Journal of Bone and Mineral Metabolism (2019) 37:854–863
https://doi.org/10.1007/s00774-018-0984-2

ORIGINAL ARTICLE

A simple questionnaire for the prediction of vitamin D deficiency in Japanese adults (Vitaimn D Deficiency questionnaire for Japanese: VDDQ-J)

Akiko Kuwabara[1] · Naoko Tsugawa[2] · Kei Mizuno[3] · Honami Ogasawara[2] · Yasuyoshi Watanabe[3] · Kiyoshi Tanaka[4]

Received: 1 November 2018 / Accepted: 17 December 2018 / Published online: 5 February 2019

Abstract

Vitamin D deficiency (VDD) is associated with an increased risk of various diseases. Serum 25-hydroxyvitamin D [25(OH)D] concentration is the best marker for vitamin D status and its concentration < 20 ng/mL indicates VDD. However, its measurement is not easily applicable for the evaluation of vitamin D status in the general population because of its cost. Therefore, we aimed to develop a simple questionnaire for easily identifying the risk of VDD. From the total sample (649 healthy subjects aged 19–70 years), 434 and 215 subjects were randomly assigned to the derivation and the validation cohort, respectively. Prediction model for VDD was developed by backward logistic regression analysis. The regression β coefficients of the significant predictors were transformed into integral numbers and used for the individual score. These individual scores were summed to calculate the total risk score (VDD questionnaire for Japanese score: VDDQ-J score). VDD was present in 54.1% of the total subjects. The model for the prediction of VDD consisted of 7 predictors. Areas under the curve were 0.78 and 0.75 in the data set of internal validation and of the external validation, respectively. The cutoff value was determined to be 31 points (range 0–54) with the sensitivity/specificity and positive predictive value/negative predictive value of 61%/79%, and 81%/57%, respectively. Our VDDQ-J score is easy to answer by the wide range of subjects, and well predicts VDD. This risk score would be useful to identify subjects at risk for VDD both in clinical and epidemiological settings.

Keywords Vitamin D deficiency · Questionnaire · Japanese · Sun exposure · Fish intake

Introduction

Vitamin D deficiency (VDD) is associated with increased risk of various diseases, such as fracture [1, 2], fall [3], cardiovascular disease [4], cancer [5], infection [6], and mortality [7]. Serum concentration of 25-hydroxyvitamin D [25(OH)D] is widely recognized as the best marker of vitamin D status. There is a general consensus that serum 25(OH)D concentration < 20 ng/ml, 20 to < 30 ng/mL and ≥ 30 ng/mL indicate VDD, vitamin D insufficiency (VDI), and vitamin D sufficiency, respectively [8]. High prevalence of VDD is not limited to Japan [9, 10], but a worldwide problem. Although vitamin D status can ideally be evaluated by serum 25(OH)D concentration, its measurement is costly and not easily applicable to the healthy subjects. Then, development of a simple questionnaire to screen the vitamin D status would be of much epidemiological value. In addition, detection of VDD by a simple questionnaire would enable an early intervention for improving vitamin D status. Therefore, a

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00774-018-0984-2) contains supplementary material, which is available to authorized users.

✉ Akiko Kuwabara
akuwabara@rehab.osakafu-u.ac.jp

[1] Department of Clinical Nutrition, Faculty of Comprehensive Rehabilitation, Osaka Prefecture University, 3-7-30 Habikino, Habikino, Osaka 583-8555, Japan

[2] Department of Health and Nutrition, Osaka Shoin Women's University, 4-2-26 Hishiyanishi, Higashiosaka, Osaka 577-8550, Japan

[3] RIKEN Compass to Healthy Life Research Complex Program, 6-7-1 Minatojima-minamimachi, Chuo-ku, Kobe, Hyogo 650-0047, Japan

[4] Department of Faculty of Nutrition, Kobe Gakuin University, 518, Ikawadanicho-Arise, Nishi-ku, Kobe, Hyogo 651-2180, Japan

screening tool of predicting VDD would be useful for both clinicians and staffs in public health.

Previously, determinants of serum 25(OH)D concentration have been reported [11–15]. Additionally, simple questionnaires to assess vitamin D status also reported in the US and Europe included such items as skin type (Fitzpatrick phototype), race [12, 16], milk fortified with vitamin D [17], and use of tanning booth [18]. However, they are not applicable to Japanese subjects. In our pilot study for a questionnaire for VDD [19], sunscreen use was an important determinant of vitamin D status. In this study, we describe the development and validation of a simple questionnaire for the prediction of VDD in Japanese adults (VDD questionnaire for Japanese: VDDQ-J).

Materials and methods

Subjects

All subjects were recruited at RIKEN in Kobe (34.7°N) between August 2017 and August 2018 including 346 men and 439 women aged 19–70 years living in Kinki Area, Japan (34.7–35.0°N). We excluded subjects with liver diseases, chronic kidney disease, inflammatory bowel diseases, cancer, diabetes mellitus, and osteoporosis. We have excluded the subjects taking vitamin D supplementation considering the low percentage of these people in Japan. Finally, 649 subjects with full set of data were used for analyses. Detailed information was given and written consent was obtained from the subject or the proxy. The study protocol was approved by the ethical committee in RIKEN (Approval number: Kobe2 2017-04(6)).

Study design

From the total sample (649 subjects), 434 subjects (67%) and 215 subjects (33%) were randomly selected to be the derivation cohort sample and the validation cohort sample, respectively. The derivation cohort sample was used to develop the prediction model for the presence of VDD.

Data collection

At the visit, we obtained the subjects' data on age, gender, self-reported medical history, and medication. The 11-item Food Diversity Score Kyoto (FDSK-11) was used for food intake evaluation [20]. Calcium intake was assessed by "Self-assessment Table for Calcium Intake" [21]. The participants also have given information on the status of sun exposure, sunscreen use, vitamin D supplement use, and habitual fish intake. These items were selected with reference to VIDSUN questionnaire [17]. "Paying attention to UV exposure" asked the subjects about their habit of using a parasol or wearing long sleeve clothes for avoiding sun exposure. "Fish containing high vitamin D" was defined as fish containing more than 10 μg of vitamin D in the habitual intake value of Japanese [22], and included salmon, sardine, saury, flounder, eel, herring and grunt. Subjects were asked to list up to three fishes they often eat with their names, volume at each intake, and weekly consumption frequency. A score of one was given to "fish containing high vitamin D" and multiplied by the weekly frequency. Zero was given to no fish intake or intake of other fishes. Then, scores were summated.

Assay of serum 25(OH)D concentration

After centrifugation, serum was stored at − 80 °C until determination. Serum vitamin D metabolites were measured by modified method of liquid chromatography tandem mass spectrometry (LC-APCI-MS/MS) [23]. Modification point is derivation of extracted vitamin D metabolites by 4-[2-(6,7-dimethoxy-4-methyl-3-oxo-3,4-dihydroquinoxalyl) ethyl]-1,2,4-triazoline-3,5-dione (DMEQ-TAD) to obtain high sensitivity by increasing ionization efficiency [24]. Coefficient of variation (CV) for intra- and inter-assay was 3.4–9.2% and 11.9% for 25(OH)D, and 13.1–19.3% and 14.7% for 24,25$(OH)_2$D, respectively. Total serum 25(OH)D level was calculated by their summation. Individuals with serum 25(OH)D less than 20 ng/ml were categorized to VDD. Serum intact parathyroid hormone (iPTH) was measured at SRL, Inc. (Tokyo, Japan).

Statistical analysis

Data were expressed as median (interquartile range). To compare the characteristics of subjects with and without VDD, Mann–Whitney *U* test (continuous data) or the Fisher exact test (categorical data) was used. For developing the VDD predictor model, univariate logistic regression analysis and multivariate logistic regression analysis with stepwise backward selection method were done in the derivation cohort. All continuous variables were categorized or dichotomized. The multivariate model was performed adjusted by all indices shown in Table 2. The regression β coefficients of the significant predictors were multiplied by 8 for transformation into integral numbers. For example, multiplication of β-coefficient of 0.850 for winter in the season of blood draw by 8 yielded a score of 6.8, and it was rounded off to the closest whole number of 7 (see Tables 2 and 3). These individual scores were summed to calculate the total risk score (VDDQ-J score). The discriminative capacity of the VDD score was analyzed by the receiver operator characteristic (ROC). External validation was also performed by calculating the AUC in the validation cohort using the

internally validated regression coefficients. In the validation cohort, the appropriate cutoff value was determined using Youden's index [25]. To assess the validity of the cutoff value, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and positive and negative likelihood ratio (with 95% confidence intervals; 95% CI) were calculated. All statistical analyses were carried out using SPSS for Windows (version 25.0; SPSS Inc., Tokyo, Japan). Statistical significance was defined as a two-tailed $P < 0.05$ for all analyses.

Results

Median serum 25(OH)D concentration was 19.1(IQR: 14.7, 24.5) ng/mL in the whole subjects. Percentage of the subjects with VDD and VDI was 54.1% and 33.4%, respectively. The characteristics and questionnaire response according to vitamin D status in each cohort sample are shown in Table 1. The prevalence of VDD was not significantly different between the derivation cohort and validation cohort ($p = 0.103$). Percentage of subjects with the following characteristics was higher in the validation cohort than in the derivation cohort; female, no suntan within the past 12 months, and ≥ 40 min/day of time regularly spent outside (see Supplemental Table 1).

Both in the derivation and validation cohorts, the percentage of subjects with the following profiles was higher in the VDD group than in the non-VDD group; younger subjects, female, blood draw in fall and winter, having less exercise habit, having less sun exposure in the last 3 months, <40 min/day of time regularly spent outside, "More often than not" to "always" of sunscreen use. Significant differences were found in the derivation cohort only for the following items: alcohol consumption, suntan within the past 12 months, spending time outside in holidays, paying attention to UV exposure, and ≥ 2 per week of intake of fish containing high vitamin D score. The percentage of subjects with the smoking status and calcium intake score was significantly different in the validation cohort only.

Table 2 shows the univariate odds ratio for VDD and the final prediction model for detecting VDD using a backward selection procedure in the derivation cohort. In our preliminary analysis, the significant interaction was found between suntan and sunscreen use ($p = 0.015$). Thus, we made a combined variable (suntan × sunscreen use) consisting of four categories depending on the presence or absence of suntan and with or without sunscreen use. The following parameters were identified as the significant contributing variables in the multivariate analysis; age (< 40 y), sex (female), the season of blood draw (fall and winter), exercise habit (never), suntan × sunscreen use (without suntan × with sunscreen use), sun exposure in the last 3 months(never), intake of fish containing high vitamin D (< 2 per week). The Hosmer–Lemeshow goodness-of-fit test for the multiple logistic regression was not significant, which indicated that the model fit the data well. According to the predicted probability thus obtained, the subjects were categorized into quintiles. In each quintile of the validation cohort, there was no significant difference between the predicted and observed probability for VDD (Chi squared test, $p = 0.424$: see supplemental Fig. 1), indicating that the logistic model was well calibrated. All regression coefficients with its odds ratio ≥ 1.5 were transformed into simple scores for the ease of use to predict the probability of VDD (Table 3). A score of 54 represents the highest probability of VDD. The discriminative ability of the VDDQ-J score was analyzed by the ROC analysis. AUC was 0.78 (95% CI 0.74–0.82) and 0.75 (95% CI 0.69–0.82) in the derivation cohort and in the validation cohort, respectively. As shown in Fig. 1, there was no significant difference between predicted and observed probabilities in each of the quintiles of the deviation cohort. Thus, the validity of the VDDQ-J score was confirmed. Then, the detective ability and cutoff value of the VDDQ-J score for the presence of VDD were evaluated by ROC analysis in the validation cohort (Table 4). The cutoff value was determined to be 31 points with the sensitivity and specificity being 61% and 79%, respectively. PPV and NPV were 81% and 57%, respectively.

Discussion

In this study, we have developed a simple questionnaire for the prediction of VDD in Japanese subjects including both dietary intake and ultraviolet irradiation. Before going into the detail, the characteristics of the study subjects will be described.

The prevalence of VDD and VDI was 54.1% and 33.4%, respectively, in the present study subjects. In a study in Niigata including 9084 subjects aged 40–74 years, 53.6% and 37.4% of them were VDD and VDI, respectively [10]. In another Japanese study involving 1790 subjects aged 18–69 years, 40.8% and 51.4% of them were VDD and VDI, respectively [26]. The prevalence of VDD and VDI in the current study was similar to that in the former study. The prevalence of VDD was lower in the latter despite similar age distribution. Subjects in the latter study were workers at a metal industry, while most of our subjects were engaged in the inactive works. Anyway, high prevalence of VDD/VDI was consistent in these Japanese studies including ours.

The logistic regression analysis has identified seven variables as independent and significant predictors for VDD: age, sex, the season of blood draw, exercise habit, suntan × sunscreen use, sun exposure in the past 3 months, intake of fish containing high vitamin D. Regarding age,

Table 1 Demographic characteristics and questionnaire response according to subjects' 25(OH)D concentration in the derivation cohort and the validation cohort

Demographics	Derivation cohort ($n=434$)			Validation cohort ($n=215$)		
	VDD ($n=222$)	Non-VDD ($n=212$)	P value	VDD ($n=129$)	Non-VDD ($n=86$)	P value
Serum 25(OH)D (ng/mL)	14.9 (12.6–17.3)	25.4 (22.2–30.5)	< 0.001	15.4 (12.8–17.4)	25.0 (21.5–30.1)	< 0.001
Serum iPTH (pg/mL)	53.4 (42.5–64.1)	47.6 (39.2–57.8)	< 0.001	51.6 (41.3–60.9)	44.3 (34.8–56.0)	0.013
Age(y)	44.0 (29.0–52.5)	47.0 (37.0–55.0)	0.012	45.0 (31.0–52.0)	48.5 (40.0–55.0)	0.019
≥ 50 y	71	83	0.015	43	38	0.136
40 to < 50 y	53	64		39	27	
< 40 y	98	65		47	21	
Sex (M/F)			< 0.001			0.008
M	71	127		37	40	
F	151	85		92	46	
BMI (kg/m^2)			0.468			0.186
< 25 kg/m^2	186	172		109	78	
≥ 25 kg/m^2	36	40		20	8	
The season of blood draw			< 0.001			< 0.001
Summer (July to September)	49	82		18	38	
Fall (Octobery to December)	76	72		52	24	
Winter (January to March)	97	58		59	24	
Smoking status			0.101			0.019
Never smoked	167	154		109	62	
Formerly smoked	43	35		12	20	
Currently smoked	12	23		8	4	
Alcohol consumption			0.038			0.382
Never	40	31		21	18	
Less than once per month	62	40		34	20	
2 to 3 times per month	56	52		39	18	
2 to 3 times per week	25	31		10	6	
More than 4 times per week	39	58		25	24	
Exercise habit			< 0.001			0.004
More than twice per week	32	57		16	20	
Once per week	23	35		20	23	
1 to 2 times per month	45	40		32	9	
Rarely	122	80		61	34	
Suntan within the past 12 months			0.002			0.074
Yes	114	140		53	46	
No	108	72		76	40	
Sun exposure in the last 3 months			< 0.001			< 0.001
Always	18	31		8	18	
More often than not	35	52		21	20	
Sometimes	30	42		17	17	
Infrequently	65	63		35	19	
Never	74	24		48	12	
Regularly outside spending time			0.016			< 0.001
≥ 40 min/d	100	120		63	64	
< 40 min/d	122	92		66	22	
Sun exposure in the past week			0.014			0.006
≥ 30 min/d	84	110		40	44	
15 to < 30 min/d	78	67		56	33	
5 to < 15 min/d	50	29		30	7	

Table 1 (continued)

Demographics	Derivation cohort ($n=434$)			Validation cohort ($n=215$)		
	VDD ($n=222$)	Non-VDD ($n=212$)	P value	VDD ($n=129$)	Non-VDD ($n=86$)	P value
< 5 min/d	10	6		3	2	
Spending time outside in holidays			0.046			0.152
≥ 3 h/d	71	85		43	41	
2 to < 3 h/d	28	36		16	12	
1 to < 2 h/d	51	47		31	18	
< 1 h/d	52	35		28	12	
Rarely	20	9		11	3	
Sunscreen use			< 0.001			0.012
"Never" to "sometimes"	140	172		76	65	
"More often than not" to "always"	82	40		53	21	
Sunscreen use for arms and legs			0.163			0.140
No	161	166		87	66	
Yes	61	46		42	20	
Paying attention to UV exposure			0.016			0.315
No	121	91		57	44	
Yes	101	121		72	42	
FDSK-11 score			0.730			0.197
11 points	122	120		68	53	
< 11 points	100	92		61	33	
Calcium intake score			0.410			0.003
≥ 16 (≥ 600 mg)	6	11		5	3	
8–15 (400-600 mg)	123	115		57	58	
0–7 (< 400 mg)	93	86		67	25	
Intake of fish containing high vitamin D score			0.005			0.385
≥ 2 per week	17	35		17	8	
< 2 per week	205	177		112	78	

Represented number was number of subjects. For serum 25(OH)D, iPTH, and age, median (Q1,Q3) were shown. Chi-squared test and Mann–Whitney test were applied for categorical indices and continuous variables, respectively. p value for the difference within each cohort was represented

VDD vitamin D deficiency

younger age was a positive risk factor for VDD in the present study, whereas older age was a positive risk in the previous reports [18, 27, 28]. Subjects aged < 40 y were characterized by a high percentage of subjects having no suntan within the past 12 months, never having sun exposure in the past week, and paying attention to UV exposure compared with those aged ≥ 50 years. Therefore, the chance and time of sun exposure in subjects < 40 years were considered lower than those aged ≥ 50 years, which would be partially the basis for younger age as a risk factor. Female gender was a significant risk for VDD, which is consistent with previous reports. For example, a recent study has described that the prevalence of vitamin D sufficiency (plasma 25(OH)D concentration ≥ 30 ng/mL) was extremely low (9.1%) in 9084 Japanese adults, and male gender was a significant positive predictor for vitamin D sufficiency [10].

Season was one of the strongest predictors in our models, which is in accordance with the previous reports [12, 16, 27, 29, 30]. Our results suggested that more dietary vitamin D intake or vitamin D supplementation is required in fall and winter. Percentage of subjects with alcohol consumption ≥ 4 times per week was higher in non-VDD group of the deviation cohort, but not the validation cohort, than in the VDD group, probably reflecting the high percentage of aged ≥ 50 years and male gender, which are protective against VDD. Less exercise habit was significantly associated with VDD, which is in agreement with the previous reports that recreational physical activity was a significant variable in models predicting 25(OH)D concentrations [11–15].

Sunscreen use has been reported to be the positive significant predictors of VDD. For example, Looker et al. [31] reported that higher frequency of sunscreen use decreased

Table 2 Univariate analysis and multivariate analysis for predicting VDD in the derivation cohort

	Univariate model		Odds(95%CI)	Multivariate model		Odds(95%CI)
	β	*P* value		β	*P* value	
Age						
≥ 50 y = ref	0			0		
40 to < 50y	−0.032	0.895	0.97 (0.60–1.57)	0.049	0.893	1.05 (0.60–1.83)
< 40 y	0.567	0.013	1.76 (1.13–2.75)	0.594	0.033	1.81 (1.05–3.13)
Sex (M/F)						
M	0			0		
F	1.156	< 0.001	3.18 (2.14–4.71)	1.007	< 0.001	2.74 (1.63–4.60)
BMI (kg/m^2)						
< 25 kg/m^2 = ref	0					
≥ 25 kg/m^2	−0.184	0.468	0.83 (0.51–1.37)	–	–	–
The season of blood draw						
Summer (July to September) = ref	0			0		
Fall (October to December)	0.569	0.020	1.77 (1.09–2.85)	0.539	0.054	1.75 (0.99–3.09)
Winter (January to March)	1.029	< 0.001	2.80 (1.73–4.53)	0.850	0.006	2.34 (1.28–4.29)
Smoking status						
Never smoked = ref	0					
Formerly smoked	0.125	0.623	1.13 (0.69–1.86)	–	–	–
Currently smoked	0.732	0.050	0.48 (0.23–1.00)	–	–	–
Alcohol consumption						
Never = ref	0					
Less than once per month	0.183	0.559	1.20 (0.65–2.22)	–	–	–
2 to 3 times per month	−0.181	0.556	0.84 (0.46–1.52)	–	–	–
2 to 3 times per week	−0.470	0.192	0.63 (0.31–1.27)	–	–	–
More than 4 times per week	−0.652	0.039	0.52 (0.28–0.97)	–	–	–
Exercise habit						
More than twice per week = ref	0			0		
Once per week	0.157	0.651	1.17 (0.59–2.31)	0.060	0.881	1.06 (0.49–2.32)
1 to 2 times per month	0.695	0.025	2.00 (1.09–3.68)	0.678	0.056	1.97 (0.98–3.95)
never	0.999	< 0.001	2.72 (1.62–4.55)	0.842	0.006	2.32 (1.28–4.22)
Suntan × Sunscreen use						
Suntan × without sunscreen use = ref	0			0		
Suntan × with sunscreen use	0.855	0.003	2.35 (1.33–4.15)	0.290	0.427	1.34 (0.65–2.73)
Without suntan × without sunscreen use	0.564	0.016	1.76 (1.11–2.78)	0.226	0.408	1.25 (0.73–2.14)
Without suntan × with sunscreen use	1.586	< 0.001	4.88 (2.45–9.73)	1.138	0.009	3.12 (1.33–7.31)
Sun exposure in the last 3 months						
Always = ref	0			0		
More often than not	0.148	0.688	1.16 (0.56–2.59)	0.099	0.809	1.10 (0.50–2.46)
Sometimes	0.207	0.586	1.23 (0.58–2.59)	0.073	0.868	1.08 (0.46–2.54)
Infrequently	0.575	0.096	1.78 (0.90–3.49)	0.717	0.071	2.05 (0.94–4.46)
Never	1.670	< 0.001	5.31 (2.53–11.1)	1.146	0.011	3.15 (1.31–7.57)
Regularly outside spending time						
≥ 40 min/d = ref	0					
< 40 min/d	0.465	0.016	1.59 (1.09–2.33)	–	–	–
Sun exposure in the past week						
≥ 30 min/d = ref	0					
15 to < 30 min/d	0.422	0.056	1.53 (0.99–2.35)	–	–	–
5 to < 15 min/d	0.814	0.003	2.26 (1.32–3.87)	–	–	–
< 5 min/d	0.780	0.146	2.18 (0.76–6.24)	–	–	–

Table 2 (continued)

	Univariate model		Odds(95%CI)	Multivariate model		Odds(95%CI)
	β	*P* value		*β*	*P* value	
Spending time outside in holidays						
≥3 h/d = ref	0					
2 to < 3 h/d	−0.978	0.024	0.38 (0.16–0.88)	–	–	–
1 to < 2 h/d	−1.050	0.027	0.35 (0.14–0.89)	–	–	–
< 1 h/d	−0.717	0.111	0.49 (0.20–1.18)	–	–	–
Rarely	−0.403	0.378	0.67 (0.27–1.64)	–	–	–
Sunscreen use for arms and legs						
No = ref	0					
Yes	0.313	0.163	1.37 (0.88–2.12)	–	–	–
Paying attention to UV exposure						
No = ref	0					
Yes	0.466	0.016	1.59 (1.09–2.33)	–	–	–
FDSK-11 score						
≥11 pointe = ref	0					
< 11 points	0.067	0.730	1.07 (0.73–1.56)	–	–	–
Calcium intake score						
≥16 (≥600 mg) = ref	0					
8–15 (400–600 mg)	0.673	0.199	1.96 (0.70–5.47)	–	–	–
0–7 (< 400 mg)	0.684	0.196	1.98 (0.70–5.59)	–	–	–
Intake of fish containing high vitamin D						
≥2 per week = ref	0			0		
< 2 per week	0.869	0.005	2.39 (1.29–4.40)	1.123	0.002	3.08 (1.50–6.31)

Multivariate logistic analysis with stepwise backward selection method was adjusted for all the factors presented in Table 2

VDD vitamin D deficiency

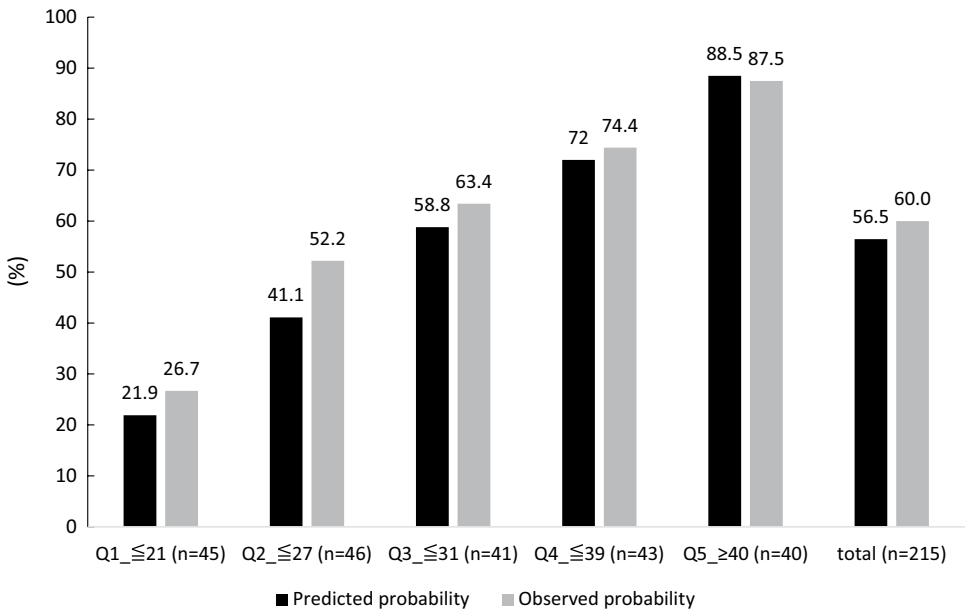

Fig. 1 Observed and predicted probability across the quintile of the VDDQ-J score (in the validation cohort). Subjects were divided into five groups based on the quintile of the VDDQ-J score. Black bar and gray bar represented the average predicted probability and observed probability, respectively. There was no significant difference in the pattern between the predicted and observed probability (Chi-squared test, $p = 0.413$). VDDQ-J: Vitamin D deficiency questionnaire for Japanese

serum 25(OH)D concentration. Suntan is also a negative significant predictor for VDD. Indeed, Nabak et al. [17] reported the suntan index as the significant predictor of VDD. Since those risk factor might be counterbalanced, a composite "suntan × sunscreen use index" was employed in the present study to avoid the multicollinearity between

Table 3 The VDDQ-J Score

	Score
Age	
≥ 50 y = ref	0
40 to < 50y	0
< 40 y	5
Sex (M/F)	
M = ref	0
F	8
The season of blood draw	
Summer (July to September) = ref	0
Fall (October to December)	4
Winter (January to March)	7
Exercise habit	
More than twice per week = ref	0
Once per week	0
1 to 2 times per month	5
Never	7
Suntan × Sunscreen use	
Suntan × without sunscreen use = ref	0
Suntan × with sunscreen use	2
Without suntan × without sunscreen use	2
Without suntan × with sunscreen use	9
Sun exposure in the last 3 months	
Always = ref	0
More often than not	0
Sometimes	0
Infrequently	6
Never	9
Intake of fish containing high vitamin D	
≥ 2 per week = ref	0
< 2 per week	9

These individual scores were summed to calculate the total risk score (VDDQ-J score). A score of 54 represents the highest probability of VDD. The combined variable (suntan × sunscreen use) consists of four categories depending on the presence or absence of suntan and with or without sunscreen use

VDDQ-J: Vitamin D deficiency questionnaire for Japanese

suntan and sunscreen use. Then, no suntan with sunscreen use was strongly associated with VDD. Sun exposure has been reported to be related with vitamin D status. In the previous studies, sun exposure was a strong significant predictor for serum 25(OH)D concentration [11, 14, 15]. Brouwer-Brolsma et al. [32] have shown that sun exposure still remained as the significant predictor of VDD even after adjustment by genetic variation that may affect 25(OH)D status. Sun exposure was a significant contributor to VDD in the current study, and it was included in the questionnaire in previous studies [16, 17].

The frequency of intake of fish containing high vitamin D was a significant predictor of VDD in the current study. Although the data on the absolute value of vitamin D intake could not be obtained, it is likely that our data regarding the consumption of fish containing high vitamin D well reflect the actual vitamin D intake, considering that foods containing high vitamin D are extremely limited. In the previous papers, taking vitamin D supplement was associated with a lower probability of VDD [12, 17, 18, 27, 28]. Even if taking vitamin D supplement was included in the multivariate regression model analysis, dietary vitamin D intake remained as the significant positive predictors for circulating concentration of 25(OH)D in the previous study [12]. Thus, dietary vitamin D intake was still considered to be one of the important predictors for VDD.

The validity of our model was evaluated by ROC analysis. In the derivation cohort, AUC exhibited a good value of 0.78. After the external validation of the VDD model, the AUC was still 0.75. Development of questionnaires to predict VDD has been reported from abroad [12, 16–18, 27–30]. In Lopes et al. [30], the clinical independent factors for VDD were female gender, diabetes and season, and an index for VDI based on these had a sensitivity/specificity of 55.9%/72.3% and ROC of 0.685. In models by Tran et al. [28], gender, age, BMI, ambient UVR, time outdoors, physical activity, vitamin D intake, and self-reported health status well predicted VDD (25(OH)D < 10 ng/mL) with AUC of 0.82 in older Australian adults. The model for the prediction of VDD the model by Sohl et al. [27] consisted of 13 predictors: age, sex, smoking, alcohol use, season of draw, vitamin use, habit of bicycling, sporting, and gardening, medication use, presence of appetite, and partner status. AUC, sensitivity/specificity and PPV/NPV were 0.71, 61%/82% and 77.5%/67.1%, respectively. In Bolek-Berquist et al. [18], the significant predictors for VDD (25OHD < 16 ng/mL) in 184 Caucasian young adults were suntan, tanning booth use, and daily ingestion of two or more servings of vitamin D fortified milk, which provided a sensitivity/specificity of 79%/78%. Nabak et al. [17] reported that black race, BMI, suntan within one year, sun exposure in the past 3 months, sunscreen use and supplemental vitamin D intake were the significant predictors of VDD, yielding the sensitivity/specificity of 89%/35% for VDI in 609 postmenopausal women. In our analysis, PPV was quite high suggesting that VDDQ-J score higher than 31 is indicative of VDD with moderate to high accuracy.

Our strength is as follows. First, serum 25(OH)D concentration was measured by a gold standard LC-APCI-MS/MS. In addition, the study subjects were not limited to the elderly but included the young or middle age subjects. Since VDD is prevalent in the younger generation also, our study population is suited for the development of a questionnaire for VDD.

We have to mention some limitations of this study. First, the predicted probability was somewhat lower than

Table 4 Sensitivity and specificity for the prediction of VDD for each value of the score (in the validation cohort)

Cutoff in the VDD score	*N* (%)	Sensitivity	Specificity	PPV	NPV	+LR	−LR
≥ 26	136 (63.3)	0.78 (0.73–0.83)	0.59 (0.52–0.66)	0.74 (0.69–0.79)	0.65 (0.56–0.72)	1.92 (1.51–2.46)	0.37 (0.26–0.52)
≥ 27	131 (60.9)	0.76 (0.71–0.81)	0.62 (0.54–0.69)	0.75 (0.70–0.80)	0.63 (0.55–0.70)	1.98 (1.53–2.38)	0.39 (0.28–0.54)
≥ 28	124 (57.6)	0.72 (0.67–0.77)	0.64 (0.56–0.71)	0.75 (0.70–0.80)	0.60 (0.53–0.67)	2.00 (1.52–2.67)	0.44 (0.33–0.59)
≥ 29	120 (55.8)	0.71 (0.66–0.76)	0.67 (0.60–0.75)	0.77 (0.71–0.82)	0.61 (0.54–0.68)	2.19 (1.63–2.98)	0.43 (0.32–0.57)
≥ 30	114 (53.0)	0.68 (0.63–0.73)	0.70 (0.62–0.77)	0.77 (0.71–0.83)	0.59 (0.53–0.65)	2.26 (1.65–3.15)	0.46 (0.35–0.60)
≥ 31	96 (44.7)	0.61 (0.55–0.65)	0.79 (0.71–0.86)	0.81 (0.74–0.87)	0.57 (0.52–0.62)	2.89 (1.94–4.45)	0.50 (0.41–0.63)
≥ 32	83 (38.6)	0.52 (0.47–0.56)	0.81 (0.74–0.88)	0.81 (0.73–0.87)	0.53 (0.48–0.57)	2.79 (1.79–4.49)	0.59 (0.50–0.72)
≥ 33	75 (34.9)	0.48 (0.43–0.52)	0.85 (0.78–0.91)	0.83 (0.74–0.89)	0.52 (0.48–0.56)	3.18 (1.93–5.44)	0.61 (0.53–0.73)

Cutoff value of VDD predict score, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV), positive likelihood ratio (+LR), negative likelihood ratio (−LR) profiles for the detection of VDD. The numbers in the parentheses show the 95% CI. The cutoff value was calculated as 31 by Youden Index in the derivation cohort

VDD vitamin D deficiency

the observed probability in Q1 and Q2 of the VDDQ-J score, indicating the underestimation of VDD. However, the predicted probability was not different in Q4, Q5. Therefore, the VDDQ-J score was considered to have a good prediction in the participants with a high prevalence of VDD. Second, there were no subjects with their blood draw in the spring. Since the multivariate model was not affected after excluding the season of blood draw, the above lack of data was considered as not impairing the analysis. Finally, our subjects were restricted to those in Kinki area in Japan. Therefore, another study including subjects living in other regions is also needed for further validation of the VDDQ-J score. Despite some limitations, to the best of our knowledge, our study is the first to develop a questionnaire to predict VDD in the general Japanese population. Our questionnaire is simple to use and allows to quickly assess VDD.

In summary, we have developed a questionnaire for predicting VDD and presented the cutoff values for the VDDQ-J score to detect VDD in the Japanese population for the first time. It would be useful in clinical practice and public health. In the future, both validity and reproducibility must be studied further in additional subjects.

Acknowledgements This work was supported by JSPS KAKENHI Grant number 16K16292.

Author contributions We thank Takahito Kitayoshi for helpful support; Kyoko Ebisu, Satoshi Kume, Yusuke Morito, Miho Iwasaki, Kyosuke Watanabe and Yoshiko Takahashi for their contribution for data collection.

Compliance with ethical standards

Conflict of interest All authors have no conflicts of interest.

Statement of human rights All procedures in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

References

1. Cauley JA, Lacroix AZ, Wu L, Horwitz M, Danielson ME, Bauer DC et al (2008) Serum 25-hydroxyvitamin D concentrations and risk for hip fractures. Ann Inter Med 149:242–250
2. Feng Y, Cheng G, Wang H, Chen B (2017) The associations between serum 25-hydroxyvitamin D level and the risk of total fracture and hip fracture. Osteoporos Int 28:1641–1652
3. Shimizu Y, Kim H, Yoshida H, Shimada H, Suzuki T (2015) Serum 25-hydroxyvitamin D level and risk of falls in Japanese community-dwelling elderly women: a 1-year follow-up study. Osteoporos Int 26:2185–2192
4. Brøndum-Jacobsen P, Benn M, Jensen GB, Nordestgaard BG (2012) 25-hydroxyvitamin d levels and risk of ischemic heart disease, myocardial infarction, and early death: population-based study and meta-analyses of 18 and 17 studies. Arterioscler Thromb Vasc Biol 32:2794–2802
5. Gandini S, Boniol M, Haukka J, Byrnes G, Cox B et al (2011) Meta-analysis of observational studies of serum 25-hydroxyvitamin D levels and colorectal, breast and prostate cancer and colorectal adenoma. Int J Cancer 128:1414–1424
6. de Haan K, Groeneveld AB, de Geus HR, Egal M, Struijs A (2014) Vitamin D deficiency as a risk factor for infection, sepsis and mortality in the critically ill: systematic review and meta-analysis. Crit Care 18:660
7. Schöttker B, Jorde R, Peasey A, Thorand B, Jansen EH et al (2014) Vitamin D and mortality: meta-analysis of individual participant data from a large consortium of cohort studies from Europe and the United States. BMJ 348:g3656
8. Okazaki R, Ozono K, Fukumoto S, Inoue D, Yamauchi M et al (2017) Assessment criteria for vitamin D deficiency/insufficiency in Japan: proposal by an expert panel supported by the Research Program of Intractable Diseases, Ministry of Health, Labour and Welfare, Japan, the Japanese Society for Bone and Mineral

Research and the Japan Endocrine Society [Opinion]. J Bone Miner Metab 35:1–5
9. Yoshimura N, Muraki S, Oka H, Morita M, Yamada H et al (2013) Profiles of vitamin D insufficiency and deficiency in Japanese men and women: association with biological, environmental, and nutritional factors and coexisting disorders: the ROAD study. Osteoporos Int 24:2775–2787
10. Nakamura K, Kitamura K, Takachi R, Saito T, Kobayashi R et al (2015) Impact of demographic, environmental, and lifestyle factors on vitamin D sufficiency in 9084 Japanese adults. Bone 74:10–17
11. Millen AE, Wactawski-Wende J, Pettinger M, Melamed ML, Tylavsky FA et al (2010) Predictors of serum 25-hydroxyvitamin D concentrations among postmenopausal women: the Women's Health Initiative Calcium plus Vitamin D clinical trial. Am J Clin Nutr 91:1324–1335
12. Bertrand KA, Giovannucci E, Liu Y, Malspeis S, Eliassen AH et al (2012) Determinants of plasma 25-hydroxyvitamin D and development of prediction models in three US cohorts. Br J Nutr 108:1889–1896
13. Bjørn Jensen C, Thorne-Lyman AL, Vadgård Hansen L, Strøm M, Odgaard Nielsen N et al (2013) Development and validation of a vitamin D status prediction model in Danish pregnant women: a study of the Danish National Birth Cohort. PLoS One 8:e53059
14. Cheng TY, Millen AE, Wactawski-Wende J, Beresford SA, LaCroix AZ et al (2014) Vitamin D intake determines vitamin d status of postmenopausal women, particularly those with limited sun exposure. J Nutr 144:681–689
15. Touvier M, Deschasaux M, Montourcy M, Sutton A, Charnaux N et al (2015) Determinants of vitamin D status in Caucasian adults: influence of sun exposure, dietary intake, sociodemographic, lifestyle, anthropometric, and genetic factors. J Invest Dermatol 135:378–388
16. Deschasaux M, Souberbielle JC, Andreeva VA, Sutton A, Charnaux N et al (2016) Quick and easy screening for vitamin D insufficiency in adults: a scoring system to be implemented in daily clinical practice. Medicine 95:e2783
17. Nabak AC, Johnson RE, Keuler NS, Hansen KE (2014) Can a questionnaire predict vitamin D status in postmenopausal women? Public Health Nutr 17:739–746
18. Bolek-Berquist J, Elliott ME, Gangnon RE, Gemar D, Engelke J et al (2009) Use of a questionnaire to assess vitamin D status in young adults. Public Health Nutr 12:236–243
19. Kuwabara A, Tsugawa N, Okada S, Kogirima M, Tada-Oikawa S et al (2018) Development of a simple questionnaire to assess vitamin D deficiency in Japanese subjects—pilot study- (in Japanese). Vitamin (Japan) 92:303–312
20. Kimura Y, Wada T, Ishine M, Ishimoto Y, Kasahara Y et al (2009) Food diversity is closely associated with activities of daily living, depression, and quality of life in community-dwelling elderly people. J Am Geriate Soc 57:922–924
21. Ishii M, Uenishi K, Ishida H, Kushima Y (2005) Development of the "self–assessment table for calcium intake" and evaluation of its validity. Osteoporos Jpn 13:497–502
22. Report of the Subdivision on Resources the Council for Science and Technology Ministry of Education (in Japanese). (2015) Standard Table of Food Composition in Japan 2015 (seventh revised version) Official Gazette Cooperation of Japan
23. Tsugawa N, Suhara Y, Kamao M, Okano T (2005) Determination of 25-hydroxyvitamin D in human plasma using high-performance liquid chromatography–tandem mass spectrometry. Anal Chem 77:3001–3007
24. Higashi T, Awada D, Shimada K (2001) Simultaneous determination of 25-hydroxyvitamin D2 and 25-hydroxyvitamin D3 in human plasma by liquid chromatography-tandem mass spectrometry employing derivatization with a Cookson-type reagent. Biol Pharm Bull 24:738–743
25. Akobeng AK (2007) Understanding diagnostic tests 3: receiver operating characteristic curves. Acta Paediatr 96:644–647
26. Akter S, Eguchi M, Kurotani K, Kochi T, Kashino I et al (2017) Serum 25-hydroxyvitamin D and metabolic syndrome in a Japanese working population: the Furukawa Nutrition and Health Study. Nutrition 36:26–32
27. Sohl E, Heymans MW, de Jongh RT, den Heijer M, Visser M et al (2014) Prediction of vitamin D deficiency by simple patient characteristics. Am J Clin Nutr 99:1089–1095
28. Tran B, Armstrong BK, McGeechan K, Ebeling PR, English DR et al (2013) Predicting vitamin D deficiency in older Australian adults. Clin Endocrinol 79:631–640
29. Janssen HC, Emmelot-Vonk MH, Verhaar HJ, van der Schouw YT (2013) Determinants of vitamin D status in healthy men and women aged 40–80 years. Maturitas 74:79–83
30. Lopes JB, Fernandes GH, Takayama L, Figueiredo CP, Pereira RM (2014) A predictive model of vitamin D insufficiency in older community people: from the São Paulo Aging & Health Study (SPAH). Maturitas 78:335–340
31. Looker AC, Pfeiffer CM, Lacher DA, Schleicher RL, Picciano MF et al (2008) Serum 25-hydroxyvitamin D status of the US population: 1988–1994 compared with 2000–2004. Am J Clin Nutr 88:1519–1527
32. Brouwer-Brolsma EM, Vaes AMM, van der Zwaluw NL, van Wijngaarden JP, Swart KMA et al (2016) Relative importance of summer sun exposure, vitamin D intake, and genes to vitamin D status in Dutch older adults: the B-PROOF study. J Steroid Biochem Mol Biol 164:168–176