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REVIEW

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Circulating levels of 25-hydroxyvitamin D in relation to hypertension in children and adolescents: a systematic review and dose–response meta-analysis of epidemiologic studies with GRADE assessment

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Abstract

Aims Findings of previous observational investigations about the relation between circulating 25-hydroxyvitamin D (25(OH)D) and hypertension (HTN) in children and adolescents were inconsistent. This systematic review and dose–response meta-analysis summarized the relation between circulating 25(OH)D and childhood HTN in epidemiologic studies.

Data synthesis A systematic search of four electronic databases, MEDLINE (PubMed), Web of Science (ISI) and Scopus and Google Scholar was performed up to April 2025. A total of 21 observational investigations that examined the relation of circulating 25(OH)D among children and adolescents and HTN, and reported RRs or ORs with 95% CIs were included. Findings demonstrated that greater circulating 25(OH)D had an association with a 19% decline in odds of HTN (95%CI 0.70, 0.93). Although a significant inverse relation was seen among highest 25(OH)D concentrations and odds of HTN in cross-sectional studies (OR = 0.81; 95% CI 0.69, 0.96), cohorts did not illustrate a significant relation (RR = 0.76; 95% CI 0.52, 1.12). Also, the observed relation of 25(OH)D levels and odds of HTN was significant in non-Asian societies (OR = 0.66; 95% CI 0.53, 0.82), but not in Asian societies (OR = 0.99; 95% CI 0.88, 1.12). Linear dose–response analysis demonstrated that each 25 nmol/L increment in 25(OH)D concentrations was related with a 5% marginal decrease in odds of HTN (OR = 0.95; 95% CI 0.90, 1.01). Furthermore, a significant U-shape nonlinear association was found between 25(OH)D concentrations and HTN.

Conclusion In conclusion, greater levels of circulating 25(OH)D levels was linked to a significantly decreased odds of childhood HTN. Moreover, the association was mostly observed in cross-sectional studies and non-Asian countries. Also, non-linear analysis has found a U-shape significant association between circulating 25(OH)D concentrations and HTN in children. The most reduction in odds of HTN was seen in optimum levels of circulating 25(OH)D levels from 35 to 75 nmol/L.

Systematic review registration PROSPERO registration no. CRD42022380969.

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Statement of significance This meta-analysis of epidemiologic studies disclosed an inverse association among circulating 25(OH)D levels and odds of elevated blood pressure among children and adolescents.

Keywords Circulating 25-hydroxy vitamin D, Hypertension, Children, Adolescents, Meta-analysis, Epidemiologic studies

Introduction

Hypertension (HTN), or elevated blood pressure (BP), as a common known risk factor for cardiovascular disease (CVD) and renal disorders, is also associated with a variety of other diseases that significantly contribute to mortality [1, 2]. Elevated blood pressure in childhood is specifically recognized as a considerable public health condition [3]. Unlike adults, in children (5–12 years) or adolescents (12–18 years), it is a complex process to evaluate blood pressure values. Childhood HTN is defined as having systolic blood pressure (SBP) and/or diastolic blood pressure (DBP) equal or greater than 95 th percentile by sex, age, and height [4]. Elevated BP in children and adolescents is defined as HTN and pre-hypertension, which means having SBP and/or DBP equal to or greater than 90 th percentile by sex, age, and height [4]. Evidence reveals that HTN in childhood is transferred to high blood pressure and atherosclerosis in adulthood [5]. Nowadays, one of the most important causes of increased HTN prevalence in childhood is the elevated prevalence of obesity in this age group [6, 7]. Global prevalence of children with elevated BP has become 4%, especially in adolescents during puberty and children with overweight or obesity [3].

Several factors are known to affect childhood blood pressure including age, gender, diet, obesity and stress as long as genetics, race and body size [8–11]. Furthermore, previous investigations suggested that decreased circulating 25(OH)D level have an association with poor health outcomes among children, notably those chronic health conditions which are related to obesity, most specifically HTN [12, 13]. Low concentrations of 25(OH)D, described as vitamin D deficiency, are prevalently observed among children and adolescents all over the world, even in locations rich in sunlight all-year round [14, 15].

Despite the fact that several previous studies illustrated the relation of circulating 25(OH)D levels and childhood HTN, the data were contradictory. Some investigations revealed that declined circulating 25(OH)D level was significantly correlated with enhanced risk of elevated BP in children [16, 17], while others did not report significant associations [18, 19]. For instance, in a study by Nam et al. that examined the relationship between vitamin D adequacy and cardiometabolic risk among Korean adolescents, no significant association was found between vitamin D deficiency ($\leq$ 50 nmol/L) and elevated BP (P = 0.673), although there was a significant difference in DBP values of adolescents with deficient and those with sufficient vitamin D concentration (P = 0.002) [18]. On the other hand, some other reports revealed a non-significant decreased risk of childhood HTN in vitamin D deficient ones [20, 21]. Moreover, finding of investigations that used different definitions for high blood pressure or different 25(OH)D cut-points were contradictory [20, 22, 23]. A previous systematic review of 85 investigations on vitamin D and HTN in adolescents reported that the findings of studies mainly indicated a lack of association, but this conclusion was based on a narrative method and a meta-analysis was not conducted [24]. In order to have an accurate finding, the weight of the studies (not the number of studies) should be considered. Performing a meta-analysis could dedicate a weight to each eligible study based on its sample size, and study design, and facilitate more accurate conclusions. As far as we know, no previous systematic review or meta-analysis has summarized the relation between circulating 25(OH)D and childhood HTN in observational studies. We therefore performed a systematic review and meta-analysis of epidemiologic studies to evaluate the relationship between 25-hydroxyvitamin D and elevated BP in children and adolescents. We also examined whether 25(OH)D concentrations could reduce the odds of HTN in a linear or nonlinear fashion. Our study was based on the hypothesis that optimal 25(OH)D levels might be related to a decreased risk of HTN in children and adolescents.

Methods and materials

Search strategy

A systematic search was conducted on electronic MEDLINE (PubMed), Web of Science (ISI) and Scopus databases to find all published articles up to April 2025, with no language or publication time limitation. Keywords and medical subjects' headings (MeSH) terms that were applied in the systematic literature search are documented in details in Supplemental Table 1. Besides that, the first 200 search records within Google Scholar were checked according to title/abstract and full-text, without Boolean operators or parentheses. Moreover, to identify additional studies, a manual search was conducted through bibliographies of the relevant studies. Grey literature, such as conference proceedings, conference abstract, theses, dissertations and unpublished articles

were not considered. The process of selecting article was performed independently by two investigators (E.M. and P.R.) through title and abstract screening and the principal investigator (P.S.) resolved any disagreement to reach a consensus. We carried out this systematic review and meta-analysis according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) [25] statement, as shown in Supplemental Table 2. Furthermore, registration of the study protocol was done at Prospero (http://www.crd.york.ac.uk/Prospero; no. CRD42022380969).

Inclusion criteria

According to PICO-framework (Population, Intervention, Comparison, Outcome), all original investigations with the following criteria were included in this meta-analysis: (1) performed on children or adolescents (≤ 18 years old); (2) considered 25(OH)D concentrations as the exposure; (3) considered HTN or elevated BP as the outcome; (4) were epidemiologic studies with cross-sectional or cohort design; (5) reported odds ratios (ORs), prevalence ratios (PRs) or risk ratios (RRs) with corresponding 95% confidence intervals (or sufficient data to calculate these values) for the association between levels of 25(OH)D and HTN. Table 1 illustrates details of population, intervention/exposure, comparison/control, outcome, and study design (PICOS) criteria.

Exclusion criteria

Two reports were published from the School-based Cardiovascular and Bone Health Promotion Program (SCVBH) cohort [26, 27]; they had the same follow-up period (2 years), so the investigation with more participants was included in our analysis [26], and the other one was excluded. More relevant excluded articles are presented in details in Supplemental Table 3. Exclusion criteria were studies which: (1) reported mean systolic or diastolic BP or prevalence of HTN; (2) included more than 18 years old individuals with no separate reports for the under 18-year population; (3) documented correlation coefficient or ß regression coefficients for the relationship. Studies reported correlation coefficients were excluded because these effect sizes could not be converted to OR/RR/HR.

Data extraction

Extraction the following data from each eligible investigation was performed based on a pre-designed table: the first author's last name, publication year, study design, health status of participants, country, age range or mean age, number of included participants, number of cases with HTN, gender, latitude, methods of circulating 25(OH)D assessment, 25(OH)D concentrations categories, unit of circulating vitamin D, OR or RR and 95% CI for the relation between 25 (OH) D and HTN, cut-off-points utilized in order to define HTN, adjustments for potential confounders. Data was extracted independently by two researchers (E.M. and P.R.) and the principal investigator (P.S.) supervised the process.

Quality assessment of included studies

Quality of all eligible investigations was assessed by the use of Newcastle–Ottawa quality assessment scale (NOS) [28] (adapted for cross sectional and cohort studies). In this scale, a total of 9 scores can be allocated to a cohort study, as the greatest quality: 4 scores for selection of participant, 2 scores for comparability (including adjustments of season of blood collection or sun exposure and body mass index (BMI)), and 3 scores for assessment of outcome. NOS allocates a total of 10 scores to a cross sectional studies as the highest quality: 5 scores for participants' selecting process, 2 scores for comparability, and 3 scores for assessment of outcome. Besides that, the quality of evidence was assigned by the use of Grading of Recommendations, Assessment, Development and Evaluations (GRADE) [29] through GRADEpro (GRADEproGDT, www.gradepro.org) [30]. Based on GRADE approach, the body of evidence certainty can be classified as high, moderate, low or very low.

Table 1 PICOS criteria for inclusion of studies

Parameter	Criteria
Participants	Children or adolescents (≤ 18 years old)
Intervention/exposure	Different categories of circulating 25-hydroxyvitamin D
Control/comparison	Individuals in the lowest category of circulating 25-hydroxyvitamin D
Outcome	Hypertension
Study design	Observational studies including prospective cohort, casecohort, cross-sectional, and case–control studies

Statistical analysis

Calculation of log OR or RR and its standard error was done by using the reported RR, OR or PR and 95% CI for the relation of circulating 25(OH)D and childhood HTN. In case of studies that provided sufficient data to calculate these values, OR and SE were calculated [31–34]. For those investigations which illustrated the estimate for the lowest versus the greatest level of circulating 25(OH)D, OR was changed to estimate for the greatest versus the lowest level. For obtaining the overall effect size, a fixed-effect model was applied for low heterogeneity ($I^2 <$ 50%) and a random-effects model was used for high heterogeneity ($I^2 >$ 50%). Between-study heterogeneity was evaluated by using Cochran's Q test and I^2. In case of significant between-study heterogeneity, subgroup analysis was done based on confounders/moderators (including study design [cross-sectionals vs. cohorts], study location [Asian vs. non-Asian countries], sex, 25(OH)D levels used for comparison, HTN definition cut-off points, method of 25(OH)D assessment, participants health status, having adjustments, and quality scores of investigations) to obtain possible sources of heterogeneity. For quality assessment of the studies, since there is no specific cut-off point, the median score of included studies (score 8) was considered as the cut point to categorize studies into low and high quality; such that the studies with a score of 8 or more was considered as high quality and those with lower scores were deemed to low quality studies. Then, subgroup analysis was performed in case of significant between-study heterogeneity. Meta-regression was also performed for continuous variables (including age range and latitude). Sensitivity analysis was also conducted to check the extent to which inferences might be dependent to a particular study. Publication bias assessment was performed by visual inspection of funnel plots. Begg's and Egger's test was also obtained for Formal statistical assessment of funnel plot asymmetry.

Dose–response analysis was performed based on a previously described method by Greenland and Longnecker [35] and Orsini et al. [36]. The natural logs of the ORs/RRs/PRs and 95% CIs across different circulating 25(OH)D levels were obtained for calculation of study specific slopes (linear trends) and 95%CIs for 25 nmol/L (or 10 ng/mL). In this method, the distribution of participants with HTN and the OR/RR/PR with the variance estimates for at least three quantitative categories of 25(OH)D for nonlinear trends were needed. The mean or median level of circulating 25(OH)D in each category was used to define the corresponding OR/RR/PR for each study. For studies that illustrated the 25(OH) D concentrations as ranges, the midpoint in each category was estimated by calculation of the average of the lower and upper bounds. In case of open-ended highest category, the length of the open-ended interval was supposed to be similar to that of the adjacent interval. In case of open-ended lowest category, the lower border for 25(OH)D was set to zero. If 25(OH)D levels were reported as ng/mL, the values were converted to nmol/L by multiplying the ng/mL by 2.5. For examination of potential nonlinear dose–response associations between 25(OH)D and odds of HTN restricted cubic splines (3 knots at fixed percentiles of 10, 50, and 90% of the distribution) were used.

Statistical analyses were carried out through STATA version 14.0 (STATA Crop, College Station, TX, USA). P values < 0.05 were considered as statistically significance for all tests including Cochran's Q test.

Results

The primary systematic search resulted in 7502 articles, after excluding duplicate studies. Two authors (E.M. and P.R.) have separately screened titles and abstracts at first. In the second round, the full texts of 495 articles were examined. Finally, 21 studies were included in the current systematic review and meta-analysis. Details of flow diagram search strategy and study selection are showed in Fig. 1.

Study characteristics

Details of all 21 eligible investigations are showed in Table 2. The publication date of reports was between 2009 and 2024. Eighteen investigations had cross-sectional design, while 3 others were cohort studies. Overall, 27,923 and 10,001 individuals were respectively included in cross-sectional and cohort studies. Of the included cross-sectional investigations, four studies were conducted in Korea [13, 18, 31, 37], two studies in China [20, 21], Spain [16, 33], three studies in United States [22, 34, 38], and the remaining in Turkey [32], Brazil [23], Portugal [39], Australia [17], Italy [40], Iran [41] and Ukraine [42]. One of the cohort studies was conducted in Denmark [43], another in China [26] and the last one was done in the United States [19]. Only one of the studies was done on girls [31], while others were conducted on both sexes. Circulating 25(OH)D concentrations were measured by use of different methods, including chemiluminescence immunoassay (CLIA) (n = 10), radioimmunoassay (RIA) (n = 4 studies), electrochemiluminescence immunoassay (ECLIA) (n = 2), high-performance liquid chromatography (HPLC) (n = 2), enzyme immunoassay (EIA) (n = 2); while, another study did not mention the applied method for measuring 25(OH)D levels. In case of outcome of interest, ten studies illustrated the relation between levels of circulating 25(OH)D and HTN which was defined as systolic and/or diastolic BP ≥ 90 th national percentile for age, sex, and height [13, 16–18, 23, 38–41, 43], six others used systolic and/or diastolic BP

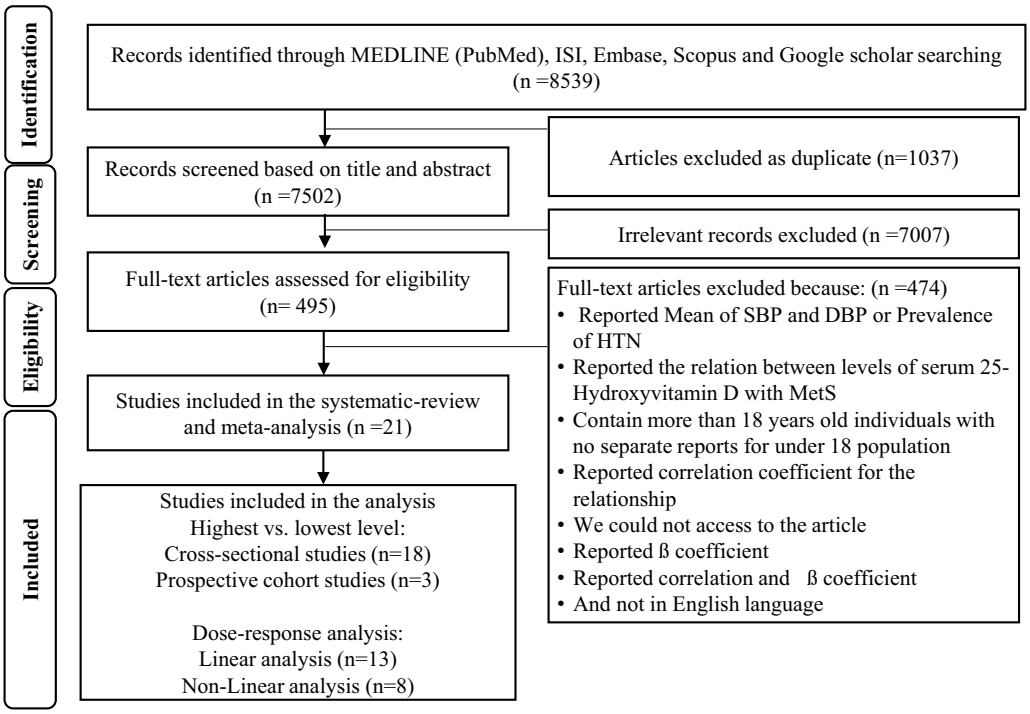

Fig. 1 Flowchart of the study selection process

≥95 th country-specific percentiles to define HTN [21, 22, 26, 32–34], four studies defined HTN as BP ≥130/85 mmHg [20, 31, 37, 42], and the last one used the cut-off-point BP ≥75 th percentile [19]. Although a great number of investigations were carried out on healthy participants, four of the investigations were conducted on adolescents with obesity [17, 32, 33, 42] and one study was conducted on children with chronic kidney disease (CKD) [34]. Confounders which were mostly controlled in the studies were age (n =15), sex (n =12), BMI (n =9), and physical activity (n =7). Adjustments for other important confounders were as follows: 1 study made adjustment for sunlight exposure, 2 studies for dietary vitamin D intake, 5 studies for socioeconomic status, and 4 studies for race and ethnicity. Details of quality assessment for eligible studies are illustrated in Supplemental Table 4. One of the cohort studies was categorized as high quality, while two others were deemed to low quality category. Among cross-sectional investigations, ten investigations had high quality and eight others were low quality.

Meta-analysis of highest versus lowest circulating 25(OH)D level in relation to childhood hypertension

Combined 21 effect sizes from 21 studies (n =37,924) resulted to an overall effect of 0.81 (95% CI 0.70, 0.93) which means that great levels of 25(OH)D in comparison to low level could decrease odds of childhood HTN by 19% (Fig. 2). Heterogeneity was low (I^2= 47.2%, $P_{Q\text{-test}}$= 0.009). Subgroup analyses were done and the results are presented in Figs. 2, 3 and Table 3. Statistically significant relations between level of 25(OH)D and elevated BP were found in most of the subgroups. In cross-sectional studies, an inverse association was observed (OR =0.81; 95% CI 0.69, 0.96), while no significant relationship was observed in cohorts (RR =0.76; 95% CI 0.52, 1.12) (Fig. 2). Levels of 25(OH)D was inversely related to odds of HTN in children of non-Asian societies (OR =0.66; 95% CI 0.53, 0.82), while in Asian children, the relation was not statistically significant (OR =0.99; 95% CI 0.88, 1.12) (Fig. 3). In subgroup analysis for Asian versus non-Asian societies, heterogeneity was low in both subgroups (Asian countries: I^2= 0.0%, $P_{Q\text{-test}}$= 0.95 and non-Asian countries: I^2= 46.6%, $P_{Q\text{-test}}$= 0.04) (Fig. 3). Meta-regression was also conducted to investigate the probable effect of age and latitude on the overall effect. Findings showed that mean age (β =0.0309, P= 0.33, I^2 residual =48.36%) and latitude (β =0.0002, P= 0.99, I^2 residual =49.46%) did not significantly affect the association of circulating 25(OH)D with childhood HTN. Sensitivity analysis determined that excluding each of the eligible studies did not significantly influence the overall estimate. No evidence for publication bias was observed (Begg's test =0.17, Egger's test =0.10).

Table 2 Detailed characteristics of the eligible epidemiologic studies included in the systematic review and meta-analysis for circulating 25(OH)D concentration in relation to high blood pressure in children

First Author (Year)	Design	Health status of participants	Country	Age Range/ mean ± SD	No. Participants/ No. HTNcases	Gender (n)		Latitude, °N/S	25(OH) D Levels, (nmol/L or ng/mL)	OR/RR (95%CI)	Method 25(OH)D Assessment	Sample (Serum or plasma)	Definition Of high blood pressure/ Device or the way of assessment	Adjustments	Quality score
						Girls	Boys								
Kumar et al. [34]	Cross-sectional (CKiD) (2005–2020)	Children with Chronic Kidney Disease	US	11 ± 5.18	370/72	139	231	37.0902°N	< 50 nmol/L ≥ 50 nmol/L	1.00 (reference) 0.95 (SE:0.32)	CLIA	Serum	95 th age-sex-height-specific BP percentile/ by auscultation the right arm (aneroid sphygmomanometer (Mabis MedicKit 5))	–	5
Xiao et al. [26]	Cohort/2 years follow-up (SCVBH) (2017–2019)	Healthy	China	10.9 ± 3.3	8857/591	NR	NR	35.8617°N	< 30 nmol/L ≥ 30	0.96 (0.73, 1.27) 1.00 (reference)	CLIA	Serum	SBP and/or DBP ≥ 95 th sex, age and height-specific percentile/ From the right brachial artery three measurements with 1–2 min intervals (OMRON-HBP-1300)	1, 2, 4, 5, 10, 11, 41, 43, 44, 45	6
Shulhai et al. [42]	Cross-sectional	Adolescents with obesity or overweight	Ukraine	12–17 15.1 ± 2.1	136/95	NR	NR	48.3794°N	< 20 ng/mL ≥ 20	0.93 (0.57, 1.68) 1.00 (reference)	EIA	Serum	SBP ≥ 130 or DBP ≥ 85 mmHg (NHBP)/ On both upper limbs 3 measurements in a sitting position using a mechanical sphygmomanometer	1, 2, 4, 5, 28, 37, 46	7
Qorbani et al. [41]	Cross-sectional (CASPIAN-V study)	Healthy	Iran	7–18 12.18 ± 3.04	2596/267	1166	1430	32.4279°N	< 10 ng/mL 10–30 > 30	1.10 (0.68, 1.77) 0.92 (0.68, 1.25) 1.00 (reference)	CLIA	Serum	SBP or DBP ≥ 90 th percentile/ In a sitting position two measurements with a 5-min interval using a standardized mercury sphygmomanometer	1, 2, 4, 7, 13, 28	7

Table 2 (continued)

First Author (Year)	Design	Health status of participants	Country	Age Range/ mean ±SD	No. Participants/ No. HTNcases	Gender (n)		Latitude, °N/S	25(OH) D Levels, (nmol/L or ng/mL)	OR/RR (95%CI)	Method 25(OH)D Assessment	Sample (Serum or plasma)	Definition Of high blood pressure/ Device or the way of assessment	Adjustments	Quality score
						Girls	Boys								
Tang et al. [20]	Cross-sectional (2013)	Healthy	China	7–18 11.1 ±3.3	2112/NR	1055	1057	35.8617°N	Q1(≤ 16.19 ng/mL) Q2 (16.20–19.74) Q3(19.75–22.99) Q4 (≥ 23.00)	0.86 (0.45, 1.64) 0.49 (0.23, 1.02) 1.04 (0.56, 1.95) 1.00 (reference)	EIA	Serum	SBP ≥ 130 or DBP ≥ 85 mmHg (NHBP)/Two measurements at 1-min intervals after a 5-min rest, with a validated mercury sphygmomanometer (model XJ1ID, China)	1, 2, 4, 5, 12–15, 34	9
Xiao et al. [21]	Cross-sectional (2013–2014)	Healthy	China	6–18 11.9 ±3.7	6091/706	3034	3035	35.8617°N	T1 (≥ 50 nmol/L) T2 (30–50) T3 (< 30)	1.00 (reference) 1.23 (1.01, 1.50) 1.08 (0.87, 1.34)	CLIA	Plasma	SBP and/or DBP ≥ 95 th sex, age and height-specific percentile/ Three measurements with 1–2 min intervals (OMRON HEM-7012) in a sitting position from the right arm	1–5, 9–11, 16–18	9
Durá-Travé et al. [33]	Cross-sectional (2015–2016)	Adolescents with severe obesity	Spain	10.2–15.8 13.4 ± 1.49	236/113	82	154	40.4637°N	T1 (< 50 nmol/L) T2 (50–75) T3 (> 75)	1.00 (reference) 0.48 (SE:0.26) 1.01(SE:0.32) SBP	CLIA	Plasma	SBP and/or DBP ≥ 95 th sex, age and height, American reference charts (NHBP)/In the right arm, with the patient in the supine position, using a Visomat comfort 20/40 (Roche Diagnostics Inc., Amman, Jordan) digital blood pressure monitor	–	5
									T1 (< 50 nmol/L) T2 (50–75) T3 (> 75)	1.00 (reference) 0.25 (SE:0.61) 1.43 (SE:0.44) DBP					

Table 2 (continued)

First Author (Year)	Design	Health status of participants	Country	Age Range/ mean ±SD	No. Participants/ No. HTNcases	Gender (n)		Latitude, °N/S	25(OH) D Levels, (nmol/L or ng/mL)	OR/RR (95%CI)	Method 25(OH)D Assessment	Sample (Serum or plasma)	Definition Of high blood pressure/ Device or the way of assessment	Adjustments	Quality score
						Girls	Boys								
Wang et al. [19]	Cohort/3–18 years follow-up (CHS: 2004–2018)	Healthy	US	3–18	760/298			37.0902°N	< 11 ng/mL ≥ 11	1.35(0.98, 1.84) 1.00 (reference)	High-performance LC–MS	NR	SBP ≥ 75 Percentile (AAPG) American Academy of Pediatrics Guidelines/ On the right arm with child in a sitting position using the validated automatic sphygmomanometer Masimo SET	1, 2, 6, 8, 11, 19–27, 33	7
Kim et al. [37]	Cross-sectional (KNHANES 2010–2014)	Healthy	Korea	12–18 15.14 ±0.3	2314/95	1070	1244	35.9078°N	≥ 20 ng/mL < 20	1.00 (reference) 0.72 (0.28, 1.89)	NR	NR	SBP ≥ 130 mmHg or DBP ≥ 85 mmHg (IDF)/Three measurements on the right arm after a 5-min resting	1, 2, 4, 7, 28–32	5
Larsen et al. [43]	Cohort/3 years-follow-up	Healthy	Denmark	3	384/NR	NR	NR	56.2639°N	≤ 45.1 nmol/L > 45.1 ≤ 45.1 nmol/L > 45.1	1.00 (reference) 0.36 (0.15, 0.85) SBP 1.00 (reference) 0.58 (0.28, 1.22) DBP	LC/MS	NR	SBP > 90 th percentile DBP > 90 th percentile/ In the left arm by a Welch Allyn device using a cuff of appropriate size	1, 8, 33–35	8
Gul et al. [32]	Cross-sectional (2012–2016)	Adolescents with obesity	Turkey	6–17	310/60	178	132	38.9637°N	< 15 ng/mL 15–29 ≥ 30	1.00 (reference) 1.67 (SE:1.04) 6.2 (SE:2.34)	CLIA	NR	BP ≥ 95 th percentile according to age, sex, and height/ BP details were collected from the electronic medical records used at the hospital	–	5

Table 2 (continued)

First Author (Year)	Design	Health status of participants	Country	Age Range/ mean ±SD	No. Participants/ No. HTNcases	Gender (n)		Latitude, °N/S	25(OH) D Levels, (nmol/L or ng/mL)	OR/RR (95%CI)	Method 25(OH)D Assessment	Sample (Serum or plasma)	Definition Of high blood pressure/ Device or the way of assessment	Adjustments	Quality score
						Girls	Boys								
Milagres et al. [23]	Cross-sectional	Healthy	Brazil	8–9	378/25	197	181	14.2350° S	< 75 nmol/L ≥ 75	1.79 (0.93, 3.43) 1.00 (reference)	CLIA	Serum	SBP or DBP ≥ 90 th percentile/In sitting position after resting for at least 5-min at three different measurements using an automatic inflation BP monitor (OMRON, HEM 907)	1–3, 6–9, 36, 37, 42	8
Cabral et al. [39]	Cross-sectional (EPITeen 2003–2004)	Healthy	Portugal	13	514/169	270	244	39.3999° N	Q1 (< 13.0 ng/mL) Q2 (13.0–16.0) Q3(17.0–20.0) Q4(> 20.0)	1.08 (0.62, 1.90) 1.29 (0.70, 2.36) 1.06 (0.58, 1.96) 1.00 (reference)	CLIA	Serum	SBP or DBP ≥ 90 th percentile for age, sex, and height/Two measurements after 10 min of rest separately by at least 5 min with a mercury sphygmomanometer	2–5, 8	9
Kao et al. [17]	Cross-sectional (2008–2011)	Adolescents with obesity	Australia	12.1 ± 3	208/148	NR	NR	25.2744° S	Q1 (≤ 36 nmol/L) Q2 (37–47) Q3 (48–56) Q4 (57–71) Q5 (≥ 72)	4.00 (1.34, 11.91) 3.81 (1.31, 11.08) 1.82 (0.69, 4.77) 1.68 (0.65, 4.37) 1.00 (reference)	Competitive ECLIA	Serum	SBP or DBP ≥ 90 th percentile for age and sex/ By auscultation of the right brachial artery via a manual sphygmomanometer	1–3, 5	8
Belmonte et al. [16]	Cross-sectional	Healthy	Spain	8–13 10.7 ± 1.0	314/29	156	158	40.4637°N	T1 (4.0–19.4 ng/mL) T2 (19.5–25.3) T3 (25.4–55.5)	1.00 (reference) 0.59 (0.28, 1.24) 0.50 (0.32, 0.79)	CLIA	Plasma	SBP or DBP ≥ 90/ In sitting position on the right arm by digital sphygmomanometer	1, 2	7

Table 2 (continued)

First Author (Year)	Design	Health status of participants	Country	Age Range/ mean ±SD	No. Participants/ No. HTNcases	Gender (n)		Latitude, °N/S	25(OH) D Levels, (nmol/L or ng/mL)	OR/RR (95%CI)	Method 25(OH)D Assessment	Sample (Serum or plasma)	Definition Of high blood pressure/ Device or the way of assessment	Adjustments	Quality score
						Girls	Boys								
Nam et al. [18]	Cross-sectional (KNHANES IV 2008–2009)	Healthy	Korea	12–18 14.7 ± 1.6	1504/434	712	792	35.9078°N	≤ 50 nmol/L >50	1.07 (0.77, 1.50) 1.00 (reference)	RIA	Serum	SBP or DBP ≥ 90 th percentile for age and sex, use of blood pressure-lowering medication or a previous diagnosis of hypertension/ By a standard mercury sphygmomanometer on the right arm	1, 2, 4, 5, 10, 38	8
Jang et al. [31]	Cross-sectional (KoCAS)	Healthy	Korea	13	320/18	320	-	35.9078°N	< 20 ng/mL ≥ 20	1.00 (reference) 1.14 (SE:0.35)	RIA	Serum	≥ 130/85 mmHg/On the right arm using a mercury sphygmomanometer	–	5
Lee et al. [13]	Cross-sectional (KMOSES)	Healthy	Korea	9 NR	1649/770	758	891	35.9078°N	Q1(< 15.5 ng/mL) Q2(15.5–18.3) Q3(18.4–21.6) Q4(> 21.6)	0.91 (0.69, 1.20) 0.94 (0.71, 1.23) 0.91 (0.69, 1.20) 1.00 (reference)	CLIA	Plasma	SBP or DBP ≥ 90 th percentile for age, sex, and height/ By a standard brachial cuff technique	5	8
Pacifico et al. [40]	Cross-sectional	Healthy	Italy	11 11.2 ± 0.2	452/164	241	211	41.8719°N	T1(< 17.0 ng/mL) T2(17.0–27.0) T3(> 27.0)	1.72 (1.02, 2.92) 1.18 (0.90, 1.55) 1.00 (reference)	ECLIA	Serum	SBP or DBP ≥ 90 th percentile for age, gender, and height/At the right arm after a 10-min rest in the supine position by using an automated oscillatory system	1, 2, 5, 39	8

Table 2 (continued)

First Author (Year)	Design	Health status of participants	Country	Age Range/ mean ±SD	No. Participants/ No. HTNcases	Gender (n)		Latitude, °N/S	25(OH) D Levels, (nmol/L or ng/mL)	OR/RR (95%CI)	Method 25(OH)D Assessment	Sample (Serum or plasma)	Definition Of high blood pressure/ Device or the way of assessment	Adjustments	Quality score
						Girls	Boys								
Reis et al. [38]	Cross-sectional (NHANES 2001–2004)	Healthy	US	12–19 15.4 ± 2.0	3430/213	NR	NR	37.0902°N	Q1(< 15 ng/mL) Q2(15.0–21.0) Q3(21.1–26.0) Q4(> 26.0)	2.36 (1.33, 4.19) 1.26 (0.65, 2.44) 1.04 (0.55, 1.97) 1.00 (reference)	RIA	Serum	SBP or DBP ≥ 90 th percentile for age, sex, and height (NHBP)/4 measurements in seated subjects after a 5-min rest with a mercury-gravity sphygmomanometer	1, 2, 4–7	9
Kumar et al. [22]	Cross-sectional (NHANES 2001–2004)	Healthy	US	1–21	4989/164	NR	NR	37.0902°N	< 15 ng/mL 15–29 ≥ 30	2.50 (1.00, 5.90) 1.00 (0.50, 2.00) 1.00 (reference)	RIA	Serum	SBP or DBP > 95 th percentile of levels for the median height of each participant's specific age and gender or > 140/90 mm Hg in those ≥ 17 years of age (NHBP)/3 measurements for all of the participants	1, 2, 6, 7, 13, 24, 40–41	8

Adjustments: 1, Age; 2, Sex or gender; 3, Season of blood collection; 4, Physical activity; 5, BMI or zBMI or SDS-BMI; 6, Race or ethnicity; 7, Socioeconomic status; 8, Maternal educational level; 9, Dietary vitamin D intake; 10, Alcohol drinking; 11, Smoking; 12, Sun exposure time; 13, Screen time or television and computer use; 14, Intake of fruit & vegetables; 15, Intake of meat products; 16, Geographical location; 17, FMP; 18, MMI; 19, Maternal age; 20, Parity; 21, Preterm birth; 22, Birthweight; 23, Breastfeeding; 24, Child current overweight or obesity; 25, Maternal hypertensive disorder; 26, Diabetes mellitus; 27, Prepregnancy obesity; 28, Resident area; 29, Self-perceived health status; 30, Self-Perceived stress status; 31, Family history of chronic disease; 32, Sleep; 33, Season of birth; 34, Height; 35, Weight; 36, Parathyroid hormone; 37, Sedentary behavior; 38, Use of multivitamin or mineral supplements; 39, Tanner stage; 40, Milk intake; 41, Vitamin D supplementation; 42, Body fat percentage; 43, Dietary habits; 44, Family history of cardiometabolic risk factors; 45, Sexual maturity; 46, Income per family member

BMI, body mass index; BP, Blood pressure; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; CI, confidence interval; CKiD: Chronic Kidney Disease in Children OR, Odds ratio; RR, Relative risk; NR, Not reported; No, Number; HBP, High blood pressure; LC–MS, liquid chromatography–tandem mass spectrometry; CHS, Children's Health Study; NHBP, National high blood pressure Program; FMP, fat mass percentage; MMI, muscle mass index, KoCAS, Korean Children Adolescents Study; NHANES, National Health and Nutrition Examination Survey; ECLIA, Electro-chemiluminescence immunoassay; RIA, Radioimmunoassay; SCVBH, School-based Cardiovascular and Bone Health Promotion Program; KNHANES, Korea National Health and Nutrition Examination Survey; US, United States; Nmol/L, nanomoles per litter; ng/mL, nanogram/milliliter; N, Number; SE, standard error, CLIA; chemiluminescent immunoassay; EIA, enzyme immunoassay; T, tertiles; Q, quartiles; Q, Quintiles; KMOSES, The Korean Metabolic Disorders and Obesity Study in Elementary School Children; EPITeen, Epidemiological Health Investigation of Teenagers; AAPG, American Academy of Pediatrics Guidelines; IDF, International Diabetes Federation; CASPIAN-V, Childhood and Adolescence Surveillance and Prevention of Adult Non-communicable disease. The Newcastle–Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-Analyses. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

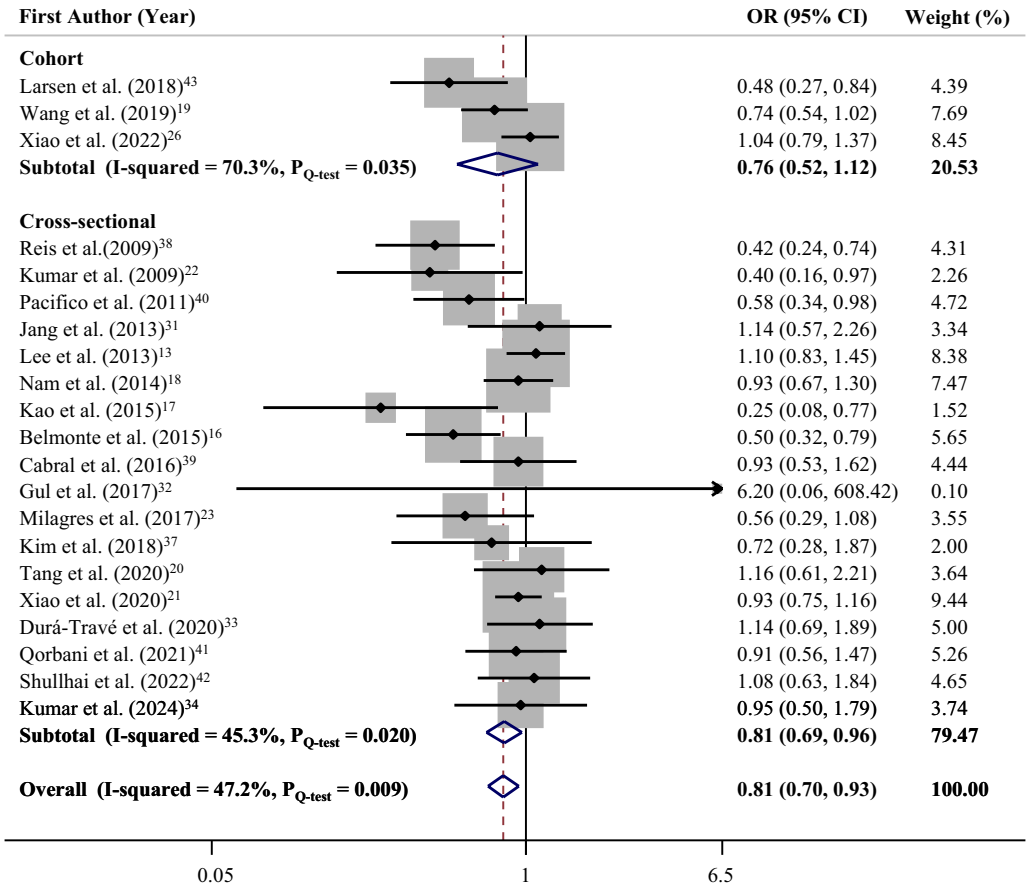

Fig. 2 Forest plot of prospective and cross-sectional studies that examined the association between highest versus lowest level of circulating 25(OH)D and odds of childhood HTN

Dose–response meta-analysis of circulating 25(OH)D concentrations and odds of childhood hypertension

Combination of effect sizes of 13 studies with a total of 19,212 subjects and 3105 children with HTN revealed that each 25 nmol/L increment in circulating 25(OH)D levels led to a non-significant 5% decrease in odds of elevated BP (OR = 0.95; 95% CI 0.90, 1.01) (Fig. 4). Moreover, a significant nonlinear relation among circulating 25(OH)D concentrations and childhood HTN was seen ($P_{nonlinearity} < 0.001$). As circulating 25(OH)D levels raised from 35 to 75 nmol/L, a steeper drop was observed in the odds of childhood HTN; however, the odds did not decline anymore for greater 25(OH)D levels and eventually started rising (Fig. 5).

GRADE assessment

The certainty of evidence was graded as high by using the GRADE approach. Results of GRADE assessment of the evidence are illustrated in Supplemental Table 5.

Discussion

This meta-analysis found that the greatest versus lowest level of circulating 25(OH)D was significantly related to a declined odds of HTN in children and adolescents. This inverse significant relation was mostly observed in cross-sectional studies (compared to cohorts) and non-Asian countries (compared to Asian societies). A U-shape relation between circulating 25-hydroxyvitamin D and HTN was also obtained in non-linear dose–response analysis which was statistically significant. The maximum odds reduction was seen in the range of 35–75 nmol/L (from deficiency to sufficiency or normal values) of 25(OH)D concentrations.

HTN is considered as a prevalent known risk factor for CVD and a considerable public health condition, specifically in childhood [1–3]. Previous investigations revealed that childhood HTN is transferred to elevated BP and atherosclerosis in adulthood [5]. Based on previous literature, vitamin D deficiency is described as 25(OH)D levels of < 50 nmol/L and the normal range for health

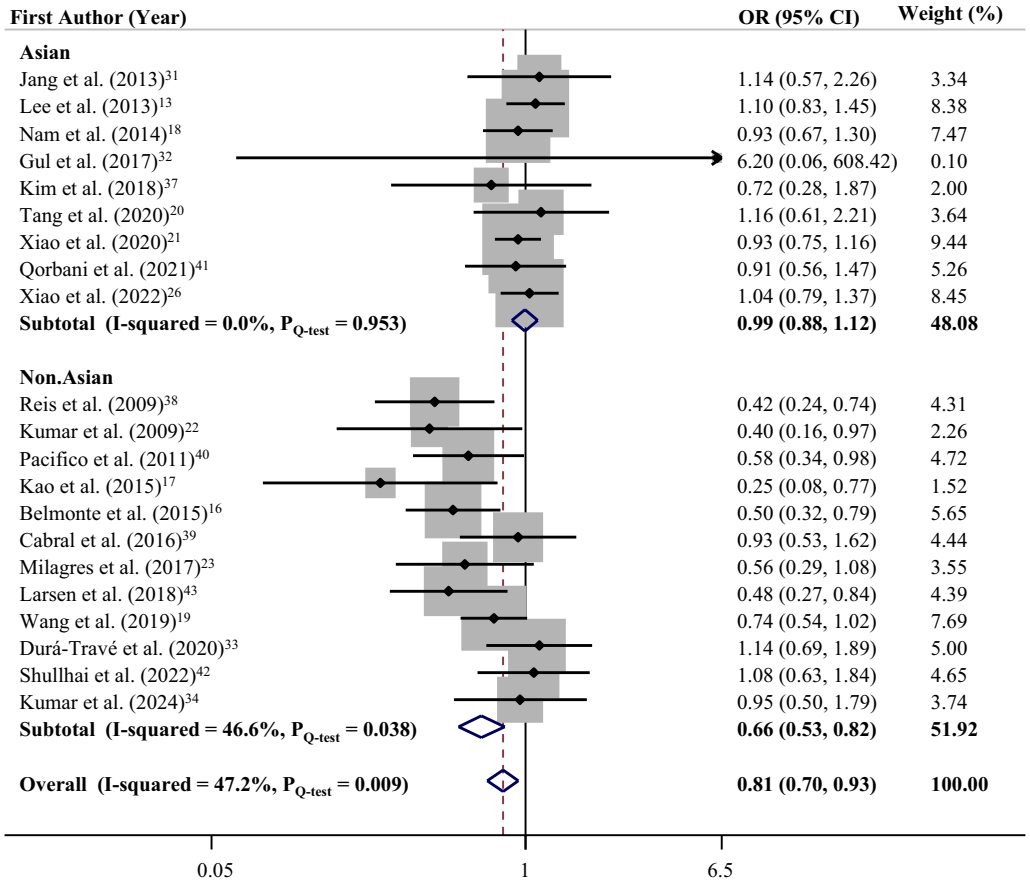

Fig. 3 Forest plot of studies conducted in Asian and Non-Asian countries that examined the association between highest versus lowest level of circulating 25(OH)D and odds of childhood HTN

maintenance is between 75 and 100 nmol/L [44]. The current meta-analysis demonstrated that normal circulating 25(OH)D levels were connected to a lower likelihood of having HTN in children and adolescents, but lowering odds did not continue after elevating circulating 25(OH)D above normal levels. Therefore, it could be considered by healthcare professionals to screen serum 25(OH)D levels of children and adolescents and consider the ways of improving the levels of 25(OH)D to prevent HTN and its associated morbidity. Over-supplementation of vitamin D should also be avoided; recommending high-dose vitamin D supplements only in children with deficient and insufficient vitamin D status and with caution should be taken.

Consistent with our findings, some previous studies have indicated the relationship between circulating 25(OH)D concentrations and risk of different non-communicable conditions among children and adolescents. A previous meta-analysis published in 2014 documented that pooling estimates of 17 cross-sectional studies with 25,394 subjects could result in a more favorable lipid profile in children with greater 25(OH)D concentrations [45]. In other words, individuals with more favorable levels of circulating 25(OH)D have lower serum HDL-c and higher total cholesterol (TC), LDL-c and triglyceride (TG) [45]. Based on the findings of another dose–response analysis, each 10 ng/mL increment in circulating 25(OH)D levels in children was linked to a 12% decreased odds of metabolic syndrome [46]; the same finding was obtained among investigations which were conducted on representative populations of children [46]. But a previous systematic review of vitamin D and HTN in adolescents had a narrative investigation on 85 studies and showed no association [24]. Most of the studies included in the mentioned systematic review were studies that examined SBP or DBP in relation to vitamin D values and did not examine the risk or odds of HTN in different categories of vitamin D. Heterogeneity between included studies in the mentioned review was high, and following studies (without considering their effect sizes) were grouped together: (1) those with a correlation between

Table 3 Results of subgroup-analysis for circulating 25(OH)D levels and odds of childhood hypertension

	No. of effect sizes	OR (95% CI)	I^2 (%)	P within[1]	P between[2]
Overall	21	0.81 (0.70, 0.93)	47.2	0.01	
Study Design					0.77
Cross-sectional	18	0.81 (0.69, 0.96)	45.3	0.02	
Cohort	3	0.76 (0.52, 1.12)	70.3	0.04	
Asian versus Non-Asian countries					< 0.001
Asian	9	0.99 (0.88, 1.12)	00.0	0.95	
Non-Asian	12	0.66 (0.53, 0.82)	46.6	0.04	
Sex					0.41
Both	20	0.80 (0.68, 0.93)	48.9	0.01	
Girls	1	1.14 (0.57, 2.26)	–	–	
Comparison vitamin D25(OH)D levels					0.13
Q5 VS Q1	1	0.25 (0.08, 0.77)	–	–	
Q4 VS Q1	4	0.86 (0.55, 1.32)	67.8	0.03	
T3 VS T1	7	0.75 (0.57, 1.00)	52.3	0.05	
SUF VS DIF	9	0.85 (0.72, 1.02)	21.9	0.25	
Method of 25(OH)D assessment					0.06
IA	18	0.84 (0.71, 0.98)	47.6	0.01	
Others	3	0.67 (0.51, 0.87)	00.0	0.42	
Outcome Definition					0.04
SBP or DBP ≥ 90 th percentile	10	0.67 (0.52, 0.87)	63.8	0.01	
Others	11	0.95 (0.82, 1.06)	0.0	0.56	
Health Status of participants					0.40
Healthy	16	0.79 (0.67, 0.92)	50.6	0.01	
Individuals with obesity and CKD	5	0.90 (0.58, 1.41)	41.4	0.15	
Having adjustments					0.14
Yes	17	0.77 (0.65, 0.91)	54.2	0.01	
No	4	1.09 (0.78, 1.53)	00.0	0.85	
Time of blood draw or season adjustment					0.14
Adjusted	8	0.72 (0.57, 0.92)	47.8	0.06	
Not adjusted	13	0.86 (0.71, 1.05)	46.2	0.03	
BMI adjustment					0.01
Adjusted	11	0.88 (0.74, 1.05)	46.2	0.05	
Not adjusted	10	0.71 (0.56, 0.89)	32.1	0.15	
Quality Status[3]					0.55
High quality	11	0.72 (0.57, 0.91)	61.4	0.01	
Low quality	10	0.88 (0.74, 1.06)	22.6	0.24	

[1] P for heterogeneity, within subgroup

[2] P for heterogeneity, between subgroups

[3] Quality scores were according to Newcastle–Ottawa Scale

CKD: Chronic kidney disease

vitamin D and SBP and DBP; (2) those with differences between SBP and DBP values across vitamin D levels; (3) those with differences in prevalence of HTN and high SBP/DBP across vitamin D status groups; (4) those with differences of vitamin D level among hypertensive versus normotensive participants. In contrast, in the current meta-analysis, only studies that provided odds or risk of HTN across levels of vitamin D were included and revealed a significant relation. A bi-directional mendelian randomization analysis of multiple adult cohorts revealed that greater BMI levels leads to lower 25(OH)D levels, which could confirm the hypothesis that obesity can be assumed as a causal risk factor for vitamin D deficiency development [47]. Considering these findings together, future studies should further clarify the relation between circulating 25(OH)D levels

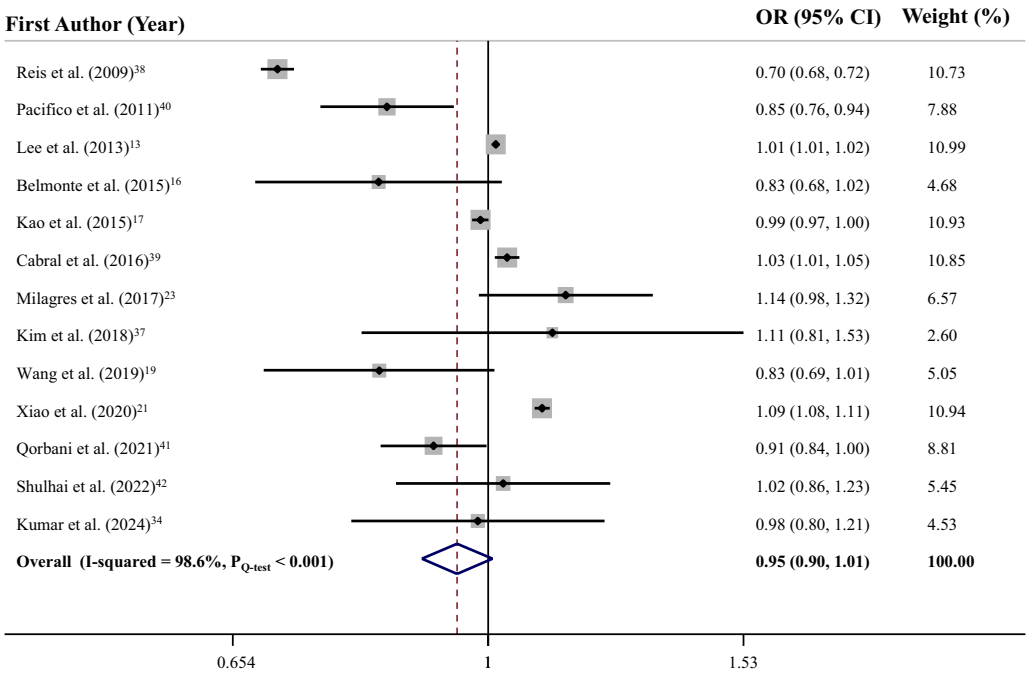

Fig. 4 Linear dose–response meta-analysis of circulating 25(OH)D and odds of childhood HTN

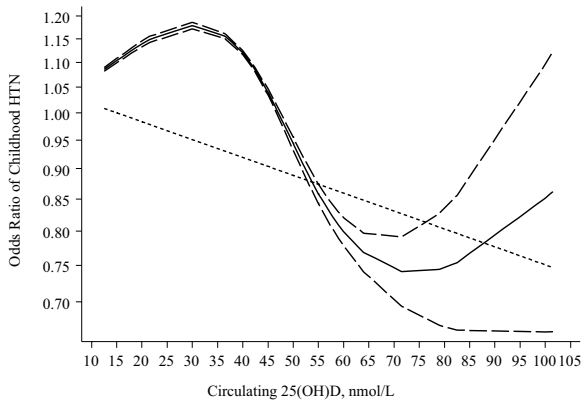

Fig. 5 Non-Linear dose–response meta-analysis of circulating 25(OH)D and odds of childhood HTN

and non-communicable diseases in children, especially among those with overweight or obesity.

A previous cross-sectional study on treated adults with HTN has documented that vitamin D deficiency was related with a less favorable BP profile and an increased risk of uncontrolled BP management as compared with vitamin D sufficiency [48]. On the other hand, a double-blind randomized trial showed that although ultraviolet radiation on people with vitamin D deficiency (25(OH)D < 50 nmol/L) could rise serum 25(OH)D to normal values (> 90 nmol/L) during 12 weeks, this change did not affect systolic or diastolic blood pressure [49]. Another meta-analysis on 5 observational studies demonstrated that vitamin D supplementation in early childhood might protect individuals against developing 1 diabetes [50]. However, a meta-analysis on 5 trials showed that supplementing children and adolescents with vitamin D did not change systolic and diastolic BP [51]. Furthermore, another meta-analysis on 14 RCTs with a number of 1088 subjects aged 4–19 years did not recommend vitamin D supplementation to improve cardio-metabolic health (including BP) in childhood. Besides that supplementation might increase LDL-c, and this unfavorable impact might be a concern [52]. Considering these conflicting results of previous research could suggest that other factors, such as weight status, comorbidities, and physical activity, might increase blood pressure and also decrease 25(OH)D without implying causality. It is suggested that obesity could have structural effects on the kidneys through the release of leptin that may cause HTN due to increasing sodium absorption [53]. On the other hand, an inverse relation between body fat content and serum 25(OH)D concentration was reported, and this association seems to be stronger than those obtained between 25(OH)D and BMI or body weight [54]. There are two basic types of assays in use for assessment of 25(OH)D: (1) automated immunoassays and (2) chromatography-based assays such as HPLC or LC–MS/MS [55]. However, there is a great deal of variability among the results for the levels of 25(OH)D in different assays [56]. So, one possible explanation for the heterogeneity between

included articles might be the differences between assays for measurement of 25(OH)D. This discrepancy between 25(OH)D concentration assessments might lead to a lack of standardization and measurement bias.

Although different cofounders were considered in the analysis of the included articles, there was little consistency among some of the articles. Moreover, some of the included articles have not controlled the analysis for critical cofounders such as BMI, time of measurement for 25(OH)D, race or ethnicity, genetic factors, environmental, lifestyle, and dietary differences across different countries and ethnicities. A complex interplay of these confounders could influence vitamin D status, hypertension, and its relation. Previous studies revealed that black versus white Americans had lower circulating vitamin D levels, and consequently a higher incidence of hypertension [57]. This could mostly be due to their skin pigmentation, which could explain the racial disparity in hypertension prevalence. In addition, genetic factors (such as variations in vitamin D receptor (VDR) polymorphisms [58]) were not controlled in the studies. The link between vitamin D status and HTN was also shaped by environment, lifestyle, and dietary intake across different regions. For instance, populations living in high-latitude regions experience reduced UVB radiation and limited vitamin D synthesis [59]. Cultural practices, such as sun-avoidant clothing and predominantly indoor lifestyles, are also lowered sun exposure and increased risk of vitamin D deficiency [60]. Dietary differences also play a significant role; traditional diets with high fatty fish consumption in some regions, like Japan, can result in better vitamin D status. In contrast, rice-based diets in South Asia lack natural vitamin D sources [61–63]. One of the important mechanisms in the pathogenesis of HTN is renin–angiotensin–aldosterone system (RAAS), but none of the articles has demonstrated a report about the RAAS activity among participants. More investigations are needed to clarify the relation between 25(OH)D and HTN through different factors that may influence both of these variables.

Subgroup analysis for Asian versus non-Asian countries revealed that higher levels of circulating 25-hydroxyvitamin D is associated with a great reduction in odds of HTN in children from non-Asian societies, but no significant relation was observed among Asian countries. Some possible explanations are needed to be considered. First, according to previous studies prevalence of hypertension in Asians countries have been reported to be similar to white societies [64]. However, in some other studies, Chinese participants seem to have the highest incidence rate of HTN compared to other ethnic groups including whites, African-American and Hispanics [65]. This might explain the role of region and genetic in the pathogenesis of HTN. Second, the synthesis of vitamin D depends on the color of the skin; and those participant whose skin tend to be darker, require more amount of sunlight to produce vitamin D [66]. So, due to the fact that Asians have lighter color skin compared with those African-Americans in non-Asian societies, the prevalence of vitamin D deficiency could be lower in Asian countries. Moreover, the skin is unable to transform 7-dehydrocholesterol to vitamin D from the sun at latitudes above 37°N and below 37°S [67, 68]. However, most of the studied Asian countries are located below 37°N and have plentiful sunny days for participant to make vitamin D. Therefore, lower prevalence of vitamin D deficiency among Asians might be the reason for independency of the odds for childhood HTN and circulating 25(OH)D.

In the current review, a U-shape relation between circulating 25-hydroxyvitamin D and childhood HTN was obtained in the non-linear dose–response analysis. The values of 35–75 nmol/L 25(OH)D were associated with a favorably decreasing odds of HTN, while the increased levels above 75 nmol/L were probably associated with greater odds of HTN. This U-shape relation indicated that both too high and too low vitamin D levels could result in disruption and dysfunction of vitamin D pathways, such as the regulation of gene expression and hormonal feedback disruption. In previous evidence, vitamin D deficiency leads to increased renin and impairs endothelial function by reducing nitric oxide production, which increases BP. On the other hand, excess vitamin D leads to hypercalcemia, which may lead to hypertension, as well [69, 70]. However, it is worth noting that only four of the included studies with 3570 participants reported the levels of 25(OH)D above 75 nmol/L. Therefore, further investigations in this regard are needed to shed a light of this relation.

Circulating 25(OH)D levels could be related to BP through multiple mechanisms. First, 25(OH)D has a critical role in regulating RAAS [71]. Additionally, 1, $25(OH)_2D$ has been proved to inversely regulate the renin gene transcription by a vitamin D receptor-mediated mechanism [72]. Therefore, 1, $25(OH)_2D$ might be a negative regulator for prevention of RAAS over-stimulation. Actually, 1, $25(OH)_2D$ is the activator of the receptor of vitamin D that is binding to the cyclic adenosine mono phosphate response element binding protein and terminates the activity of renin gene promoter, finally resulted in a declined renin secretion [73]. Second, 1, $25(OH)_2D$ may play a role in vascular smooth muscle cells and endothelial cells developing and functioning that can express both vitamin D receptor and 1α-hydroxylase [74]. Third, 1, $25(OH)_2D$ has an indirect association with BP, according to the role of 25(OH)D in regulating intestinal absorption of calcium as long as calcium homeostasis

through its interaction with parathyroid hormone (PTH) [75, 76]. Fourth, declined levels of 25(OH)D concentrations have a relation with insulin resistance, and supplementing participants with vitamin D may lead to an improvement in production of insulin and insulin sensitivity, which has been suggested to have a role in HTN pathogenesis [77, 78]. Fifth, 25(OH)D is suggested to has positive influences on vascular health, due to decreasing the production of free radicals [79].

Some strength in the present meta-analysis could be identified. To our knowledge, this investigation is the first meta-analysis that illustrates the relation between circulating 25(OH)D concentration and childhood HTN. Moreover, neither the exposure nor the outcome in eligible studies was collected by self-reporting, and the data were gathered objectively. GRADE approach demonstrated high certainty for the obtained evidence in the analysis. Besides these strengths, some limitations of this review should be considered. Most of the studies that were included were cross-sectional investigations, and only 3 cohorts were included. So, more prospective cohorts are needed to confirm the causality of the association. In addition, due to having small number of prospective studies (n = 3), we combined both cross-sectional and cohort studies in the analyses, while it would be better to analyze these studies separately. Besides that, none of the included articles had stratified the analysis by gender, so we could not calculate separate estimates for girls and boys. Furthermore, the effects of certain confounders, such as physical activity and time of 25(OH)D measurement were not considered in most of the eligible studies. In addition, different definitions of HTN were applied in eligible studies, and this variability could lead to misclassification bias.

In conclusion, this meta-analysis illustrated that children and adolescents with the highest level of circulating 25(OH)D had a significantly declined chance of HTN in comparison to those with the lowest level, mostly in cross-sectional studies and non-Asian countries. Moreover, A U-shape significant relation between circulating 25(OH)D concentrations and childhood HTN was found. The non-linear results illustrated that a considerable reduction was observed in the odds of childhood HTN as circulating 25(OH)D levels raised from 35 to 75 nmol/L. Since most of the included studies was cross-sectional investigations, we were not able to find causality; So, more RCTs are needed to illustrate the causality between 25(OH)D concentrations and childhood HTN.

Abbreviations

25(OH) D	25-Hydroxyvitamin D
95% CI	95% Confidence intervals
BMI	Body mass index
BP	Blood pressure
CLIA	Chemiluminescent immunoassay
DBP	Diastolic blood pressure
ECLIA	Electrochemiluminescence immunoassay
EIA	Enzyme immunoassay
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
HDL-c	High density lipoprotein cholesterol
HPLC	High-performance liquid chromatography
HR	Hazard ratio
HTN	Hypertension
LDL-c	Low density lipoprotein cholesterol
NOS	Newcastle-Ottawa scale
OR	Odds ratio
PICO	Population, Intervention, Comparison, Outcome
PR	Prevalence ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
CKD	Chronic Kidney Disease
PTH	Parathyroid hormone
RAS	Renin angiotensin system
RCT	Randomized controlled trial
RIA	Radioimmunoassay
RR	Relative risks
SBP	Systolic blood pressure
TC	Total cholesterol
TG	Triglyceride
WC	Waist circumference

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12967-025-06668-z.

Additional file 1

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E.M., Z.M, P.R, and P.S. contributed to conception, design, statistical analyses, data interpretation, and manuscript drafting. All authors approved the final manuscript for submission.

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Data availability
The data underlying this article will be shared on reasonable request to the corresponding author.

Declarations

Ethics approval and consent to participate
Not applicable.

Competing interests
The authors have no relevant interests to declare.

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