Research Paper

Vitamin D status in Mainland of China: A systematic review and meta-analysis

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ABSTRACT

Background: Low vitamin D (VitD) status is becoming a global health issue. Previous heterogenous results are urging a meta-analysis to delineate a panorama of VitD conditions in the general population in Mainland of China.

Methods: We performed a systematic review and meta-analysis by searching PubMed, Web of Science, EMBASE, China National Knowledge Infrastructure, WanFang, and VIP databases up to June 4, 2021. The inclusion criteria were as follows: (1) original articles or dissertations focused on VitD status of people in Mainland of China; and (2) studies were population-based, cross-sectional, or longitudinal cohort with baseline data. The outcomes were serum 25(OH)D concentration and the prevalence of low VitD status. Low VitD status included VitD deficiency (25(OH)D < 30 nmol/L) and VitD inadequacy (25(OH)D < 50 nmol/L). Data were estimated by Hierarchical Bayesian methods. All included studies were cross-sectional or longitudinal cohort studies about VitD status of people in Mainland of China. (Registration: PROSPERO CRD42021226130).

Findings: A total of 105 eligible studies including 234,519 subjects were included. In adults, the overall mean 25(OH)D concentration was 44.3 nmol/L (95% Credible Interval [CrI]: 39.8–48.7). The pooled prevalence of VitD deficiency and inadequacy was 20.7% (95% CrI: 11.9–37.2) and 63.2% (95% CrI: 53.5–72.3), respectively. In children and adolescents, the overall mean 25(OH)D concentration was 52.2 nmol/L (95% CrI: 46.7–57.5). The pooled prevalence of VitD deficiency and inadequacy was 23.0% (95% CrI: 8.9–44.3) and 46.8% (95% CrI: 37.2–56.6), respectively. Specially, we identified that the prevalence of VitD inadequacy increased with age in populations with age ≥18 years and ≥60 years.

Interpretation: Low VitD status is prominent in general population of Mainland of China, especially for adults.

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1. Introduction

Low vitamin D (VitD) status including inadequacy and deficiency is becoming a severe public health issue [1]. About 14% of people are estimated as low VitD status worldwide, and the conditions are severer in Middle East, Africa and Asia [2–4]. VitD is primarily obtained from skin synthesis by sunlight exposure and also absorbed from diet, which is further converted to 25-hydroxyvitamin D (25(OH)D) by 25-hydroxylase in the liver. It plays an essential role in bone metabolism, hormone-related conditions, and even the health of gut microbiome [5–8]. Low VitD status is associated with various infectious and non-communicable diseases [9].

As a large country including 1.4 billion people, China has a vast territory that stretches from the tropical and subtropical zones in the south to the cold-temperate zones in the north. Although some studies have investigated VitD conditions in Mainland of China, the reported prevalence of low VitD status varied from 22.3 to 81.9% in adults [10,11], and from 19.6 to 78.1% in children and adolescents [12,13]. Differences may result from geographical disparity, dietary habits, and imbalance in urban and rural economic developments. Another considerable issue is no consensus on the definition of VitD sufficiency. Measurement of serum 25(OH)D concentrations is widely considered as the best indicator of VitD nutritional status [14]. The
Research in context

Evidence before this study

The reported prevalence of low vitamin D (VitD) status in Mainland of China varied from 22.3% to 81.9% in adults, and from 19.6% to 78.1% in children and adolescents. Characteristics of study populations such as geographical disparity, different sampling methods and inconsistent criteria may contribute to the heterogenous results. Although there were some national studies, they often focused on a specific crowd.

Added value of this study

This study presents the largest assessment to delineate the overall VitD conditions of general people in Mainland of China, based on 105 high-quality studies with 234,519 subjects. Results revealed that the prevalence of VitD inadequacy in adults were strikingly up to 63.2%, which was much higher than that in children and adolescents (46.8%). Specially, the estimated prevalence of VitD inadequacy significantly increased with age in populations with age < 18 years or > 60 years.

Implications of all the available evidence

Low VitD status is prominent in Mainland of China, especially for adults. It may help public health experts and officials pay more attention and more encouragement on VitD investigation and control strategies in Chinese adults. In view of significant association between age and VitD inadequacy in children/adolescents, and in older people, we advocate more detailed guidelines on VitD supplementation in these people.

2. Methods

2.1. Protocol and guidance

This study was registered with PROSPERO (CRD42021226130). It was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [24].

2.2. Literature search and selection criteria

We searched PubMed, Web of Science, EMBASE databases for relevant articles without language or date restriction. Chinese authoritative databases including China National Knowledge Infrastructure (CNKI), WanFang, and VIP were also searched. The full search strategy was detailed in Supplementary file 1. Papers that occurred in the references of the selected full-text papers were also manually reviewed, but yielded no additional eligible articles. The literature search was updated to June 4, 2021.

Studies were eligible for inclusion if they met the following criteria: (1) original articles or dissertations about measurement of serum 25(OH)D concentrations were published; (2) studies were population-based, cross-sectional, or longitudinal cohort with baseline data; and (3) participants resided in Mainland of China. We excluded studies that were case reports, case series, commentary, review or meeting abstracts; and were measured 25(OH)D concentrations after a clinical intervention. Because we focused on VitD status of general people, studies on special populations were also excluded, including pregnant or lactating women, industry workers, and subjects from hospital, military or nursing home. Besides, studies that not specified the random sampling methods or not provide necessary data were excluded. Two independent investigators (WL and JH) performed these procedures and disagreements in study selection were resolved by discussion and consensus. All data were double checked by another author (YF).

2.3. Data extraction and quality evaluation

Two independent investigators (PW and YL) extracted the following items from each eligible study: first author's name, publication year, sampling method, sample size, age, geographical region, mean 25(OH)D concentrations, prevalence of low VitD status, and so on. If two studies had overlapping data, we kept the one with a larger sample size. The outcomes were mean serum 25(OH)D concentration (nmol/L) and the prevalence of low VitD status. Low VitD status included VitD deficiency (< 30 nmol/L, or < 12 ng/mL) and inadequacy (< 50 nmol/L, or < 20 ng/mL), based on the latest Chinese health industry standard of "Method for vitamin D deficiency screening (WS/T 677–2020)" [16].

The quality of the included studies was evaluated by a tool by Hoy [25]. This tool sets ten items and each with a score of one (yes) or zero (no) for assessment. Quality ratings were reported for each study according to an overall score of high (0–3), moderate (4–6), or low (7–10) risk of bias.

2.4. Statistical analysis

Given the patterns of data sparsity and the hierarchical structure of extracted data, we used HB approaches to perform the meta-analysis [26,27]. HB analysis combines the prior information and sample information to obtain the posterior distribution, and then estimates the pooled effect sizes. However, there is not an “ideal” statistics such as I² in HB methods to directly quantify the heterogeneity between the included studies. As a compromise, the between-study variances could indicate the heterogeneity to some extent. Therefore, we provided all the between-study variances from each HB model to show the heterogeneity between the studies. In view of obvious differences between children/adolescents and adults, we evaluated their outcomes, respectively. First, overall mean 25(OH)D concentrations and low VitD status were estimated. Second, possible effects of sex, age, sampling frame, latitude, urbanization, season and detection assays on outcomes were evaluated using the HB meta-regression model, separately. For the univariate HB meta-regression analysis, the number of the studies for analysis in each level of a covariate should be 3 or more. The sampling frame of the included studies were classified into three levels as follows: nationwide level, province/city level (≥ 3 districts/counties), and county level (one or two districts/counties). The latitude of Mainland of China is defined as north and south, based on the Qinling Mountains–Huaibei River line boundary. So the latitude of the included studies was divided into north, south, and both. The
urbanization of the included studies was divided into Urban, Rural, and both. Seasons were divided into three categories as follows: summer/autumn (June to November), winter/spring (December to May), and both (investigation lasting for 12 months or more). Detection assays were also evaluated, including enzyme-linked immunosorbent assays (ELISA), chemiluminescent assays (CLIA), electrochemiluminescence immunoassays (ECLIA), radioimmunoassays (RIA), and chemical assays. Chemical assays included high-performance liquid chromatography (HPLC) and liquid chromatography coupled with mass spectrometry (LC-MS/MS). It should be noted that the included studies rarely provided sex-age-specific outcomes, so we extracted sex-specific and age-specific outcomes to explore the effects of sex and age on outcomes, respectively. We used the mid-point values of each age group as continuous variables to construct the trend HB model. All HB models were fitted with the Markov chain Monte Carlo (MCMC) algorithm and Gibbs sampling to estimate the posterior distribution of interest outcomes. Difference, the odds ratio (OR) and credible interval (CrI) were used to measure the effects of potential factors on the outcomes of interest. The CrI represents the 2.5–97.5 percentiles of the posterior distribution of the estimation. Inferences were based on 5000 iterations, and the first 2500 of which were used as burn-in. Non-informative prior was specified for all parameters. HB analyses were performed using the R software (version 4.0.3) with “R2jags” package. The HB methods were detailed in Supplementary file 2.

2.5. Role of the funding source

This work was supported by National Major Scientific and Technological Special Project for “Significant New Drugs Development” (2017ZX09304022). The funder had no role in study design, data collection, data analysis, result interpretation, or writing. All authors had full access to the full data in the study and accept responsibility to submit for publication.

3. Results

3.1. Characteristics of the eligible studies

We searched a total of 19,827 records by multiple databases, and then removed 3964 duplicates. After exclusion of irrelevant records by title and abstract screening, we got 824 full-text records for eligibility assessment. Finally, a total of 105 eligible studies including 234,519 subjects were included. A flowchart of study selection is shown in Fig. 1.

These studies were published between 2001 and 2021, with data collection period ranging from 1995 to 2019. 99 studies were cross-sectional design and 6 studies were baseline data of cohorts. All these studies applied the random sampling methods to recruit subjects. 54 studies included only adults, 48 included only children and adolescents, and 3 included both. Other characteristics are shown in Supplementary Table S1. The quality assessment showed that all the included studies had a low risk of bias, based on the overall scores ranging from 8 to 10 (Supplementary Table S2).

3.2. Overall VitD conditions of general population

As shown in Supplementary Fig. S1, there were 34 studies including 88,065 adults to estimate the overall mean 25(OH)D

![Flowchart of study selection](image-url)
concentration, which was 44.3 nmol/L (95% CrI: 39.8–48.7). The results of low VitD status are summarized in Fig. 2. The pooled prevalence of VitD deficiency of adults was 20.7% (95% CrI: 11.9–32.9) based on eight studies including 18,296 subjects. The pooled prevalence of VitD inadequacy of Chinese adults was 63.2% (95% CrI: 53.5–72.3) based on 43 studies including 87,742 subjects.

As shown in Supplementary Fig. S2, there were 36 studies including 59,863 children and adolescents to estimate the overall mean 25(OH)D concentration, which was 52.2 nmol/L (95% CrI: 46.7–57.5). The results of low VitD status are summarized in Fig. 3. The pooled prevalence of VitD deficiency of Chinese children and adolescents was 23.0% (95% CrI: 8.9–44.3) based on 9 studies including 36,509 subjects. The pooled prevalence of VitD inadequacy of Chinese children and adolescents was 46.8% (95% CrI: 37.2–56.6) based on 39 studies including 85,494 subjects.

Between-study heterogeneity of overall VitD conditions was evaluated by $\sigma^2$ and 95% CrI (Supplementary Fig. S1 and S2, Figs. 2 and 3). In view of high levels of heterogeneity, we further explored effects of potential factors contributing to VitD conditions.

### 3.3. Effects of potential factors on the outcomes of Chinese adults

The effects of some potential factors on the outcomes of Chinese adults were evaluated separately by the HB meta-regression analysis, including sex, age, sampling frame, latitude, urbanization, season and detection assays. For low VitD status, we only evaluated the VitD inadequacy since the number of the studies about VitD deficiency was limited. The results are summarized in Table 1. Relevant parameters including study number and between-study variance were shown in Supplementary Table S3 and S4. We observed that sex was
the most significant factor influencing the outcomes of Chinese adults (the pooled prevalence of VitD inadequacy: OR = 1.7, 95% CrI = 1.5–2.0; the overall mean 25(OH)D concentration: difference = −4.8 nmol/L, 95% CrI = −6.4 to −3.2). Compared with men, women had a lower overall mean 25(OH)D concentration and a higher pooled prevalence of VitD inadequacy (Supplementary Fig. S3, female: 42.9 nmol/L [95% CrI: 37.9–48.1], 64.9% [54.8–74.2]; male: 47.7 nmol/L [95% CrI: 42.8–52.8], 52.1% [45.8–74.2]). Relevant forest plots for the VitD outcomes of adults based on sex are shown in Supplementary Figs. S4 and S5. Latitude seemed to be a marginally significant factor of VitD inadequacy, but the effect was not shown on the overall mean 25(OH)D concentration. Other factors such as sampling frame, season and detection assays showed no obvious effect on the outcomes of Chinese adults.

Previous studies have reported that adults with age ≥ 60 years have a higher risk of VitD inadequacy, due to limited sun exposure, inadequate dietary VitD intake, and worse physical function [2,28]. Several studies have reported that elderly people had a poorer VitD condition than that of young and middle-aged people [29,30]. Besides, the expert consensus on clinical application of VitD in Chinese elderly people demonstrated that VitD inadequacy seemed to be severer with age in elderly people [31]. Therefore, when we found no significant effect of age on the outcomes of all adults, we further performed a subgroup analysis on adults with age ≥ 60 years. It is worth noting that a significant negative association between age and the overall mean 25(OH)D concentration was identified in elderly people (≥ 60 years) (Difference = −0.18 nmol/L/year, 95% CrI = −0.36 to −0.01), as shown in Fig. 4A. Consistently, our results showed an
increased risk of VitD inadequacy with age, with an OR of 1.02 (95% CrI: 1.01–1.04) (Fig. 4B).

### 3.4. Effects of potential factors on the outcomes of Chinese children and adolescents

Similar analyses were performed in children and adolescents. Results demonstrated a significant sex difference (difference = −4.1 nmol/L, 95%CrI = −5.4 to −2.8, as shown in Table 1) that girls had a lower overall mean 25(OH)D concentration (51.3 nmol/L [95% CrI: 44.4–58.4]) than boys (55.4 nmol/L [95% CrI: 48.6–62.2]) (Supplementary Fig. S6).

As shown in Table 1, the HB model also suggested that sex, age, and latitude were significantly associated with the pooled prevalence of VitD inadequacy. Although CLIA showed a significant effect on VitD inadequacy, the small number of the included studies (n = 4) and the wide range of CrI limited the reliability of this result. Because the included studies rarely provided sex-age-specific prevalence based on latitude, we failed to include all these factors in a model. Therefore, we estimated sex-specific prevalence of VitD inadequacy based on latitude (Fig. 5A). The estimated prevalence of VitD inadequacy was highest in northern girls (67.7% [95% CrI: 52.6–79.9]) and lowest in southern boys (23.9% [95% CrI: 13.0–38.0]). Besides, we explored the latitude-specific association between age and the prevalence of VitD inadequacy. As shown Fig. 5B, the estimated prevalence of VitD inadequacy of children and adolescents significantly increased with age, no matter in the north or in the south.
4. Discussion

Our work suggests that low VitD status is a public health issue in Mainland of China, especially for adults. We found that 20.7% of the adults were VitD deficiency and 63.2% were VitD inadequacy. Women had a lower overall mean 25(OH)D concentration and a higher prevalence of VitD inadequacy than men. For children and adolescents, the pooled prevalence of VitD deficiency and inadequacy was 23.0% and 46.8%, respectively. The pooled prevalence of VitD inadequacy was highest in northern girls and lowest in southern boys. Particularly, we identified that the prevalence of VitD inadequacy significantly increased with age in populations with age ≤ 18 years or ≥ 60 years.

Prevalence of VitD inadequacy varies throughout the world, with the reported prevalence of 20% in Australia [32], 23.3% in the United States [33], 34.2% in Africa [4], 40.4% in Europe [34], and 53.6% in Japan [35]. Notably, we identified that adults in Mainland of China had a higher prevalence of VitD inadequacy (63.2%). We also found that the overall mean 25(OH)D concentration was 44.3 nmol/L, which was much lower than that of populations in the Asia/Pacific regions (61.39 nmol/L) [36]. Poor VitD conditions in Mainland of China seem to be a public health issue. Plausible explanations are as follows: (1) several factors result in low exposure of sunshine and reduced VitD cutaneous production, such as air pollution, sun-avoiding behavior, and decreased outdoor activities due to busy and heavy work [37,38]; (2) VitD supplements and relative fortification foods are...
Vitamin D inadequacy in adults. That may be because adults have more technology and instruments, these assays are comparable; serum vitamin D levels. In general, although there are some variations due to short sunshine time, which results in less endogenous production of vitamin D. However, we did not observe the in effect of sun season on the pooled outcomes, which was possibly due to the insufficient study power in this study. Fourth, some factors such as pollution may be potential determinants of serum 25(OH)D. We did not evaluate their effects in this work due to lacking of sufficient data from the included studies. At last, we observed the significant association between vitamin D conditions and age in children/adolescents, and in older people, respectively. However, we did not evaluate the association between vitamin D conditions and all ages. There also may be a quadratic relationship of vitamin D conditions with age. More studies are needed for this investigation in the future.

In summary, this study suggests that low vitamin D status is a general public health issue in the population of Mainland of China, particularly in adults. In view of the trend between age and vitamin D inadequacy in children/adolescents, and in older people, additional strategies and more detailed guidelines for vitamin D intake should be provided targeting these populations.

**Authors' contributions**

NS conceived the study and designed the protocol. WL, JH and YF performed the literature search and study selection. PW and YL extracted the relevant information and validated the data. WL conducted the data analysis with support from NS. WL wrote the first draft of the paper. All authors critically revised successive drafts of the paper and approved the final version. WL and NS are the study guarantors. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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**Data sharing statement**

All the data are available in the paper/supplementary material.

**CRediT authorship contribution statement**

Wenhua Liu: Data curation, Formal analysis, Writing – original draft, review & editing. Jing Hu: Data curation, Writing – review & editing. Yuanyuan Fang: Data curation, Writing – review & editing. Peng Wang: Investigation, Writing – review & editing. Yanjun Lu: Investigation, Writing – review & editing. Na Shen: Visualization, Funding acquisition, Writing – review & editing.

**Declaration of Competing Interest**

WL was supported from the National Major Scientific and Technological Special Project for “Significant New Drugs Development” (2017ZX09304022) during the conduct of the study. All the other authors declare no competing interests.

**Supplementary materials**

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.eclinm.2021.101017.
