Eur J Pediatr (2013) 172:1607–1617
DOI 10.1007/s00431-013-2119-z

ORIGINAL ARTICLE

Vitamin D status and predictors of hypovitaminosis D in Italian children and adolescents: a cross-sectional study

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Received: 8 June 2013 / Accepted: 23 July 2013 / Published online: 20 August 2013

Abstract Hypovitaminosis D affects children and adolescents all around the world. Italian data on vitamin D status and risk factors for hypovitaminosis D during pediatric age are lacking. Six hundred fifty-two children and adolescents (range 2.0–21.0 years) living in the northwestern area of Tuscany were recruited at the Department of Pediatrics, University Hospital Pisa. None of them had received vitamin D supplementation in the previous 12 months. 25-hydroxyvitamin D (25-OH-D) and parathyroid hormone (PTH) levels were analyzed in all subjects. Severe vitamin D deficiency was defined as serum levels of 25-OH-D<25.0 nmol/L (10.0 ng/mL) and vitamin D deficiency as<50.0 nmol/L (20.0 ng/mL). Serum 25-OH-D levels of 50.0–74.9 nmol/L (20.0–29.9 ng/mL) indicated vitamin D insufficiency, whereas 25-OH-D levels≥75.0 nmol/L (30.0 ng/mL) were considered sufficient. Hypovitaminosis D was defined as 25-OH-D levels<75.0-nmol/L (30.0 ng/mL). The median serum 25-OH-D level was 51.8 nmol/L, range 6.7–174.7 (20.7 ng/mL, range 2.7–70.0), with a prevalence of vitamin D deficiency, insufficiency, and sufficiency of 45.9, 33.6, and 20.5 %, respectively. The prevalence of severe vitamin D deficiency was 9.5 %. Adolescents had lower median 25-OH-D levels (49.8 nmol/L, range 8.1–174.7; 20.0 ng/mL, range 3.2–70.0) than children (55.6 nmol/L, range 6.8–154.6; 22.3 ng/mL, range 2.7–61.9, $p=0.006$). Non-white individuals ($n=37$) had median serum 25-OH-D levels in the range of deficiency (28.2 nmol/L, range 8.1–86.2; 11.3 ng/mL, range 3.2–34.5), with 36/37 having hypovitaminosis D. Logistic regression showed significant increased risk of hypovitaminosis D in the following: blood samples taken in winter (odds ratio (OR) 27.20), spring (OR 26.44), and fall (OR 8.27) compared to summer; overweight (OR 5.02) and obese (OR 5.36) subjects compared to individuals with normal BMI; low sun exposure (OR 8.64) compared to good exposure, and regular use of sunscreens (OR 7.06) compared to non-regular use. Gender and place of residence were not associated with vitamin D status. The 25-OH-D levels were inversely related to the PTH levels ($r=-0.395$, $p<0.0001$). Sixty-three out of the 652 (9.7 %) subjects showed secondary hyperparathyroidism. *Conclusion* Italian children and adolescents who were not receiving vitamin D supplementation had high prevalence of hypovitaminosis D. Careful identification of factors affecting vitamin D status is advisable to promptly start vitamin D supplementation in children and adolescents.

Keywords Vitamin D deficiency · Vitamin D insufficiency · 25-hydroxivitamin D · Parathyroid hormone · Children · Adolescents

Abbreviations

25-OH-D	25-hydroxyvitamin D
BMI	body mass index
OR	odds ratio

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PTH	parathyroid hormone
SPF	sun protector factor

Conversion factors (international units=conventional units)

25-hydroxyvitamin D	nmol/L=ng/mL×2.496
Parathyroid hormone	pg/mL=ng/L
Calcium	mmol/L=mg/dL×0.25
Phosphate	mmol/L=mg/dL×0.323

Introduction

Nutritional rickets, the most evident consequence of vitamin D deficiency, still affects children and adolescents worldwide [41]. More often, hypovitaminosis D may develop subtly and remain undetected, negatively affecting bone health and muscle function [2, 47]. Serum 25-hydroxyvitamin D (25-OH-D) concentration is the best marker of vitamin D status as it is the major circulating form of vitamin D, reflecting both the amount produced in the skin after sun exposure and the amount contained in foods [27]. Sunlight is the main source of vitamin D and contributes up to 90–95 % of vitamin supply, while the number of foods naturally containing a significant quantity of vitamin D is very limited except for some oily fishes and sun-exposed mushrooms, rarely consumed by children and adolescents [30]. The efficacy of sunlight promotion of vitamin D synthesis is influenced by several factors such as latitude, seasons, and time of the day [34]. Cutaneous vitamin D synthesis is also affected by skin pigmentation and topical application of sunscreens: non-white children need more time of sun exposure to obtain the same amount of vitamin D than white ones [21]. Furthermore, sunscreens with a sun protector factor (SPF) of at least 15 practically prevent skin vitamin D synthesis [27].

There is still no agreement on which serum 25-OH-D level should define a sufficient vitamin D status. The Endocrine Society Clinical Practice Guidelines suggested to consider deficiency when 25-OH-D<50 nmol/L (20 ng/mL), insufficiency if the 25-OH-D levels are between 52.5 and 72.5 nmol/L (21–29 ng/mL), and sufficiency for 25-OH-D concentration≥75 nmol/L (30 ng/mL) [31], while 25-OH-D levels<25 nmol/L (10 ng/mL) are generally considered as cut-off for severe vitamin D deficiency [8]. The relationship between serum concentrations of 25-OH-D and parathyroid hormone (PTH) has been used as a possible way to define vitamin D status. Conflicting results emerged from studies conducted in adults, while few studies have been performed in pediatric subjects [48].

Several studies evaluated the prevalence of vitamin D deficiency and insufficiency during pediatric age, reporting high percentages of hypovitaminosis D all around the world [54]. Limited data on the prevalence of hypovitaminosis D are available among healthy Italian children and adolescents, and there is no study assessing the PTH levels in these age groups [10, 35-37, 39]. Furthermore, there is paucity of data on the predictors of vitamin D status in Italian children. We investigated vitamin D status in Italian children and adolescents, evaluating the role of some accepted predictors of vitamin D status: age, gender, residence, season the blood sample was taken, ethnicity, body mass index (BMI), sun exposure, and use of sunscreens. The aims of this study were to (1) evaluate the prevalence of hypovitaminosis D in Italian children and adolescents living in the northwestern area of Tuscany, Central Italy, (2) identify risk factors for hypovitaminosis D, and (3) assess the relationship between vitamin D status and PTH levels.

Materials and methods

We enrolled 652 Italian children (2.0–10.9 years) and adolescents (11.0–21.0 years) recruited at the Pediatric Unit of the University of Pisa in a 24-month period (October 2010 to September 2012). All of them were living in the northwestern area of Tuscany, Central Italy (latitude between 43°N and 44°N). None had diseases known to affect vitamin D metabolism, and none had received vitamin D supplementation in the 12 months prior to the enrolment to the study. Ethnicity was categorized as white or non-white. Auxological assessment was available for 496 subjects (76.1 %); standing height and body weight were measured with a wall-mounted stadiometer and a mechanical balance. Both height and weight were the mean of three measurements. BMI was calculated using the formula weight (kg)/height $(m)^2$. Height, weight, and BMI were expressed as *Z*-score according to the LMS method of Cole and Green [12]. Weight status was categorized as normal, overweight, and obese according to Cole et al. for subjects under 18 years [11] and according to the World Health Organization for subjects aged 18–21 years (BMI<25.0, 25.0–29.9, and ≥30.0 kg/m^2, respectively). A detailed interview was administered to 385 individuals (59.0 %) to provide general information about lifestyle and dietary habits. Residence was categorized as urban or rural. For children and adolescents enrolled in fall, winter, and spring, sun exposure was evaluated as the number of days with significant exposure to sunlight during the summer months prior to the enrolment in the study. Conversely, for children included in the study during summer, we evaluated sun exposure during the same season of enrolment. Indeed, we had previously demonstrated that no vitamin D is produced as a result of sun exposure at the latitude of Pisa during late fall, winter, and the beginning of spring [43]. Adequate sun exposure was defined by Holick [27] as the exposure of the arms

and legs for 5–30 min (depending on season, latitude, and skin pigmentation) between 10 a.m. and 3 p.m. twice a week. Based on this assumption, we arbitrarily defined significant sun exposure as the exposure of the arms and legs for at least 15 min between 10 a.m. and 3 p.m. without the application of sunscreens. Sun exposure was categorized as poor (less than 15 days with significant exposure to sunlight), moderate (15–30 days), and good (more than 30 days). We evaluated the use of sunscreens, defining it as regular when a sunscreen with a SPF of 15 or higher was always applied at least 30 min before the exposure to sunlight and reapplied every 2 h and after swimming, as recommended by the American Academy of Pediatrics [13]. Depending on the age, the subject and/or his/her parents were interviewed with the use of food models or serving containers to assist in estimating serving size. We evaluated the diet of 1 week, and the resulting nutrient analysis was performed with the software WinFood© 1.5 (Medimatica, Teramo, Italy) to assess daily dietary intakes of vitamin D and calcium. The characteristics of the enrolled subjects are summarized in Table 1, and the distribution of the presumed risk factors for hypovitaminosis D by age groups is reported in Table 2. A higher percentage of females regularly used sunscreens compared to males (39.7 vs. 27.4 %, $p=0.011$), while the distribution of the other presumed predictors of hypovitaminosis D did not differ by gender (data not shown).

Table 1 Characteristics of the subjects

	Number	Median (range)	*p* Value
Age (years)			<0.0001
Entire sample	652	12.0 (2.0–21.0)	
Children	283	8.0 (2.0–10.9)	
Adolescents	369	15.1 (11.0–21.0)	
Stature (SDS)			0.106
Entire sample	496	−0.5 (−2.1–2.3)	
Children	178	−0.2 (−2.1–2.3)	
Adolescents	318	−0.6 (−2.1–2.3)	
Weight (SDS)			0.144
Entire sample	496	0.4 (−2.1–3.9)	
Children	178	0.8 (−2.1–3.8)	
Adolescents	318	0.3 (−2.1–3.9)	
BMI (SDS)			0.047
Entire sample	496	0.7 (−2.2–3.9)	
Children	178	1.0 (−2.2–3.8)	
Adolescents	318	0.7 (−2.2–3.9)	
Calcium intake (mg/day)			0.173
Entire sample	385	603.8 (200.2–1,280.9)	
Children	145	592.7 (223.4–998.5)	
Adolescents	240	614.4 (200.2–1,280.9)	
Vitamin D intake (IU/day)			0.0005
Entire sample	385	14.0 (2.4–282.8)	
Children	145	10.8 (2.4–223.2)	
Adolescents	240	15.2 (2.4–282.8)	

Table 2 Distribution of presumed risk factors for hypovitaminosis D by age

	Children Number/total (%)	Adolescents Number/total (%)	*p* Value
Gender			0.595
Male	144/283 (50.9)	180/369 (48.8)	
Female	139/283 (49.1)	189/369 (51.2)	
Residence			0.002
Urban	125/283 (44.2)	208/369 (56.4)	
Rural	158/283 (55.8)	161/369 (43.6)	
Season blood sample was taken			0.0003
Winter	95/283 (33.5)	114/369 (30.9)	
Spring	40/283 (14.1)	102/369 (27.6)	
Summer	44/283 (15.6)	53/369 (14.4)	
Fall	104/283 (36.8)	100/369 (27.1)	
Ethnicity			0.018
White	260/283 (91.9)	355/369 (96.2)	
Non-white	23/283 (8.1)	14/369 (3.8)	
Weight status			0.121
Normal	98/178 (55.1)	190/318 (59.8)	
Overweight	30/178 (16.9)	64/318 (20.1)	
Obese	50/178 (28.0)	64/318 (20.1)	
Sun exposure			0.135
Low	22/145 (15.2)	42/240 (17.5)	
Moderate	31/145 (21.4)	70/240 (29.2)	
Good	92/145 (63.4)	128/240 (53.3)	
Use of sunscreens			0.026
Regular	59/145 (40.7)	71/240 (29.6)	
Non-regular	86/145 (59.3)	169/240 (70.4)	

A fasting blood sample was obtained from all to evaluate the 25-OH-D and PTH levels. Vitamin D deficiency was defined as serum levels of 25-OH-D<50.0 nmol/L (20.0 ng/mL); serum 25-OH-D levels of 50.0–74.9 nmol/L (20.0–29.9 ng/mL) were considered as vitamin D insufficiency, whereas levels of 75.0 nmol/L (30.0 ng/mL) or greater were considered sufficient. Severe vitamin D deficiency was defined as 25-OH-D levels<25.0 nmol/L (10 ng/mL). Serum levels of 25-OH-D less than 75.0 nmol/L (30.0 ng/mL) identified hypovitaminosis D and PTH levels≥65.0 ng/L were suggestive of hyperparathyroidism. 25-hydroxyvitamin D in serum was quantitatively determined by radioimmunoassay (25-hydroxyvitamin $D^{125}I$ RIA Kit, DiaSorin, intra- and inter-assay CV=11 %). Biologically active intact hPTH 1–84 in plasma was quantitatively determined by immunoradiometric assay (N-tact® PTH SP Irma Kit, DiaSorin, intra-assay CV=3.6 %, inter-assay CV=4.9 %). In a subgroup of

Table 3 Serum 25-OH-D levels and vitamin D status related to presumed risk factors for hypovitaminosis D

	Number/total (%)	25-OH-D (nmol/L) Median (range)	25-OH-D (ng/mL) Median (range)	*p*	Number/total (%) with 25-OH-D <50.0 nmol/L (20.0 ng/mL)	Number/total (%) with 25-OH-D 50.0–74.9 nmol/L (20.0–29.9 ng/mL)	Number/total (%) with 25-OH-D ≥75.0 nmol/L (30.0 ng/mL)	*p*
Age				0.006				0.019
Children	283/652 (43.4)	55.6 (6.8–154.6)	22.3 (2.7–61.9)		114/283 (40.3)	99/283 (35.0)	70/283 (24.7)	
Adolescents	369/652 (56.6)	49.8 (8.1–174.7)	20.0 (3.2–70.0)		185/369 (50.1)	120/369 (32.5)	64/369 (17.4)	
Sex				0.897				0.175
Male	324/652 (49.7)	51.2 (6.8–174.7)	20.5 (2.7–70.0)		151/324 (46.6)	99/324 (30.6)	74/324 (22.8)	
Female	328/652 (51.3)	52.3 (8.1–174.3)	20.9 (3.2–69.8)		148/328 (45.1)	120/328 (36.6)	60/328 (18.3)	
Residence				0.994				0.988
Urban	333/652 (51.1)	51.6 (6.8–174.7)	20.7 (2.7–70.0)		153/333 (46.0)	111/333 (33.3)	69/333 (20.7)	
Rural	319/652 (49.9)	52.9 (8.1–147.1)	20.8 (3.2–58.9)		146/319 (45.8)	108/319 (33.8)	65/319 (20.4)	
Season blood sample was taken				<0.0001				<0.0001
Winter (January–March)	209/652 (32.1)	44.1 (6.8–147.1)	17.7 (2.7–58.9)		120/209 (57.4)	62/209 (29.7)	27/209 (12.9)	
Spring (April–June)	142/652 (21.8)	47.8 (12.1–122.3)	19.2 (4.8–49.0)		79/142 (55.6)	47/142 (33.1)	16/142 (11.3)	
Summer (July–September)	97/652 (14.9)	67.1 (10.8–174.3)	27.1 (4.3–69.8)		25/97 (25.8)	32/97 (33.0)	40/97 (41.2)	
Fall (October–December)	204/652 (31.2)	56.6 (8.7–174.7)	22.7 (3.5–70.0)		75/204 (36.8)	78/204 (38.2)	51/204 (25.0)	
Ethnicity				<0.0001				<0.0001
White	615/652 (94.3)	53.2 (6.8–174.7)	21.3 (2.7–70.0)		266/615 (43.3)	216/615 (35.1)	133/615 (21.6)	
Non-white	37/652 (5.7)	28.2 (8.1–86.2)	11.3 (3.2–34.5)		33/37 (89.2)	3/37 (8.1)	1/37 (2.7)	
Weight status				0.020				0.001
Normal	288/496 (58.1)	53.0 (13.5–174.7)	21.2 (5.4–70.0)		128/288 (44.4)	89/288 (30.9)	71/288 (24.7)	
Overweight	94/496 (19.0)	50.5 (10.0–107.9)	20.2 (4.0–43.2)		45/94 (47.9)	38/94 (40.4)	11/94 (11.7)	
Obese	114/496 (22.9)	48.8 (10.8–94.6)	19.6 (4.3–37.9)		59/114 (51.8)	45/114 (39.5)	10/114 (8.7)	
Solar exposure				<0.0001				<0.0001
Low	64/385 (16.6)	36.1 (10.0–97.7)	14.4 (4.0–25.8)		50/64 (78.1)	11/64 (17.2)	3/64 (4.7)	
Moderate	101/385 (26.2)	53.2 (13.5–174.7)	21.3 (5.4–70.0)		41/101 (40.6)	40/101 (39.6)	20/101 (19.8)	
Good	220/385 (57.2)	58.3 (17.5–154.6)	23.3 (7.0–61.9)		81/220 (36.8)	67/220 (30.5)	72/220 (32.7)	
Use of sunscreens								
Low sun exposure				0.749				0.641
Regular	37/64 (57.8)	34.7 (10.0–97.7)	13.9 (4.0–39.1)		29/37 (78.4)	7/37 (18.9)	1/37 (2.7)	
Non-regular	27/64 (42.2)	37.5 (17.7–87.2)	15.0 (7.1–34.9)		21/27 (77.8)	4/27 (14.8)	2/27 (7.4)	
Moderate sun exposure				0.565				0.008
Regular	39/101 (38.6)	53.9 (13.5–90.8)	21.6 (5.4–36.4)		14/39 (35.9)	22/39 (56.4)	3/39 (7.7)	
Non-regular	62/101 (61.4)	52.8 (17.2–174.8)	21.1 (6.9–70.0)		27/62 (43.5)	18/62 (29.0)	17/62 (27.5)	
Good sun exposure				<0.0001				<0.0001
Regular	54/220 (24.6)	47.4 (17.5–87.0)	19.0 (7.0–34.8)		30/54 (55.6)	20/54 (37.0)	4/54 (7.4)	
Non-regular	166/220 (75.4)	66.4 (18.1–154.6)	26.6 (7.2–61.9)		51/166 (30.7)	47/166 (28.3)	68/166 (41.0)	

subjects, we also evaluated serum levels of total calcium (n=564, 86.5 %) and phosphate (n=485, 74.4 %). Written informed consent to participate in the study was obtained from all the participants of the study or their parents, as requested. The study was approved by the Ethics Committee for Human Investigation at our institution.

Statistical analyses

All continuous variables were not normally distributed; thus, non-parametric Mann–Whitney test and Kruskal–Wallis test were used to compare the groups. The data were reported as median and range. Chi-square test was used to compare the groups of categorical variables. A multiple logistic regression analysis was performed to study the association between each presumed risk factor and hypovitaminosis D. Spearman's correlation coefficients were adopted to explore the relationship between serum 25-OH-D levels and age, BMI, biochemical findings, and dietary calcium and vitamin D intake. All statistical analyses were carried out using the Statistical Package of Social Sciences (Chicago, IL, USA) for Windows software program version 19.0. A p value <0.05 was considered significant.

Results

Vitamin D status and presumed risk factors for hypovitaminosis D

Analyzing the entire sample, the median serum 25-OH-D level was 51.8 nmol/L, and the range was 6.7–174.7 (20.7 ng/mL, range 2.7–70.0). Overall, 79.5 % of the subjects showed hypovitaminosis D (deficiency 45.9 % and insufficiency 33.6 %). Sixty-two individuals (9.5 %) had severe vitamin D deficiency.

Table 3 summarizes the serum 25-OH-D levels and vitamin D status in relation to the presumed risk factors for hypovitaminosis D. Adolescents showed lower circulating serum 25-OH-D levels and a higher prevalence of hypovitaminosis D than children. However, the prevalence of severe vitamin D deficiency was the same among the age groups (9.5 %).

Significant seasonal differences in vitamin D status have been detected; particularly, we observed higher prevalence of severe vitamin D deficiency during winter and spring (winter 31/209, 14.8 %; spring 20/142, 14.1 %; summer 1/97, 1.0 %; fall 10/204, 4.9 %; $p<0.0001$). Figure 1 shows the trend of serum 25-OH-D levels during the year, with higher levels in July (68.0 nmol/L, range 34.7–174.3; 27.2 ng/mL, range 13.9–69.8) and August (65.4 nmol/L, range 26.0–144.8; 26.2 ng/mL, range 10.4–58.0), and lower levels in February (41.4 nmol/L, range 6.8–87.4; 16.6 ng/mL, range 2.7–35.0) and March (40.4 nmol/L, range 8.1–147.1; 16.2 ng/mL, range 3.24–58.9).

Ethnicity was strongly associated with vitamin D status; indeed, only one adolescent of non-white ethnicity had vitamin D sufficiency, and median serum 25-OH-D levels were double in white subjects compared with non-white ones. Obese and overweight children and adolescents had significantly lower vitamin D levels than subjects with normal BMI. Serum 25-OH-D levels were strongly associated with sun exposure: individuals who reported low exposure to sunlight had lower vitamin D levels and higher prevalence of hypovitaminosis D. Regular use of sunscreens also affected vitamin D status of children and adolescents, reporting moderate or good sun exposure. Gender and residence did not affect vitamin D status. Figures 2 and 3 show the seasonal variation of 25-OH-D levels related to sun exposure and use of sunscreens, respectively.

The logistic regression for the presumed predictors of vitamin D status is represented in Table 4. Subjects who underwent blood sampling in winter, spring, or fall had an odds ratio (OR) of having hypovitaminosis D of 27, 26, or 8 times higher than those who were evaluated in summer, confirming marked seasonal variation in vitamin D status. Overweight and obese children and adolescents had an OR of hypovitaminosis D five times higher than those with normal BMI. Individuals with low sun exposure had an OR of hypovitaminosis D eight times higher than those with good sun exposure. The regular use of sunscreens was associated with a seven times higher OR of hypovitaminosis D. Non-white children and adolescents were at higher risk for severe vitamin D deficiency (OR 9.42, C.I. 95 % 4.60–19.29, $p<0.0001$) and for vitamin D deficiency (OR 10.82, C.I. 95 % 3.79–30.93, $p<0.0001$) than white subjects, as assessed by chi-square test. Adolescent age, female gender, and urban

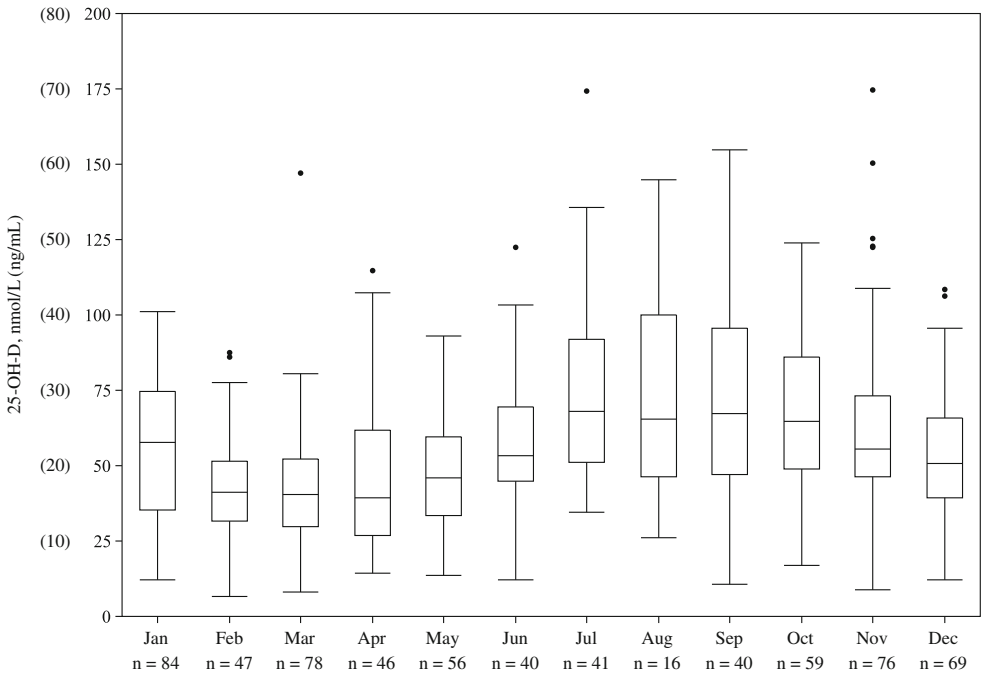

Fig. 1 Box plot of serum 25-OH-D levels according to month the blood samples were taken. $p<0.0001$ between groups

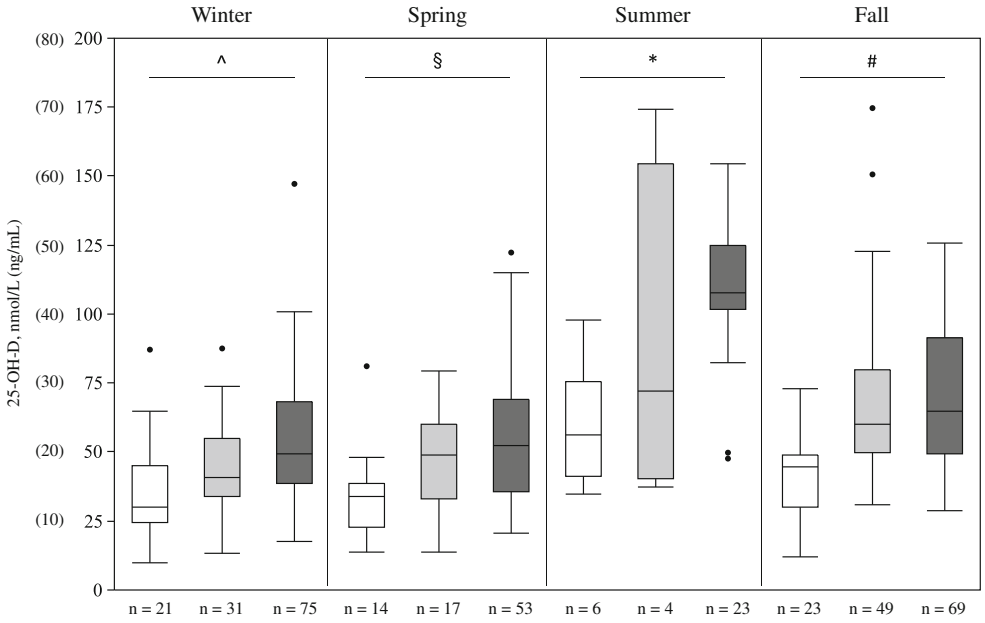

Fig. 2 Box plot of seasonal variation of serum 25-OH-D levels according to sun exposure. *White boxes*, low sun exposure; *light gray boxes*, moderate sun exposure; *dark gray boxes*, good sun exposure. *Caret symbol* denotes $p=0.0005$, *section sign* $p=0.004$, *asterisk* $p=0.0065$, *number sign* $p<0.0001$

residence were not associated with an increased risk of hypovitaminosis D.

Vitamin D status and calcium and phosphate metabolism

Overall, 9.7 % (63/652) of the subjects showed secondary hyperparathyroidism. Elevated PTH was detected in 21.1 % (52/247) of individuals with vitamin D deficiency. Notably, hyperparathyroidism was found in 37.1 % (23/62) of subjects with severe vitamin D deficiency. Secondary hyperparathyroidism was also detected in 5.3 % (11/208) of subjects with vitamin D insufficiency. No subjects with vitamin D sufficiency had elevated PTH.

Serum PTH levels were significantly different, depending on vitamin D status (severe deficiency 51.0 ng/L, range 17.2–138.6; deficiency 39.9 ng/L, range 11.7–139.3; insufficiency 31.0 ng/L, range 10.0–95.4; sufficiency 24.0 ng/L, range 10.0–52.2; $p<0.0001$). Serum PTH levels also differed by age (children 29.0 ng/L, range 10.0–138.6; adolescents 35.0 ng/L, range 10.0–139.3; $p<0.0001$), season the blood sample was

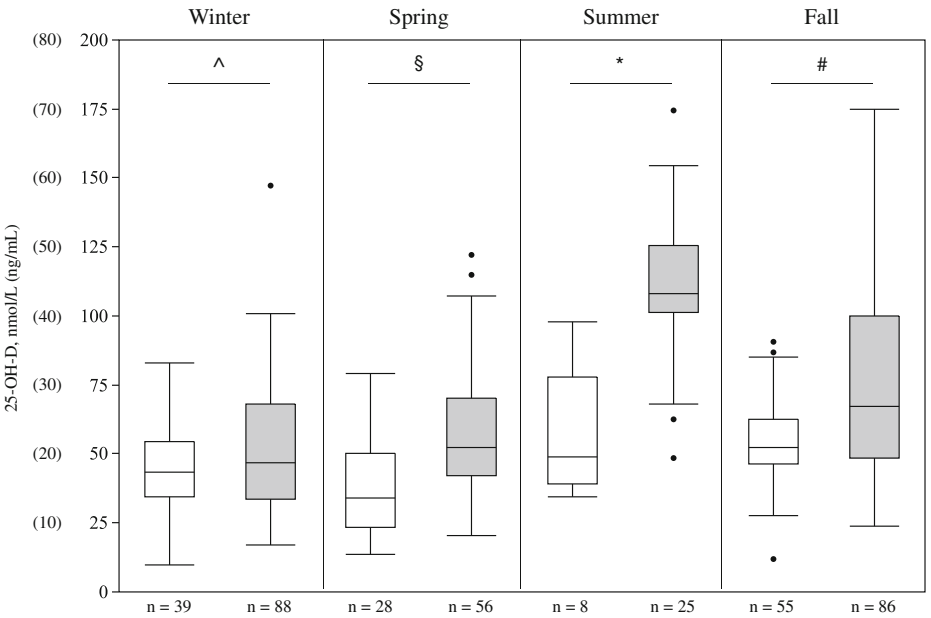

Fig. 3 Box plot of seasonal variation of serum 25-OH-D levels according to use of sunscreens. *White boxes* signify regular use. *Gray boxes* represent non-regular use. *Caret symbol* denotes $p=0.1701$, *section sign* $p<0.0001$, *asterisk* $p=0.0002$, *number sign* $p=0.0005$

Table 4 Logistic regression for presumed risk factors for hypovitaminosis D

	B (SE)	OR	C.I. 95 %	*p* Value
Age (adolescence vs. childhood)	0.24 (0.35)	1.27	0.64–2.53	0.502
Sex (female vs. male)	−0.05 (0.32)	0.96	0.52–1.78	0.886
Residence (urban vs. rural)	0.11 (0.33)	1.12	0.59–2.11	0.737
Season blood sample was taken				
Summer		1 (reference)		
Fall	2.11 (0.60)	8.27	2.59–26.45	<0.0001
Winter	3.30 (0.63)	27.20	7.93–93.31	<0.0001
Spring	3.28 (0.66)	26.44	7.25–96.48	<0.0001
BMI				
Normal		1 (reference)		
Overweight	1.61 (0.54)	5.02	1.73–14.53	0.003
Obese	1.68 (0.78)	5.36	1.17–24.57	0.031
Sun exposure				
Good		1 (reference)		
Moderate	0.35 (0.36)	1.42	0.70–2.88	0.329
Low	2.16 (0.71)	8.64	2.15–34.70	0.002
Use of sunscreens (regular vs. non-regular)	1.95 (0.46)	7.06	2.86–17.40	<0.0001
Constant	−2.46 (0.68)	0.09		<0.0001

Ethnicity was not included in the analysis because only one non-white subject had vitamin D sufficiency

C.I. coefficient interval

χ^2 =98.81 p<0.0001

Cox R^2 =0.244

Nagelkerke R^2 =0.384

Hosmer and Lemeshow test p=0.350

taken (winter 39.1 ng/L, range 13.3–139.3; spring 34.0 ng/L, range 13.3–97.6; summer 29.0 ng/L, range 11.0–69.0; fall 28.4 ng/L, range 10.0–103.0; p<0.0001), sun exposure (low 38.7 ng/L, range 10.0–103.0; moderate 33.0 ng/L, range 11.5–139.3; good 32.2 ng/L, range 10.0–138.6; p=0.034), and use of sunscreens (regular 35.0 ng/L, range 10.0–138.6; non-regular 32.8 ng/L, range 10.0–139.3; p=0.034). Blood samples obtained during the winter–spring period was associated with an increased OR of hyperparathyroidism of three times (OR 3.33, C.I. 95 % 1.80–6.16, p<0.0001 by chi-square test) in comparison with blood samples obtained during summer–fall. Non-white subjects had higher non-significant serum PTH levels than white individuals (35.0 ng/L, range 11.6–82.0; and 32.2 ng/L, range 10.0–139.3, respectively; p=0.453) but had higher significant prevalence of hyperparathyroidism (non-white 11/37, 29.7 %; white 53/615, 8.5 %; p<0.0001) with an increased OR of nearly five times (OR 4.58, C.I. 2.14–9.80, p<0.0001 by chi-square test). Gender, residence, and weight status did not affect PTH levels (data not shown).

We found a slight but significant difference in calcium levels according to vitamin D status (deficiency n=260, 2.42 mmol/L, range 2.13–2.68; insufficiency n=184, 2.43 mmol/L, range 2.19–2.70; sufficiency n=120, 2.45 mmol/L, range 2.17–2.65; p=0.033), while there was no difference in phosphate

Table 5 Correlations between serum 25-OH-D levels and auxological and biochemical data

	Unadjusted		Adjusted[a]		Adjusted[b]	
	r	*p*	*r*	*p*	*r*	*p*
Age (years)	−0.097	0.013				
BMI (SDS)	−0.123	0.006	−0.181	0.003		
PTH (ng/L)	−0.395	<0.0001	−0.301	<0.0001	−0.275	<0.0001
Calcium (mmol/L)	0.162	<0.0001	0.114	0.057	0.112	0.063
Phosphorus (mmol/L)	0.058	0.201	−0.014	0.823	−0.019	0.749
Calcium intake (mg/day)	−0.082	0.110				
Vitamin D intake (IU/day)	0.047	0.362				

[a] Adjusted for age, season blood sample was taken, ethnicity, calcium intake, vitamin D intake, sun exposure, and use of sunscreens

[b] Adjusted for BMI SDS, age, season blood sample was taken, ethnicity, calcium intake, vitamin D intake, sun exposure, and use of sunscreens

levels (data not shown). Serum 25-OH-D levels were inversely related to age, BMI, and PTH, and positively related to calcium levels (Table 5). The relationship between vitamin D and PTH was significant, also adjusting for potential confounders.

Discussion

To our knowledge, this is the largest pediatric Italian series assessing the prevalence of hypovitaminosis D, searching for a correlation between vitamin D status and several presumed risk factors and evaluating the relationship between PTH and 25-OH-D levels.

Although we identified a small but considerable group of subjects with severe vitamin D deficiency, we nevertheless observed a high prevalence of vitamin D deficiency and insufficiency, as only one child or adolescent out of five had a sufficient vitamin D status. These results are comparable to those reported by other studies [1, 24, 26, 33, 46].

Few studies have evaluated vitamin D status in Italian pediatric population [10, 35-37, 39]. Analyzing the laboratory database of the University Hospital of Verona (45°N), Lippi et al. reported that 6.2 % of 192 children and adolescents (aged 1 week–17.9 years) had serum 25-OH-D levels<27.5 nmol/L (11 ng/mL) [36]. Marrone et al. evaluated 93 subjects (aged 2 months–18.3 years) afferent to the Pediatric Department of Udine (46°N), reporting 54.8 % of subjects with serum 25-OH-D levels<50 nmol/L (20 ng/mL). In this series, a significant percentage of subjects (33 %) were receiving vitamin D supplementation at the time of evaluation, and this could have possibly influenced their results [37]. Recently, Lippi et al. assessed vitamin D status in 270 presumably healthy Caucasian adolescents, aged 12.0–20.9 years, acquiring data from the database of a local Laboratory Information System in the northeast of Italy over a 3-year period. They reported a lower prevalence of vitamin D deficiency (19.3 %) and a similar prevalence of vitamin D insufficiency (36.3 %) in comparison to our series [35]. This discrepancy may be explained because in this study, vitamin D supplementation had not been thoughtfully checked in all subjects, possibly biasing the results. Moreover, seasonal distribution of blood samples was not reported, making it difficult to compare their results with our study. Finally, data regarding Italian pediatric population may be obtained from the Healthy Lifestyle in Europe by Nutrition in Adolescence (HELENA) study conducted in nine European countries [22]. Overall, the HELENA study (n=1,006 aged 12.5–17.5 years) reported that the prevalence of vitamin D deficiency (42 %) and insufficiency (39 %) was high among European adolescents. Enrolled Italian adolescents (n=104, aged 12.6–17.4 years) living in Rome (42°N) had a prevalence of vitamin D deficiency of 26.4 %. Furthermore, the HELENA study also did not account for possible vitamin D supplementation nor personal sun exposure habits. Several studies reported high percentages of vitamin D deficiency and insufficiency during adolescence [15, 22, 23, 26, 45, 46, 49]. In the present study, adolescents had a slightly but significantly higher prevalence of hypovitaminosis D than children. Sun exposure and weight status did not differ among the age groups, but more adolescents were enrolled during winter and spring than children, partly explaining our results.

Contrary to other reports [4, 5, 17], we did not observe any difference in vitamin D status in relation to gender and residence. In our series, females had similar serum 25-OH-D levels and a higher not significant prevalence of hypovitaminosis D than males. Indeed, except for the regular use of sunscreens, the presumed predictors of hypovitaminosis D did not differ by sex.

Ultraviolet radiation efficacy in promoting skin vitamin D synthesis varies according to season [34], and between 23.5° and 66.5° of latitude sunlight-derived vitamin D production is ineffective for at least 1 month during the year [7]. Our data confirmed that the prevalence of hypovitaminosis D was higher during winter and spring in Italian children and adolescents, as reported by Marrone et al. [37] and other European studies [1, 6, 25, 55]. The serum 25-OH-D levels peaked in summer and physiologically reached their nadir in February and March, highlighting that wintry vitamin D status depends on the amount of vitamin D produced and stored during the previous summer. Seasonal variation may be taken in particular consideration because we reported that children and adolescents had higher prevalence of severe vitamin D deficiency during winter and spring. Moreover, we observed an increased threefold OR of secondary hyperparathyroidism during winter and spring in comparison with summer and fall. The results of our study stress the need to carefully evaluate the administration of vitamin D supplementation during winter and spring in Italian children and adolescents. However, other targeted studies are needed before giving national recommendations on supplementation.

Ethnicity was a strong determinant of vitamin status, in agreement with other reports [1, 37, 45, 51, 52]. In the present study, non-white subjects had extremely low 25-OH-D levels, close to severe deficiency. Dark-skinned subjects require a higher time of exposure to sunlight compared to Caucasian subjects to produce the same amount of vitamin D [21]. Moreover, non-white immigrant or adopted children frequently had minimal exposure due to cultural reasons [9, 44]. As non-white children and adolescents had an 11-fold increased risk of vitamin D deficiency and a nearly 5-fold increased risk of secondary hyperparathyroidism, they may benefit from vitamin D supplementation.

Weight status also influenced vitamin D status as we found a significant difference in the prevalence of hypovitaminosis D in relation to BMI. Moreover, we demonstrated that overweight and obese subjects had a fivefold increased OR of hypovitaminosis D, and we confirmed a negative correlation

between 25-OH-D levels and BMI. A few recent pediatric series reported a high prevalence of hypovitaminosis D in obese children and adolescents [3, 19, 40, 42, 53]. Vitamin D is a fat-soluble vitamin, possibly stored in the adipose tissue with decreased bioavailability [16, 57]. Decreased sun exposure due to sedentary lifestyle may contribute to explain the lower 25-OH-D levels seen in obese children [40].

In Italian children and adolescents, exposure to sunlight was an important predictor of vitamin D status, while the amount of vitamin D obtained from diet was negligible. We also took into account the use of sunscreens, considering that it notably affects vitamin D production [27, 28]. Indeed, in subjects with good sun exposure, the regular use of sunscreens was associated with significant lower 25-OH-D levels and higher prevalence of hypovitaminosis D. Both low sun exposure and regular application of sunscreens were associated with an increased OR of hypovitaminosis D of 8 and 7, respectively. Moreover, we found that the effect of summer sun exposure persisted during all the remaining seasons, as we showed lower 25-OH-D levels in subjects with low exposure to sunlight. These results possibly reflect a combination of a lifestyle distinguished by spending more time outside and vitamin D store produced by sun exposure in summer. The regular use of sunscreens was also associated with lower 25-OH-D levels in spring, summer, and fall. Although excessive exposure to sunlight increases the risk of non-melanoma skin cancer, there is no evidence that sensible sun exposure may increase this risk [30]. Moreover, melanoma skin cancer occurs on the least sun exposed areas and is less likely to occur in adults who have outdoor occupations [18, 32]. Therefore, it is not unreasonable to consider sensible sun exposure as a good source of vitamin D [29]. The multitude of factors that influence cutaneous vitamin D synthesis makes it difficult to determine the adequate sun exposure for any given child, and more studies are necessary to develop recommendations for safe sun exposure [56]. However, pediatricians should monitor sun exposure of children and adolescents, considering vitamin D supplementation in subjects with low exposure or regular use of sunscreens, particularly during winter and spring.

At present, this is the first study assessing the relationship between vitamin D status and PTH levels in an Italian pediatric series. We found a negative correlation between serum 25-OH-D and PTH levels, also adjusting for confounders. Interestingly, some children and adolescents with vitamin D insufficiency showed secondary hyperparathyroidism. This observation is in accordance with Srivastava et al. who found that 14.2 % of a group of 553 children and 15.7 % of another group of 304 children with vitamin D insufficiency (25-OH-D levels 50–75 nmol/L, 20–30 ng/mL) and normal serum creatinine values had elevated serum PTH levels (≥75 ng/L) [50]. Their results supported the use of 75 nmol/L (30 ng/mL) as 25-OH-D cut-off for a sufficient vitamin D status, as proposed by the Endocrine Society [31]. In a mixed population of children and adults, Ginde et al. found that PTH levels started to plateau at serum 25-OH-D levels of 75–100 nmol/L (30–40 ng/mL), suggesting 100 nmol/L (40 ng/mL) as 25-OH-D cut-off for optimal vitamin D status [20]. Other few pediatric studies analyzed the relationship between vitamin D and PTH with conflicting results, but generally confirming that only a relative small percentage of children and adolescents with hypovitaminosis D developed secondary hyperparathyroidism [14, 23, 38].

Some strong points of this study were the large number of subjects enrolled, similar to other series from European and non-European countries. We enrolled only children and adolescents who were not receiving vitamin D supplementation, giving an exact picture of the role of presumed risk factors for hypovitaminosis D during pediatric age. Our study also had some limitations. Being a cross-sectional study, we did not consider a follow-up that may help in clarifying the impact of some risk factors on vitamin D status, particularly season of blood sample. In addition, the sample of the subjects we examined was not a random sample of a community, and thus, our results might not reflect the entire healthy Italian pediatric population. Furthermore, auxological assessment and detailed interview to evaluate the role of presumed risk factors were not available for the entire series. Finally, some presumed risk factors, as sun exposure and use of sunscreens, were only indirectly evaluated by questionnaire administration, so recall bias may have partially influenced our results.

Conclusions

Italian children and adolescents who were not receiving vitamin D supplementation had high prevalence of hypovitaminosis D. Winter–spring period, non-white ethnicity, weight excess, low sun exposure, and regular use of sunscreens were the factors that mostly influenced vitamin D status. Careful identification of factors affecting vitamin D status is advisable to promptly start vitamin D supplementation in children and adolescents.

Competing interests The authors declare that they have no competing interests.

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