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Original article

A validated screening tool correctly identifies the majority of pregnant women at high risk of vitamin D deficiency

Linnea Bärebring [1], Anna Amberntsson [1], Hanna Augustin*

Department of Internal Medicine and Clinical Nutrition, Sahlgrenska Academy, University of Gothenburg, Sweden

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SUMMARY

Background & aim: The objective was to develop and validate a non-invasive screening tool to identify pregnant women at high risk of vitamin D deficiency.
Methods: Data from the Swedish prospective cohort GraviD, 2125 pregnant women, were randomly split in halves; one for developing the screening tool, and one for validation. Risk factors of vitamin D deficiency (serum 25-hydroxyvitamin D < 30 nmol/L) were identified using logistic regression analyses and odds ratios were translated into scores. Cutt offs to indicate high risk of vitamin D deficiency were evaluated by receiver operator characteristics.
Results: Five variables (season, clothing, eye color, fortified milk intake and vitamin D supplement use) were included in the screening tool. The possible total score was 0–42. Mean (95% CI) area under the curve for classification of vitamin D deficiency was 0.921 (0.893–0.948) ($p < 0.001$). A score of ≥15 points had 92% sensitivity and 76% specificity to identify women with 25OHD <30 nmol/L. This cut off had a positive predictive value of 31% and a negative predictive value of 99%.
Conclusion: This short non-invasive screening tool is valid as it correctly identified the majority of the vitamin D deficient pregnant women, who may benefit from further investigation for definite diagnosis and subsequent treatment.

1. Introduction

One of the most known functions for vitamin D in the human body is to regulate the calcium homeostasis [1]. The role of adequate vitamin D status during pregnancy is less well studied. Associations between poor maternal vitamin D status and several gestational complications have been found, both for the mother (preeclampsia [2,3]), and the infant (small for gestational age [4], preterm delivery [5]). In addition, vitamin D supplementation during pregnancy in winter improves the bone health of the newborn child [6].

Vitamin D can be produced in the human skin following exposure to sunlight [1]. However, the production depends on several factors, i.e. skin pigmentation [1]. For countries at northern latitudes, the dermal production is absent during the winter season [7]. Studies from these latitudes simultaneously reveals an overall low intake of vitamin D from diet alone [8]. Fortified dairy products and fatty fish are major dietary sources of vitamin D for the adult population in Sweden [9]. Supplemental vitamin D intake is also an important contributor to vitamin D status [10]. Due to differences in latitude, diet and lifestyle, the determinants of vitamin D status vary between populations. There is variation within the Nordic region, due to differences in fortification policies and supplemental intake, reflected by higher vitamin D intake in Finland and Norway [8].

We have previously shown the overall prevalence of vitamin D deficiency (serum concentrations of 25-hydroxyvitamin D (25OHD) < 30 nmol/L) in a multi-ethnic population of pregnant women living in Sweden to be 10% [5,11]. Among women born in Africa and Asia, the prevalence was approximately 50%. Other research groups have also confirmed poor vitamin D status among pregnant women in Scandinavia [12,13]. We and others have

Abbreviations: 25OHD, 25-hydroxyvitamin D; ROC, receiver operator characteristic; PPV, positive predictive value; NPV, negative predictive value; AUC, area under the curve.

* Corresponding author. Department of Internal Medicine and Clinical Nutrition, Sahlgrenska Academy, University of Gothenburg, Medicinaregatan 13, 405 30, Gothenburg, Sweden.
E-mail addresses: Linnea.barebring@gu.se (L. Bärebring), anna.amberntsson@gu.se (A. Amberntsson), hanna.augustin@gu.se (H. Augustin).
[1] Shared first authorship.

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investigated determinants for vitamin D status during pregnancy. Some of the variables significantly associated with vitamin D status were; country of origin [11,14], vitamin D supplementation [11,14,15], season of blood sampling [11,15] and clothing style [11]. Eye color has also been related to vitamin D status in an adult population [16]. Both skin pigmentation and eye color as a proxy for skin pigmentation has been associated with vitamin D status in different populations [17].

Vitamin D status can be assessed by measuring the biomarker 25OHD from serum or plasma [18]. Thus, a blood sample is necessary to detect vitamin D deficiency, but to test the general population by blood sampling is not cost-effective [19]. Considering the risk of poor vitamin D status in the Nordic countries [8], a simpler tool to screen for vitamin D deficiency is desired. A screening tool enables the maternal health care to identify women at risk, in order to provide treatment (such as recommending a vitamin D supplement), and thereby improve health for both the woman and fetus. Screening tools to detect vitamin D deficiency and insufficiency with good validity have been developed in countries such as India and France [20,21]. However, it is crucial to use a population specific tool, when screening for individuals with low vitamin D status due to the variation of determinants between populations. The objective of this study was to establish and validate a screening questionnaire to identify pregnant women at high risk of vitamin D deficiency (25OHD <30 nmol/L).

2. Materials and methods

2.1. Study population

The GraviD study is a population-based pregnancy cohort conducted in south western Sweden (latitude 57–58°N) [11]. Pregnant women registering for antenatal care in the first trimester were invited to participate. In total, 2125 women were included in the study during fall 2013 and spring 2014. The only exclusion criterion for the GraviD study was gestational age >16 weeks at inclusion. For the current analyses, only women (n = 1758) with complete data on vitamin D status in first trimester and candidate variables of interest for vitamin D status, as previously published [11], were included. The study was approved by the Regional Ethics Committee in Gothenburg (Dnr 897-11, T439-13) and conducted in accordance to the Declaration of Helsinki. Informed written consent was provided by all participants after receiving both written and oral information.

2.2. Data and sample collection

In the first trimester (gestational week <17), questionnaires were distributed and collected by the midwife at a routine visit at the antenatal care. An interpreter was present if needed, in line with standard care. The questions to the participants included background information (i.e. education, country of origin, and eye color), and lifestyle factors (i.e. sun habits and dietary intake). Also, a non-fasting venous blood sample was drawn at this routine visit to the antenatal care.

2.3. Laboratory analysis

The drawn non-fasting venous blood sample was centrifuged within 3 h of sampling. Serum was thereafter aliquoted and banked in −80°C until analysis. Serum 25OHD was analyzed by liquid chromatography tandem mass spectrometry (LC-MS/MS), performed by the central laboratory in the region Skåne, certified by Vitamin D External Quality Assessment Scheme [22].

2.4. Statistical analysis

All women with complete data (N = 1758) were included and the data set was randomly divided into two parts; a development (N = 891) and a validation data set (N = 867).

The development of the screening tool was performed using the development data set. In the development data set, candidate variables for the screening tool were selected from the questionnaire of determinant variables of vitamin D status collected within the GraviD study. The distribution of maternal vitamin D status and the determinants of this distribution have been previously published [11]. Fixed variables were selected based on their strong correlation with vitamin D deficiency in previous analyses [11]. In the current analyses, the variable eye color was included instead of country of origin (North Europe, Continental Europe, America, Asia or Africa) as these were too correlated to both be include in the same model. Thus, fixed variables were: season (November–April or May–October), eye color (blue/green, hazel or dark brown), clothing in warm weather (often, seldom or never show skin to sun) and vitamin D supplement use (yes/no). Secondly, potential candidate variables added were age (<30, 30–40 or >40 years), skin type (Fitzpatrick's scale 1–6), BMI (>30 kg/m^2; yes/no), fish intake (eats fatty fish; yes/no), fortified milk intake (drinks fortified milk; yes/no) and sun habits (prefers sun, shade or both). A logistic regression model was built by adding the fixed candidate variables as independent variables and vitamin D deficiency (defined as 25OHD <30 nmol/L) as dependent. The potential candidate variables were subsequently added one by one to the fixed model. Akaike's Information Criterion [23] was used to build the best balanced logistic regression model to avoid both under- and overfitting. The variable fortified milk intake was included in the final model, while all others potential candidate variables were excluded as they did not improve the model. The odds ratios of vitamin D deficiency for the included independent variables in the final model were translated into rounded off scores. Each woman obtained a sum total, and the higher sum of score corresponded to the higher odds of vitamin D deficiency. To identify a cut off for the scores for prediction of high risk of vitamin D deficiency (25OHD <30 nmol/L), receiver operator characteristic (ROC) curves were used [24]. The ROC curve plots sensitivity versus 1-specificity. The optimal cut off of scores for high risk of vitamin D deficiency was determined based on the highest possible sensitivity and specificity on the ROC curve, called Youden's index. Thereafter, the area under the curve (AUC) was calculated. AUC is an index ranging from 0 to 1 with high values indicating that the diagnostic tool has good ability to differentiate between the risk of vitamin D deficieny and non-deficiency. Positive predictive value (PPV) and negative predictive value (NPV) were calculated and defined as true positives/total positives and true negatives/total negatives, respectively. PPV is the probability that the individuals identified as vitamin D deficient by the screening tool truly have a 25OHD <30 nmol/L. True positives were individuals with a score above the cut off and serum 25OHD <30 nmol/L. Total positives are all with serum 25OHD <30 nmol/L. NPV is the probability that the individuals identified as not vitamin D deficient by the screening tool truly have a 25OHD ≥30 nmol/L. True negatives were individuals with a score below the cut off and serum 25OHD ≥30 nmol/L. Total negatives are all with serum 25OHD ≥30 nmol/L.

To validate the screening tool, the scores and the cut off obtained in the development data set was applied in the validation data set. In addition, the ROC statistics were applied on validation data set, to validate the sensitivity and specificity of the scores and selected cut off. Also, PPV and NPV were calculated in the validation data set for each score.

3. Results

3.1. Study population

Among the 1758 women included in this study, 75% were born in North Europe, 7% in Continental Europe, 9% in Asia, 7% in Africa and 2% in South or North America. Mean (SD) age was 31.3 (4.8) years and mean BMI in early pregnancy was 24.5 (4.2) kg/m^2. In total, 60% had a university level education, 33% a secondary level education, and 7% a primary level education or less. The potential candidate variables for the screening tools are shown in Table 1 for all women and for the two data sets (development and validation) separately.

3.2. Development of the screening tool

Based on the Akaike's Information Criterion, the final model for the screening tool included season of blood sampling, eye color, clothing in warm weather, fortified milk intake, and vitamin D supplement use. The score attributed to each answer are shown in Table 2 and Supplement 1. In total, the score ranged from 0 to 42 (including whole and half units). The mean (95% CI) AUC was 0.925 (0.902–0.947) ($p < 0.001$), Fig. 1a. The cut off was selected based on the coordinates of the ROC curve, showed the highest sensitivity and specificity (i.e. Youden's index) at a score equal to or greater than 14.75 points, which was rounded to 15.0, indicating high risk of vitamin D deficiency. The screening tool is presented in Supplement 2.

3.3. Validation of the screening tool

ROC statistics was applied also to the validation data set, where the scores performed equal to the development data set (Fig. 1b). Mean AUC was 0.921 (95% CI 0.893–0.948) ($p < 0.001$). The cut off of 15 points showed 92% sensitivity and 76% specificity to identify women with vitamin D deficiency (25OHD <30 nmol/L). This cut off had a PPV of 31% and a NPV of 99% in the validation data set (Table 3).

Table 2
The final model and the score attributed to the questions in the screening tool.

	B	S.E.	P	OR	SCORE
Season at blood sampling					
Summer (May–October)					0
Winter (November–April)	1.40	0.31	<0.001	4.07	4
Eye color					
Blue/green					0
Hazel	2.16	0.45	<0.001	8.67	8.5
Dark brown	2.78	0.41	<0.001	16.05	16
Clothing in warm weather					
Often					0
Seldom	0.65	0.38	0.088	1.91	2
Never	2.53	0.42	<0.001	12.58	12.5
Drinks fortified milk					
Yes					0
No	0.91	0.30	0.002	2.47	2.5
Vitamin D supplement user					
Yes					0
No	1.94	0.40	<0.001	6.96	7

B; Beta, S.E; Standard Error, P; P-value, OR; Odds Ratio.

4. Discussion

The novelty of this paper is that we have developed and validated a screening tool with high specificity and sensitivity for identifying pregnant women at high risk of vitamin D deficiency, defined as 25OHD <30 nmol/L. The results show that a cut off at

Table 1
Potential candidate variables for the screening tool of the women in the development and validation data set.

	All women (N = 1758) N (%)	Development data set (N = 891) N (%)	Validation data set (N = 867) N (%)
Age			
<30 years	709 (40.3)	348 (39.1)	361 (41.6)
30–40 years	979 (55.7)	512 (57.5)	467 (53.9)
>40 years	70 (4.0)	31 (3.5)	39 (4.5)
BMI (first trimester)			
<18.5 kg/m^2	31 (1.8)	15 (1.7)	16 (1.9)
18.5–24.9 kg/m^2	1094 (62.4)	567 (63.7)	527 (61.4)
25–29.9 kg/m^2	451 (25.7)	233 (26.2)	218 (25.2)
≥30 kg/m^2	178 (10.1)	75 (8.4)	103 (11.9)
Vitamin D deficiency (25OHD <30 nmol/L)	176 (10.0)	84 (9.4)	92 (10.6)
Season at sampling			
November–April	665 (37.8)	342 (38.4)	323 (37.3)
May–October	1093 (62.2)	549 (61.6)	544 (62.7)
Eye color			
Blue/green	1157 (65.8)	592 (66.4)	565 (65.2)
Hazel brown	224 (12.7)	119 (13.4)	105 (12.1)
Dark brown	377 (21.4)	180 (20.2)	197 (22.7)
Skin color			
Fitzpatrick scale 1–4	1585 (91.0)	800 (91.0)	785 (91.1)
Fitzpatrick scale 5–6	156 (9.0)	79 (9.0)	77 (8.9)
Clothing in warm weather			
Often show skin	1414 (80.4)	732 (82.2)	682 (78.7)
Seldom show skin	234 (13.3)	112 (12.6)	122 (14.1)
Never show skin	110 (6.3)	47 (5.3)	63 (7.3)
Sun preference			
Prefer sun	297 (16.9)	149 (16.4)	151 (17.5)
Prefer both sun and shade	1392 (79.3)	712 (80.0)	680 (78.6)
Prefer shade	66 (3.8)	32 (3.6)	34 (3.9)
Drinks fortified milk	1228 (69.9)	626 (70.3)	602 (69.4)
Eats fatty fish	1613 (91.8)	822 (92.3)	791 (91.2)
Vitamin D supplement user	763 (43.4)	390 (43.8)	373 (43.0)

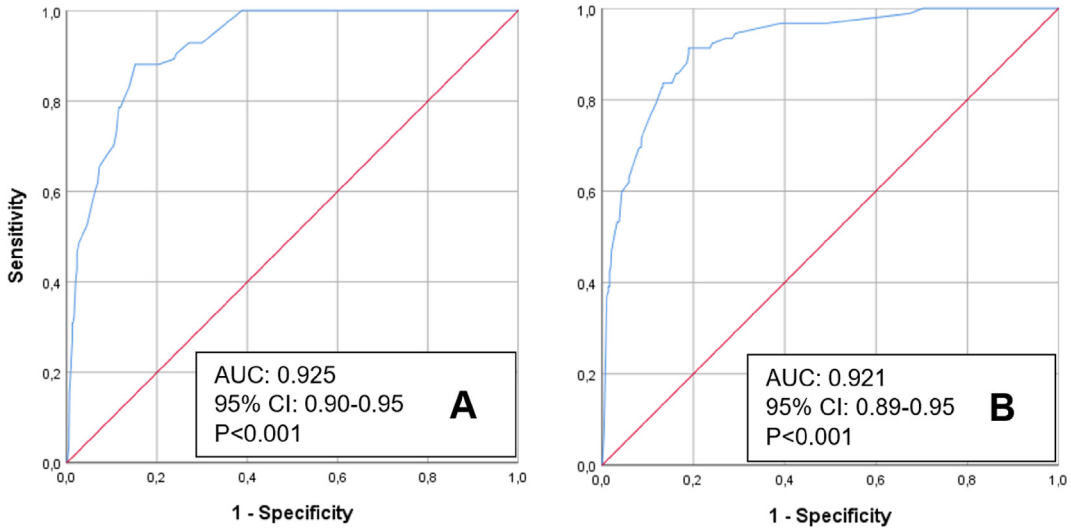

Fig. 1. Receiver Operating Characteristic curve data for the screening tools prediction of vitamin D deficiency (25-hydroxyvitamin D < 30 nmol/L) in the A) development data set and B) validation data set. *AUC; area under the curve, CI; confidence interval, P; P-value.*

Table 3
Sensitivity, specificity, positive and negative predictive values for different cut offs of the score derived from the vitamin D deficiency screening tool.

Cut off (points)	Development data set N = 891					Validation data set N = 867				
	N (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	N (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
≥5	642 (72.1)	100.0	30.9	13.1	100.0	643 (74.2)	100	28.9	14.3	100.0
≥10	400 (44.9)	100.0	60.8	21.0	100.0	393 (45.3)	96.7	60.8	22.6	99.4
≥15	272 (30.5)	90.5	75.7	27.9	98.7	272 (31.4)	92.4	75.9	31.3	98.8
≥20	182 (20.4)	83.3	86.1	38.5	98.0	196 (22.6)	83.7	84.6	39.3	97.8
≥25	103 (11.6)	60.7	93.6	49.5	95.8	127 (14.6)	69.6	91.9	50.4	96.2
≥30	40 (4.5)	32.1	98.4	67.5	93.3	59 (6.8)	46.7	97.9	72.9	93.9
≥35	26 (2.9)	21.4	99.0	69.2	92.4	46 (5.3)	38.0	98.6	76.1	93.1
≥40	3 (0.3)	1.2	99.8	33.3	90.7	9 (1.0)	6.5	99.6	66.7	90.0

PPV; Positive predictive value, NPV; Negative predictive value.

total sum of score ≥15 points from the five item screening questionnaire (possible score 0–42 points), has high sensitivity (92%) and reasonable specificity (76%) for detecting women with vitamin D deficiency. In addition, the NPV of the cut off was high (99%), whereas the PPV was low (31%).

We found that a suitable cut off was a score at or above 15 points, to indicate a high risk of vitamin D deficiency. The high sensitivity (92%) of this cut off means that the score correctly identifies the majority with actual vitamin D deficiency (25OHD <30 nmol/L). However, the specificity of 76% means that some (24%) false positives will be included. The high NPV (99%) means that the score can predict who does not have vitamin D deficiency, with high accuracy. The PPV of 31% means that each single individual with a high risk of vitamin D deficiency (≥15 points) will still have a quite low probability (31%) of actually having 25OHD <30 nmol/L.

A score of ≥15 points should thus warrant further blood testing for vitamin D status, in order to make an accurate diagnosis. However, blood testing may not be required as the supplemental intake required to correct vitamin D deficiency is well below the tolerable upper intake levels of 100 μg/day [25]. Thus, a supplement of 10–20 g/day is safe to recommend without blood testing, also during pregnancy. Women with a score of ≥15 points who already takes a vitamin D supplement, can be encouraged to maintain supplemental intake and be guided to the appropriate dose. The tool is simple to use and can easily be implemented as a routine procedure in the maternal health care, to identify women at high risk of vitamin D deficiency.

The final screening tool included five variables; season at blood sampling, eye color, clothing in warm weather, fortified milk intake and vitamin D supplement use. Information on season at blood sampling and clothing in warm weather were both major determinants of vitamin D status, which is expected at the Northern latitudes of Sweden [26]. Eye color was included as a proxy for skin pigmentation. Skin pigmentation was assessed in the GraviD cohort using Fitzpatrick's scale [27] but eye color was a greater determinant of vitamin D deficiency. The reason for this can be due to the difficulty to estimate and correctly classify ones skin color according to the Fitzpatrick's scale. The variable fish intake did not improve the model and was therefore not included in the screening tool. Instead, the variable fortified milk intake improved the model and was thus included. In Sweden, mean milk and yoghurt intake per day is 226–244 g for women 18–44 years of age [9]. At the time of data collection, low fat dairy products were fortified with 0.38–0.50 μg vitamin D3/100 g [28]. Thus, if intake of fortified milk is regular and frequent, it can be a significant contributor to vitamin D intake and status. Since 2018, the fortification policy in Sweden has changed, and more products (such as plant-based milk drinks, full fat milk and fermented dairy products) are now fortified with 0.75–1.10 μg vitamin D/100 g [29]. It is therefore likely that milk

intake is an even greater determinant of vitamin D status today. Lastly, information on vitamin D supplementation was included in the tool, which was also expected as this is a major determinant of vitamin D repletion [6,30].

The methodological approach used in the current paper, is similar to that of Deschasaux et al. [21], Garg et al. [20] and Tran et al. [31], who also developed scoring systems for vitamin D insufficiency (defined as 25OHD <50 nmol/L) och deficiency (defined as 25OHD <25 nmol/L) risk. We chose vitamin D deficiency instead of insufficiency and found higher sensitivity and higher or similar specificity than the previous studies. Previous studies have developed the screening tool in a different population [20,21,31,32], or in a very small study population [20]. None of the previous studies have developed the screening tool in a pregnant population or in northern parts of Europe. Of the previous studies, only the study by Sohl et al. [32] has used Akaike's Information Criterion for model selection. While a complex model is not always the best, it is beneficial to use such a technique to select the model who best balances the fitting of the model to the data with the loss of information by including more variables [23].

4.1. Strengths and limitations

A strength of this study is that the cohort used allowed for a large number of candidate variables to be tested and included in the screening tool. The large sample size also allowed for both the development and the validation of the screening tool, by splitting the data set. Further, the cohort is representative of the pregnant Swedish population with regards to country of origin, pre-pregnancy BMI and parity [11]. Therefore, the tool can likely be extrapolated to all geographical areas of Sweden. This study also has some limitations. Possible reasons for the fish intake not being included as a question in the screening tool is that it is difficult to estimate the intake of fatty fish due to infrequent and irregular intake. Together with changes in food preferences during pregnancy, this could potentially lead to a low mean fish intake not high enough to contribute substantially to vitamin D status in this population. Also, since the score included fortified milk intake, it is likely that the tool will not perform as well in a population with other fortification practices. Another limitation is that the development and validation data sets were both derived from the same study population. To get an even better perception of the performance of the screening tool, an additional validation study in another study sample should be performed.

In conclusion, we here present the development and validation of a short screening tool for identifying pregnant women at high risk of vitamin D deficiency. A score $\geq$15 points will correctly identify the vast majority of vitamin D deficient women, who may benefit from further blood testing for definite diagnosis and subsequent treatment.

Author contributions

Conceptualization, L.B., A.A and H.A.; methodology, L.B., A.A and H.A. validation, L.B., A.A and H.A.; formal analysis, L.B., A.A and H.A.; resources, H.A.; data curation, L.B.; writing—original draft preparation, L.B. and A.A.,; writing—review and editing, L.B., A.A and H.A.; funding acquisition, H.A. All authors have read and agreed to the published version of the manuscript.

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Data availability statement

The data presented in this study are available on request from the corresponding author. The data are not publicly available due to The General Data Protection Regulation under Swedish law.

Declaration of competing interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.clnesp.2022.03.034.

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