Importance of vitamin D in critically ill children with subgroup analyses of sepsis and respiratory tract infections: a systematic review and meta-analysis

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Summary

Background

Critical care and sepsis remain high priority concerns in children. Observational studies report high prevalence of vitamin D deficiency and present mixed results regarding the correlation between vitamin D status and adverse outcomes. Associations between deficiency and mortality, particularly in children with sepsis, remain unclear. We performed a systematic review and meta-analysis to address this uncertainty.

Methods

PubMed, OVID and Google Scholar were searched for observational studies in critically ill children. We obtained pooled prevalence estimates for vitamin D deficiency and odds ratios for the association of mortality in critically ill children treated in intensive care units, with subgroup analysis for children with sepsis. Meta-regression and sensitivity analyses were used to investigate heterogeneity.

Findings

Forty-eight studies were included. The total sample size was 7,199, with 1,679 (23%) children acting as controls in case-control studies. Of 5,520 critically ill children, 2,664 (48%) were vitamin D deficient (< 50 nmol/L). Results of the random effects model demonstrated a pooled prevalence of vitamin D deficiency of 54.9% (95% CI 48.0-61.6, I^2=95.0%, 95% CI 94.0-95.8, p < 0.0001). In subgroup analysis of children with sepsis (16 studies, 788 total individuals) we observed higher prevalence of deficiency (63.8%, 95% CI 49.9-75.7, I^2=90.5%, 95% CI 86.2-93.5%, p < 0.0001). In patients admitted to intensive care for respiratory tract infections (24 studies, 1,683 total individuals), prevalence was 49.9% (95% CI 37.6-62.2; I^2 = 93.9%, 95% CI 92.1-95.3, $p < 0.0001$). Only one identified study assessed vitamin D levels in sepsis and mortality. The meta-regression model with all available variables (year of publication, total study sample size, quality score, study design, country group and clinical setting) explained 37.52% of I^2 ($F = 5.1119$, $p = 0.0005$) with clinical setting and country groups being significant predictors for prevalence.

Our meta-analysis (18 studies, 2,463 total individuals) showed an increased risk of death in vitamin D deficient critically ill children both with the random (OR 1.81, 95% CI 1.24-2.64, p-value = 0.002) and fixed effects (OR 1.72, 95% CI 1.27-2.33, p= 0.0005) models with low heterogeneity (I^2 = 25.7%, 95% CI 0.0-58.0, p = 0.153) and low evidence of publication bias (p = 0.084, Egger's test).

Interpretation

Circulating vitamin D deficiency is common amongst critically ill children, particularly in those with sepsis. Our results suggest that vitamin D deficiency in critically ill children is associated with increased mortality. Clinical trials, studies with larger sample sizes and standardized approaches are needed to further assess associations between circulating levels of vitamin D and mortality or other outcomes in the pediatric population.

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Short title Meta-analysis of vitamin D deficiency in paediatric critical care and sepsis

Introduction

Vitamin D is an essential nutrient[1, 2] representing a group of fat soluble secosteroids with key endocrine functions[3]. It is synthesized in the skin upon sunlight exposure[4] while dietary sources, such as oily fish, egg yolk, certain fungi and supplements, are usually secondary sources.

Vitamin D is essential in regulating bone metabolism[5] and calcium homeostasis.[6] It also regulates extra-skeletal metabolic processes,[7] the cardiovascular and immune systems.[8] Many observational and laboratory studies have observed the anti-inflammatory properties of vitamin D, [9] including direct regulation of endogenous anti-microbial peptide production.[10]

It is therefore crucial for humans to have sufficient vitamin D levels to maintain bone health and possibly improve response to infection.[6, 11, 12] Infants and children are especially dependent on vitamin D to achieve healthy bone development and growth.[13, 14] Well-known functional outcomes of adequate vitamin D levels in children include rickets prevention, higher bone mineral content and reduced bone fracture rates.[5, 14] In otherwise healthy children in the United States, the reported prevalence of vitamin D deficiency (25OHD levels of < 25 nmol/L) ranges from 9 to 18%.[15] The Endocrine Society Clinical Practice Guidelines and the Institute of Medicine (IOM) suggest that vitamin D levels less than 50 nmol/L (20 ng/mL) reflect a deficient state.[4, 16]

Studies in adults reflect a high prevalence of vitamin D deficiency both in general intensive care unit (ICU) and sepsis patients and strongly suggest an association between low vitamin D and poor clinical outcomes, including increased mortality, particularly in those suffering from sepsis.[2, 17] Recent clinical trials of vitamin D supplementation in adults appear promising in both general critical care[18, 19] and sepsis.[20]

Sepsis remains a challenging clinical entity with high social and economic costs.[21] Each year there are approximately 123,000 sepsis cases and around 37,000 deaths in England alone.[22] Recent reports show an increased prevalence of pediatric sepsis,[23] likely a reflection of an increased population with chronic comorbidities, higher rates of opportunistic infections and multidrug resistant organisms.[24] Respiratory tract infections account for a large proportion of underlying diagnoses in acute and critical care conditions[24, 25] but remain understudied.[26]

The magnitude and relevance of vitamin D deficiency in children receiving acute care is not clear. Several recent studies have addressed these questions with mixed results. We sought to summarise the evidence regarding the implications of vitamin D deficiency and its prevalence in general ICU, respiratory tract infection and sepsis patients in the pediatric population. We carried out a systematic review and meta-analysis of circulating vitamin D levels to assess the prevalence of vitamin D deficiency (≤ 50 nmol/L) and its association with mortality in these conditions.

Research in context

Evidence before this study

We searched PubMed, OVID, Google Scholar and the Cochrane Library from inception up until 5th November 2017, with no language restrictions. Search terms used across these databases included: “critical care”, “vitamin D”, “pediatric”, “child”, “neonate”, “toddler”, “intensive care unit”, “sepsis” and “septic shock”. Reference lists of identified papers including reviews were also checked. The extend of vitamin D deficiency in children receiving acute care is unclear and only recently has gained more attention. Most identified papers (81.3%) were published between 2014 and 2017. Specific outcomes such as sepsis are not adequately studied in relation to vitamin D status in this population. Only a single meta-analysis was identified on this topic which has been published by McNally et al. (2017). They demonstrated that 50% of pediatric patients admitted to intensive care units were vitamin D deficient (≤ 50 nmol/L). They also associated deficiency with multiple organ dysfunction, illness severity and higher mortality. However, they did not investigate the prevalence of deficiency separately in children with acute lower respiratory tract infections or sepsis and only included studies where mortality was the primary clinical outcome.

Added value of this study

This systematic review and meta-analysis is in full support of the findings by McNally et al. (2017) and updates and extends their work further. We have included additional publications in critically ill children with respiratory tract infections and sepsis and identified high prevalence of vitamin D deficiency in those subgroup populations. Our work provides additional sensitivity analyses using fixed effects model, by country group, age (neonates versus other ages), by study design and sample size. Our meta-analysis demonstrated that vitamin D deficient critically ill children are at higher risk of mortality compared to vitamin D non-deficient critically ill children.

Implications of the available evidence

Prevalence of vitamin D deficiency in children treated in intensive care units, children with sepsis and children with respiratory tract infections is high. Our review demonstrates a very heterogeneous population and emphasizes the need for future adequately powered longitudinal studies with larger sample sizes and multiple time-points for measurement of vitamin D levels. We also identified absence of sufficient studies looking at the correlation of vitamin D deficiency with mortality in children with sepsis although it is becoming more prevalent in the pediatric population and has high economic costs.

Methods

We planned and conducted our systematic review and meta-analysis according to the PRISMA guidelines[27] and since we did not include randomized controlled trials we reported following the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines.[28]

Search strategy and selection criteria

Our population of interest consists of pediatric patients with acute conditions and/or treated in ICU or emergency units for acute conditions whose vitamin D status was assessed prior to or during admission. We included published cross sectional, case-control and cohort studies that measured circulating 25(OH) D levels and either reported prevalence, odds ratios (OR) or data to enable calculation. Studies were excluded if they were reviews, case reports, surveys, commentaries, replies, not original contributions, experimental *in vitro* or if they recruited patients who were not treated in emergency, neonatal intensive care units (NICUs), pediatric intensive care units (PICUs) or for acute conditions. Studies were also excluded if they only enrolled vitamin D deficient patients, investigated healthy populations only or did not measure circulating 25(OH) D levels as an indicator of vitamin D status. When we identified more than one publication utilising the same cohort, we included the publication which shared our review's objective to investigate vitamin D levels and prevalence of deficiency.

For purposes of our review, we classified vitamin D deficiency as being less than 50 nmol/L (equivalent to 20 ng/mL) as suggested by the IOM.[16] Different age categories were used to designate patients as "children" in the studies reviewed. We therefore included all "children" as defined by each treating facility and this included "neonates", "infants", "toddlers", "children" and "adolescents".

We searched PubMed, OVID, Google Scholar and the Cochrane Library from inception up until 5th November 2017, with no language restrictions. Search terms used across these databases included: "critical care", "vitamin D", "pediatric", "child", "neonate", "toddler", "intensive care unit", "sepsis" and "septic shock". Search terms used in OVID and PubMed are listed in the *Additional Tables 1A and 1B*. Literature searches were performed by two investigators (MC and AJBT) independently and included initial screening of titles and abstracts, followed by full text screening. Any disagreements for study eligibility were resolved by discussion between the authors. Reference lists of the selected papers, including reviews, were also checked for relevant titles. Abstracts of relevant titles were then assessed for eligibility. A data extraction form was designed a priori.

Study quality assessment

The quality of each included study was assessed using the Newcastle-Ottawa Scale (NOS) for cohort, case-control and cross-sectional study designs.[29] We classified studies as low (1-3), medium (4-6) or high quality (7-9) for purposes of sensitivity analysis (*Additional Table 2 A, B* and *C*).

Prevalence and mortality outcomes

In the majority of studies (n = 36), prevalence of vitamin D deficiency was extracted as reported with a threshold of ≤ 50 nmol/L. If prevalence was not reported directly, it was calculated using data provided in each study (cases ≤ 50 nmol/L / total number of study participants, *Additional Table 3 A* and *B*). Extracted or calculated prevalence values were then combined in a meta-analysis. For mortality, we calculated unadjusted odd ratios (OR) as:

OR = (vitamin D deficient patients who died * vitamin D non-deficient patients who did not die)/ (vitamin D deficient patients who did not die * vitamin D non-deficient patients who died)

We had sufficient information to calculate ORs < 50 nmol/L for 36 studies (75%). For the 12 studies with insufficient information, we used the lower cut-off values reported as a conservative approximation (*Additional Table 4*). We converted 25(OH) D values using: nmol/L = ng/mL * 2.496.

Data analysis

We obtained proportions of vitamin D deficiency with 95% confidence intervals (CI) using the Clopper-Pearson method[30] in R. We used a random effects model[31] to account for the variation observed within and between studies due to the different ages and acute conditions in the populations considered. For mortality, we also obtained pooled proportions and pooled ORs with fixed effect model for sensitivity analysis and to avoid false conclusions that could result from small-study effects.[32]

We investigated possible sources of heterogeneity using sensitivity and subgroup analyses. The I^2 statistic was used to estimate the percentage of total variation across studies which can be attributed to heterogeneity. A Q value of < 0.05 was considered significant and an I^2 statistic greater or equal to 75% indicated a high level of variation due to heterogeneity.[33, 34] We used

Egger's regression test to present results for publication bias and funnel plot asymmetry[35] and generated funnel plots for visual assessment and screen for evidence of publication bias.

To further assess heterogeneity, we utilised meta-regression to identify predictor variables that could explain variation in study prevalence estimates. We used restricted maximum likelihood (REML) estimations in the model to account for residual heterogeneity[36] and the Knapp-Hartung method to adjust confidence intervals and test statistics. This method estimates between study variance using a t-distribution, rather than a z-distribution, yielding a more conservative inference.[37] We tested the following continuous predictors: year of study publication, total sample size and quality score. Categorical variables included study setting (PICU, NICU), study design (case-control, cross-sectional and cohort) and country group by geographic region and economic development (group 1, group 2, and group 3) and were dummy coded.

We used R version 3.5.0 and Microsoft Excel 2010 for analyses and data collection. The R packages "meta"[38] and "metafor"[39] were used for analyses. Only results of the random effects model are reported for prevalence due to the expected heterogeneity between populations being considered. Our protocol is registered in PROSPERO (CRD42016050638).

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Screening and study characteristics

After title and abstract screening, we identified 2,890 potentially relevant studies (*Figure 1*) and eighty-five full text articles were assessed for eligibility. Rationale for study exclusion included: studies including adults, study populations other than critically ill children or with acute conditions, studies of circulating vitamin D levels and deficiency in healthy children or in children with chronic conditions. Four studies[40-43] were excluded due to insufficient data reporting (*Additional Table 5*). We also excluded three studies[44-46] that used the same cohort of children and included a single study to represent the cohort.[47] Ultimately, 48 studies met criteria for inclusion (*Additional Table 6*).

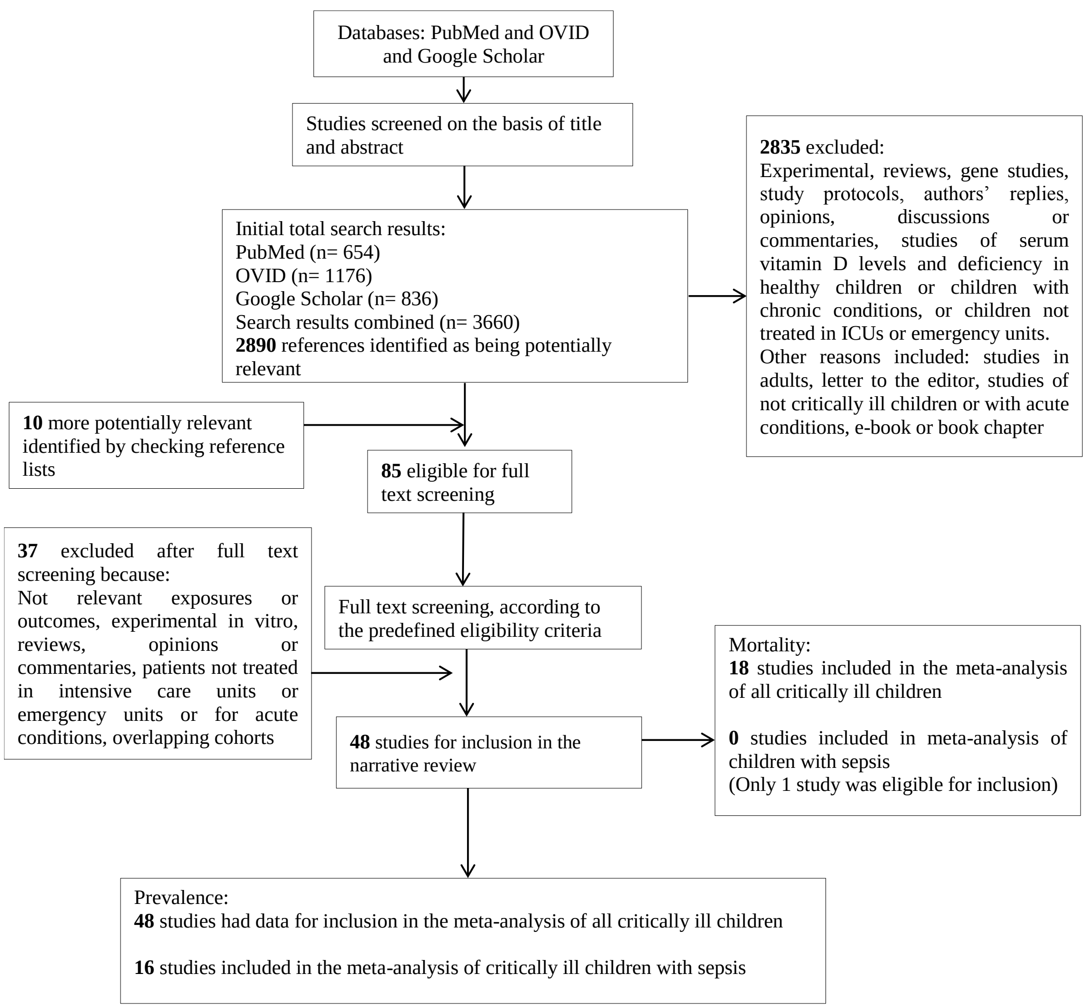

Figure 1 Flow chart of study selection process

The primary objective of the majority of studies was to determine circulating vitamin D concentration ("status") in children and/or prevalence of vitamin D deficiency. Secondary objectives included investigation of associations between deficiency of circulating vitamin D and various outcomes, such as hospital mortality length of stay, requirement of ventilation and/or illness severity (*Additional Table 7*).

All included studies reported vitamin D measurement assay methods used (*Additional Table 8*) and stated samples were collected and analysed within the first 24 hours of hospital admission. Studies reported ethical approval and consent for participation from parents or guardians (*Additional Table 9*). Included studies were published between 2004 and 2017, with the majority (n = 39, 81.3%) published between 2014 and 2017 (*Additional Table 6*). In total, 5,520 children were hospitalized in pediatric or neonatal intensive care units or emergency units. Sample sizes of critically ill children ranged from 25[48] to 511.[49] In 16 studies the total number of cases was greater than 100.

Studies originated from 15 countries, with the majority from India[8, 50-58] (n = 10) or Turkey[48, 59-64] (n = 7) (*Additional Table 6*). All were of medium or high quality (NOS score mean 6.6, range 4-8). The score range for cohort studies was 6 to 8 (n = 20), for case-control studies 5 to 8 (n = 24) and for cross sectional 4 to 6 (n=4). Studies used a broad range of ages to classify patients as "children". Six studies (12.5%)[48, 60, 62-65] included only neonates. In two[60, 65] of these six studies, neonates were preterm. The largest age range was seen in the study of Ayulo et al 2014, which included individuals between 1 and 21 years of age (*Additional Table 10*).

All studies included both female and male participants. For mortality, four of the 18 studies (22%) carried out multivariate regression analysis with adjustment for confounders. The remaining studies presented results using a variety of methods, including Spearman's correlation analysis, chi-square or Fisher's exact tests or descriptive statistics.

Prevalence of vitamin D deficiency

We included 48 studies representing a total of 5,220 critically ill children. Of these, 2,664 (48%) were classified as vitamin D deficient (< 50 nmol/L). Prevalence of deficiency ranged from 5%[66] to 95%[54] (*Additional Table 11*). Sample sizes ranged from 25 to 511, with a median of 82 individuals (*Additional Table 12*). Using a random effects model, the pooled prevalence estimate of vitamin D deficiency was 54.9% (95% CI 48.0-61.6) with a high proportion of variation attributed to heterogeneity (I^2 = 95.0%, 95% CI 94.0-95.8, p < 0.0001) (*Figure 2*) and evidence of funnel plot asymmetry (p = 0.015, Egger's test) (*Table 1* and *Additional Figure 1*).

Table 1 Pooled estimates of vitamin D deficiency in critically ill children and critically ill children with sepsis

Patient category	Number of studies (Total number of individuals; number of deficient individuals)	Pooled proportion % (95% CI)		Heterogeneity (I^2) % (95% CI)	Q value, d.f. p-value	Eggers p-value
		Random effects	Fixed effects			
Critically ill children (includes those with sepsis)	48 (5,520; 2,664)	54.9% (48.0-61.6)	46.8 (45.4-48.3)	95.0% (94.0-95.8)	931.46, 57, < 0.0001	0.015
Critically ill children (only those with sepsis)	16 (788; 499)	63.8% (49.9-75.7)	62.6% (58.6-66.5)	90.5% (86.2-93.5)	157.99, 15, < 0.0001	0.828

CI = confidence intervals; I^2 = heterogeneity; df = degrees of freedom. Vitamin D deficiency defined in our study as < 50 nmol/L (20 ng/mL). I^2 statistic used to estimate heterogeneity between pooled studies: : $I^2 \geq 75\%$ was considered as high heterogeneity [(1)]

1. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ: British Medical Journal. 2003;327(7414):557.

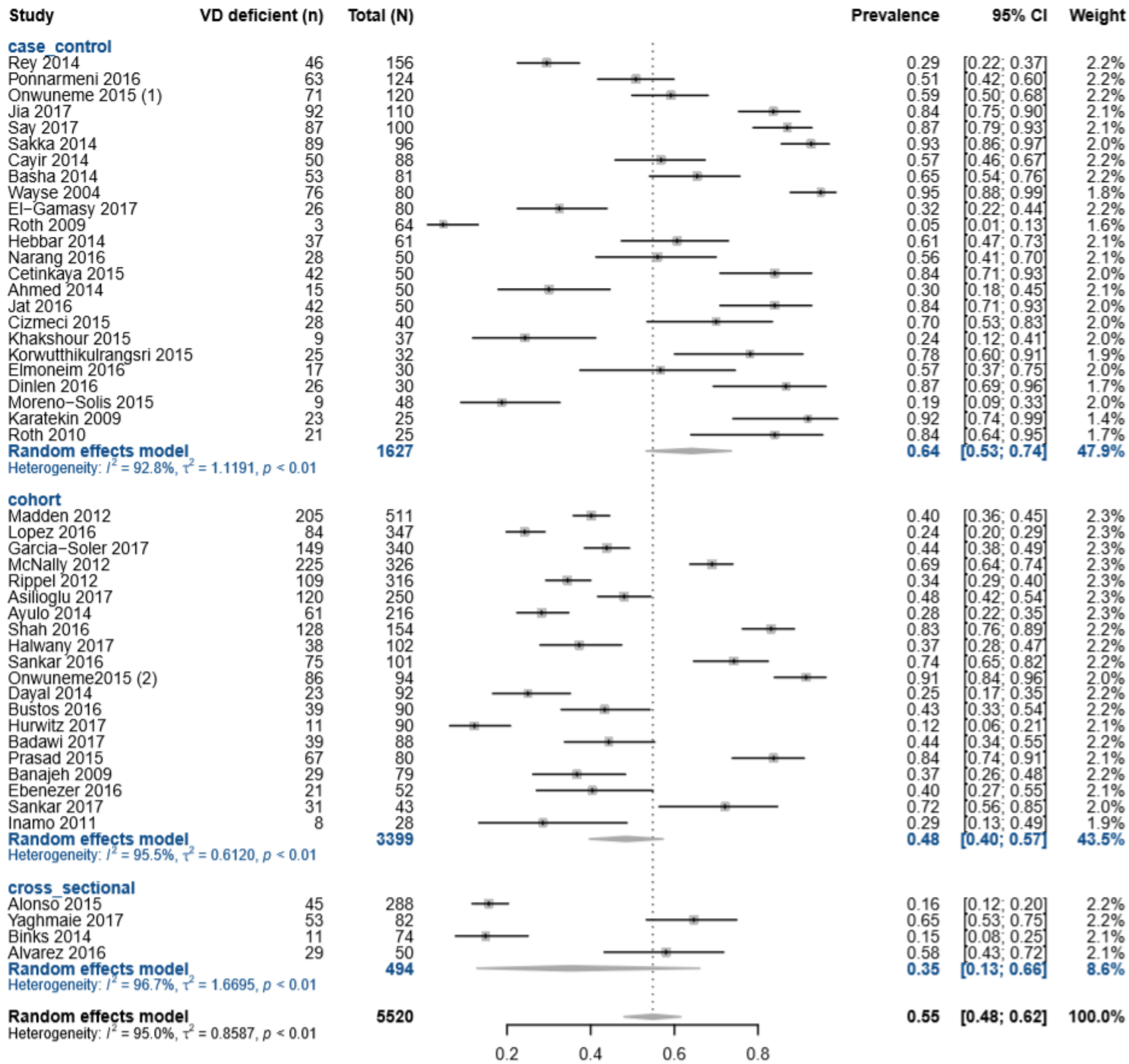

Figure 2 Pooled prevalence estimate for vitamin D deficiency in critically ill children by study design. Forest plot shows results from the random effects model. Each diamond represents the pooled proportion of vitamin D deficiency for each of the subgroups (case-control, cohort, cross-sectional study designs). The diamond at the bottom represents the overall pooled proportion of all the 48 studies together. Each square shows the prevalence estimate of each study and the horizontal line across each square represents the 95% confidence interval (CI) of the prevalence estimate.

Sensitivity analysis for prevalence

We did not detect material differences in prevalence after exclusion of the 12 studies which did not directly report prevalence < 50 nmol/L (53.1%, 95% CI 45.6-60.4; I^2 = 95.1%, 95% CI 93.9-96.0, p < 0.0001) (*Additional Table 13*).

When examining results by sample size (defining "large" as ≥ 100 and "small" as < 100), we found that the 16[8, 47, 49-51, 59, 60, 67-75] studies with larger sample size included 3,561 total individuals and gave a prevalence estimate of 50.8% (95% CI 40.5-61.1; I^2 = 96.9%, 95% CI 95.9-97.6, p < 0.0001). The remaining 32 studies with "smaller" sample sizes included 1,959 total children and estimated pooled prevalence as 57.2% (95% 47.3-66.7; I^2= 92.7, 95% CI 90.7-94.3, p < 0.0001) (*Additional Table 13*).

We also conducted analysis by study design. Cohort studies (n = 20) yielded a prevalence estimate of 48.4% (95% CI 39.7-57.3; I^2 = 95.5%, 95% CI 94.1-96.5, p < 0.0001). In case-control studies (n = 24) the estimate was 64.1% (95% CI 53.2-73.6; I^2 = 92.8%, 95% CI 90.5-94.6, p < 0.0001) and in cross-sectional (n = 4) 34.8% (95% CI 12.8-66.0; I^2 = 96.7%, 95% CI 94.0-98.2, p <0.0001) (*Additional Table 13*, *Figure 2*).

We assessed whether studies' country of origin influenced results. Studies in India gave an estimate of 69.5% (95% CI 53.0-81.5; I^2 = 93.6%, 95% CI 90.2-95.8, p < 0.0001). Similarly, we found slightly higher pooled prevalence estimates for studies from Turkey (76.3%, 95% CI 60.9-87.0; I^2 = 91.1%, 95% CI 84.2-95.0, p < 0.0001). We also grouped studies by geography and economic development. Group 1: USA, Chile, Australia, Canada, Ireland, Japan, Spain; group 2: South Africa, China, Egypt, Iran, Turkey, Saudi Arabia; and group 3: Bangladesh, Thailand, and

India. Prevalence was 36.1% (95% CI 27.8-45.4) for group 1 (n = 18), 62.7% (95% CI 52.2-72.2) for group 2 (n = 18) and 71.4% (95% CI 57.9-82.0) for group 3 (n = 12), *(Additional Figure 2).* Variation attributable to heterogeneity was still high in the three subgroups ($I^2 > 90\%$).

Given the broad age range in included studies, we combined studies with only neonates[48, 60, 62-65] and observed a prevalence estimate of 85.6% (95% CI 78.5-90.6) with moderate variation attributable to heterogeneity ($I^2 = 54.3\%$, 95% CI 0.0-81.7, p value = 0.05). In all other studies (n = 42) that included children of broad age ranges, estimated prevalence was lower at 49.7% (95% CI 42.9-56.5; $I^2 = 94.7\%$, 95% CI 93.6-95.6, p value < 0.0001) (*Additional Table 13, Additional Figure 3*).

Post-hoc investigation to determine sources of heterogeneity

To investigate the substantial heterogeneity observed in prevalence estimates, we incorporated study-specific characteristics (year of publication, total study sample size, quality score, study design, country group and clinical setting) as covariates in a random effects meta-regression model. We identified clinical setting and country groups as significant predictors *(Figure 3).* We found that the model fitted with all available covariates can explain 37.52% of I^2 with F = 5.1119, p = 0.0005 *(Additional Table 14).* We also conducted univariate meta-regressions for each of the six predictors *(Additional Figure 4).*

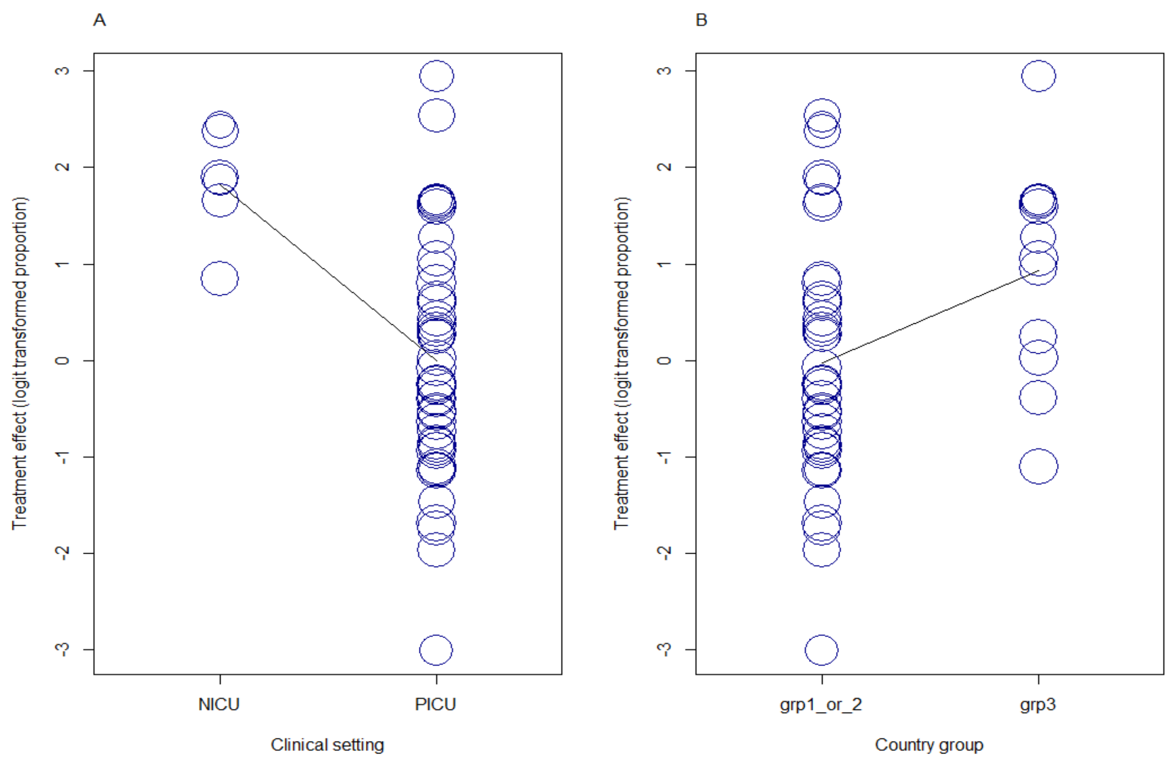

Figure 3 Bubble plots of univariate meta-regressions. Each study is represented by a circle. Predictor variables; A clinical setting and B country groups are shown on the x-axis and the effect measure logit transformed proportion shown on the vertical (y-axis). NICU = Neonatal Intensive Care Unit; PICU = Pediatric Intensive Care Unit; country group 1 = USA, Chile, Australia, Canada, Ireland, Japan, Spain; country group 2 = South Africa, China, Egypt, Iran, Turkey, Saudi Arabia; and country group 3 = Bangladesh, Thailand, and India

Prevalence of vitamin D deficiency in critically ill children with sepsis and in those with respiratory tract infections

A total of 788 (median 41.5, range 9-160) patients had a diagnosis of sepsis, of which 499 (63.3%) were vitamin D deficient. Nine of the sixteen studies including septic patients were cohort (56.3%) and seven (43.8%) case-control *(Additional Table 15).* Most studies originated from India (n = 6) Turkey (n = 3) or Ireland (n = 2) and 15 were published between 2014 and 2017. Thirteen studies took place in a PICU and the remaining[60, 63, 65] in NICUs. We found that all studies were of medium to high quality (median NOS score 6.5, range 5 – 8). Pooled prevalence of vitamin D deficiency was 63.8% (95% CI 49.9-75.7) *(Figure 4)*. Variation attributable to heterogeneity was high (I^2 = 90.5%, 95% CI 86.2-93.5%, p < 0.0001).

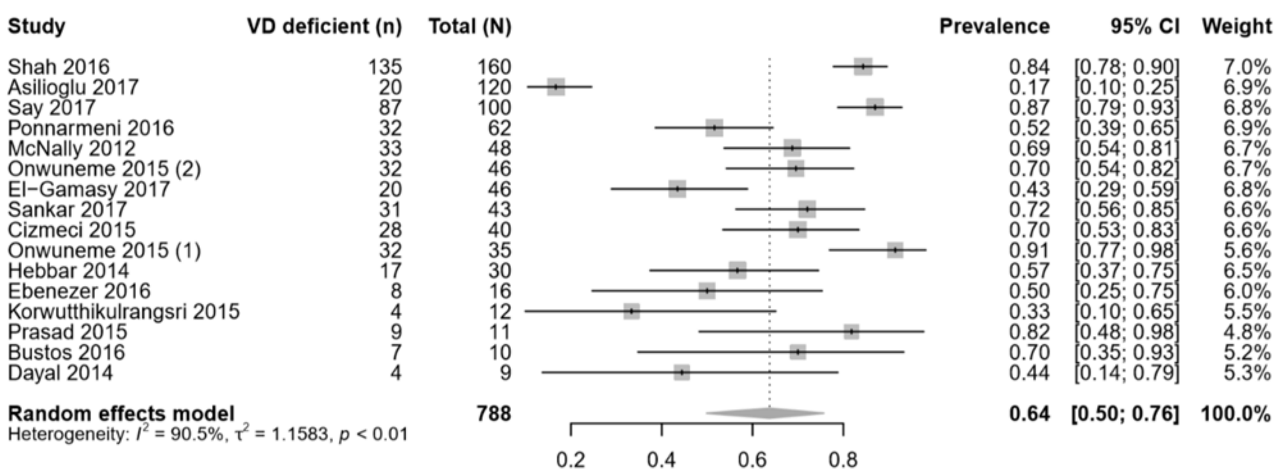

Figure 4 Pooled prevalence estimate for vitamin D deficiency in critically ill children with sepsis. Forest plot shows result from the random effects model. The diamond represents the overall pooled proportion of vitamin D deficiency from the meta-analysis of the 16 studies. Each square shows the prevalence estimate of each study and the horizontal line across each square represents the 95% confidence interval (CI) of the prevalence estimate.

Funnel plot was symmetric suggesting no publication bias (p = 0.828, Egger's test) *(Additional Figure 5).*

We also analysed studies of patients admitted for respiratory tract infections (n = 24, 1,683 total individuals) including acute lower respiratory tract infection (ALRTI), pneumonia and bronchiolitis, and found a prevalence estimate of 49.9% (95% CI 37.6-62.2; I^2 = 93.9%, 95% CI 92.1-95.3, p < 0.0001) *(Additional Table 13)*. Two of these studies[50, 76] also investigated sepsis.

Sensitivity analysis for prevalence in children with sepsis

Exclusion of the studies[58, 60, 65, 77] utilising thresholds other than < 50 nmol/L for deficiency yielded a similar estimate of prevalence at 61.4% (95% CI 43.5-76.6; I^2 = 91.2% 86.5-94.2, p < 0.0001) *(Additional Table 16).*

We examined pooled prevalence estimates according to sample size (< 40 versus ≥ 40). Studies with a small sample size (n = 7; 123 total individuals) showed a prevalence estimate of 63.2% (95% CI 45.0-78.2) with moderate variation attributable to heterogeneity (I^2 = 66.2%, 95% CI 24.5-84.9, p = 0.0068). For the remaining nine studies (sample sizes ≥ 40, 665 total individuals) the estimate was 63.9% (95% CI 44.9 - 79.4) with high variation attributable to heterogeneity (I^2 = 94.3%, 95% CI 91.2-96.3, p < 0.0001).

There was no material change in prevalence estimates when analysed according to study design. The nine cohort studies (463 total individuals) gave an estimate of 62.6% (95% CI 40.7-80.4) with high variation attributable to heterogeneity (I^2 = 92.8%, 95% CI 88.6-95.5, p < 0.0001). Case-control studies (n = 7; 325 total individuals) showed a prevalence of 65.2% (95% CI 47.3-79.7; I^2 = 87.0%, 95% CI 75.5-93.1, p < 0.0001) *(Additional Table 16, Additional Figure 6).*

Studies from India (n = 6) gave a prevalence estimate of 66.4% (95% CI 48.3-80.7; I^2 = 83.6%, 95% CI 65.7-92.2, < 0.0001). The three studies from Turkey assessing septic patients gave a pooled estimate of 59.2% (95% CI 13.6-93.1; I^2 = 97.8%, 95% CI 95.8- 98.8, p < 0.0001) *(Additional Table 16).*

The prevalence estimate in the three studies[60, 63, 65] including neonates with sepsis was 76.9% (95% CI 61.9-87.3, I^2 = 74.7%, 95% CI 15.9-92.4, p-value 0.019). The thirteen studies with children of different ages, excluding neonates, gave a pooled estimate of 60.1% (95% CI 43.7-74.5; I^2 = 90.8%, 95% CI 86.1-93.9, p value < 0.0001) *(Additional Table 16).*

Mortality in critically ill children

We identified 18 studies[8, 47, 50-53, 55, 58, 59, 65, 68, 69, 71, 76-80] assessing vitamin D status and mortality. These studies included a total of 2,463 individuals, from which 220 deaths (17.2%) were observed in 1,278 (51.9%) individuals with vitamin D deficiency and 99 deaths (8.4%) were observed in 1,185 individuals without deficiency (48.1%).

All 18 studies took place in a PICU apart from one[65] in a NICU. Sixteen of these studies (89%) were published between 2014 and 2017. Fourteen were cohort (77.8%) and four case-controls (22.2%). Almost half (n = 7) of the studies originated from India. Quality scores ranged from 5 to 8 with a median of 6.

Using a random effects model, we found that vitamin D deficiency in critically ill children significantly increased the risk of death (OR 1.81, 95% CI 1.24-2.64, p-value = 0.002) with low, non-significant heterogeneity (I^2 = 25.7%, 95% CI 0.0-58.0, p = 0.153) (*Table 1, Figure 5*). We did not identify evidence of publication bias (p = 0.084, Egger's test) (*Additional Figure 7*).

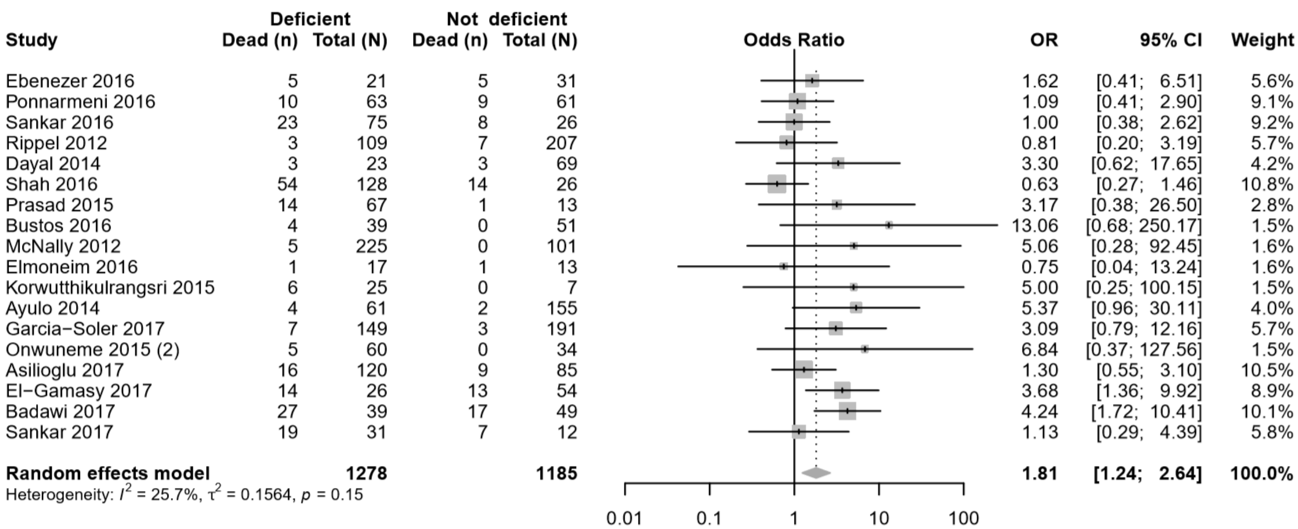

Figure 5 Pooled odds ratio (OR) of risk of mortality in vitamin D deficient versus vitamin D non-deficient critically ill children. Forest plot shows result from the random effects model. Diamond represents the overall OR (with corresponding 95% Confidence Interval). Each square shows the odds ratio of each study and the horizontal line across each square represents the 95% confidence interval (CI) of the estimate.

Sensitivity analysis for mortality in critically ill children

We obtained similar results through the fixed effects model (OR 1.72, 95% CI 1.27-2.33, p = 0.0005) (*Table 1, Additional Figure 8*). When excluding studies with thresholds other than < 50 nmol/L indicating deficiency, we found the association between vitamin D deficiency and increased risk of mortality still significant but lower, both with the random (OR 1.59, 95% CI 1.05-2.41, p = 0.028; I^2 = 24.3%, 95% CI 0.0-59.9, p = 0.191) and fixed effect models (OR 1.52, 95% CI 1.08-2.13, p = 0.016) with no indication of publication bias (p = 0.12, Egger's test) *(Additional Table 17).*

A significant association was also observed in analysis of the 14 cohort studies, both with the random effects model (OR 1.80, 95% CI 1.15-2.81, p = 0.01) and the fixed effects model (OR 1.65, 95% CI 1.17-2.34, p-value = 0.004) with low variation attributable to heterogeneity (I^2 = 31.3%, 95% CI 0.0-63.7). Pooling the four case-control studies together we obtained a significant positive association with the fixed (OR 1.97, 95% CI 1.02-3.82, p = 0.044) effects model but non-significant with the random effects model (OR 1.97, 95% CI 0.88-4.42, p = 0.098). The association was not-significant when pooling the seven studies from India with the random effects model (OR 1.08, 95% CI 0.70-1.69, p-value = 0.710; I^2 = 0.0% 0.0-62.4, p = 0.589) and a similar result with fixed effects (OR 1.08, 95% CI 0.70-1.69, p = 0.710) *(Additional Table 16).*

Mortality in patients with sepsis

We were unable to identify a sufficient number of studies assessing vitamin D and mortality for meta-analysis in individuals with sepsis. Three studies[8, 58, 60] measured vitamin D levels in pediatric patients with sepsis. One study[8] assessed mortality and did not find a significant association in children from 1 to 12 years with sepsis (n=124).

Discussion

Vitamin D deficiency is highly prevalent worldwide, even in countries with abundant sunshine. Studies demonstrated a high prevalence of vitamin D deficiency in otherwise healthy children from high-income countries (9 to 24%) but also from middle and low-income countries in Indian subcontinents (36 to 90%).[8]

We identified 48 studies representing a total of 5,520 children treated in ICU or emergency units for acute conditions who had blood vitamin D levels measured close to or upon admission. Our analysis shows that prevalence of vitamin D deficiency is high (range 5%[66] to 95%[54]) across ICU and emergency units in the pediatric population, particularly in individuals with sepsis. Importantly, our pooled estimates identified a significantly increased risk of mortality in critically ill children with vitamin D deficiency.

A recently published meta-analysis by McNally et al. 2017[81] also investigated prevalence of vitamin D deficiency in critically ill children and its association with risk of mortality. Our inclusion criteria were similar to McNally et al.,[81] except that they included only cohort and case-control study designs, excluded publications focusing on specific diseases or interventions, such as ALRI, and only used studies in which mortality was the primary clinical outcome. In addition, they did not include any studies in neonates. All studies in their review (n = 17) were also included in the present study except one.[82] Our results are in agreement with their findings both for prevalence of vitamin D deficiency and risk of mortality. McNally et al 2017 did not carry out subgroup analyses for prevalence of vitamin D deficiency in children with sepsis or respiratory tract infections. However, they investigated the relationship between vitamin D deficiency and vasopressor use, need for mechanical ventilation and bacterial or nosocomial infections. We carried out additional sensitivity analyses using fixed effects models, by study design, country group, age and sample size and found consistent results. Sub-group analyses in patients with sepsis or respiratory tract infections demonstrated a high prevalence of vitamin D deficiency, consistent with the increased risk of bacterial or nosocomial infection in vitamin D deficient individuals identified in McNally et al 2017. Finally, we carried out meta-regression analysis to investigate the high level of heterogeneity across studies and found that clinical setting and country groups are significant predictors.

Although sepsis is a leading cause of pediatric mortality and morbidity worldwide,[83] we found few studies assessing the relationship between vitamin D status and mortality in this population. We were unable to identify sufficient studies including patients with sepsis to perform a meta-analysis of vitamin D status and mortality. Sepsis remains an area of unmet need with high social and financial costs.[24] Diagnostic criteria,[84] a lack of adequate biomarkers[85] and targeted treatment remain important challenges in research on sepsis.

Strengths of our review include the large number of studies and large sample size, allowing for a high-powered investigation to identify meaningful associations. For our systematic review and meta-analysis, we followed pre-specified eligibility criteria and used the PRISMA[27] and MOOSE guidelines[28] for reporting. We carried out sensitivity analyses with few material differences in results. However, we note that the relationship between vitamin D deficiency and mortality was sensitive to study design. Only the prevalence analysis with neonates indicated lower variation attributable to heterogeneity (I^2 = 54.3%) along with a higher prevalence estimate (86%) compared to other analyses. As expected, heterogeneity across studies is high overall, particularly for prevalence estimates. Sources of this heterogeneity may include clinical setting, age, and ethnicity, country of study, measurement assays, case mix and seasonality, amongst many others.

We utilised meta-regression to investigate this substantial heterogeneity around prevalence estimates. From the six variables in our multivariate model, only clinical setting and country groups were found to be significant predictors of pooled prevalence estimates of vitamin D deficiency and the full model could explain 37.52% of I^2. Studies in NICU yielded higher prevalence estimates compared to studies in PICU. Studies from group 3 countries were also associated with higher prevalence estimates compared to studies from countries of group 1 and 2. Other variables, mainly individual patient characteristics such as age and ethnicity, were not directly available to us and may account for significant heterogeneity. Future research should also investigate biological heterogeneity in order to strengthen the evidence and produce generalisable results.

Our systematic review did not identify longitudinal studies with multiple time-point, pre-disease or pre-admission vitamin D measurements. The majority of studies were single centre with heterogeneous patient groups and relatively small sample sizes. Few studies accounted for important confounders that influence vitamin D levels, such as age, gender, BMI, season of measurements, vitamin D supplementation and comorbidities. The relationship observed between vitamin D deficiency and mortality could be due to reverse causation and future studies will need to control for these covariates and other confounders.

Although included studies were generally of good quality, sample sizes varied considerably and were typically small. Over half of studies included less than 100 cases and only 10 studies (19.6%) had a total sample size of more than 200 individuals. In addition, studies used a variety of definitions and age ranges to designate individuals as children. Our analysis only included mortality as a clinical outcome. A further general limitation is the difference in thresholds for vitamin D deficiency, particularly in the levels which are considered normal for infants and young children. Our assessment used the currently recommended threshold for deficiency (≤ 50 nmol/L)[16] and used a conservative estimate for studies which used different criteria.

Vitamin D remains an attractive biomarker and potential therapeutic agent in acute and critical care patients. Carefully designed and adequately powered studies are needed to determine the importance and therapeutic value of vitamin D in the general and septic pediatric critical care population.

Availability of data and materials

Data and computational code used for processing and analysis are available at https://github.com/margarc/VitaminD_children

Contributors

AJBT conceived the study. AJBT and IT designed the study. MC collected data and performed the analysis with input from MAC, IT, ABJT and EE. MC and AJBT wrote the manuscript with contributions from all authors.

Declaration of interests

The authors declare no conflicts of interest.

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Additional Files

Additional Tables

Additional Table 1A Search terms used in OVID

Additional Table 1B Search terms used in PubMed

Additional Table 2A Newcastle Ottawa study quality scoring system (cohort studies)

Additional Table 2B Newcastle Ottawa study quality scoring system (case-control studies)

Additional Table 2C Newcastle Ottawa study quality scoring system (cross sectional studies)

Additional Table 3A Circulating 25(OH) D threshold levels used in the selected studies

Additional Table 3B Circulating 25(OH) D threshold levels used in the selected studies for prevalence in sepsis

Additional Table 4 Studies with thresholds other than <50 nmol/L

Additional Table 5 Excluded studies

Additional Table 6 Characteristics of the 48 included studies

Additional Table 7 Objectives and outcomes of included studies

Additional Table 8 Assay used in each study to measure Vitamin D levels

Additional Table 9 Funding and ethical approval of included studies

Additional Table 10 Age groups of children in each study

Additional Table 11 Prevalence of vitamin D deficiency in each study of critically ill children (sorted from highest to lowest)

Additional Table 12 Characteristics of studies used in the meta-analysis for prevalence

Additional Table 13 Sensitivity analyses for prevalence of vitamin D deficiency in all critically ill children

Additional Table 14 Multivariate meta-regression model for prevalence

Additional Table 15 Characteristics of studies included in the meta-analysis for prevalence in individuals with sepsis

Additional Table 16 Sensitivity analyses for prevalence of vitamin D deficiency in critically ill children with sepsis

Additional Table 17 Sensitivity analyses for mortality

Additional Figures

Additional Figure 1 Funnel plot of studies of prevalence of vitamin D deficiency in critically ill children

Additional Figure 2 Pooled prevalence estimate for vitamin D deficiency in critically ill children (subgroup analysis by country group)

Additional Figure 3 Pooled prevalence estimate for vitamin D deficiency in critically ill children (subgroup analysis of neonates versus all other age groups)

Additional Figure 4 Bubble plots of univariate meta-regressions.

Additional Figure 5 Funnel plot for prevalence of vitamin D deficiency in critically ill children with sepsis

Additional Figure 6 Pooled prevalence estimate for vitamin D deficiency in critically ill children with sepsis (subgroup analysis by study design)

Additional Figure 7 Funnel plot of risk of mortality in vitamin D deficient versus vitamin D non-deficient critically ill children

Additional Figure 8 Pooled odds ratio and 95% CI for risk of mortality in vitamin D deficient versus vitamin D non-deficient critically ill children (fixed effects model)