



Prevalence of vitamin D deficiency in healthy Iranian children: A systematic review and meta-analysis

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Abstract

Background: Vitamin D deficiency is related to rickets in children, and it can increase the risk of osteoporosis in adulthood. The aim of our study was to estimate the prevalence of vitamin D deficiency among healthy Iranian children and adolescents. Vitamin D levels less than 20ng/ml and between 20 and 30ng/ml was considered as vitamin D deficiency and insufficiency, respectively.

Methods: Relevant observational studies evaluating the prevalence of vitamin D deficiency through 1 January 1990 to 28 Dec 2016, were searched in several electronic databases including Iran-Medex, Scientific Information Database (SID), Irandoc, PubMed and NLM Gateway (for MEDLINE), Web of Science, and Scopus with no restriction on language. Only full-text articles were used for data extraction and synthesis after considering the inclusion/exclusion criteria.

Results: 11 studies included; the data of four studies of Iranian newborns were withdrawn because of their high heterogeneity. The prevalence of vitamin D deficiency in Iranian boys and girls were 35% (CI 95% 34–37) and 61% (CI 95% 60–63), respectively. The prevalence of vitamin D insufficiency in Iranian children and adolescents was 31% (CI 95% 30–31).

Conclusion: It seems that the prevalence of vitamin D deficiency is very high among Iranian children and adolescents. The present findings could provide practical information for healthcare decision makers.

Keywords: Vitamin D deficiency, Insufficiency, Prevalence, Children, Iran

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Introduction

The 25-hydroxy vitamin D plays an important role in bone growth, mineralization and other metabolic processes in the human body such as calcium and phosphate homeostasis (1-3). Lack of vitamin D in all stages of life has been considered an important health issue (4). The bone mass in childhood can prognosticate the occurrence of osteoporosis risk in adulthood (5). Due to its principal role in maintaining serum calcium and phosphorus, vitamin D deficiency can have long-term effects for children, particularly it causes rickets, leading to skeletal abnormalities, short stature, delayed development or failure to thrive (6).

The prevalence of Vitamin D deficiency in healthy children and adolescents has been estimated 30 to 50% (7). To date, several researchers have published their data on the prevalence of vitamin D deficiency in children around the world. However, data from children in Iran is sporadic in different settings and regions. As a result, there is a gap in the estimate of vitamin D deficiency at the national level. We, therefore, for the first time, conducted a systematic review and meta-analysis to estimate the prevalence of Vitamin D deficiency among healthy Iranian children and adolescents.

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↑What is “already known” in this topic:

Vitamin D has important role in children and adolescents' life. Many studies have investigated the prevalence of Vitamin D deficiency and insufficiency in Iran during past decades.

→What this article adds:

This systematic review and meta-analysis revealed the very high prevalence of vitamin D deficiency among Iranian children and adolescents.

Methods

The protocol for this systematic review has been registered in the International Prospective Register of Systematic Reviews (PROSPERO). The registration number is CRD42016036786; <http://www.crd.york.ac.uk/PROSPERO>.

Identification and selection of studies

Inclusion criteria: Observational studies describing the prevalence of vitamin D deficiency in healthy Iranian children under the age of 18 years were included. It was considered published articles in any language, with full English abstracts. Also, studies included in this review, accomplished the following defined set of criteria: (a) contained a well-defined sample of children, (b) included only healthy children, (c) presented data on serum 25-hydroxyvitamin D concentrations, (d) were published before 28 December 2016, and (e) were conducted in Iran. Articles that included only children with vitamin D-deficient rickets were excluded because the goal was to review vitamin D status in healthy children.

Exclusion criteria: (a) Duplicate publications of the same material. When the study has been published in more than one journal, the most complete recent version was used. (b) Narrative reviews, opinion pieces, letters or any other publications lacking primary data and/or explicit method descriptions. (c) Studies which report the prevalence in ages higher than 18 years.

Full-text articles that potentially met inclusion criteria were identified by the search for the titles; abstracts were obtained for data synthesis. Studies were screened against predefined inclusion and exclusion criteria. Two authors (M.J and H.R. B) were assigned to evaluate and appraise the results of the searches, based on the title and abstract. The reviewers then either marked the studies as included or excluded. Once all the studies had been reviewed independently, the reviewers together compared their scripts; discrepancies were discussed and, if necessary, a third reviewer was called on to resolve any disagreements.

Search strategy

The relevant original articles on vitamin D status in Iranian children were identified by searching several electronic databases: Main domestic databases; Iran-Medex, Scientific Information Database (SID), Irandoc, PubMed and NLM Gateway (for MEDLINE), Institute of Scientific Information (ISI), and SCOPUS, between 1 January 1990 to 28 Dec 2016.

In PubMed database, the search syntax was: ("vit D" OR "vitamin D" OR "calciferol" OR "25-hydroxyvitamin D" OR "25(OH) D") AND (deficiency OR insufficiency OR hypo vitaminosis OR "hypo vitaminosis D") AND (Prevalence OR incidence OR frequency OR outbreaks OR occurrence OR epidemiology OR epidemiologic studies OR "population-based" OR status) AND (Iran (tiab) OR Iran (ad) OR Iran (PI)). The search syntax was modified in other databases.

Data extraction and quality assessment

Data were critically reviewed according to a standard

protocol independently by two authors. Disagreement was resolved by discussion between them. In cases could not reach a consensus, a third author was consulted. The extracted information from literature included the name of the first author, the year of publication, the study region, total sample size, age, sex groups, and prevalence of vitamin D deficiency. According to Endocrine Society Clinical Practice Guideline the serum level of 25(OH) D under 50 nm/L or 20 ng/ml and between 20 and 30 ng/ml were considered respectively as vitamin D deficiency and insufficiency (8, 9).

To determine age-related differences, we defined five age groups: newborns (0-1month), infants (1month-2 years); young children (2-6years), children (6-12 years) and adolescents (12-18 years).

Risk of bias assessment

The quality of each study was assessed according to Hoy et al. quality assessment tool (10). The Hoy et al. statement provides guidance to authors about how to improve the reporting of observational studies and facilitates critical appraisal and interpretation of studies by reviewers, journal editors, and readers (10).

Statistical analysis

We used fixed and random effects models based on the absence or presence of heterogeneity, respectively. Heterogeneity was assessed using Q Cochrane test and I² index. Forest plot was implemented for showing the results of the individual and pooled effect of all studies. Egger and Begg tests and Funnel plot were used for evaluating the presence of publication bias. Trim and fill method was also used for overcoming the publication bias. Different subgroup analyses were implemented for finding different sources of heterogeneity. P-values of all statistical tests were considered significant at 0.05 except for Q Cochrane, meta-regression, Begg and Egger tests which were set at less than 0.1. All statistical tests and figures were implemented using Stata12.0 (STATA Corp. LP).

Results

In this study, a total of 659 articles were extracted from primary studies, only eleven studies finally remained and included for meta-analysis of 9993 children and adolescents to estimate the prevalence of vitamin D deficiency (Fig. 1). Table 1 indicates the main results of single studies on 25(OH) vitamin D deficiency (cut off <20ng/ml) and insufficiency in Iranian children (11-23). Four studies were related to the newborns (24-27). Table 2 shows the vitamin D deficiency and insufficiency in Iranian newborns. These data could not be meta-analyzed because of the high heterogeneity of studies.

Table 1. Main results from single studies on 25(OH) vitamin D deficiency (cut off <20ng/ml) and insufficiency in Iranian children (20 <Vitamin D< 30ng/ml)

| Author | City/Region | Sample size | Gender | Age (years old) | Prevalence of vit D Def and Insuff (%) male | Prevalence of vit D Def and Insuff (%) female | Prevalence of vit D Def and Insuff (%) Total | 25(OH)D (ng/ml) (mean± SD) |
|------------------------------|---------------|-------------|-------------------|-----------------|---|---|--|-------------------------------------|
| Mussavi et al. (11) (2005) | Isfahan | 318 | M (153) F(165) | 14-18 | Def: 18.3 | Def; 72.1 | Def; 46.2 | M: 37.29±18.76 F: 16.76±8.37 |
| Shakiba et al. (12) (2008) | Yazd | 167 | F(167) | 12.5-15.5 | NP | Def; 39 | Def; 39 | NP |
| Rabbani et al. (13) (2009) | Tehran | 963 | M(424) F(539) | 7-18 | Def; 11.3 | Def; 53.6 | Def; 34.9 | M: 46.53±21.63 F: 24.17±18.46 |
| Ardestani et al. (14) (2010) | Isfahan | 513 | M(271) F(242) | 6-7 | Def; 3.7 | Def; 2.1 | Def; 3 | 46.01±17 |
| Neyestani et al. (15) (2011) | Tehran | 1111 | M(573) F(538) | 9-12 | Def; 62.3 Insuff; 26.5 | Def; 76.4 Insuff; 18.4 | Def; 69.1 Insuff; 22.6 | 9.45±8.89 |
| Olang et al. (16) (2011) | 11 Regions | 4013 | NP | 1.3-2 | NP | NP | Def; 2.8 Insuff; 32.9 | 24.55±12.58 |
| Talaei et al. (17) (2012) | Arak | 420 | M(200) F(220) | 10-16 | Def; 66.5 | Def; 99.1 | Def; 84 | M: 18±5.3 F: 10.5±2.8 |
| Shakeri et al. (18) (2014) | Bojnurd | 361 | M(175) F(186) | 7-18 | Def; 0.65 Insuff; 10.8 | Def; 30.6 Insuff; 38.7 | Def; 16.1 Insuff; 25.2 | 36.36±15.55 |
| | | | | A: (7-10) | Def; 0% Insuff; 6.7 | Def; 2.9% Insuff; 28.6 | Def; 1.5% Insuff; 18.5 | |
| | | | | B: (11-14) | Def; 1.3% Insuff; 16.9 | Def; 29.9% Insuff; 43.3 | Def; 17.2% Insuff; 31.6 | |
| | | | | C: (15-18) | Def; 0% Insuff; 5.9 | Def; 50% Insuff; 37 | Def; 22.1% Insuff; 19.7 | |
| Ebrahimi et al. (19) (2014) | Shahroud | 1047 | M(442) F(605) | 11-19 | Def; 24.7 Insuff; 32.2 | Def; 87.9 Insuff; 5.5 | Def; 61.2 Insuff; 18.9 | 14.7±9.4 |
| Mellati et al. (20) (2014) | Zanjan | 297 | M(134) F(163) | 7-11 | Def; 16.4 Insuff; 74.6 | Def; 42.9 Insuff; 57.1 | Def; 31 Insuff; 65 | 14.12±8.2 |
| Kelishadi et al. (21) (2014) | Isfahan | 97 | M(45) F(52) | 4-10 | NP | NP | De; 37.9 Insuff; 46.3 | 14.98 † |
| Jari et al. (22) (2015) | 27 provinces | 1090 | M(568) F(522) | 10-18 | Def; 40.7 Insuff; 36.6 | Def; 39.3 Insuff; 41.4 | Def; 40 Insuff; 38.9 | NP |
| Saki et al. (23) (2015) | Karwar (Fars) | 477 | M(241) F(236) | 9-18 | Def; 68 Insuff; 17 | Def; 68 Insuff; 13 | Def; 68 Insuff; 15 | 15.2± 5.6 |

Abbreviations: NP, not reported; M, male; F, female; vit D, vitamin D; Def, deficiency; Insuff, insufficiency. † 25(OH) D median values

Assessment of Pooled Prevalence

Eleven studies from different settings remained for meta-analysis to have a pooled prevalence estimation; vitamin D deficiency was estimated to be 30% (CI 95% 30–31) in Iranian children and adolescents (Fig. 2). Also, subgroup analysis for gender, results showed in Iranian boys and girls were 35% (CI 95% 34–37) and 61% (CI 95% 60–63), respectively (Figs. 3 and 4). The prevalence of vitamin D insufficiency in Iranian children and adolescents was 31% (CI 95% 30–31) (Fig. 5). Also, the results showed that prevalence of vitamin D insufficiency in Iranian boys and girls were 31% (CI 95% 29–33) and 24% (CI 95% 23–26), respectively (Figs. 6 and 7).

Meta-Regression

Meta-regression was used to explore the sources of between-study heterogeneity, including age and gender. According to the results, the prevalence of deficiency and

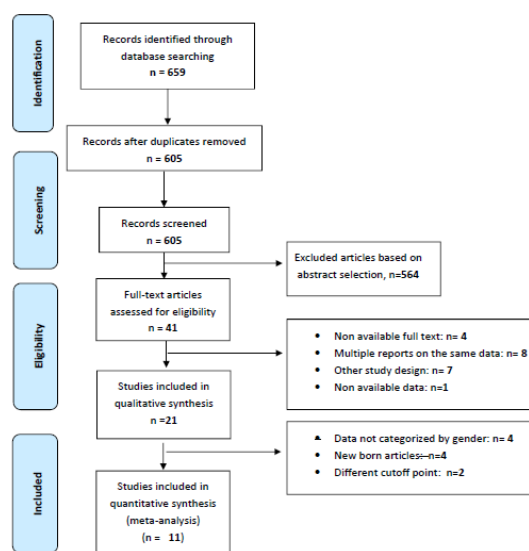


Fig. 1. PRISMA flow diagram

insufficiency were related to age ($p < 0.10$) and gender ($p < 0.10$).

Discussion

Vitamin D deficiency is associated with rickets in children, and it can cause osteoporosis in adulthood (5). Vitamin D is assayed by measuring plasma levels of 25-hydroxyvitamin D. (25 (OH) D is the best indicator and

the main form of circulating vitamin D (1, 3).

In this study, for the first time, we determined the prevalence of vitamin D deficiency in healthy Iranian children. In our meta-analysis, we considered the serum level of 25(OH) D under 20ng/ml or (50 nm /l) as vitamin D deficiency based on The Institute of Medicine report (28). Also, the level of 25(OH) D between 20ng/ml and 30ng/ml were considered as vitamin D insufficiency (28).

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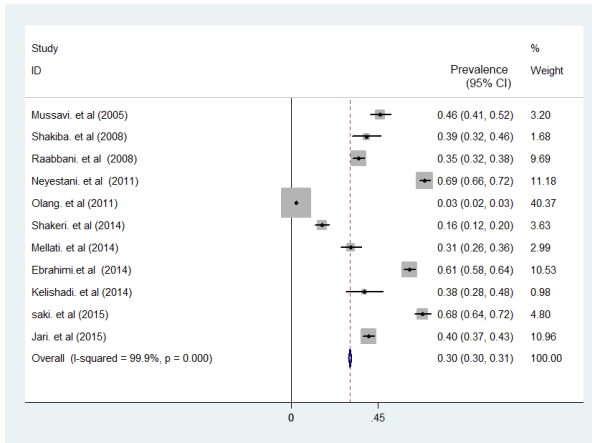


Fig. 2. Frost plot for the prevalence of vitamin D deficiency in Iranian children and adolescents

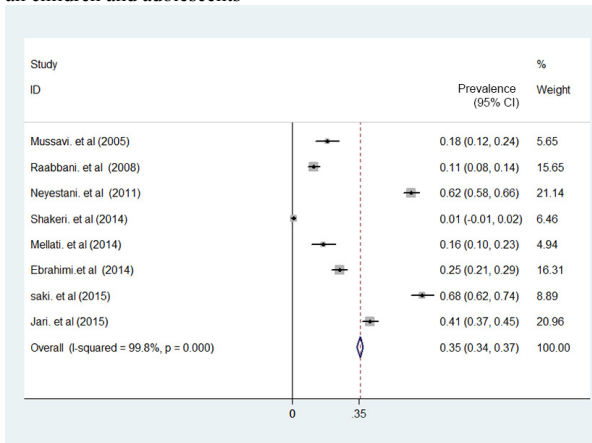


Fig. 3. Frost plot for the prevalence of vitamin D deficiency in Iranian boys children and adolescents

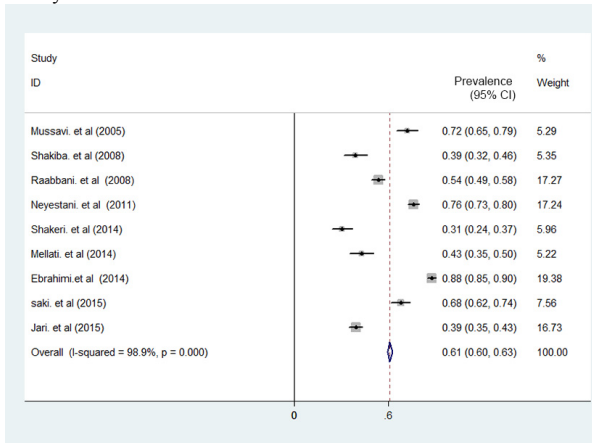


Fig. 4. Frost plot for the prevalence of vitamin D deficiency in Iranian girl children and adolescents

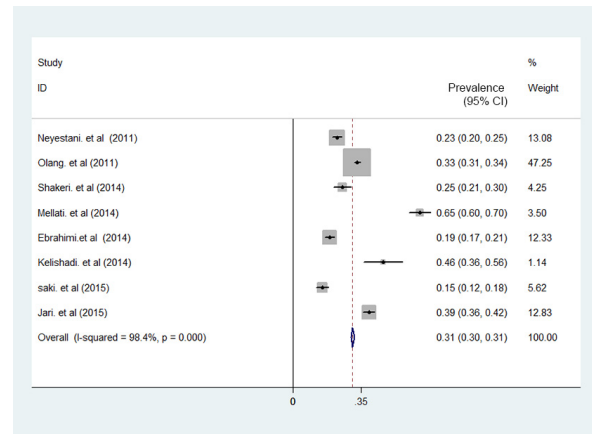


Fig. 5. Frost plot for the prevalence of vitamin D insufficiency in Iranian children and adolescents

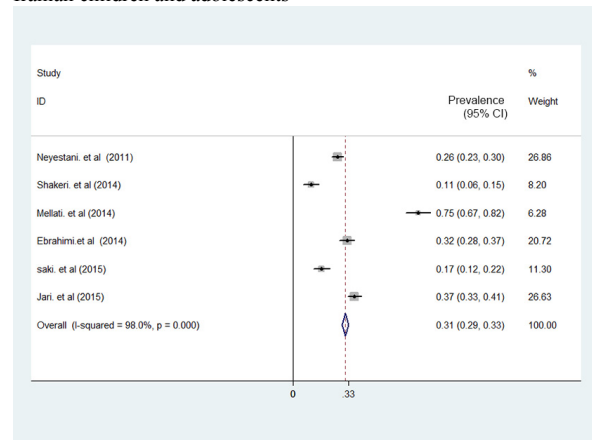


Fig. 6. Frost plot for the prevalence of vitamin D insufficiency in Iranian boys children and adolescents

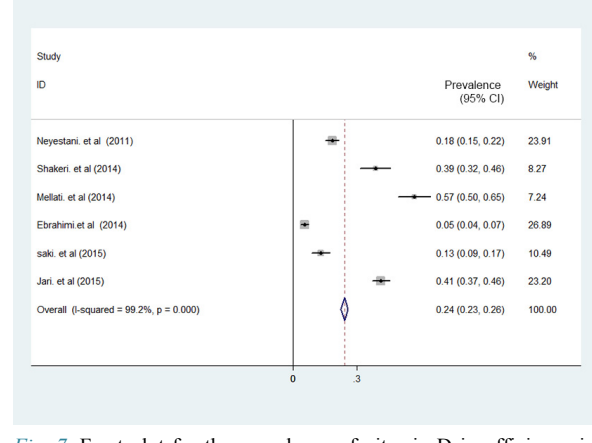


Fig. 7. Frost plot for the prevalence of vitamin D insufficiency in Iranian girl children and adolescents

Table 2. Main results from single studies on 25 (OH) vitamin D deficiencies in Iranian newborns

| Author | City/Region | Sample size | Prevalence of Vit D Def (%) Total | 25(OH)D (ng/ml) (mean± SD) | Cut off for vit D Def (ng/ml) |
|------------------------------|-------------|-------------|-----------------------------------|----------------------------|-------------------------------|
| Bassir et al. (24) (2001) | Tehran | 44 | 81.8 | 1.97±3.76 | Def < 10 |
| Maghbooli et al. (25) (2007) | Tehran | 552 | 93.3 | 7.25±4.64 | Def < 14 |
| Salek et al. (26) (2008) | Urmia | 88 | 4.5 | 27.42±11.4 | Def < 12.5 |
| | Tehran | | 21.6 | | Def < 30 |
| Kazemi et al. (27) (2009) | Zanjan | 67 | 67 | 6.69±1.16 | vit D < 10 |

Abbreviations: vit D, vitamin D; Def, deficiency

The results of the meta-analysis showed that the prevalence of the vitamin D deficiency in Iranian children is about 30% (female 61% (CI 95% 60–63) and male 35% (CI 95% 34–37). The findings of our systematic review and meta-analysis indicated a high rate of Vitamin D deficiency and insufficiency in Iranian children and adolescents. This is in line with some reports particularly in the Middle East region (29, 30). However, vitamin D deficiency varies in different parts of the world (31). Most studies from Middle Eastern regions indicated that the prevalence of vitamin D deficiency in children especially adolescents varies from 30 to 75% (32). In Saudi Arabia and Qatar, vitamin D deficiency seems to have a higher rate than other ME countries. The prevalence of vitamin D deficiency and insufficiency in Qatari children was estimated around 85% by consideration of 25 (OH) D levels < 30 ng/ml (33).

It is noticed that the prevalence of vitamin D deficiency in Iranian girls was much higher than Iranian boys; similar to Saudi Arabia and Qatar (32), the possible explanation of this finding could be the dress code and body coverage in public places which cause not enough sun exposure in addition to inadequate physical activities either in indoor or outdoor. Another justification could be due to a high rate of obesity and overweight in girls in Iran since previous studies showed higher vitamin D deficiency in obese children (34, 35).

We have also noticed that the prevalence of vitamin D deficiency varies in different regions of Iran (Table 1). However, Iran has more frequent sunlight days during the year compared with European countries and North America but enough UVB radiation may be varied in different regions.

It seems air pollution is one of the major reasons for the vitamin D hypovitaminosis. Air pollution can prevent the UVB radiation to the earth considerably and therefore the vitamin D synthesis is remarkably reduced by the skin (36). Kelishadi et al. showed the prevalence of vitamin D deficiency is increased in Iranian children living in regions with high air pollution (21). Also, the relationship between air pollution and vitamin D deficiency has been observed in Indian children (37).

We found only four studies for vitamin D deficiency and insufficiency among Iranian newborns (24–27). Due to high heterogeneity, we could not make a point estimate of prevalence by meta-analysis. Investigations in Saudi Arabia, Kuwait, United Arab Emirates, and Iran reveal that 10–60% of mothers and 40–80% of their neonates had undetectable low 25(OH) D levels (0–25 nmol/L) at delivery (32). This high rate in comparison with developed countries could be justified as in industrialized

countries such as North America effective interventions on fortification of some foods such as milk or juice have been implemented in their national health program (31).

Limitation

We found the heterogeneity between the studies due to different methods for vitamin D assay and experimental variations; therefore, they were not directly comparable. Also, we could not stratify different age groups of children.

Conclusion

It seems that the prevalence of vitamin D deficiency is very high among children and adolescents in Iran. The present findings could provide practical information for healthcare decision makers. The vitamin D status of children should be improved in Iran. As well, future studies are necessary to evaluate the 25(OH) D and parathyroid hormone (PTH) levels for obtaining the vitamin D cutoff in Iranian population.

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Conflict of Interests

The authors declare that they have no competing interests.

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