Research Paper

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

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A B S T R A C T

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 base-line data. The outcomes were serum 25(OH)D concentration and the prevalence of low VitD status. Low VitD status included VitD deficiency (< 30 nmol/L) and VitD inadequacy (< 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: 11.9−32.9) 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.

majority of experts recommend serum 25(OH)D above 50 nmol/L as sufficient [15,16], but some experts recommend a concentration of higher than 75 nmol/L [17−19]. Inconsistent criteria lead to different standards of low VitD status in the previous studies, ranging from 25(OH)D < 25 nmol/L to 25(OH)D < 80 nmol/L [4,20,21]. In addition, several studies were based on hospital and lacked of representativeness of general people, or did not provide design details such as response rate and sampling methods. These factors also contribute to differences of the prevalence of low VitD status in Mainland of China.

Although some national studies have been performed, they often focus on a specific crowd [22,23]. A comprehensive study on VitD conditions of general population is still warranted to guide VitD detection, prevention and control strategies. Therefore, we performed this systematic review and meta-analysis to delineate a panorama of VitD conditions of general population in Mainland of China. The mean serum 25(OH)D concentrations and the prevalence of low VitD status were estimated by a Hierarchical Bayesian (HB) method, and the variations of the outcomes were also assessed based on the potential factors including age, sex and latitude.

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 I^2 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-Huaihe 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

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
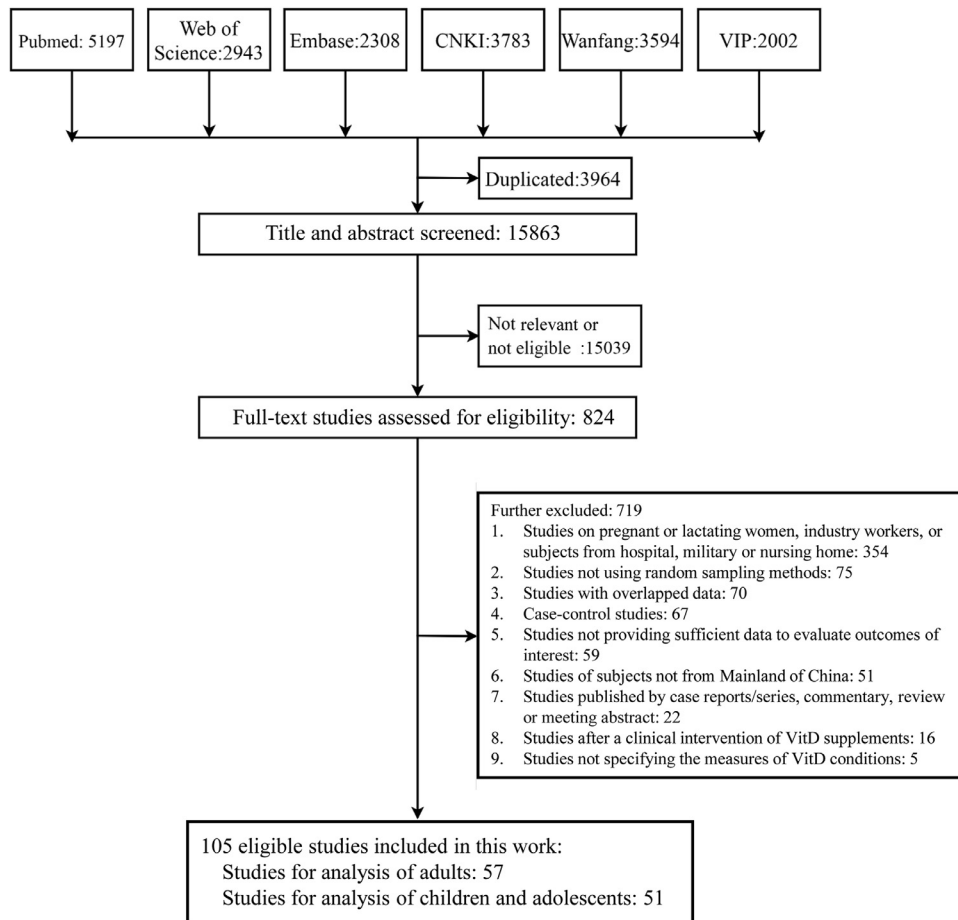

Fig. 1. Study selection. The search date was updated to June 4, 2021. A total of 105 eligible studies were finally included. Of these eligible studies, 54 included only adults, 48 included only children and adolescents, and 3 included both children/adolescents and adults. Abbreviations: VitD = Vitamin D.
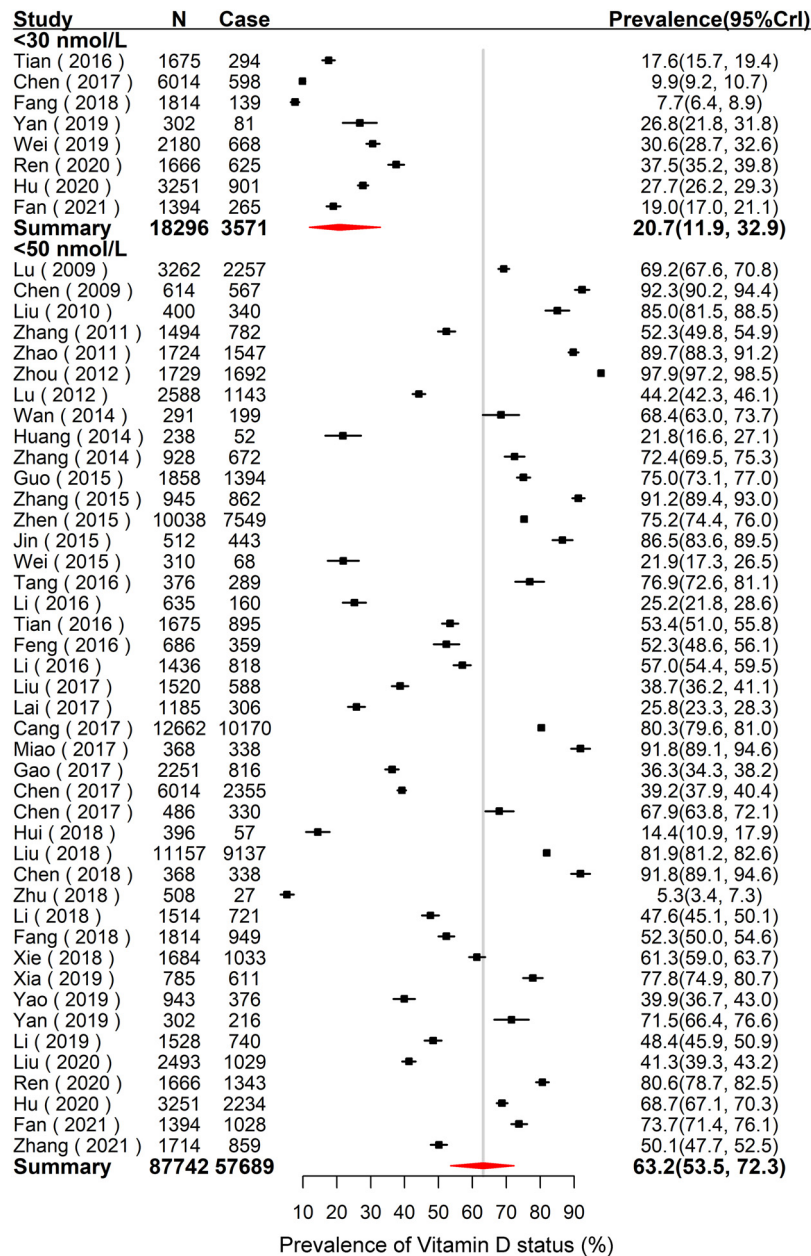
Study	N	Case		Prevalence(95%CrI)
<30 nmol/L				
Tian (2016)	1675	294		17.6(15.7, 19.4)
Chen (2017)	6014	598		9.9(9.2, 10.7)
Fang (2018)	1814	139		7.7(6.4, 8.9)
Yan (2019)	302	81		26.8(21.8, 31.8)
Wei (2019)	2180	668		30.6(28.7, 32.6)
Ren (2020)	1666	625		37.5(35.2, 39.8)
Hu (2020)	3251	901		27.7(26.2, 29.3)
Fan (2021)	1394	265		19.0(17.0, 21.1)
Summary	**18296**	**3571**		**20.7(11.9, 32.9)**
<50 nmol/L				
Lu (2009)	3262	2257		69.2(67.6, 70.8)
Chen (2009)	614	567		92.3(90.2, 94.4)
Liu (2010)	400	340		85.0(81.5, 88.5)
Zhang (2011)	1494	782		52.3(49.8, 54.9)
Zhao (2011)	1724	1547		89.7(88.3, 91.2)
Zhou (2012)	1729	1692		97.9(97.2, 98.5)
Lu (2012)	2588	1143		44.2(42.3, 46.1)
Wan (2014)	291	199		68.4(63.0, 73.7)
Huang (2014)	238	52		21.8(16.6, 27.1)
Zhang (2014)	928	672		72.4(69.5, 75.3)
Guo (2015)	1858	1394		75.0(73.1, 77.0)
Zhang (2015)	945	862		91.2(89.4, 93.0)
Zhen (2015)	10038	7549		75.2(74.4, 76.0)
Jin (2015)	512	443		86.5(83.6, 89.5)
Wei (2015)	310	68		21.9(17.3, 26.5)
Tang (2016)	376	289		76.9(72.6, 81.1)
Li (2016)	635	160		25.2(21.8, 28.6)
Tian (2016)	1675	895		53.4(51.0, 55.8)
Feng (2016)	686	359		52.3(48.6, 56.1)
Li (2016)	1436	818		57.0(54.4, 59.5)
Liu (2017)	1520	588		38.7(36.2, 41.1)
Lai (2017)	1185	306		25.8(23.3, 28.3)
Cang (2017)	12662	10170		80.3(79.6, 81.0)
Miao (2017)	368	338		91.8(89.1, 94.6)
Gao (2017)	2251	816		36.3(34.3, 38.2)
Chen (2017)	6014	2355		39.2(37.9, 40.4)
Chen (2017)	486	330		67.9(63.8, 72.1)
Hui (2018)	396	57		14.4(10.9, 17.9)
Liu (2018)	11157	9137		81.9(81.2, 82.6)
Chen (2018)	368	338		91.8(89.1, 94.6)
Zhu (2018)	508	27		5.3(3.4, 7.3)
Li (2018)	1514	721		47.6(45.1, 50.1)
Fang (2018)	1814	949		52.3(50.0, 54.6)
Xie (2018)	1684	1033		61.3(59.0, 63.7)
Xia (2019)	785	611		77.8(74.9, 80.7)
Yao (2019)	943	376		39.9(36.7, 43.0)
Yan (2019)	302	216		71.5(66.4, 76.6)
Li (2019)	1528	740		48.4(45.9, 50.9)
Liu (2020)	2493	1029		41.3(39.3, 43.2)
Ren (2020)	1666	1343		80.6(78.7, 82.5)
Hu (2020)	3251	2234		68.7(67.1, 70.3)
Fan (2021)	1394	1028		73.7(71.4, 76.1)
Zhang (2021)	1714	859		50.1(47.7, 52.5)
Summary	**87742**	**57689**		**63.2(53.5, 72.3)**

10 20 30 40 50 60 70 80 90

Prevalence of Vitamin D status (%)

Fig. 2. Forest plot of the pooled prevalence of VitD deficiency (< 30 nmol/L) and VitD inadequacy (< 50 nmol/L) of adults in Mainland of China. N is the total number of subjects of the studies, and case is the number of subjects with low VitD status. The forest plot was drawn based on the observational prevalence with 95%CrI of each study, and the pooled prevalence with 95%CrI was estimated using the Hierarchical Bayesian models. For VitD deficiency, the between-study variance (σ^2) and 95%CrI was 0.8 (0.2−2.9). For VitD inadequacy, the between-study variance (σ^2) and 95%CrI was 1.8 (1.2−2.8). Abbreviations: VitD = Vitamin D; CrI = Credible Interval.

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 σ^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 summarizes 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
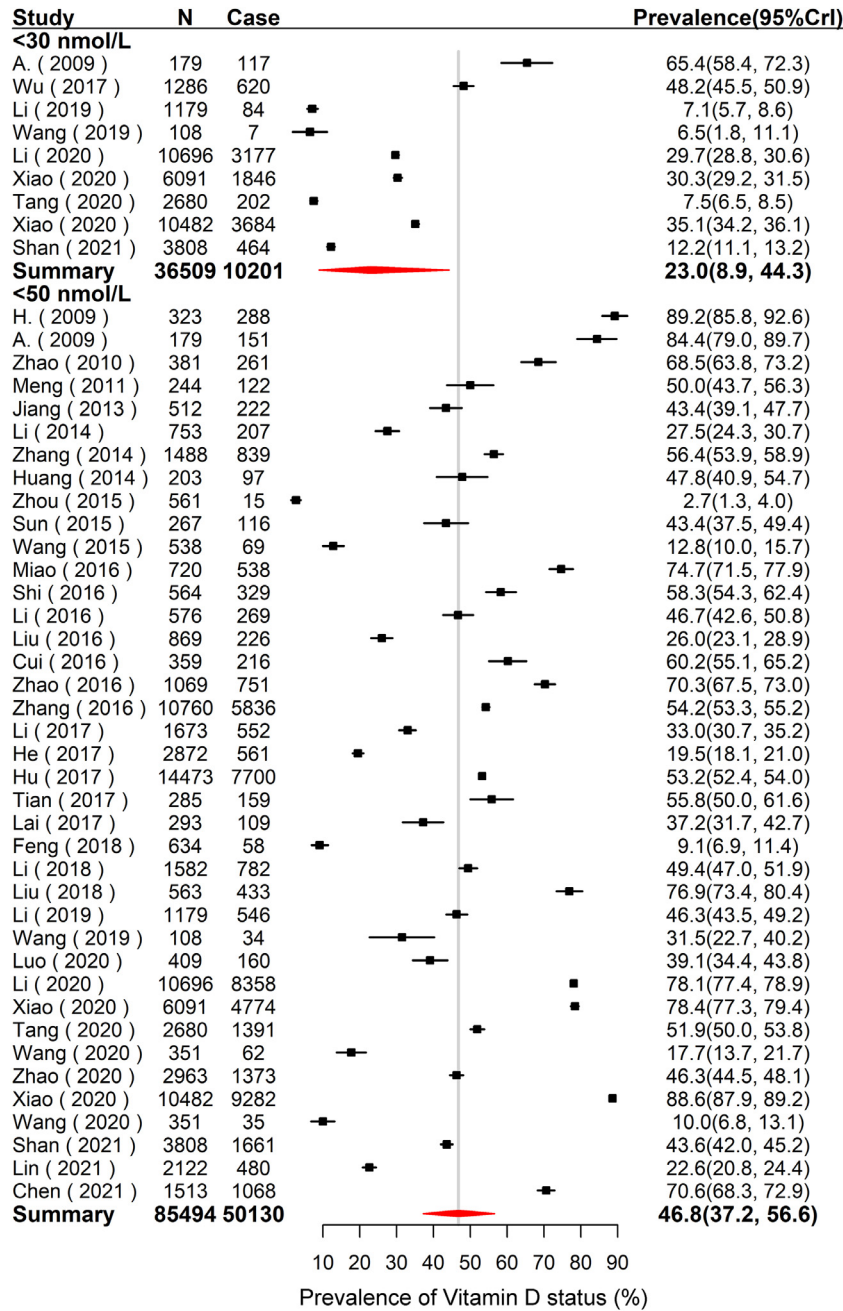
Study	N	Case	Prevalence(95%CrI)
<30 nmol/L			
A. (2009)	179	117	65.4(58.4, 72.3)
Wu (2017)	1286	620	48.2(45.5, 50.9)
Li (2019)	1179	84	7.1(5.7, 8.6)
Wang (2019)	108	7	6.5(1.8, 11.1)
Li (2020)	10696	3177	29.7(28.8, 30.6)
Xiao (2020)	6091	1846	30.3(29.2, 31.5)
Tang (2020)	2680	202	7.5(6.5, 8.5)
Xiao (2020)	10482	3684	35.1(34.2, 36.1)
Shan (2021)	3808	464	12.2(11.1, 13.2)
Summary	**36509**	**10201**	**23.0(8.9, 44.3)**
<50 nmol/L			
H. (2009)	323	288	89.2(85.8, 92.6)
A. (2009)	179	151	84.4(79.0, 89.7)
Zhao (2010)	381	261	68.5(63.8, 73.2)
Meng (2011)	244	122	50.0(43.7, 56.3)
Jiang (2013)	512	222	43.4(39.1, 47.7)
Li (2014)	753	207	27.5(24.3, 30.7)
Zhang (2014)	1488	839	56.4(53.9, 58.9)
Huang (2014)	203	97	47.8(40.9, 54.7)
Zhou (2015)	561	15	2.7(1.3, 4.0)
Sun (2015)	267	116	43.4(37.5, 49.4)
Wang (2015)	538	69	12.8(10.0, 15.7)
Miao (2016)	720	538	74.7(71.5, 77.9)
Shi (2016)	564	329	58.3(54.3, 62.4)
Li (2016)	576	269	46.7(42.6, 50.8)
Liu (2016)	869	226	26.0(23.1, 28.9)
Cui (2016)	359	216	60.2(55.1, 65.2)
Zhao (2016)	1069	751	70.3(67.5, 73.0)
Zhang (2016)	10760	5836	54.2(53.3, 55.2)
Li (2017)	1673	552	33.0(30.7, 35.2)
He (2017)	2872	561	19.5(18.1, 21.0)
Hu (2017)	14473	7700	53.2(52.4, 54.0)
Tian (2017)	285	159	55.8(50.0, 61.6)
Lai (2017)	293	109	37.2(31.7, 42.7)
Feng (2018)	634	58	9.1(6.9, 11.4)
Li (2018)	1582	782	49.4(47.0, 51.9)
Liu (2018)	563	433	76.9(73.4, 80.4)
Li (2019)	1179	546	46.3(43.5, 49.2)
Wang (2019)	108	34	31.5(22.7, 40.2)
Luo (2020)	409	160	39.1(34.4, 43.8)
Li (2020)	10696	8358	78.1(77.4, 78.9)
Xiao (2020)	6091	4774	78.4(77.3, 79.4)
Tang (2020)	2680	1391	51.9(50.0, 53.8)
Wang (2020)	351	62	17.7(13.7, 21.7)
Zhao (2020)	2963	1373	46.3(44.5, 48.1)
Xiao (2020)	10482	9282	88.6(87.9, 89.2)
Wang (2020)	351	35	10.0(6.8, 13.1)
Shan (2021)	3808	1661	43.6(42.0, 45.2)
Lin (2021)	2122	480	22.6(20.8, 24.4)
Chen (2021)	1513	1068	70.6(68.3, 72.9)
Summary	**85494**	**50130**	**46.8(37.2, 56.6)**

Prevalence of Vitamin D status (%) — 10 20 30 40 50 60 70 80 90

Fig. 3. Forest plot of the pooled prevalence of VitD deficiency (< 30 nmol/L) and VitD inadequacy (< 50 nmol/L) of children and adolescents in Mainland of China. N is the total number of subjects of the studies, and case is the number of subjects with low VitD status. The forest plot was drawn based on the observational prevalence with 95%CrI of each study, and the pooled prevalence with 95%CrI was estimated using the Hierarchical Bayesian models. For VitD deficiency, the between-study variance (σ^2) and 95%CrI was 2.4 (0.7−7.5). For VitD inadequacy, the between-study variance (σ^2) and 95%CrI was 1.6 (1.0−2.5). Abbreviations: VitD = Vitamin D; CrI = Credible Interval.

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 ~ −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% [54.8−74.2]). Relevant forest plots for the VitD outcomes of adults based on sex are shown in Supplementary Fig. 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 ~ −0.01), as shown in Fig. 4A. Consistently, our results showed an

Table 1
Hierarchical Bayesian meta-regression analyses on the VitD status in Mainland of China.

Covariates	Children and Adolescents	Adults[†]
VitD inadequacy (< 50 nmol/L), OR (95% CrI)		
Sampling frame		
(Province or City) vs. National	0.4(0.1 to 1.1)	1.6(0.4 to 4.3)
County vs. National	0.4(0.1 to 1.1)	2.1(0.4 to 7.0)
Latitude		
North vs. South	4.1(1.8 to 7.9)	2.7(1.0 to 5.9)
Urbanization		
Rural vs. Urban	1.1(0.4 to 2.2)	1.1(0.2 to 3.5)
Season		
(Summer/Autumn) vs.(Winter/Spring)	0.9(0.3 to 2.0)	1.1(0.4 to 2.6)
Detection assays		
ELISA vs. chemical assays	1.5(0.4 to 3.8)	1.4(0.2 to 4.8)
ECLIA vs. chemical assays	1.2(0.2 to 3.5)	1.1(0.2 to 4.0)
CLIA vs. chemical assays	6.3(1.3 to 19.7)	1.8(0.2 to 7.0)
RIA vs. chemical assays	2.6(0.7 to 6.9)	0.9(0.1 to 3.0)
Sex		
Female vs. Male	1.6(1.4 to 1.9)	1.7(1.5 to 2.0)
Age (years)		
OR per one year	1.13(1.07 to 1.19)	1.02(1.01 to 1.04) [*]
Mean 25(OH)D concentration (nmol/L), Diff. (95% CrI)		
Sampling frame		
Province or City vs. National	10.9(−7.8 to 29.1)	−2.8(−17.3 to 11.0)
County vs. National	11.6(−6.7 to 29.7)	−3.1(−19.5 to 13.3)
Latitude		
North vs. South	−2.8(−15.3 to 9.3)	−4.3(−14.4 to 5.3)
Urbanization		
Rural vs. Urban	−1.3(−13.6 to 10.8)	NA[†]
Season		
Summer/Autumn vs. Winter/Spring	5.6(−6.2 to 17.7)	7.5(−4.1 to 19.0)
Detection assays		
ELISA vs. chemical assays	13.4(−2.6 to 29.4)	1.0(−16.6 to 19.6)
ECLIA vs. chemical assays	−4.4(−19.1 to 10.8)	−4.9(−24.7 to 16.4)
CLIA vs. chemical assays	−14.9(−33.4 to 3.2)	−1.8(−21.4 to 17.9)
RIA vs. chemical assays	6.6(−9.9 to 23.5)	5.4(−13.8 to 25.2)
Sex		
Female vs. Male	−4.1(−5.4 to −2.8)	−4.8(−6.4 to −3.2)
Age (years)		
Diff. per one year	−1.04(−2.14 to 0.09)	−0.18(−0.36 to −0.01) [*]

Abbreviations: VitD = Vitamin D; 25(OH)*D* = 25-hydroxyvitamin D; OR = Odds Ratio; CrI = Credible Interval; Diff. = Difference; vs. = versus; NA = Not available; ELISA = Enzyme-linked immunosorbent assay; ECLIA = Electrochemiluminescence immunoassay; CLIA = Chemiluminescent assay; RIA = Radioimmunoassay.

Note: We used a Hierarchical Bayesian meta-regression model to estimate the pooled prevalence of VitD inadequacy and mean 25(OH) D concentration based on each covariate (sampling frame, latitude, urbanization, season, assays, sex, and age) separately. Diff., OR, and the corresponding 95%CrI were estimated. If the 95%CrI of the effect sizes included the null effect (OR = 1 or difference = 0), the covariate was not considered as a significant factor contributing to the between-study heterogeneity. Chemical assays included high-performance liquid chromatography (HPLC) and liquid chromatography coupled with mass spectrometry (LC-MS/MS).

† For the univariate Hierarchical Bayesian meta-regression analysis, the number of the studies for analysis in each level of a covariate should be 3 or more. The model was performed without rural category because of only two studies sampling from the rural areas.

* The results showed the data of the elderly people with age ≥ 60 years old. For all the adults, the OR and 95%CrI between age and VitD inadequacy was 1.00 (0.98 to 1.01); the diff. between age and mean 25(OH)D concentration was 0.01 (−0.13 to 0.15).

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 ∼ −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 fit 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.
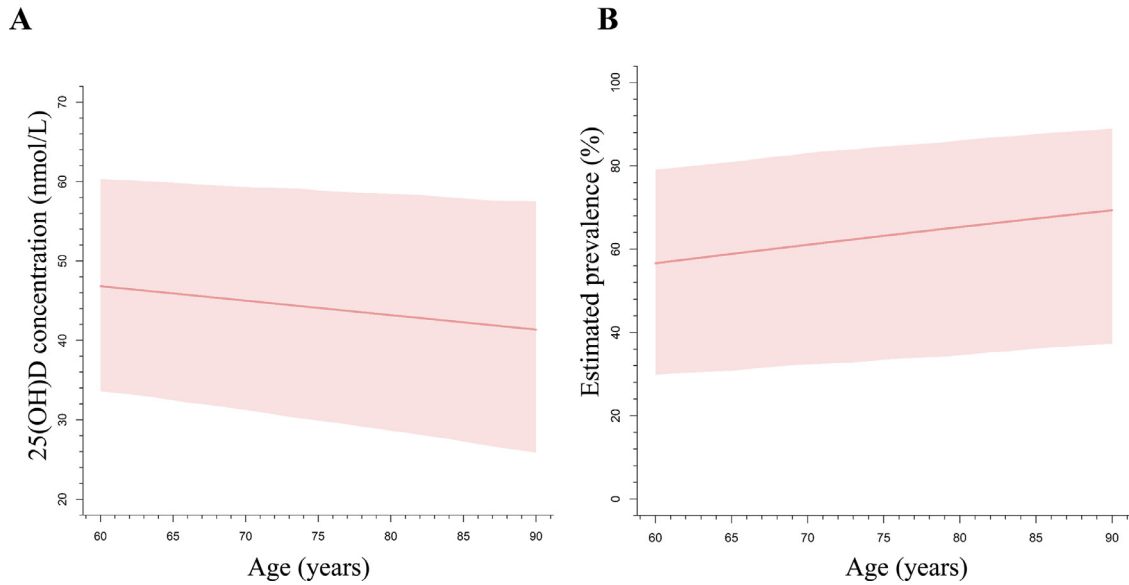
A

B

Fig. 4. The relationship of age with the estimated 25(OH)D concentration (A) and with VitD inadequacy (B) of elderly people in Mainland of China. A Hierarchical Bayesian meta-regression model was used to estimate the trend of age with the effect sizes. A random effect of age between studies was specified in the model, and both the between- and within-study variances were taken account in the model. Abbreviations: VitD = Vitamin D; 25(OH)*D* = 25-hydroxyvitamin D.
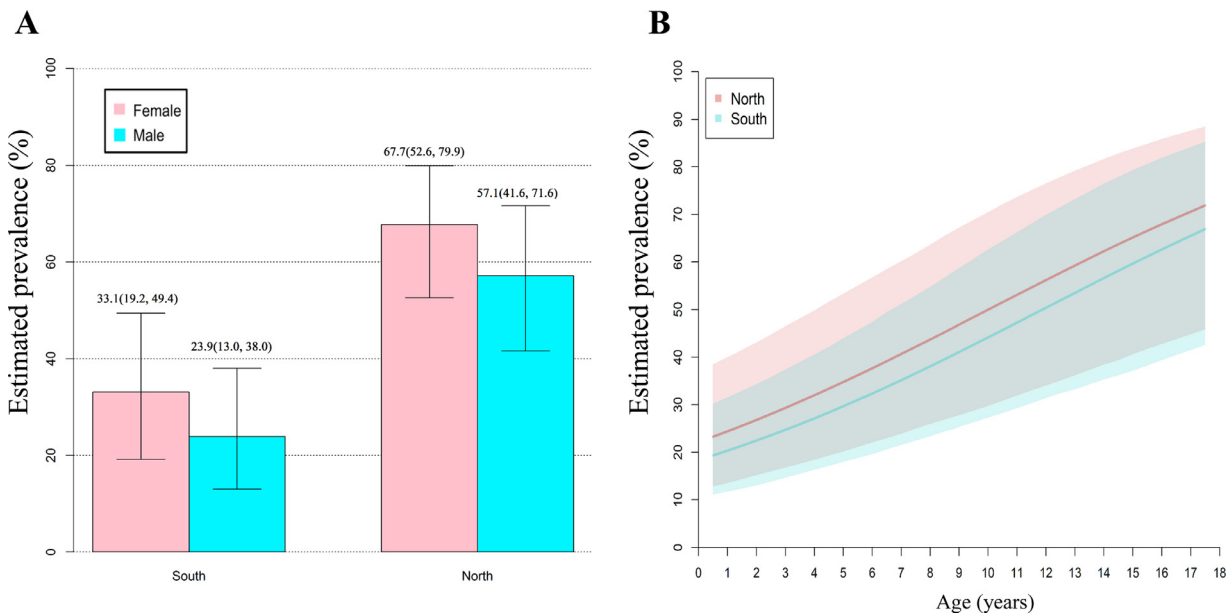
A

B

Fig. 5. Potential effects of sex, latitude and age on VitD inadequacy of children and adolescents in Mainland of China. **A** shows the estimated prevalence of VitD inadequacy based on sex and latitude. The between-study variance (σ^2) and 95%CrI was 1.2 (0.7−2.2). **B** shows the relationship between age and VitD inadequacy based on latitude. The between-study variance (σ^2) and 95%CrI was 1.0 (0.4−2.2). The detailed model and parameter estimation were described in the Supplementary file 2.2 and 2.3.

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

rarely used in Chinese individuals [39]; and (3) Insufficient dietary VitD intake including eggs, fish and sea foods are also prevalent in China [40]. Similarly, poor VitD condition of youth in Mainland of China was also prevalent, with 52.2 nmol/L of overall mean 25(OH)D concentration and 46.8% of VitD inadequacy. That was poorer than condition of children and adolescents in the US or Europe among whom 9%−20% had VitD inadequacy [34,41]. In addition, we observed that the prevalence of VitD inadequacy was higher in adults than that in children and adolescents (63.2% versus 46.8%) in Mainland of China. Our finding suggests that VitD inadequacy in Chinese adults is becoming a public health problem, which requires need of more attentions and interventions. Strategies such as adequate sunshine exposure, more dietary VitD intake, and VitD supplements could be encouraged in Chinese adults.

Another finding in our work is that the pooled prevalence of VitD inadequacy may significantly increase with age in children and adolescents, as well as in older people. In China, regular VitD supplementation is recommended for children from birth, but this health intervention is mainly performed among children under 3 years old. A survey showed that only 16.6% of children with age between 3 and 12 years old had VitD supplementation, and this percentage decreased with increasing age [42]. Additionally, dietary habits and increased schoolwork also reduce outdoor activities, which results in less sunshine exposure for VitD synthesis. That may explain why VitD inadequacy is more prevalent as children grow up. Our work also revealed an increasing trend between VitD inadequacy and age in this population. Chinese older people often advocate a bland diet with heavy on vegetables and seldom take VitD supplements. Besides of less VitD intake and less sunshine, the body function of older people significantly declines with age [43,44]. The evidence above supported our results.

In agreement with the results from other studies, we also found that Chinese women tended to have a lower 25(OH)D concentration and a higher prevalence of low VitD status than men [4,45]. A possible explanation is the effects of different sexual hormones such as testosterone [46]. Another explanation is different lifestyles between males and females, including smoking, alcohol consumption, sun exposure, physical activity and fat intake [47]. In addition, we identified that VitD inadequacy was most prevalent in northern girls and least prevalent in southern boys, suggesting that latitude is another important factor influencing VitD metabolism besides sex. Compared with southern areas, northern areas are in higher latitudes and have short sunshine time, which results in less endogenous production of VitD [22]. However, we did not observe the influence of latitude on VitD inadequacy in adults. That may be because adults have more complex dietary habits and lifestyles.

Detection assays seemed not to influence the pooled outcomes. From older RIA to new chemical assays, they are proven usable to measure serum VitD levels. In general, although there are some variations due to differences of technology and instruments, these assays are comparable; all have similar assay linearity and precision to identify low VitD status [48,49]. That may explain the non-significant effect of detection assays in this study. Curiously, we did not observe the effect of season on the overall mean 25(OH) D concentration and the pooled prevalence of VitD inadequacy. A possible reason is the insufficient number of available studies. About 1/3 of the included studies did not reported data based on seasons, such as investigation across seasons or not specifying seasons. The remaining studies used for evaluating season's effect came from different study populations and geographical regions. The effect of season may be covered by these factors, and this study might have insufficient power for identification.

This study provides the most up-to-date national representative estimates of VitD conditions in the general population in Mainland of China. However, some limitations should be considered when interpreting our findings. First, we found that sex, age and latitude were significantly associated with the prevalence of low VitD status in children and adolescents. However, we failed to establish the fit model including all these factors because of the restricted availability of primary data in eligible studies. Therefore, we explored sex-specific and age-specific prevalence based on latitude respectively. Second, although some studies used complex sampling method, we did not obtain the data adjusted by complex sampling method. We extracted the crude mean 25(OH) D concentration and the crude prevalence of low VitD status, which were handled as if obtained from simple random sampling in meta-analysis. Third, we did not observe the effect of 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 VitD conditions and age in children/ adolescents, and in older people, respectively. However, we did not evaluate the association between VitD conditions and all ages. There also may be a quadratic relationship of VitD conditions with age. More studies are needed for this investigation in the future.

In summary, this study suggests that low VitD 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 VitD inadequacy in children/ adolescents, and in older people, additional strategies and more detailed guidelines for VitD 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, Writing − 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

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Supplementary materials

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

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