intakes of vitamin D, and of the 2 SNPs of the *GC* gene in the scoring system, and following the exclusion of participants diagnosed with a cardiovascular disease or diabetes at baseline.

To perform an external validation of the obtained score, an independent sub-sample of the NutriNet-Santé study was

selected as follows: from the 860 participants with available plasma vitamin D concentration, participants were excluded for taking vitamin D supplementation (n = 79), thus leaving data from 781 participants available for analyses (see the flow chart in Supplemental Digital Content 1). The same multivariable unconditional logistic regression model was fit in that sample.

If <5% of data were missing, they were replaced by the mode value of the respective variable. If >5% of data were missing, a ''missing category'' was introduced into the model.

In both samples, receiver operating characteristic (ROC) curves were drawn (sensitivity vs 1-specificify) from a logistic regression model of vitamin D insufficiency, with the VDIP score modeled as the explanatory variable. Sensitivity, specificity, and positive and negative predictive values (PPV and NPV) were calculated for each value of the score and the area under the ROC curve (AUC) was assessed. The AUC represents the ability of the test to measure reality, an ideal test having an AUC of 1. In our study, the AUC shows the ability of the score to accurately identify people with actual vitamin D insufficiency.

SAS software version 9.3 was used for the analyses (SAS Institute, Cary, NC). All statistical tests were 2-sided and $P < 0.05$ was considered significant.

RESULTS

Mean 25OHD concentrations were 20.2 ± 10.4 ng/mL in our SU.VI.MAX analysis sample (N = 1557), and 24.1 ± 11.7 ng/mL in our NutriNet-Santé validation sample (N = 781). More than half (57.0%) of the SU.VI.MAX sample had 25OHD concentration ≤20 ng/mL (40.8% in the NutriNet-Santé validation sample).

A description of the 2 study populations and results of the logistic regression models are presented in Table 1. As expected,[11] vitamin D insufficiency in the SU.VI.MAX cohort (median age at baseline = 53 years) was associated with female sex, being overweight or obese, practicing physical activity irregularly or ≤1 h/d walking equivalent, living at Northern latitudes, blood draw occurring in winter/early spring, having low or moderate usual sun exposure, and having a very fair skin (Fitzpatrick phototype I or II). In NutriNet-Santé (median age at baseline = 47 years), the same characteristics were associated with vitamin D insufficiency (also including the darkest Fitzpatrick phototypes), except for physical activity and sex. These results were similar when excluding subjects with missing data (N = 470).

Next, a scoring system was developed from the logistic regression results obtained in the SU.VI.MAX sample (Table 2). Points were attributed to the characteristics associated with vitamin D insufficiency (ORs rounded to the closest 0.5, except for obesity, for which an additional 0.5 was assigned, given that obesity is recognized as a major determinant of vitamin D insufficiency).[21] As noted above, Fitzpatrick phototypes V and VI (dark skin color) were not represented in the SU.VI.MAX population. Hence, we extrapolated the points given to the 2 fairest phototypes (Fitzpatrick types I and II) to the 2 darkest phototypes (Fitzpatrick types V and VI) for validation purposes in the NutriNet-Santé sample, in which these phototypes were represented. In Supplemental Digital Content 2, http://links.lww.com/MD/A691, we present a simple checklist that could be completed in 5 minutes and can be used in day-to-day practice to gather personal information needed for computing the VDIP score.

In turn, Table 3 provides the distribution of the VDIP score in the SU.VI.MAX sample with the corresponding sensitivity, specificity, PPV, and NPV. The median score was 7.0 (min: 0, Q1: 5.5, Q3: 9.0, max: 14.0). A score ≥7 was observed in 54.3% of the sample, with the following properties: sensitivity = 0.67, specificity = 0.63, PPV = 0.70, and NPV = 0.59. In total, for 8.9% of the participants with a score ≥7, 25OHD concentration was >30 ng/mL, and it was >40 ng/mL for 1.8%. Among those with a score ≥9, the corresponding proportions were 4.3% and 1.0%. The ROC curve associated with the score is presented in Figure 1a. The AUC was 0.70 ± 0.01. Similar results were observed after the exclusion of participants who declared a

TABLE 2. Score Loading: Attribution of Points for Each Selected Individual Characteristic*

Characteristics	Points
Sex	
Male	0
Female	1.5
Weight status; BMI, kg/m^2	
<25	0
between 25 and 30	1.5
≥30	2.5
Physical activity	
Irregular	1.5
<1h/d walking equivalent	1.5
≥1h/d walking equivalent	0
Residential latitude	
<48°N (in France: South of a line from mid-Brittany to mid-Alsace)	0
≥48°N (in France: North of a line from mid-Brittany to mid-Alsace)	2
Season	
June–November	0
December–January	1.5
February–March	2.5
April–May	2
Usual sun exposure	
Low/very low	3
Moderate	1.5
High	0
Fitzpatrick phototype	
I: always burns easily, never tans	1.5
II: burns easily, tans minimally	1.5
III: burns moderately, tans gradually	0
IV: burns minimally, tans well	0
V: burns rarely, tans profusely†	1.5
VI: never burns, deep pigmentation†	1.5
	Total‡

BMI = body mass index.

* The individual characteristics with points >0 were the ones for which an increased risk of vitamin D insufficiency was observed in the SU.VI.MAX logistic regression model (Table 1). Points were attributed according to the OR value in the SU.VI.MAX logistic regression model (Table 1) rounded to the closest 0.5 to facilitate score computation. An additional 0.5 was given for the ''obese'' characteristic because obesity is a major determinant of vitamin D status.

† Fitzpatrick phototypes V and VI were not represented in the SU.VI.MAX population. We extrapolated the points given to the 2 fairest phototypes (I, II) to the 2 darkest (V, VI) for validation in the NutriNet-Santé cohort in which these phototypes were represented.

‡ Final score is comprised between 0 and 14.5.

TABLE 3. Sensitivity and Specificity for the Detection of Vitamin D Insufficiency (25OHD ≤ 20 ng/mL) for Each Value of the Score, N = 1557, SU.VI.MAX cohort, France

Score	N	%	Sensitivity	Specificity	True positives	False positives	PPV*	NPV†
≥14	1	0.06	0.00	1.00	0	1	/	0.43
≥13.5	7	0.4	0.01	1.00	5	2	0.71	0.43
≥13	13	0.8	0.01	1.00	10	3	0.77	0.43
≥12.5	24	1.6	0.02	0.99	19	5	0.79	0.43
≥12	57	3.7	0.06	0.99	49	8	0.86	0.44
≥11.5	79	5.1	0.08	0.99	69	10	0.87	0.45
≥11	111	7.1	0.10	0.97	93	18	0.84	0.45
≥10.5	181	11.6	0.17	0.95	148	33	0.82	0.46
≥10	237	15.2	0.22	0.94	195	42	0.82	0.48
≥9.5	290	18.6	0.27	0.92	236	54	0.81	0.49
≥9	396	25.4	0.36	0.88	316	80	0.80	0.51
≥8.5	492	31.6	0.43	0.84	385	107	0.78	0.53
≥8	569	36.6	0.49	0.80	433	136	0.76	0.54
≥7.5	725	46.6	0.59	0.69	520	205	0.72	0.56
≥7	845	54.3	0.67	0.63	595	250	0.70	0.59
≥6.5	926	59.5	0.72	0.57	635	291	0.69	0.60
≥6	1086	69.8	0.81	0.45	719	367	0.66	0.64
≥5.5	1178	75.7	0.86	0.38	765	413	0.65	0.68
≥5	1226	78.8	0.89	0.34	787	439	0.64	0.69
≥4.5	1360	87.4	0.94	0.22	835	525	0.61	0.73
≥4	1387	89.1	0.95	0.19	845	542	0.61	0.75
≥3.5	1410	90.6	0.96	0.17	854	556	0.61	0.77
≥3	1514	97.3	0.99	0.05	880	634	0.58	0.81
≥2.5	1520	97.7	0.99	0.04	880	640	0.58	0.78
≥2	1522	97.8	0.99	0.04	881	641	0.58	0.80
≥1.5	1555	99.9	1.00	0.00	888	667	0.57	1.00
≥0	1557	100	1.00	0.00	888	669	0.57	/

PPV = positive predictive value, NPV = negative predictive value.

* Positive predictive value = $\frac{\text{True positives(individuals with a score} \geq \text{cut off and 25OHD} \leq 20\,\text{ng/mL)}}{\text{Total positives (individuals with a score} \geq \text{cut off)}}$, which corresponds to the proportion of participants with actual vitamin D insufficiency among individuals with a score above the chosen cut off.

† Negative predictive value = $\frac{\text{True negatives(individuals with a score} < \text{cut off and 25OHD} > 20\,\text{ng/mL)}}{\text{Total negatives (individuals with a score} < \text{cut off)}}$, which corresponds to the proportion of participants without vitamin D insufficiency among individuals with a score below the chosen cut off.

cardiovascular disease or diabetes at baseline (N = 1476, AUC = 0.70 ± 0.01). Likewise, similar AUC were observed with a modified VDIP score that included the SNPs *GC* rs4588 (0 point for the genotype GG, 1.5 for GT and 2 for TT) and rs7041 (0 point for the genotype CC, 1.5 for AC and AA) (AUC = 0.71 ± 0.01) or with a modified VDIP score that included dietary intake of vitamin D (0 point for quartiles 3 and 4, 1.5 for quartiles 1 and 2) (AUC = 0.70 ± 0.01) [data not tabulated].

In the NutriNet-Santé validation sample (Table 4), the median VDIP score was 6.0 (min: 0, Q1: 4.5, Q3: 8.0, max: 14.5). A score ≥7 was observed in 45.2% of the sample, with the following properties: sensitivity = 0.61, specificity = 0.66, PPV = 0.55, and NPV = 0.71. In total, for 19.3% of subjects with a score ≥7, 25OHD concentration was >30 ng/mL, and it was >40 ng/mL for 7.6%. Among those with a VDIP score ≥9, the corresponding proportions were 17.9% and 6.4%. The ROC curve associated with the score is presented in Figure 1b. The AUC was 0.67 ± 0.02.

DISCUSSION

In this study, a simple scoring system based on easy-to-assess individual characteristics was developed in a population of nonsupplemented middle-aged French adults to predict vitamin D insufficiency. The VDIP score computation uses information on individual characteristics associated with vitamin D status (sex, BMI, physical activity, residential latitude, season, usual sun exposure, and Fitzpatrick skin phototype) that could feasibly be gathered in clinical practice using a 5-minute checklist (Supplemental Digital Content 2). The VDIP score performed well, with an AUC of 0.70 ± 0.01 (0.67 ± 0.02 in the validation sample). It thus constitutes a useful tool to be integrated in clinical practice to obviate unnecessary supplementation and blood testing.

As indicated by the PPV, 70% of the participants with a score ≥7 were vitamin D-insufficient (80% in those with a score ≥9). Any patient with a VDIP score ≥7 to <9 could be regarded as moderately at risk of vitamin D insufficiency and any patient with a score ≥9 could be regarded as being at high risk.

In practice, if a patient has a VDIP score higher than a selected cut off, a vitamin D supplementation could be recommended. The choice of the cut off depends on the context and on the clinical and/or public health objectives, and should undergo a validation in clinical laboratories. This is why all characteristics (sensitivity, specificity, PPV, and NPV) for all cut offs are provided in Tables 3 and 4. A cut-off score of 7 represents a balance between relatively high sensitivity and high specificity.

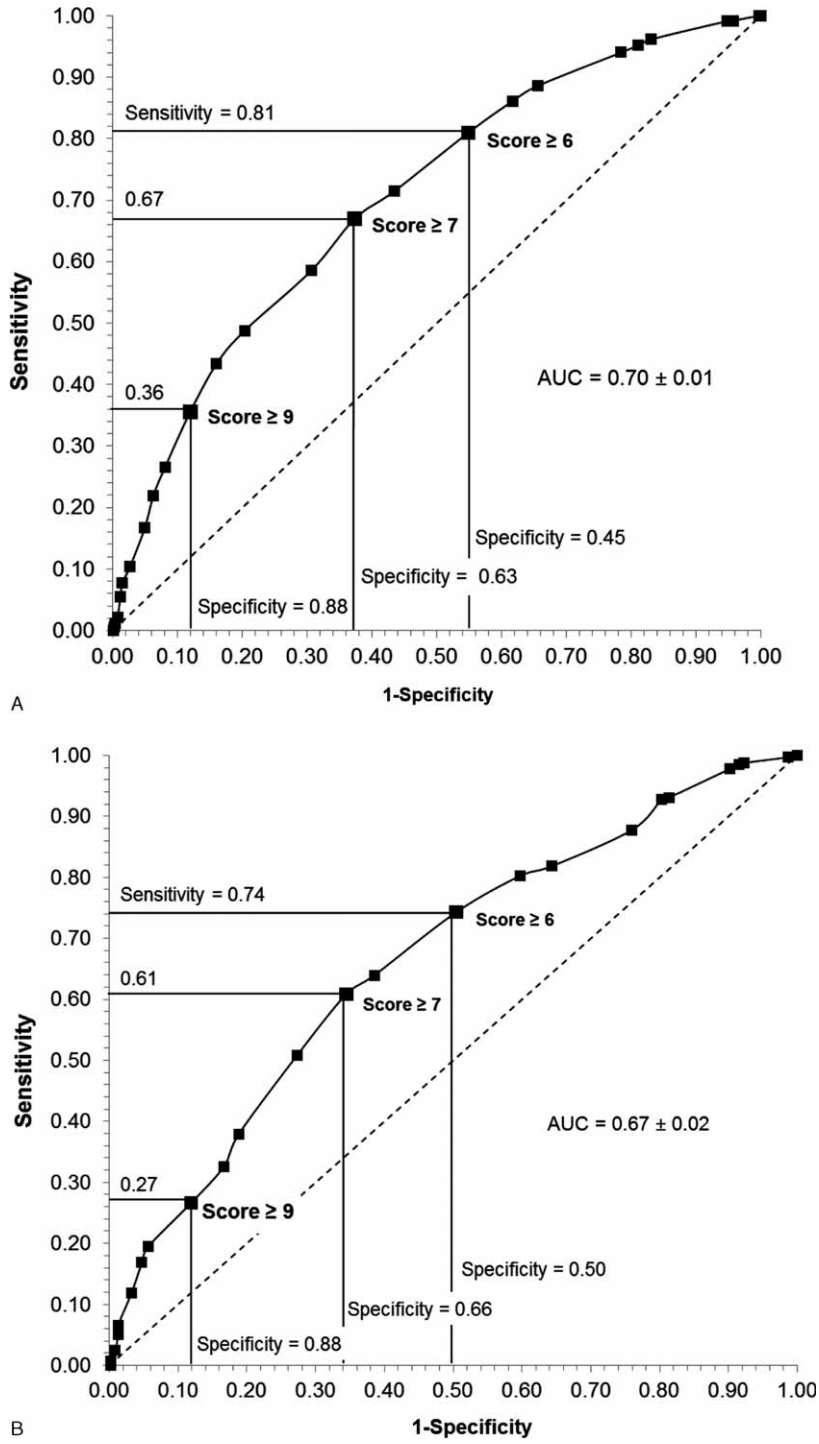

FIGURE 1. ROC curves for the VDIP score in the detection of vitamin D insufficiency (25-hydroxyvitamin D ≤20 ng/mL), (A) SU.VI.MAX cohort (N = 1557), (B) NutriNet-Santé cohort (N = 781), France. The ROC curve of the VDIP score (solid line) draws the sensitivity vs 1 minus the specificity. For each value of the VDIP score, the sensitivity is the probability to accurately classify a person with vitamin D insufficiency (true positive) and the specificity is the probability to accurately classify a person who does not have a vitamin D insufficiency (true negative). Conversely, 1 minus the specificity is the probability for a person to be classified as ''vitamin D insufficient'' while this person does not have vitamin D insufficiency (false positive). For instance, in (A), a VDIP score ≥7 corresponded to a sensitivity = 0.67, and a specificity = 0.63. The first bisector (dotted line) represents the ROC curve of a test that would be no better than random. The more a ROC curve is away from the first bisector toward the upper left corner, the better the screening ability of the test is. The AUC represents the ability of the score to accurately identify people with actual vitamin D insufficiency. AUC = area under curve, ROC = receiver operating characteristic, VDIP = Vitamin D Insufficiency Prediction score.

TABLE 4. Sensitivity and Specificity for the Detection of Vitamin D Insufficiency (25OHD ≤ 20 ng/mL) for Each Value of the Score, N = 781, NutriNet-Santé cohort, France

Score	N	%	Sensitivity	Specificity	True positives	False positives	PPV*	NPV†
=14.5	1	0.1	0.00	1.00	0	1	0.00	0.59
≥13	2	0.3	0.00	1.00	1	1	0.50	0.59
≥12.5	3	0.4	0.01	1.00	2	1	0.67	0.59
≥12	12	1.5	0.03	0.99	8	4	0.67	0.60
≥11.5	22	2.8	0.05	0.99	16	6	0.73	0.60
≥11	27	3.5	0.07	0.99	21	6	0.78	0.60
≥10.5	53	6.8	0.12	0.97	38	15	0.72	0.61
≥10	76	9.7	0.17	0.95	54	22	0.71	0.62
≥9.5	88	11.3	0.19	0.94	62	26	0.70	0.63
≥9	140	17.9	0.27	0.88	85	55	0.61	0.63
≥8.5	181	23.2	0.33	0.83	104	77	0.57	0.64
≥8	208	26.6	0.38	0.81	121	87	0.58	0.65
≥7.5	288	36.9	0.51	0.73	162	126	0.56	0.68
≥7	353	45.2	0.61	0.66	194	159	0.55	0.71
≥6.5	382	48.9	0.64	0.61	204	178	0.53	0.71
≥6	470	60.2	0.74	0.50	237	233	0.50	0.74
≥5.5	532	68.1	0.80	0.40	256	276	0.48	0.75
≥5	558	71.5	0.82	0.36	261	297	0.47	0.74
≥4.5	631	80.8	0.88	0.24	280	351	0.44	0.74
≥4	667	85.4	0.93	0.20	296	371	0.44	0.80
≥3.5	673	86.2	0.93	0.19	297	376	0.44	0.80
≥3	729	93.3	0.98	0.10	312	417	0.43	0.87
≥2.5	737	94.4	0.98	0.08	314	423	0.43	0.89
≥2	741	94.9	0.99	0.08	315	426	0.43	0.90
≥1.5	774	99.1	1.00	0.01	318	456	0.41	0.86
≥0	781	100	1.00	0.00	319	462	0.41	/

PPV = positive predictive value, NPV = negative predictive value.

* Positive predictive value $= \frac{\text{True positives(individuals with a score} \geq \text{cut off and 25OHD} \leq 20\,\text{ng/mL)}}{\text{Total positives (individuals with a score} \geq \text{cut off)}}$, which corresponds to the proportion of participants with actual vitamin D insufficiency among individuals with a score above the chosen cut off.

† Negative predictive value $= \frac{\text{True negatives(individuals with a score} < \text{cut off and 25OHD} > 20\,\text{ng/mL)}}{\text{Total negatives (individuals with a score} < \text{cut off)}}$, which corresponds to the proportion of participants without vitamin D insufficiency among individuals with a score below the chosen cut off.

If the objective is to detect a maximum of patients with vitamin D insufficiency (increased sensitivity), then lower cut-off scores such as 5.5 or 6 could be selected. However, this strategy would also lead to a higher proportion of people wrongly classified as vitamin D insufficient (false positives) because of a decreased specificity. In contrast, if the objective is to minimize the proportion of wrongly classified people (increased specificity), then higher cut-off scores, such as 9, could be selected. However, this strategy would also lead to a decreased sensitivity and thus a decreased number of detected people.

Among those who would be identified as vitamin D-insufficient based on the score, a small yet nonnegligible proportion (especially in the validation sample) had a 25OHD concentration >40 ng/mL. Cautious dosing of vitamin D supplements may thus be advised, in line with the recommendations made by the Institute of Medicine.[4,10]

Admittedly, a few studies have already advanced scoring guidelines to predict vitamin D status, either in order to identify a proxy for blood 25OHD concentration in large cohorts,[22] or with the objective to detect at-risk individuals in clinical practice.[23–27] However, most of these investigations were either based on relatively restricted samples,[24,26,27] or were focused on specific population subgroups,[24] or included a very limited number of individual characteristics,[23,27] or included characteristics that are practically impossible to assess in a quick and easy fashion (as dietary vitamin D intake and precise UV exposure),[22,26] or provided complex, hard-to-interpret coefficients,[22] or did not perform external validation in an independent sample.[23,24,26,27] Sohl et al[25] were the first who successfully developed models to predict vitamin D deficiency in the general elderly European population. This study focused on older subjects (mean age = 76 years) and thus included frailty indicators associated with cognitive and physical decline in the elderly. In contrast, our VDIP score is designed to be implemented in a non–vitamin D-supplemented noninstitutionalized middle-aged adult population.

These scores had similar discrimination performances when predicting vitamin D insufficiency (25OHD ≤ 20 ng/mL) compared to ours: Nabak et al[24] observed a sensitivity/specificity of 89%/35% at their chosen cut off; Lopes et al[23] observed an AUC of 0.68; Tran et al[26] observed an AUC of 0.73; Bolek-Berquist et al[27] observed a sensitivity/specificity of 79%/78% at their chosen cut off (detection of people with 25OHD <16 ng/mL); and Sohl et al[25] observed an AUC of 0.78 (0.71 in the external validation).

Our analyses showed that inclusion of characteristics that would require a time-consuming, costly and/or invasive assessment, such as dietary vitamin D intake or *GC* rs4588 and rs7041 SNPs, did not improve substantially the discriminatory performance of the score.

Our study had several strengths such as a large sample size and an independent cohort available for validation purposes. The score we developed accounts for a relatively small number of individual-level parameters that could be easily assessed and computed with a simple checklist. This scoring system is therefore a noninvasive method for a quick and efficient assessment of the likelihood of vitamin D insufficiency.

However, some limitations should be acknowledged. First, in both the cohorts, subjects were volunteers participating in long-term studies on nutrition and health and thus may not be representative of the French population. Also, the large majority of the participants were non-Hispanic whites. In SU.VI.MAX, people < 45 years or those with darker skin tones were not represented, even though these categories were included in the NutriNet-Santé cohort. Next, we did not have information on individual clothing habits. Overall, the use of the VDIP score in other Western nonsupplemented population requires caution given that the modeled latitudes are in a relatively narrow range, and also that dietary vitamin D intake in France is rather limited and thus, is not a major determinant of vitamin D status.[11] This may be different in other countries with higher dietary vitamin D intake. Second, our score was built in a non–vitamin D-supplemented population. Indeed, spontaneous dietary supplement use was not allowed in the SU.VI.MAX trial and we excluded participants who declared taking drugs containing vitamin D in our analyses. In the NutriNet-Santé sample, we excluded participants using vitamin D supplements or drugs. Supplementation is supposed to have a great influence on vitamin D status. However, the primary goal of our study was to provide a tool to detect vitamin D insufficiency prior to medical decision (ie, prior to supplementation). Third, in the NutriNet-Santé study, there were some missing data on covariates, especially for sun exposure, Fitzpatrick phototype, and physical activity. A missing class was entered into the logistic regression model and individuals were kept in the sample for score computation, with no point attributed for the missing characteristics. This may have induced some misclassification and thus decreased the performance of the score. Exclusion of participants with missing data provided similar results but induced loss of statistical power in the analyses. In addition, weight and height were self-reported in the NutriNet-Santé cohort, thus classification bias could not be excluded. However, in a previous validation study, we showed that self-reported weight and height data from the NutriNet-Santé study were valid and strongly correlated with anthropometric data measured by study staff.[28] Fourth, although main analyses excluded participants with epilepsy and renal failure at baseline and sensitivity analyses excluded participants with cardiovascular diseases or diabetes at baseline, analyses that excluded participants with other autoimmune diseases at baseline could not be performed since this information was not validated in the present study. Finally, vitamin D status also is likely determined by other complex biological parameters beyond the simple individual characteristics included in the VDIP score, which could explain the remaining variability.

The simple VDIP score, developed and externally validated in this study, performed well in identifying middle-aged nonsupplemented adults at risk of vitamin D insufficiency who might benefit from vitamin D supplementation. The score was designed to be used in daily clinical practice, given that it is based on a quick and simple checklist that could be administered in physician waiting rooms. Computation of the VDIP score is easy and costless, yet its potential as a primary screening tool for vitamin D insufficiency should not be underestimated. This score could help to better target at-risk individuals and thus to avoid unnecessary systematic supplementation or blood testing.

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