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Meta-analyses

Association between vitamin D status and sepsis in children: A meta-analysis of observational studies

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SUMMARY

Background: The consequences of vitamin D deficiency regarding sepsis in children remain controversial. We conducted a meta-analysis of studies evaluating the association between vitamin D status and sepsis in children.

Methods: We used EMBASE, Ovid Medline and Cochrane Library to conduct a meta-analysis of studies published in English before November 21, 2017.

Results: Among 1146 initially identified studies, we included 13 studies according to predefined inclusion criteria comprising 975 patients and 770 control participants. According to a random effects model, the mean difference in 25(OH)D levels (nmol/L) between participants with sepsis (444) and controls (528) was (mean difference, −18.55; 95% confidence interval (CI), −19.45 to −17.66, $p < 0.05$). The association between vitamin D deficiency and sepsis was significant, with an odds ratio (OR) = 1.13 (95% CI, 1.18 to 1.50, $p < 0.05$). Factors that could explain differences in the results include the study location/medical conditions, study design, 25(OH)D assay methods, diagnostic sepsis at different ages, diagnostic criteria for sepsis, and sepsis with comorbidities.

Conclusions: The association between vitamin D deficiency/lower 25(OH)D levels and sepsis was significant in children and neonates. Further studies are required to confirm the results by considering more confounders.

1. Introduction

Vitamin D deficiency (VDD) is highly prevalent in children [1–3] and leads to immune dysregulation and systemic inflammation [4]. VDD is defined as a serum concentration of 25(OH)-vitamin D (25(OH) D) below 50 nmol/L in critically ill patients [5], with severe deficiency developing at 25–30 nmol/L [6]. The availability of vitamin D in most foods is limited, and most endogenous vitamin D is synthesized through exposure to ultraviolet radiation B [7]. However, vitamin D levels can be influenced by several factors, such as sun exposure, fat absorption and skin pigmentation. Darker skin pigmentation often leads to higher levels of melanin, which reduces vitamin D production after sun exposure [7]. Madden et al. [8] showed that race and age were associated with VDD in critically ill children. Finally, the genotype and concentration of vitamin D-binding protein (DBP) can affect the 25(OH)D half-life [9].

The pathogenesis of sepsis is related to an imbalance of the inflammatory response, immune dysfunction, and more [10]. Innate and acquired immune dysfunction also contributes to the progression of sepsis [7,11]. The common mechanisms by which VDD associates with sepsis are related to its modulation of the immune system [7]. First, vitamin D binds to vitamin D receptors (VDRs) controlling major immune cells, including macrophages, neutrophils, and dendritic cells, and the production of cytokines [12–14]. Second, vitamin D induces the expression of cathelicidin and β-defensin, which contribute to the modulation of innate immunity via chemotactic action and toxin neutralization [11].

Multiple research groups have recently evaluated vitamin D in children with sepsis and in critically ill children [1,2,15–20], but the

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results are controversial. Say et al. [18] demonstrated that VDD was an insignificant risk factor of neonatal sepsis in premature infants, whereas Gamal et al. [19] showed that the serum vitamin D level can be a sensitive predictor of early-onset sepsis (EONS) in neonates. Overall, few studies have evaluated the association between vitamin D status and sepsis or septic shock in children. Furthermore, the sample sizes in existing studies have been small, and many studies have thus lacked sufficient data to evaluate the relationship between vitamin D status and sepsis/septic shock in children. Therefore, we conducted the present meta-analysis to overcome these limitations.

2. Methods

2.1. Retrieval of studies

The reporting of this meta-analysis was in accordance with the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guideline and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The Ovid Medline, EMBASE, and Cochrane Library databases were searched through November 21, 2017. The search consisted of three terms: sepsis, septic shock and vitamin D. We used the Medical Subject Heading (MeSH) and key words to search for the first and second terms and used "OR" to connect sepsis and septic shock. We used vitamin D and relevant key words to search for the third terms. In addition, we used "AND" to connect the third terms and combinations of the first two terms. For the MeSH terms and the search strategy, see (supplement 1). We restricted the search to human studies published in English. The retrieved studies were first screened by reading the titles and the abstracts. Two authors (Dongqiong Xiao and Xiaoyan Zhang) subsequently read the full texts of the remaining publications independently and then discussed any disagreements to reach a consensus regarding the inclusion of studies.

2.2. Definitions

A neonate is defined as an infant within the first 28 days after birth. An early neonate is defined as an infant during the first 7 days after birth. A premature infant is defined as an infant born before 37 weeks of gestation.

2.3. Study selection

The study inclusion criteria were as follows. (1) The participants were neonates or children aged <18 years who were investigated for any of the three outcomes as follows: the primary outcome was a difference in 25(OH)D levels reported as the mean and standard deviation (SD) between sepsis and control participants; secondary outcomes were the incidence, prevalence, and risk or odds ratio of sepsis/septic shock between VDD and control participants; and tertiary outcomes were the incidence, prevalence, and risk or odds ratio of VDD between sepsis and control participants. (2) The study described assessments of exposure and outcomes and reported unadjusted and/or adjusted relative ratios (RRs) and the corresponding 95% CIs or unadjusted and/or adjusted OR estimates and 95% CIs. (3) The study was published in English, and the study design was case–control, cohort, or cross-sectional.

The exclusion criteria were as follows: (1) the article described only animal experiments; (2) the participants in the study were adults; (3) the study data overlapped with those of another study; (4) the study did not report useable data; and (5) the study was a meta-analysis, review or case report.

2.4. Data extraction

The data were independently extracted from the studies by two reviewers (Dongqiong Xiao and Xiaoyan Zhang) and aggregated in a standardized form, including the study authors, publication year, country, children's ICU/hospital, sepsis definition, 25(OH)D assay, study design, number of samples (cases/controls), outcomes, comparisons, and comorbidities.

2.5. Quality evaluation

The two reviewers (Dongqiong Xiao and Xiaoyan Zhang) independently used the Newcastle-Ottawa Scale (NOS) [21] method to examine the methodological quality of all included studies (supplements 2, 3). The reviewers evaluated the quality score (with a maximum score of nine) in three domains: selection of the study population and the comparability and evaluation of exposure and outcomes. The reviewers resolved disagreements as described above.

2.6. Statistical analysis

The original studies included the mean difference and SD in 25(OH)D levels to evaluate the difference between sepsis and control groups. We pooled the mean difference and SD of each study separately using the DerSimonian-Laird formula (random effects model) [22,23]. In addition, the original studies included ORs and 95% CIs to assess the association between VDD and sepsis/septic shock among participants. All data from the included studies were converted into log(ORs) and standard errors (SEs) [24]. We pooled the log(ORs) and SEs of each study separately using the DerSimonian-Laird formula (random effects model) [22]. Statistical heterogeneity [25] among the studies was assessed using I [2] statistics [26]. Values of I [2]>50% and $p < 0.1$ indicated high heterogeneity [27].

We conducted a stratified analysis based on the study location/medical conditions (Africa, other countries), study design (cohort, case–control), 25(OH)D assay methods (enzyme-linked immunosorbent assay (ELISA), high-performance liquid chromatography (HPLC), and other methods), diagnostic sepsis at different ages (neonates, children (1 month–18 years)), diagnostic criteria for sepsis (standard sepsis, early-onset neonatal sepsis (EONS), and no definition of sepsis or culture-positive), and comorbidities (yes, not mentioned).

We used funnel plots [5] of SEs vs ORs in the meta-analysis to assess publication bias. We used Review Manager 5.3 software (Cochrane Library) to perform the statistical tests.

3. Results

3.1. Literature search

We identified 1146 potential studies, including 190 from Ovid Medline, 790 from EMBASE, and 166 from Cochrane Library (supplement 1). After careful screening, 13 studies reported the effects of 25 (OH) D levels, the risk of developing sepsis/septic shock in participants with VDD versus controls, and the risk of developing VDD in participants with sepsis versus controls (see Fig. 1). These 13 included studies are summarized in Table 1.

3.2. Characteristics and quality of the included studies

The included studies were published between 2013 and 2017 and involved 975 patients and 770 control participants. Seven studies [1,2,18–20,28,29] described vitamin D status and sepsis in

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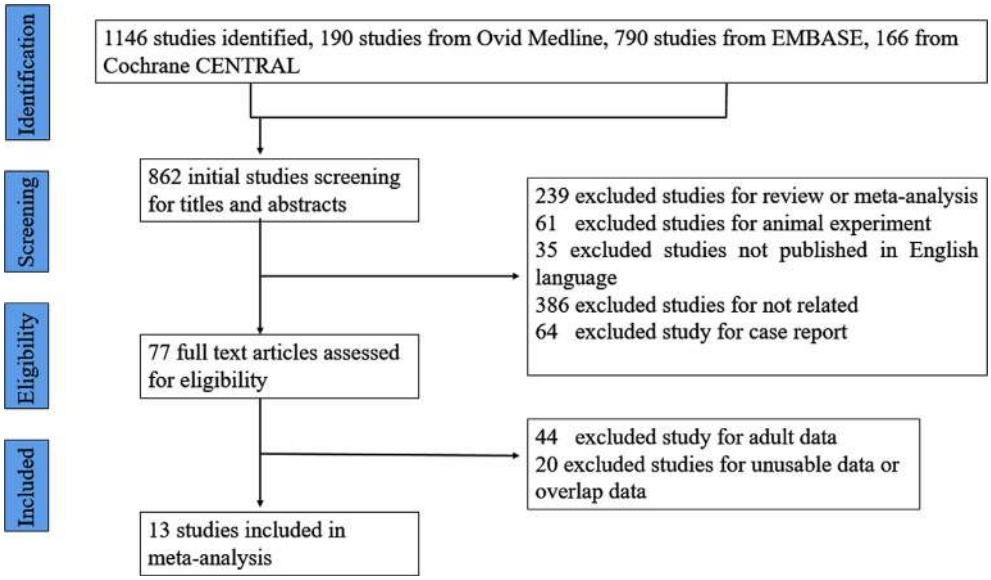

Fig. 1. Flow chart describing study selection.

neonates and six [3,15–17,30,31] studies in children, respectively. Six studies [1,3,17,19,20,28] reported the difference in 25(OH)D levels between sepsis (444) and control participants (528), three studies compared sepsis patients with healthy controls, and three studies compared patients with and without sepsis. Four of the studies evaluated the prevalence of developing sepsis in VDD versus control subjects, and two of the studies evaluated the prevalence of developing septic shock in VDD versus control subjects. Six studies evaluated the prevalence of developing VDD in sepsis versus control subjects.

3.3. Quantitative results (meta-analysis)

The meta-analysis was performed using a random effects model (Figs. 2 and 3). Figure 2 shows that the mean difference in 25(OH)D levels (nmol/L) between sepsis and control participants was −18.55 (95% CI, −19.45 to −17.66, $p < 0.00001$, $I^2 = 96\%$), with lower 25(OH)D levels in the sepsis group (444) than those in the control group (528). The association between VDD and sepsis was OR (1.13, 95% CI, 1.18 to 1.50, $p < 0.05$), with high heterogeneity (I [2] = 0.85) (Fig. 3).

4. Stratified analysis of the association between 25(OH)D status and sepsis

A stratified analysis was performed to evaluate possible sources of heterogeneity in the included studies (Table 2). The association between a lower vitamin D level and sepsis was significant, and this association was consistent when stratified by study location/medical conditions, study design, diagnostic sepsis at different ages, and the presence or absence of comorbidities. The sources of heterogeneity for the association between the vitamin D level and sepsis included the study location/medical conditions, 25(OH)D assay methods, and diagnostic criteria for sepsis.

The association between VDD and sepsis was significant, and this association was inconsistent when stratified by different factors. A stronger association between VDD and sepsis was found in Africa than in other countries. Stronger associations were found in cohort studies rather than case–control studies, in children (1 month–18 years old) rather than neonates, in participants with comorbidities or original infection rather than those without comorbidities, and when 25(OH)D was measured by HPLC rather than other methods.

4.1. Publication bias

Asymmetry and publication bias were evaluated by funnel plots of the studies. The pooled results did not support the presence of a significant publication bias (Supplements 4, 5).

5. Discussion

To our knowledge, this study is the first meta-analysis to evaluate the association between vitamin D status and sepsis in children. The results of this meta-analysis, which included 13 studies, revealed that lower vitamin D levels were observed in children with sepsis than those in control subjects, and that the association between VDD and sepsis was significant.

A lower 25(OH)D level was observed in children, including neonates (0–18 years old), with sepsis than that in control participants, and the association remained when the analysis was stratified by different factors, including study location/medical conditions, study design, 25(OH)D assay methods, diagnostic sepsis at different ages, diagnostic criteria for sepsis, and the presence or absence of comorbidities. Among these factors, study location/medical conditions, 25(OH)D assay methods, and diagnostic criteria for sepsis did not markedly affect the association between lower 25(OH)D levels and sepsis, although stronger associations were found when the analysis was stratified by study location/medical conditions, different 25(OH)D assay methods, and different diagnostic criteria for sepsis. Therefore, researchers need a uniform 25(OH)D assay method and standardized diagnostic criteria for sepsis in future studies, and the study location/medical conditions should be included as confounding factors. The causality of this association cannot be verified through the included observational studies since no evidence shows that a lower 25(OH)D level preceded sepsis in these studies [3,16,17,19,20,28]. A lower 25(OH)D level may lead to susceptibility to microbial infection in children. On the other hand, a lower 25(OH)D level may be a result of sepsis [32]. Fluid resuscitation, limited sun exposure and limited vitamin

Table 1
Characteristics of the included studies.

Study	Publication year	Country	Children ICU/hospital	Sepsis definition	25(OH)D assay	Study design	Number (case/control)	Outcomes	Comparison (meta-analysis)	Any comorbidities
Cizmeci	2015	Turkey	NICU	EONS	HPLC	Case-control	40/43	The OR of developing VDD	<30 ng/ml vs > 30 ng/ml	No
Cetinkaya	2015	Turkey	NICU	EONS	HPLC	Case-control	50/50	The OR of developing VDD in sepsis and control groups	<10 ng/ml vs 10–32 ng/ml	No
Gamal	2017	Egypt	NICU	EONS	ELISA	Case-control	50/30	25(OH)D level	<30 nmol/L vs > 50 nmol/L	No
Cekmez	2014	Turkey	NICU	EONS	Automated CI technology	Case-control	40/20	25(OH)D level	NA	No
Das	2016	India	NICU	NA	ELISA	Case-control	60/60	25(OH)D level	<20 ng/ml vs > 30 ng/ml	NA
Slavcovici	2016	Romania	Children's (1–18 years) hospital	NA	NA	Case-control	28/21	The OR of developing VDD with sepsis and without sepsis	<20 ng/ml vs > 30 ng/ml	MODS 1–18 y,
Satheesh	2013	India	PICU	Standard sepsis	ELISA	Case-control	124/40	25(OH)D level The OR of developing VDD in sepsis patients vs healthy controls The OR of developing septic shock in VDD vs VDS	<20 ng/ml vs > 30 ng/ml	MODS 1–12 y
Onwuneme	2015	Ireland	PICU	Culture-positive	Elecsys	Case-control	120/30	25(OH)D level The OR of sepsis	<50 nmol/L vs > 50 nmol/L	MODS <12 y, fluid bolus volume, adjusted
Ponnarmeni	2016	India	PICU	Standard sepsis	ELISA	Case-control	124/338	25(OH)D level The OR of developing septic shock in VDD vs VDS	<50 nmol/L vs > 75 nmol/L	MODS 1–12 y
Oleo	2015	Uganda	NICU	EONS	NA	Case-control	73/73	The OR of developing sepsis	<20 ng/ml vs > 30 ng/ml	NA
SHAH	2016	India	PICU	Standard sepsis	Auto-analyser using a CI	Cohort study	128/26	The OR of sepsis The OR of septic shock	<20 ng/ml vs > 20 ng/ml	Acute respiratory distress symptom (ARDS), liver failure, 1 month-15 y
Say	2017	Turkey	Premature NICU	EONS, LONS	Competitive CI	Case-control	63/13	The OR of developing sepsis	<5 ng/ml vs > 15 ng/ml	No
Sankar	2016	Switzerland	PICU	NA	Automated CI technology	Observational study	75/26	The OR of developing VDD in sepsis	<20 ng/ml vs > 30 ng/ml	MODS

EONS: early-onset neonatal sepsis; LONS: late-onset neonatal sepsis; NA: not available; HPLC: High-performance liquid chromatography; CI: chemiluminescent immunoassay; Elecsys: Elecsys vitamin D total automated competitive binding protein assay; VDD: vitamin D deficiency; SVDD: severe vitamin D deficiency; ARDS: Acute respiratory distress symptom.

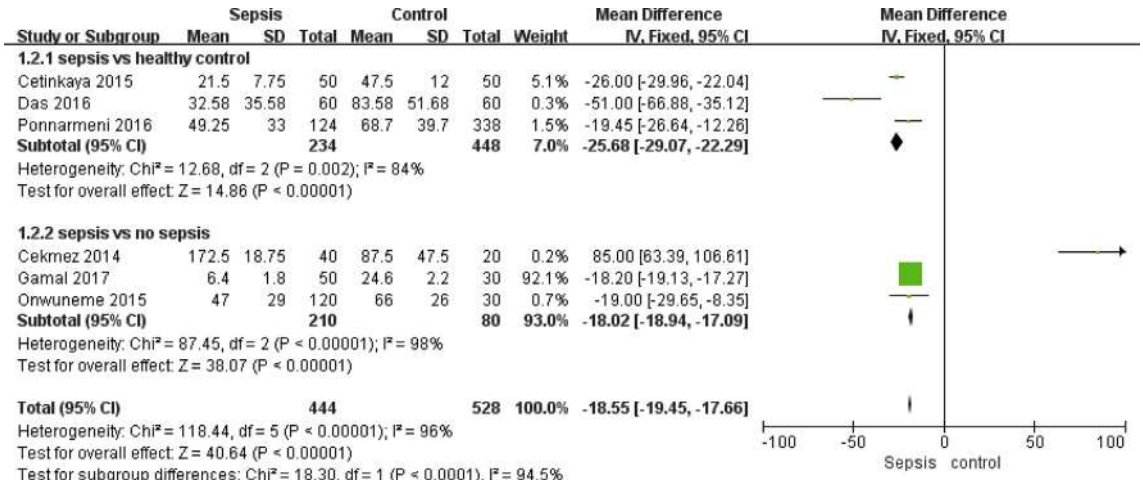

Fig. 2. Forest plot of the comparison of vitamin D levels (nmol/L) between the sepsis and control groups.

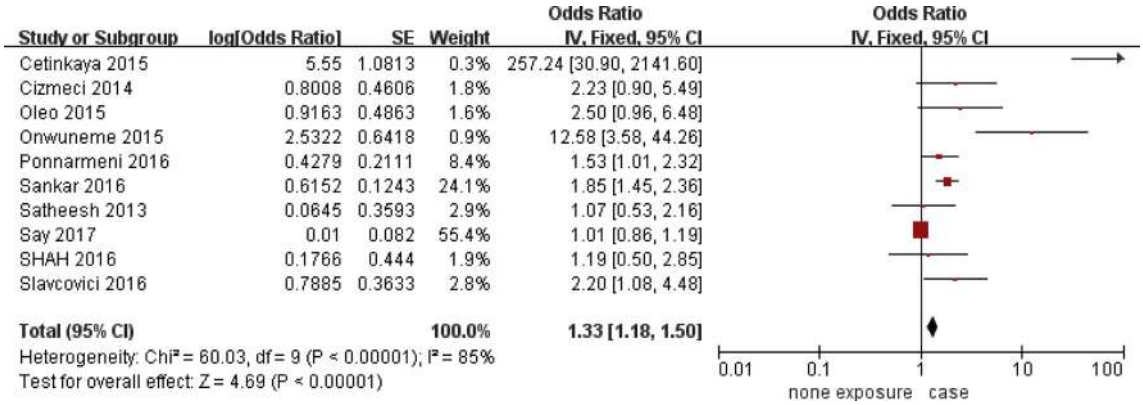

Fig. 3. Forest plot of the pooled odds ratio of the association between sepsis and vitamin D deficiency.

Table 2
Stratified analysis of the associations between the vitamin D level and sepsis and between VDD and sepsis.

Variable	Vitamin D level & sepsis			*p*	VDD & sepsis			*p*
	Studies	OR (95% CI)	I^2 (*p*-value)		Studies	OR (95% CI)	I^2 (*p*-value)	
Total	6	−18.55 (−19.45, −17.66)	0.96 (<0.05)	<**0.05**	10	1.13 (1.18−1.50)	0.85 (<0.05)	<**0.05**
Study location/medical conditions								
Africa	1	−18.20 (−19.13, −17.27)	NA	<**0.05**	1	2.50 (0.96, 6.48)	NA	<**0.05**
Other countries	5	−22.67 (−25.86, −19.74)	0.96 (<0.05)		9	1.32 (1.17, 1.49)	0.86 (<0.05)	
Study design								
Cohort	1	−19 (−29.65, −8.35)	NA	>0.05	1	1.85 (1.45, 2.36)	NA	<**0.05**
Case-control	5	−18.55 (−19.45, −17.65)	0.97 (<0.05)		9	1.20 (1.05, 1.38)	0.84 (<0.05)	
25(OH)D assay methods								
ELISA	3	−18.33 (−19.25,−17.41)	0.88 (<0.05)	<**0.05**	2	1.40 (0.98, 2.00)	0 (0.38)	<**0.05**
HPLC	1	−26 (−29.96,−22.04)	NA		2	4.62 (2.01,10.60)	0.94 (<0.05)	
Other	2	1.31 (0.97, 1.76)	0.99 (<0.05)		6	1.28 (1.13, 1.46)	0.85 (<0.05)	
Diagnostic sepsis at different ages								
Neonates	4	−18.53 (−19.44, −17.63)	0.97 (<0.05)	>0.05	4	1.09 (0.93, 1.28)	0.91 (<0.05)	<**0.05**
Children (1 month∽18 years)	2	−19.31 (−25.27, −13.35)	0 (0.95)		6	1.77 (1.47, 2.14)	0.62 (<0.05)	
Diagnostic criteria for sepsis								
Standard sepsis	1	−19.45 (−26.64, −12.26)	NA	<**0.05**	3	1.37 (0.98, 1.90)	0 (0.65)	<**0.05**
EONS	3	−18.43 (−19.33, −17.52)	0.98 (<0.05)		4	1.09 (0.93, 1.28)	0.91 (<0.05)	
No definition or culture-positive	2	−28.93 (−37.38, −20.09)	0.91 (<0.05)		3	2.00 (1.60, 2.51)	0.77 (<0.05)	
With comorbidities								
Yes	4	−18.53 (−19.44, −17.63)	0.97 (<0.05)	>0.05	6	1.77 (1.47, 2.14)	0.62 (<0.05)	<**0.05**
Not mentioned	2	−19.31 (−25.27, −13.35)	0 (0.95)		4	1.09 (0.93, 1.28)	0.91 (<0.05)	

EONS: early-onset neonatal sepsis; VDD: vitamin D deficiency; HPLC: High-performance liquid chromatography; ELISA: enzyme-linked immunosorbent assay.

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D absorption may explain the decreased vitamin D levels in children with sepsis/septic shock [3].

The association between VDD and sepsis was significant, and this association was inconsistent when the analysis was stratified by study location/medical conditions, study design, 25(OH)D assay methods, diagnostic sepsis at different ages, diagnostic criteria for sepsis, and whether participants had comorbidities. First, a stronger association between VDD and sepsis was found in other countries versus Africa, indicating that the study location/medical conditions may affect the association between VDD and sepsis. The confounding factors may include insufficient medical conditions, higher susceptibility to microbial infection, lower vitamin D absorption due to higher levels of melanin and the prevalence of VDD in Africa [7,23]. Second, a stronger association between VDD and sepsis was found in cohort study [30] versus case–control studies [1–3,15–18,29,31], indicating that the association may be affected by the study design and that the results of cohort studies should be interpreted with caution. Third, a stronger association between VDD and sepsis was found in children assayed by the HPLC method [1,2] versus ELISA/other methods [3,15–18,29–31], indicating that 25(OH)D assay methods may affect the association. Therefore, the association may have been underestimated when 25(OH)D levels were assayed by ELISA, and future studies should standardize the 25(OH)D assay methods. Fourth, a stronger association between VDD and sepsis was found in children (1 month–18 years old) [3,15–17,30,31] rather than neonates [1,2,18,29], indicating that the association may be affected by different ages at the diagnosis of sepsis. We have mentioned that VDD resulted in adverse sepsis outcomes due to immune system disruption in children, and disruption of the immune reaction by VDD may lead to susceptibility to infection in children. The immune system is immature in neonates, which may explain why the age at the diagnosis of sepsis can affect the association between VDD and sepsis [7,11]. Fifth, a stronger association between VDD and sepsis was found in participants with comorbidities or original infection [3,15–17,30,31] rather than in those without comorbidities [1,2,18,29], suggesting that future studies should include comorbidities as a confounding factor. Finally, the association between VDD and sepsis was affected by the diagnostic criteria for sepsis. A stronger association between VDD and sepsis was found in the studies with no definition of sepsis or in which sepsis was diagnosed by a positive bacterial culture [15,17,31]. Overall, VDD was associated with an increased risk of sepsis via multiple factors described above, and the source of the heterogeneity may be these same factors. For a better understanding of the relationship between sepsis and VDD in children, future studies should consider confounders or else the results of meta-analyses may overestimate the association between sepsis and VDD.

Our meta-analysis has the following limitations. First, the studies included a wide range of participants with different age groups, associated medical conditions, and original diseases that could result in biases, which may lead to an overestimation of the results of the meta-analysis. Second, we included articles only published in English, which may contribute to publication bias. Third, the results of this meta-analysis should be interpreted with caution because of the limited number of participants. Fourth, studies reporting outcomes in alternative manners were not included in our meta-analysis, which may contribute to publication bias. For example, studies that did not measure 25(OH)D levels as the mean and SD were excluded. Fourth, most of the included studies did not measure serial levels of vitamin D during the course of sepsis, which would better reflect vitamin D status when treating patients using various methods, especially fluid resuscitation. Furthermore, the bias inherent to observational studies was not eliminated in the quantitative synthesis.

The merits to this meta-analysis are as follows. First, this study evaluated the association between vitamin D status and sepsis/septic shock in children. Second, this study demonstrated that the study location, study design, 25(OH)D assay methods, diagnostic sepsis at different ages, diagnostic criteria for sepsis, and sepsis with comorbidities are all sources of heterogeneity.

6. Conclusions

In conclusion, our pooled analyses provide evidence that children with sepsis have lower vitamin D levels than control participants. Children with VDD were associated with an increased risk of sepsis.

Ethics approval and consent to participate

Not applicable; meta-analysis.

Consent for publication

Not applicable; meta-analysis.

Availability of data and materials

No additional data are available.

Clinical trial registration number and date if applicable

Not applicable; meta-analysis.

Competing financial interests

The authors declare that they have no competing financial interests.

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CRediT authorship contribution statement

Dongqiong Xiao: Conceptualization, Methodology, Software, Investigation, Writing - original draft, Writing - review & editing. **Xiaoyan Zhang:** Conceptualization, Methodology, Software, Resources, Writing - original draft, Writing - review & editing. **Junjie Ying:** Methodology, Software, Validation, Formal analysis, Investigation, Resources. **Yan Zhou:** Methodology, Software, Validation, Formal analysis, Investigation, Resources. **Xihong Li:** Methodology, Software, Validation, Formal analysis, Investigation, Resources. **Dezhi Mu:** Formal analysis, Investigation, Resources, Data curation, Writing - review & editing, Visualization, Supervision, Funding

acquisition. **Yi Qu:** Formal analysis, Investigation, Resources, Data curation, Writing - original draft, Visualization, Supervision, Funding acquisition.

Abbreviations

MD	mean difference
25(OH)D	25-hydroxyvitamin D3
RRs	relative ratios
ORs	odds ratios
DBP	vitamin D binding protein
VDRs	vitamin D receptors
CIs	confidence intervals
NOS	Newcastle-Ottawa Scale
HPLC	high-performance liquid chromatography
ELISA	enzyme-linked immunosorbent assay
EONS	early-onset neonatal sepsis

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2019.08.010.

References

[1] Cetinkaya M, Cekmez F, Buyukkale G, Erener-Ercan T, Demir F, Tunc T, et al. Lower vitamin D levels are associated with increased risk of early-onset neonatal sepsis in term infants. J Perinatol 2015;35(1):39–45.
[2] Cizmeci MN, Kanburoglu MK, Akelma AZ, Ayyildiz A, Kutukoglu I, Malli DD, et al. Cord-blood 25-hydroxyvitamin D levels and risk of early-onset neonatal sepsis: a case-control study from a tertiary care center in Turkey. Eur J Pediatr 2015;174(6):809–15.
[3] Ponnarmeni S, Angurana SK, Singhi S, Bansal A, Dayal D, Kaur R, et al. Vitamin D deficiency in critically ill children with sepsis. Paediatr Int Child Health 2016;36(1):15–21.
[4] Watkins RR, Lemonovich TL, Salata RA. An update on the association of vitamin D deficiency with common infectious diseases. Can J Physiol Pharmacol 2015;93(5):363–8.
[5] de Haan K, Groeneveld ABJ, de Geus HRH, Egal M, Struijs A. Vitamin D deficiency as a risk factor for infection, sepsis and mortality in the critically ill: systematic review and meta-analysis. Crit Care 2014;18(6).
[6] McNally JD, Nama N, O'Hearn K, Sampson M, Amrein K, Iliriani K, et al. Vitamin D deficiency in critically ill children: a systematic review and meta-analysis. Crit Care 2017;21.
[7] Esposito S, Lelii M. Vitamin D and respiratory tract infections in childhood. BMC Infect Dis 2015;15.
[8] Madden K, Feldman HA, Smith EM, Gordon CM, Keisling SM, Sullivan RM, et al. Vitamin D deficiency in critically ill children. Pediatrics 2012;130(3):421–8.
[9] Jones KS, Assar S, Harnpanich D, Bouillon R, Lambrechts D, Prentice A, et al. 25(OH)D-2 half-life is shorter than 25(OH)D-3 half-life and is influenced by DBP concentration and genotype. J Clin Endocrinol Metab 2014;99(9):3373–81.
[10] Despond O, Proulx F, Carcillo JA, Lacroix J. Pediatric sepsis and multiple organ dysfunction syndrome. Curr Opin Pediatr 2001;13(3):247–53.
[11] Franca Goi PH, Ferreira D, Olenski S, Seguro AC. Vitamin D and infectious diseases: simple bystander or contributing factor? Nutrients 2017;9(7).
[12] Zeljic K, Elkilany A, Supic G, Surbatovic M, Djordjevic D, Magic Z, et al. Vitamin D receptor gene polymorphisms association with the risk of sepsis and mortality. Int J Immunogenet 2017;44(3):129–34.
[13] Kearns MD, Alvarez JA, Seidel N, Tangpricha V. Impact of vitamin D on infectious disease. Am J Med Sci 2015;349(3):245–62.
[14] Equils O, Naiki Y, Shapiro AM, Michelsen K, Lu D, Adams J, et al. 1,25-Dihydroxyvitamin D-3 inhibits lipopolysaccharide-induced immune activation in human endothelial cells. Clin Exp Immunol 2006;143(1):58–64.
[15] Slavcovici A, Tripon R, Iubu R, Marcu C, Sabou M, Muntean M. Vitamin D deficiency and sepsis in childhood. In: BMC Infectious Diseases Conference: 12th Scientific Days of the National Institute for Infectious Diseases "Prof Dr Matei Bals" and the 12th National Infectious Diseases Conference Romania. 16; 2016. 4.
[16] Satheesh P, Verma S, Singhi S, Bansal A. Prevalence of vitamin D deficiency among children with sepsis, its association with sepsis severity and its outcome in a pediatric ICU. In: Critical Care Conference: Sepsis. 17; 2013. no pagination.
[17] Onwuneme C, Carroll A, Doherty D, Bruell H, Segurado R, Kilbane M, et al. Inadequate Vitamin D levels are associated with culture positive sepsis and poor outcomes in paediatric intensive care. Acta Paediatr Int J Paediatr 2015;104(10):e433–8.
[18] Say B, Uras N, Sahin S, Degirmencioglu H, Oguz SS, Canpolat FE. Effects of cord blood vitamin D levels on the risk of neonatal sepsis in premature infants. Korean J Pediatr 2017;60(8):248–53.
[19] Gamal TS, Madiha A-AS, Hanan MK, Abdel-Azeem ME-M, Marian GS. Neonatal and maternal 25-OH vitamin D serum levels in neonates with early-onset sepsis. Children (Basel, Switzerland) 2017;4(5).
[20] Cekmez F, Aydemir G, Yildirim S, Bulut O, Tunc T, Kul M, et al. Diagnostic value OF 25-hydroxyvitamin D level and new cytokines IN neonatal sepsis. Eur J Inflamm 2014;12(2):297–304.
[21] Zhu T, Tang J, Zhao F, Qu Y, Mu D. Association between maternal obesity and offspring Apgar score or cord pH: a systematic review and meta-analysis. Sci Rep 2015;5:18386.
[22] Hartzel J, Agresti A, Caffo B. Multinomial logit random effects models. Stat Model 2001;1(2):81–102.
[23] Gou X, Pan L, Tang F, Gao H, Xiao D. The association between vitamin D status and tuberculosis in children: a meta-analysis. Medicine (Baltim) 2018;97(35):e12179.
[24] Gou X, Yang L, Pan L, Xiao D. Association between bronchopulmonary dysplasia and cerebral palsy in children: a meta-analysis. BMJ Open 2018;8(9):e020735.
[25] Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. Bmj 2003;327(7414):557–60.
[26] Xiao D, Qu Y, Huang L, Wang Y, Li X, Mu D. Association between maternal overweight or obesity and cerebral palsy in children: a meta-analysis. PLoS One 2018;13(10):e0205733.
[27] Wu YW, Colford Jr JM. Chorioamnionitis as a risk factor for cerebral palsy: a meta-analysis. Jama 2000;284(11):1417–24.
[28] Das B, Patra S, Behera C, Suar M. Genotyping of vitamin D receptor gene polymorphisms using mismatched amplification mutation assay in neonatal sepsis patients of Odisha, eastern India. Infect Genet Evol 2016;45:40–7.
[29] Oleo C, Mugalu J, Nsibambi D, Abio A, Sekikubo M. A case control study on maternal and neonatal serum 25-hydroxyvitamin D_3 levels and the risk of very early onset neonatal sepsis in Mulago hospital. Int J Gynecol Obstet 2015;131:E528–9.
[30] Shah SK, Kabra SK, Gupta N, Pai G, Lodha R. Vitamin D deficiency and parathyroid response in critically-ill children: association with illness severity and clinical outcomes. Indian Pediatr 2016;53(6):479–84.
[31] Sankar J, Dev N, Das RR, Ismail J. Severe vitamin d deficiency at admission and after 72 hours of ICU stay in children with fluid refractory septic shock-a prospective observational study. Eur J Pediatr 2016;175(11):1474–5.
[32] Greulich T, Regner W, Branscheidt M, Herr C, Koczulla AR, Vogelmeier CF, et al. Altered blood levels of vitamin D, cathelicidin and parathyroid hormone in patients with sepsis-a pilot study. Anaesth Intensive Care 2017;45(1):36–45.