*European Journal of Public Health*, 1–6
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doi:10.1093/eurpub/ckz182

# Vitamin D deficiency in a population of migrant children: an Italian retrospective cross-sectional multicentric study

Manuela Ceccarelli [1], Elena Chiappini[2], Rosangela Arancio[3], Mauro Zaffaroni[4], Simona La Placa[5], Marianna D'Andrea[6], Chiara de Waure [7], Rosalia Maria Da Riol[8], Piero Valentini[9] on the behalf of National Working Group for the Migrant Children of the Italian Society of Pediatrics (NWGMC-ISP)[†]

1 Department of Clinical and Experimental Medicine, Unit of Infectious Diseases, University of Messina, Messina, Italy
2 Department of Health Sciences, "Meyer" Children University Hospital, University of Florence, Florence, Italy
3 Unit of Pediatrics, "San Paolo" Hospital, Milan, Italy
4 Unit of Pediatrics, "Maggiore" University Hospital, Novara, Italy
5 Department of Health Promotion Sciences and Mother and Child Sciences "G. D'Alessandro", "P. Giaccone" University Hospital, Palermo, Italy
6 Public Health Institute, Catholic University of Sacred Heart, Rome, Italy
7 Department of Experimental Medicine, University of Perugia, Perugia, Italy
8 Center of Regional Coordination for Rare Diseases, "Santa Maria della Misericordia" University Hospital, Udine, Italy
9 Department of Woman and Child Health, Fondazione Policlinico Universitario "A. Gemelli", Università Cattolica del Sacro Cuore, Rome, Italy

[†]The authors of National Working Group for the Migrant Children of the Italian Society of Pediatrics (NWGMC-ISP) are listed in Acknowledgements section.

**Correspondence:** Manuela Ceccarelli, Department of Clinical and Experimental Medicine, Unit of Infectious Diseases, University of Messina, Via Consolare Valeria, 1, 98125 Messina, ME, Italy, e-mail: manuela.ceccarelli86@gmail.com

**Background:** Vitamin D is a hot topic in the scientific community. Its deficiency and the implications for the children's health became increasingly discussed during the last 20 years. The main aim of this retrospective study was to determinate the prevalence of vitamin D metabolism disorders in a population of adopted children and their risk factors. **Methods:** We gathered data from 2140 children observed in five different National Working Group for the Migrant Children of the Italian Society of Pediatrics centers, variously located in Italy. Serum 25-hydroxy (OH)-D concentration was used to determine every child's vitamin D status, defined as *severely deficient* (serum 25-OH-D $< 10$ ng/ml), *moderately deficient* (serum 25-OH-D {$\geq 10$ ng/ml U $< 20$ ng/ml}), *mildly deficient* (serum 25-OH-D {$\geq 20$ ng/ml U $< 30$ ng/ml}) and *normal* (serum 25-OH-D $\geq 30$ ng/ml). **Results:** Mean value of serum 25-OH-D was 22.7 ng/ml (SD $\pm$ 12.1). Vitamin D status was deemed as *normal* in 483 (22.6%) children, *mildly deficient* in 718 (33.6%) children, *moderately deficient* in 730 (34.1%) children and *severely deficient* in 209 (9.8%) children. **Conclusions:** A very high percentage of migrant children is affected by hypovitaminosis D, with a strong association with age, geographic origin, season of blood sample collection and time spent in Italy after the arrival. This finding highlights the need for corrective measures. However, these measures cannot be applied without increasing the access of migrant populations to healthcare services.

## Introduction

Health of migrant populations is a highly discussed and current problem, not only because of infectious and tropical diseases, but also because of other concerns, such as cardiovascular diseases, cancer and autoimmune disorders.[1–4]

In 2017, the *Ministry of Health* and the *National Institute for Health Migration and Poverty* (NIHMP), in cooperation with *Superior Institute of Health* (SIH) and the *Italian Society of Migration Medicine* (ISMM), felt the need for the definition of a shared procedure; thus, they published the 'Guidelines for health checkups at the arrival and health pathways for migrant refugees'.[5]

Founded in 1992, the National Working Group on Migrant Children for the Italian Society of Pediatrics (NWGMC-ISP) and its affiliated clinics work every day to identify health problems of migrant children following the 'Guidelines for health checkup at the arrival of the migrant children' issued by the group itself and periodically revised (Supplementary material S1).[6–9]

Vitamin D deficiency and its implications for the children's health, especially in that subset represented by either migrant or internationally adopted children, became increasingly discussed during the last 20 years, highlighting not only the need for the definition of a universally applicable range of normality in a mixed-race population, but also the gaps in our knowledge. Current studies about hypovitaminosis in migrant children, examine only a limited number of cases.[10–24] Moreover, even the largest studies offer different conclusions, making it difficult to reach a real agreement on this topic.[25–27]

The aim of this retrospective multicentric study was to determinate the prevalence of vitamin D deficiency in a population of migrant children. Secondary aims were to determine risk factors for hypovitaminosis D and to determine if current guidelines are applicable to this population.

This is, to our knowledge, the largest study about a multi-ethnic children population.

## Methods

### Subjects

We retrospectively gathered data from 2140 children observed in five different NWGMC-ISP centers, variously located in Italy,

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during a period extending from January 2008 to December 2015. Inclusion criteria were pediatric age (< 18 years) and having undergone a serum 25-hydroxy (OH)-D dosage during the first visit.

A general written informed consent to the use of the children's data for study purposes was obtained during the first visit from their guardians.

From the paper and online documentation available, we extracted personal and clinical data such as age, sex, country of origin, time from the arrival in Italy, date of the first health check-up, serum 25-OH-D values, presence of parasitosis or latent/active tuberculosis infection.

### Assessment of vitamin D status

To define vitamin D status, we used the serum concentration of the circulating inactive metabolite 25-OH-D.[28] Serum 25-OH-D was measured with a chemo-immunoluminescence assay (CLIA) kit, produced by *DIA-SORIN* (Saluggia, VC, Italy).

Vitamin D status was defined as *severe deficiency* when serum 25-OH-D was below 10 ng/ml, *moderate deficiency* when serum 25-OH-D was between 10 ng/ml and 20 ng/ml, *mild deficiency* when serum 25-OH-D was between 20 ng/ml and 30 ng/ml and *normal* when serum 25-OH-D was above 30 ng/ml.

Cut-offs were chosen according to the Endocrine Society clinical practice guidelines even though the Institute of Medicine (IOM) of the United States of America and the European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) disagree with this definition and state that sufficiency is achieved with a serum 25-OH-D level of 20 ng/ml. We chose to use the Endocrine Society guidelines to determine vitamin D status to better compare our findings to data offered by literature, as their use is the most widespread.[29–31]

### Statistical analyses

Time since arrival in Italy was categorized in two groups (<90 days and ≥90 days).

Sampling season was defined as winter (January–March), spring (April–June), summer (July–September), fall (October–December).

Frequencies and percentages (%) were used to describe categoric variables (center of observation, month of the first visit, season of the first visit, sex, time from arrival to first visit, country and continent of origin, Vitamin D status). Mean and standard deviations (mean ± SD) were used to express continuous variables (serum 25-OH-D values, age at the arrival, age at first visit).

The Chi-square ($\chi^2$) test was used to compare categorical variables with respect to vitamin D status. We determined the normal distribution of continuous variables with a Kolmogorov–Smirnof test: the result permitted us to use parametric tests. ANOVA test was therefore used to assess correlations in quantitative variables among different vitamin D status groups.

*Post-hoc* analysis was performed for $\chi^2$ tests significant results, Bonferroni adjusted *P* values were considered to determine which couple of categorical variables significantly differed when a contingency table bigger than 2*2 was generated.

All statistical analyses were carried out using the Statistical Package of Social Sciences (Chicago, IL, USA) for Windows software program, version 22.0. A *P* value ≤ 0.05 was considered significant (confidence interval, CI, was 95%).

## Results

Data were collected from five centers: 'Meyer' Children University Hospital (Florence), 'A. Gemelli' University Hospital (Rome), 'San Paolo' Hospital (Milan), 'Maggiore' University Hospital (Novara) and 'P. Giaccone' University Hospital (Palermo). Nine hundred and sixty-two subjects (45.0%) were observed in Florence, 850 (39.7%) in Rome, 184 (8.6%) in Milan, 93 (4.3%) in Novara and 51 (2.4%) in Palermo.

### Subjects

Data about sex were available only for 2065 children of the 2140 (96.5%). One thousand and two hundred and fourteen of them were males (58.8%), while 851 (41.2%) were females. Age at the arrival was only available for 1959 (91.5%) children. Mean age at the arrival was 5.2 years (SD ± 3.0). Age at first medical examination was available for 100% of the children included in the study. Mean age at first visit was 5.6 years (SD ± 3.1).

Seven hundred and eighty-two (36.5%) children originated from Europe, largely from Russia; 491 (22.9%) of them came from America; 480 (22.4%) from Asia; while 387 (18.1%) came from Africa. Detailed data about countries of origin are resumed in Supplementary material S2.

Six hundred and five (28.3%) children were observed for the first time during winter, 560 (26.2%) came to the first visit during fall, 520 (24.3%) during spring and only 455 (21.3%) during summer. Detailed data about month at first medical examination are resumed in Supplementary material S3.

Time since arrival to the first health check-up was only available in 1959 children (91.5%). One thousand and two-hundred and sixty (64.3%) of the subjects stayed in Italy for <90 days before the first medical examination, while 699 (35.7%) for a time ≥ 90 days.

Results of stool examinations and sera tests for intestinal parasitic infections were reported in 2089 (97.6%) cases; 478 (22.9%) of them yielded a positive result.

Results of tuberculin skin test (TST) and/or Interferon-Gamma Release Assay (IGRA), such as QuantiFERON® TB Gold test (Qiagen GmbH, Hilden, Germany), for the screening *Mycobacterium tuberculosis* infection were reported in 2089 children (97.6%); 183 (8.8%) were positive. The database did not offer the complete set of data (chest X-ray, admission, therapy) to determine if these children were affected by a latent tuberculosis infection (LTBI) or an active tuberculosis (TB) infection.

### Vitamin D status and sex

Mean value of serum 25-OH-D was 22.7 ng/ml (SD ± 12.1). Vitamin D status was deemed as *normal* in 483 (22.6%) children, *mildly deficient* in 718 (33.6%) children, *moderately deficient* in 730 (34.1%) children and *severely deficient* in 209 (9.8%) children.

There was no significant association between either serum 25-OH-D value ($P = 0.672$) or vitamin D status ($P = 0.794$) and sex. It was only possible to determine this association for the 2065 children (96.5%) for whom data about sex were available. Serum 25-OH-D mean value in females was 22.6 ng/ml (SD ± 12.2) vs. 22.8 ng/ml (SD ± 12.0) in males. Vitamin D status was *normal* in 273 (22.5%) males and 194 (22.8%) females; *mildly deficient* in 406 (33.4%) males and 284 (33.4%) females; *moderately deficient* in 421 (34.7%) males and 283 (33.3%) females; *severely deficient* in 114 (9.4%) males and 90 (10.6%) females.

### Vitamin D status and age

We then studied a possible association between vitamin D status and age. Our results show a significant correlation between both age at arrival ($P < 0.001$) and age at first visit ($P < 0.001$) and vitamin D status. A better vitamin D status (higher serum 25-OH-D values) is associated to a lower mean age at first evaluation (Supplementary material S4).

### Vitamin D status and origin

We analyzed the vitamin D status by continent of origin, and we found a significant association ($P < 0.001$) between vitamin D status and macro-area of origin. African children's vitamin D status was

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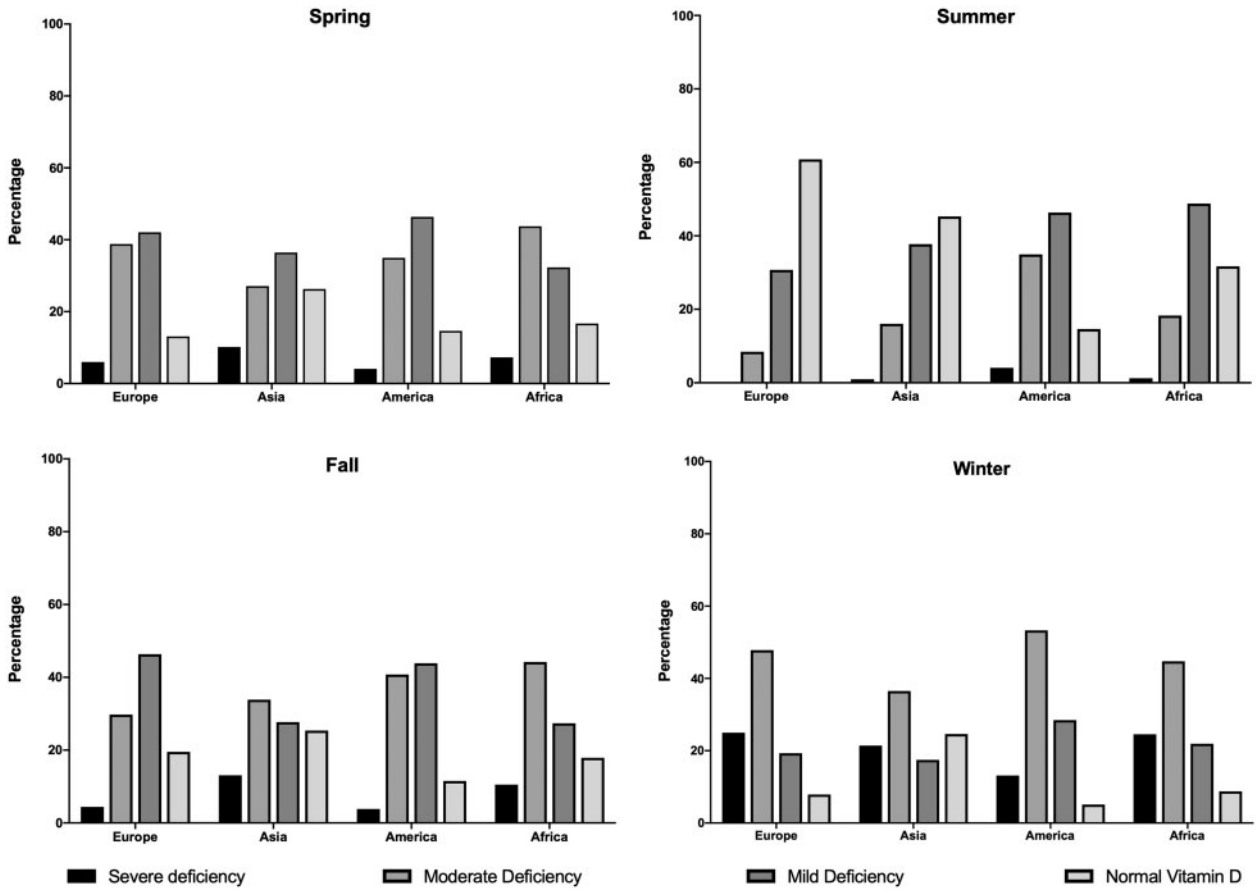


**Figure 1** Distribution of vitamin D status in relation to continent of origin and season of the first observation. This figure shows the percentage of children in every vitamin D status category per continent of origin and season of the first observation. *Severe deficiency* (25-OH-D < 10 ng/ml), *moderate deficiency* (25-OH-D {≥10 ng/ml U < 20 ng/ml}), *mild deficiency* (25-OH-D {≥20 ng/ml U < 30 ng/ml}), *normal vitamin D* (25-OH-D ≥30 ng/ml)

*severe deficiency* in 11.9% of the cases, *moderate deficiency* in 38.8%; *mild deficiency* in 31.5% and *normality* in 17.8%. American children's vitamin D status was *severe deficiency* in 5.9% of cases; *moderate deficiency* in 37.9%; *mild deficiency* in 38.3%; *normality* in 17.9%. Asian children's vitamin D status was *severe deficiency* in 11.9%; *moderate deficiency* in 29.0%; *mild deficiency* in 29.4%; *normality* in 29.8%. European children's vitamin D status was *severe deficiency* in 9.8%; *moderate deficiency* in 32.6%; *mild deficiency* in 34.1%; *normality* in 23.4%.

Detailed data about serum 25-OH-D values and vitamin D status per country of origin are resumed in Supplementary materials S5 and S6.

*Post-hoc* analysis showed that American children tend to have a worse vitamin D status than children coming from Asia, that African children have a significantly worse status than children coming from Asia when comparing moderate deficiency with normality and a significantly worst status than American children when comparing severe deficiency with mild deficiency (Supplementary material S7).

## *Vitamin D status and season of first observation*

We also found a significant association between serum 25-OH-D values ($P < 0.001$) and vitamin D status ($P < 0.001$) and the season of the first observation. Severe and moderate deficiency were prevalent during winter (21.5% and 46.1%, respectively) and spring (6.7% and 36.2% respectively), while severe deficiency was almost never found in children observed during summer (figure 1).

*Post-hoc* analysis showed how significance is maintained for most of the comparisons, except for comparison happening between children observed in Spring and Autumn. Frequencies of hypovitaminosis D in these subsets show no significant differences (Supplementary material S7).

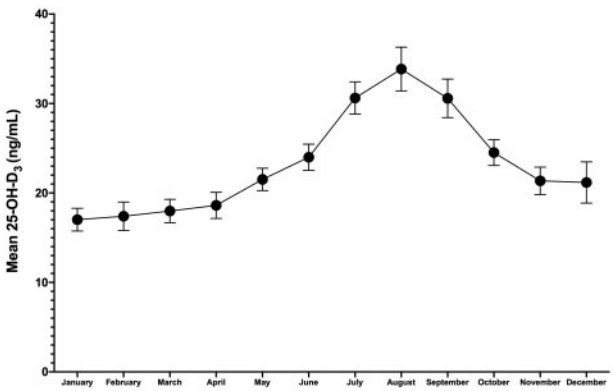


**Figure 2** Mean 25-OH-D values and 95% CI in relation to month of observation. The figure resumes mean 25-OH-D trend throughout the year, with higher values during summer and lower values during winter

Detailed data about mean values of serum 25-OH-D per month of first medical examination are resumed in figure 2.

## *Vitamin D status and time spent in Italy before the first observation*

We found a significant association between time from the arrival in Italy to the first visit and both serum 25-OH-D value ($P = 0.008$) and vitamin D status ($P < 0.001$).

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Among the children examined within the first 90 days from their arrival in Italy, serum 25-OH-D mean value was 23.4 ng/ml (SD ± 12.2 ng/ml). On the other hand, when the children were examined after 3 months from their arrival in Italy, serum 25-OH-D mean value was 21.8 ng/ml (SD ± 12.3 ng/ml).

*Post-hoc* analysis highlighted that differences are only significant when comparing a normal vitamin D status with moderate and mild deficiency (Supplementary material S7).

Detailed data about vitamin D status and its association with time from arrival in Italy to first evaluation are resumed in table 1.

### *Vitamin D status and infections*

There is no significant association between vitamin D status and either parasitosis ($P = 0.363$) or a possible *M. tuberculosis* infection ($P = 0.997$). Supplementary materials S8 and S9 resume descriptive statistics.

## Discussion

Our study provides data about the vitamin D status of a multi-ethnic population composed by migrant children coming from all over the world and living in various places in Italy.

Unsurprisingly, as reported by other authors[15,27,32] we found a strong association of vitamin D status with age, geographic origin, season of blood sample collection and time spent in Italy after the arrival. Curiously, age at the first evaluation was inversely related to serum vitamin D status. We did not find any association with sex, in opposition to what Houghton et al.[14] observed in their study, or the infectious diseases considered (parasitosis and tuberculosis).

Other recent studies[1,2,11,13,16,17,19,20] reported similar findings on smaller populations and just one ethnicity.

Interestingly, our results are similar to Stagi et al.[18] They observed 679 Italian subjects in the Florence area, with an 88.7% prevalence of hypovitaminosis D, strongly associated with season of observation and age. Our results are also similar to Vierucci et al.,[15] who studied a cohort composed by 427 Italian adolescents. They found an 82.2% prevalence of hypovitaminosis D, significantly associated with season of blood withdrawal and ethnicity, but not with sex.

On the other hand, our data largely differ from Gustafson et al.[10] As a matter of fact, they observed a prevalence of 34% of hypovitaminosis D in a cohort of 160 internationally adopted children, evaluated within 6 months after their arrival in the USA. Moreover, in this study season of observation was deemed not associated to vitamin D status. Similar to our findings, though, they observed an inverse correlation of vitamin D status with age.

The significant association between vitamin D status and time after the arrival highlights, in accordance with Chiappini et al.,[27] the importance of a well-timed check-up within the first three months upon the arrival. Curiously, it also seems to indicate that better nutrition and healthcare increase the risk for hypovitaminosis D. This result might suffer from the bias of not stratifying for the cause of migration and the migration status after three months from the arrival.

In our study, as easily expected because of the known correlation existing between skin pigmentation and serum 25-OH-D values, African children had the highest prevalence of *severe deficiency* (50.7%).[19,21,22] However, as observed in a study by Thoreson et al.,[33] African origins are associated with lower serum 25-OH-D values, but a higher bone mineral density (BMD). Moreover, the same study reported how the inflection point for parathyroid hormone (PTH), the mean serum 25-OH-D value at which PTH increases, in African people of all age is close to 20 ng/ml. It is then possible to hypothesize that the application of IOM and ESPGHAN guidelines could be more appropriate in this subset of the immigrant children population.[30,31]

In conclusion, our data show that a very high percentage of migrant children is affected by hypovitaminosis D upon their arrival in Italy, with more than 75% of them suffering from deficiency. This finding highlights the need for effective measures focused on decreasing the incidence of hypovitaminosis D in migrant population, which could be the same applied for the general population: dietary supplementation and increased exposure to sunlight.[28] A secondary measure is the creation of specific cut-offs for each ethnicity, as it is demonstrated that vitamin D influences differently African people bone density.[33]

However, these measures cannot be applied without increasing the access of migrant populations to healthcare services. In fact, previous studies showed how migrants have a lower access to the healthcare services, and to preventive healthcare services in particular.[34–37] However, these studies focused on an adult population, whose problems for the access to the healthcare services are different from those of a population variously composed by internationally adopted children, unaccompanied migrant minors and accompanied migrant minors.

Our group's job is to offer expertise on migration pediatrics and healthcare access to all the children in need. Even though the largest part of our work consists in attending internationally adopted children, during the almost 30 years of activity we established relations with and offered assistance to family homes and reception centers for minors not only to limit the spread of communicable diseases, such as tuberculosis and parasitosis, but also to evaluate the general health conditions of these children at the arrival. Moreover, it is our knowledge that during the first three months after the arrival, the conditions of internationally adopted children and migrant children are not so different.[27] As a matter of fact, a study by Valentini et al.[9] highlighted that the most frequent noninfective problems in a cohort of 358 internationally adopted children were related to growth (weight and height) and nutritional status (defined as low serum iron and 25-OH-D concentrations). Data from the International Society for Social Pediatrics and Child Health (ISSOP), however, show how our reality is not the norm.[38] Access to healthcare services is still limited to migrant children all over Europe, mostly because of cultural and language barriers, but also because of psychological hurdles caused by the migration process itself.

Limitations of our study are represented by missing data about other serum parameters than 25-OH-D, the fact we did not exclude children currently assuming supplementation at the time of the blood withdrawal, and missing data about 1,25-dihydroxy-Vitamin D (1,25-$OH_2$-D) as an indicator of supplementation and PTH activity. Moreover, we did not stratify between unaccompanied migrant minors, accompanied migrant minors and internationally adopted children.

Our study also has some strengths. First of all, the number of subjects observed and the fact it is a multicentric study. Moreover, the multi-ethnicity of our sample and the inclusion of all the age groups.

**Table 1** Vitamin D status in relation to time from the arrival to the first visit

| | | <90 days | ≥90 days | Total |
|---|---|---|---|---|
| Severe deficiency | Count | 121 | 72 | 193 |
| | % | 9.6 | 10.3 | 9.9 |
| Moderate deficiency | Count | 401 | 257 | 658 |
| | % | 31.8 | 36.8 | 33.6 |
| Mild deficiency | Count | 413 | 249 | 662 |
| | % | 32.8 | 35.6 | 33.8 |
| Normal vitamin D | Count | 325 | 121 | 446 |
| | % | 25.8 | 17.3 | 22.8 |
| Total | Count | 1260 | 699 | 1959 |
| | % | 100.0 | 100.0 | 100.0 |

Notes: Severe deficiency (25-OH-D < 10 ng/ml); moderate deficiency (10 ng/ml ≤ 25-OH-D < 20 ng/ml); mild deficiency (20 ng/ml ≤ 25-OH-D < 30 ng/ml); normal vitamin D (25-OH-D ≥ 30 ng/ml).

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## Ethical approval

As this is a retrospective study, the data were anonymously acquired, and a general written informed consent to the use of the children's data for study purposes was obtained during the first visit, there was no need for further ethical approval to this study.

## Supplementary data

Supplementary data are available at *EURPUB* online.

## Acknowledgements

In memory of Orazio Gaetano Ranno, founding member of the NWGMC-ISP, a guide in our profession and a model for every one of us.

**NWGMC-ISP Contributors:** Davide Pata (Department of Woman and Child Health, Fondazione Policlinico Universitario 'A. Gemelli', Università Cattolica del Sacro Cuore, Roma); Danilo Buonsenso (Department of Woman and Child Health, Fondazione Policlinico Universitario 'A. Gemelli', Università Cattolica del Sacro Cuore, Roma); Gilda Salerno (Department of Woman and Child Health Fondazione Policlinico Universitario 'A. Gemelli', Università Cattolica del Sacro Cuore, Roma); Valerio Faccia (Department of Gynecologic, Pediatric and Neonatologic Sciences, 'Sant'Andrea' University Hospital, Unit of Pediatrics, University 'Sapienza' of Rome, Italy); Costanza Paramithiotti (Unit of Pediatrics, 'San Paolo' Hospital, Milan, Italy); Marina Crosa (Unit of Pediatrics, 'San Paolo' Hospital, Milan, Italy); Antonella Gangemi (Department of Health Promotion Sciences and Mother and Child Sciences 'G. D'Alessandro', 'P. Giaccone' University Hospital, Palermo, Italy).

## Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

*Conflicts of interest*: None declared.

## Key points

- The prevalence of hypovitaminosis D in migrant children is above 75%.
- Offering an increased and timely access to healthcare services to migrant children is of vital importance.
- A change in daily habits, with an increase in outdoor activities and dietary supplementation is desirable.
- Determination of PTH inflection points on subsets of the migrant population could offer a chance to individualize the therapy.
- Additional studies are needed to determine if the current guidelines for the individuation of children suffering from hypovitaminosis D should be updated, in relation to the origin of the patient and their age.

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