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Original Article

Association between vitamin D deficiency and otitis media with effusion in children: a systematic review and meta-analysis

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Abstract

Background Vitamin D plays a crucial role in the regulation of inflammation. However, its effect on the development of otitis media with effusion (OME), an inflammatory disease of the middle ear without signs of infection, remains largely unknown.

Objective To assess the association between vitamin D deficiency and OME in children by systematic review and meta-analysis of the literature.

Methods Eligible studies retrieved from PubMed, ProQuest, Embase, Cochrane databases and trial registries published up to 30 October 2022 were included in this review. The risk of bias of the included articles was assessed with the JBI Critical Appraisal Checklist for observational studies. The certainty of evidence was assessed with the Grading of Recommendations Assessment, Development and Evaluation framework.

Results We included eight studies (six case-control and two cross-sectional studies) involving 1,114 children, of which four studies were eligible for meta-analysis due to the significant clinical heterogeneity. We found that vitamin D deficiency (defined as vitamin D concentration of 20 ng/mL or less, i.e., ≤50 nmol/L) might increase the odds of developing OME by 66.0% (n=514; OR 1.66; 95%CI 1.09 to 2.54; I2=20%), albeit with a very low certainty of evidence.

Conclusion There is a very low quality of evidence indicating that vitamin D deficiency is associated with the development of OME in children. Further large, high-quality cohorts and adjusting for confounding factors are warranted to confirm our findings, ideally by exploring the dose-response relationship between vitamin D concentration and the development of OME. **[Paediatr Indones. 2024;64:419-29; DOI: https://doi.org/10.14238/pi64.5.2024.419-29].**

Keywords: *otitis media effusion; systematic review; vitamin D deficiency*

Otitis media with effusion (OME), defined as the accumulation of non-infected fluid in the middle ear without any signs of acute ear infection, remains a debilitating condition in children resulting in conductive hearing loss.[1] Previous studies reported that up to 83.0% of children attending primary school with OME experienced hearing loss. Hearing loss caused by OME may remain undetected and may lead to speech and language disturbances.[2-4]

To date, several risk factors of OME have been identified, including tobacco smoke exposure, Helicobacter pylori infection, daycare attendance, history of acute otitis media (AOM) or gastroesophageal reflux disease, and atopy.[5-9] These risk factors are postulated to promote inflammation and immune reactions, contributing to rhinopharyngeal infections, which, in turn, lead to the production of proinflammatory mediators and the secretion of protein-rich exudates causing OME.[10] Vitamin D,

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known for its antioxidative properties, helps regulate inflammation by stimulating the production of anti-inflammatory cytokines and inhibiting the proliferation and activation of inflammatory mediators.[11] Through these mechanisms, vitamin D is thought to play a key role in regulating inflammatory diseases including OME.[11] However, the effect of vitamin D deficiency on the development of OME in children remains largely unexplored. Hence, this systematic review was conducted to investigate the possible association between vitamin D deficiency and the development OME in children.

Methods

The study protocol has been prospectively registered in *PROSPERO* (CRD42021230843).[11] This systematic review was conducted according to the COSMOS-E guideline and was reported based on the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) statement.[12,13]

The inclusion criteria of this systematic review were randomized controlled trials (RCTs) and observational studies (i.e., case-control, prospective and retrospective cohort studies, as well as analytical cross-sectional studies) evaluating the association between serum 25-hydroxyvitamin D [25(OH)D] level and the development of OME, as diagnosed by pneumatic otoscopy and tympanometry, in healthy children aged up to 12 years of age. Studies that had subjects with the following conditions were excluded: 1) active or history of recent ear infections, including acute otitis media (AOM) and chronic suppurative otitis media (CSOM), 2) craniofacial abnormalities, including cleft palate or cleft lip, 3) mucociliary dysfunction, 4) immunodeficiency, 5) renal impairment, or 6) children who had previously undergone ear surgery.[1]

We searched six bibliographic (*PubMed, Embase, ProQuest*) and grey literature databases [*Cochrane Central Register of Controlled Trials* (CENTRAL), *ClinicalTrials.gov*, the *World Health Organization International Clinical Trials Registry Platform* (ICTRP; http://apps.who.int/trialsearch/)] for eligible studies published up to October 30, 2022. We combined the search terms and applied the search strategy in each database (see **Appendix 1**), and did not limit our search to language, publication status, or publication year. We checked the reference lists of all primary studies, reviewed articles, web searching (e.g., *Google Scholar*), and conference abstracts or proceedings for additional references. Five review authors independently screened the titles and abstracts and reviewed the retrieved full-text studies to identify studies for inclusion. Disagreement was resolved through discussion with an independent review author.

The data from the included studies were extracted into a prespecified form that had been piloted. The following data were extracted: (1) study characteristics including first author's last name, year of publication, design, location, and setting; (2) patient characteristics including sample size, mean age, and diagnosis criteria; (3) exposure including serum 25(OH)D level and measurement methods, as well as other confounding factors; and (4) the association between vitamin D levels and the incidence of OME. The included studies were then assessed for risk of bias using the *JBI Critical Appraisal Checklist*[14] for cohort, case-control, and analytical cross-sectional studies. Four authors performed the data extraction and risk of bias assessment independently and a second reviewer subsequently checked for accuracy by.

The extracted characteristics data were tabulated and summarized qualitatively. Due to significant differences in study characteristics (e.g., design and cut-offs used to define vitamin D deficiency), we contacted the study authors for additional data in an attempt to homogenize the variable characteristics. However, as the authors could not provide the requested data, we could not pool all studies into the meta-analysis. In addition, due to the lack of studies reporting multiple categories, we also could not perform a dose-response meta-analysis. Hence, we defined vitamin D deficiency as serum 25(OH) D level of 20 ng/mL or less (≤50 nmol/L).[15] Odds ratio (OR) along with its 95.0% confidence interval (CI) was used as the common effect measure. The statistical heterogeneity between studies was assessed using Cochrane Chi-square and I2 values, and the random-effects model was used to estimate the pooled effect size when significant heterogeneity existed (I2>50%). Otherwise, we pooled the effect sizes using the fixed-effects model.[16]

Furthermore, due to the limited number of included studies, subgroup analysis was performed based only on the presence of adenoid hypertrophy.[12] All data analyses were conducted in *Review Manager ver. 5.4*.[17] Lastly, the certainty of evidence was assessed using the *Grading of Recommendations, Assessment, Development and Evaluations* (GRADE) framework, with vitamin D as the main exposure. The evidence quality was then judged as high, moderate, low, or very low.[18]

Results

We retrieved 2,892 records from electronic databases and an additional six records from web searching (i.e., *Google Scholar*) (**Figure 1**). Following title and abstract screening, 22 full-texts were assessed, of which 12 articles were excluded due to ineligible study designs and types (six studies),[19-24] inappropriate study population (two studies each included children with AOM),[25-26] and CSOM,[27-28] different exposure and outcome of interests (one study),[29] and superseded by a newer report (one study),[30] resulting in 11 articles. Among them, there were various definitions of otitis media (acute or chronic effusion) and data from the control group.[31,32] Therefore, only eight studies were included in this systematic review (1,114 children), comprising six case-control studies and two cross-sectional studies.[33-40] The characteristics of the eight included studies are summarized in **Table 1**. We further assessed the eligibility of the eight included studies to be included in the meta-analysis, resulting in the exclusion of two studies due to different cut-off definitions (only studies reporting a cut-off of <20 ng/mL were included in the meta-analysis) and two studies due to cross-sectional design.[41-44]

Seven studies were conducted in hospital settings and one study was conducted in a community setting. The study by Akcan *et al*.[33] was conducted in the Black Sea Region of Turkey, while the other studies were conducted in Egypt and Iran (three studies each) and in New Zealand (1 study). Of the eight studies, three included children who underwent tonsillectomy or adenotonsillectomy.[34,35,40] Two studies included children with adenoid hypertrophy,[38-39] and one study included children referred for tympanostomy.[36]

The methods used to measure serum 25(OH)D levels also differed among studies. Five studies used enzyme-linked immunosorbent assay (ELISA),[34,35,37-40] one used electrochemiluminescence immunoassay,[40] one used liquid chromatography-tandem mass spectrometry,[36] and another study did not state the measurement method.[33] Among the four studies that mentioned the timing of serum 25(OH)D level measurement, two were measured perioperatively,[33,34] one before the surgery,[40] and one three months after the diagnosis of OME.[45] Furthermore, we were unable to identify the exposure core set such as age, lack of breastfeeding, recurrent upper respiratory tract infection (URTI), and atopy due to the small number of included studies and incomplete data. In fact, only one study adjusted for confounding factors.[36]

Most of the included studies yielded a moderate-to-high risk of bias (**Table 2**). Most of the concerning biases were related to the identification and strategies to deal with confounding factors, as well as the duration of exposure. The four studies included in the meta-analysis also had a moderate-to-high bias risk, resulting in the overall assessment of high risk of bias for both studies.[33,38-40]

Only one of the included studies reported an adjusted estimate for at least one exposure core set.36 The study found that higher serum 25(OH)D level was associated with a lower risk of chronic OME (OR 0.86 per 10 nmol/L; 95%CI 0.77 to 0.97), independent of age, sex, ethnicity, tobacco smoke exposure, duration of breastfeeding, season of blood sampling (summer, autumn, winter, or spring), and the *New Zealand Deprivation Index*.[41] Due to the substantial clinical heterogeneity between studies, we decided to pool only the studies with similar characteristics in the meta-analysis. From the four case-control studies included in the model (n=514 children),[5-8] we found that vitamin D deficiency increased the odds of developing OME by 66% (OR 1.66; 95%CI 1.09 to 2.54; I^2=20%) (**Figure 2**). However, the quality of the evidence was judged to be very low in terms of study design, limitations, and imprecision (**Table 3**).

We initially planned to perform subgroup analyses based on the severity of vitamin D deficiency, the presence of adenoid hypertrophy, and the age of the included patients (preschool- *vs.* school-aged children). However, due to the limited number of included studies, we could only perform a subgroup analysis based on the presence of adenoid hypertrophy.

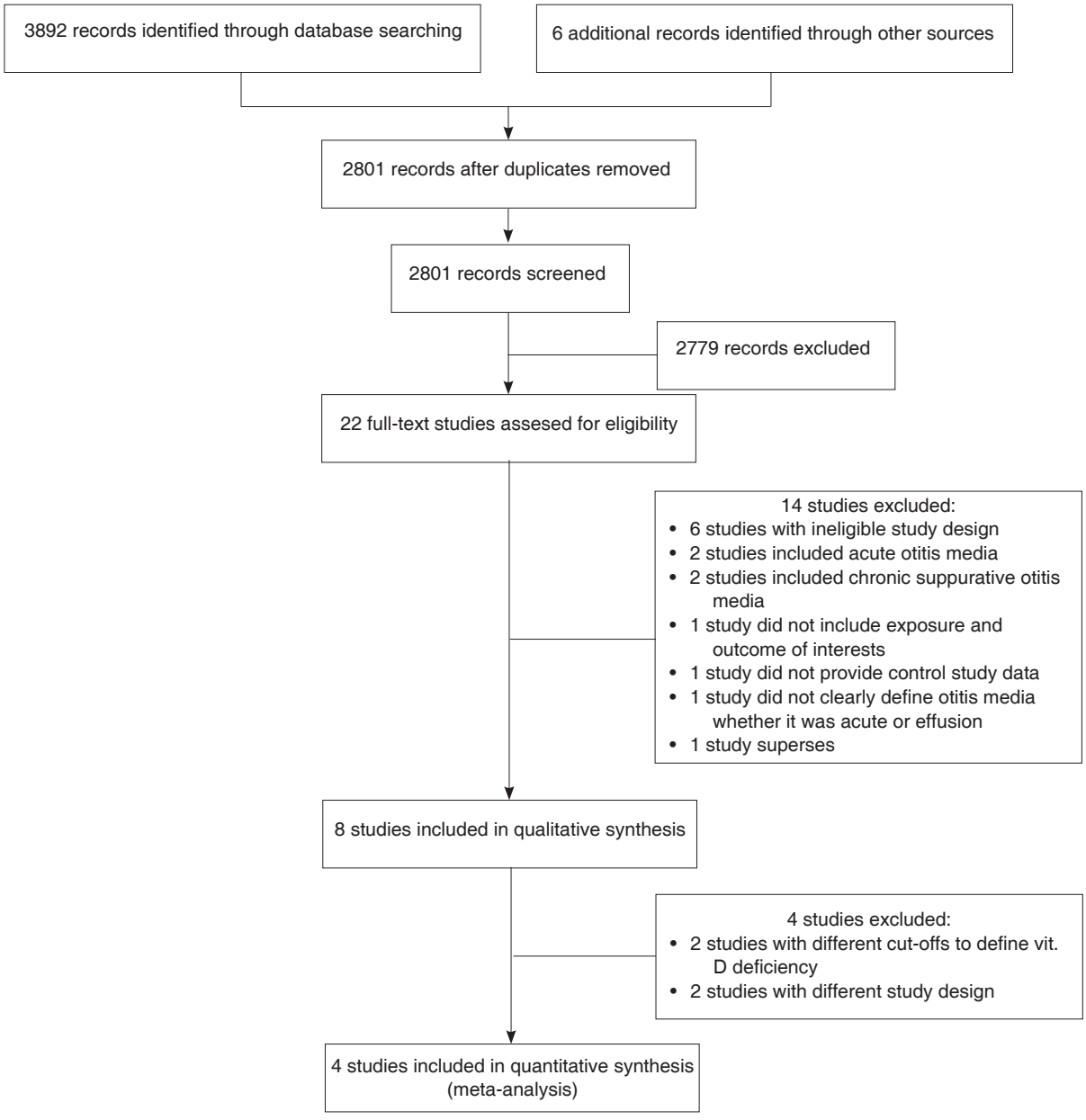

Figure 1. PRISMA flow diagram of the literature search and study selection process

The subgroup analysis revealed that children without adenoid hypertrophy had a higher risk of developing OME compared to those with adenoid hypertrophy (OR 2.10; 95%CI 1.22 to 3.65; I^2=0% *vs.* OR 1.13; 95%CI 0.57 to 2.24; I^2=19%).

Discussion

Otitis media with effusion in children, if left untreated, is known to predispose patients to hearing and speech development disorders.[42] As the underlying pathology in OME involves immune and inflammatory reactions, it is important to identify and mitigate risk factors of OME for prevention and prompt treatment of children with OME.[43] Our meta-analysis revealed that vitamin

D deficiency may increase the odds of developing OME by 66.0%. However, our findings should be interpreted cautiously, especially considering that the pooled effect size was derived from a small number of studies with a moderate-to-high risk of bias, and the certainty of evidence was very low.

The observed association between vitamin D deficiency and OME may be explained by the immunomodulatory effects of vitamin D. Vitamin D deficiency results in diminished anti-inflammatory mechanisms mediated by T-lymphocytes, leading to exacerbation of proinflammatory states and tissue damage. An animal study showed that rats with vitamin D deficiency exhibit a thicker middle ear mucosa, indicating that the inflammation exacerbated by vitamin D deficiency may induce pathological changes resulting in OME.[44] Surprisingly, the odds of developing OME were significant in children without adenoid hypertrophy, and non-significant in children with adenoid hypertrophy. We initially hypothesized that adenoid hypertrophy might increase the odds of developing OME, as adenoid enlargement could lead to Eustachian tube dysfunction, and a focus of primary infection - leading to the production of exudates in the middle ear.[45] This observation may be explained by several factors, including the severity of adenoid hypertrophy, the timing of outcome assessment, and more importantly, the limited number of patients and studies assessed. Nonetheless, due to the limited information available at this time, we were unable to further explore the possible explanations underlying the observed findings. Therefore, further studies are required to confirm adenoid hypertrophy as a risk factor for developing OME in children with vitamin D deficiency.

Vitamin D deficiency is also considered to be a risk factor in many inflammatory diseases, both in those of infectious origin e.g., acute respiratory tract infection (ARTI) and acute otitis media (AOM), as well as non-infectious origin, e.g., allergic rhinitis.[25,43,46] This is further corroborated by studies which found that vitamin D supplementation may reduce the risk of developing ARTI and AOM in children.[43,46] These observations are critical as they indicate that vitamin D may prevent OME directly through its anti-inflammatory effects in the middle ear, and indirectly by preventing infection and inflammation in the united airway system, thus preventing the accumulation of exudates in the middle ear.[44] These studies also indicate that identifying vitamin D deficiency among children at risk of developing OME may also provide valuable information for patients and clinicians to prevent OME. However, further investigations are required to determine whether such measurements should be routinely performed in daily clinical practice. Such a decision should be based on a cost-benefit analysis of implementing routine serum vitamin D level measurement and supplementation, as well as considerations from clinicians' expertise and parents' preferences.

This systematic review was not without limitations. The included studies were conducted in areas with relatively low sun exposure, thus, our findings may not be generalizable in all settings, especially considering that exposure to sunlight is known to influence serum vitamin D levels. Furthermore, only one study adjusted the observed effect of vitamin D deficiency on the development of OME with confounding factors.[36] This is important considering that the substantial clinical heterogeneity between studies, including comorbidities (e.g., adenoid enlargement and tympanostomy), seasonal sun exposure, and criteria used to diagnose OME, may limit the interpretability of our findings. In addition, the small number of studies, high risk of bias, and the very low certainty of evidence, indicate that our findings should be interpreted with caution. Despite these limitations, our study highlights the possible association between serum vitamin D concentration and OME, thus warranting further large, high-quality studies adjusting for confounding variables. These studies should ideally explore a dose-response relationship between serum vitamin D level and the incidence of OME in order to obtain a complete picture on the role of vitamin D in OME.

In conclusion, there is very low certainty of evidence that vitamin D deficiency may increase the odds of developing otitis media with effusion in children. Further large sample size, high-quality studies adjusting for confounding variables and exploring the dose-response relationship between serum vitamin D level and the development of OME are required to substantiate our findings.

Table 1. Characteristics of the studies included in systematic review

Author (publication year)	Country (setting)	Study design	Population					
			Description		Mean age (SD), years		Mean serum 25(OH) D level (SD), ng/mL	
			Study group	Control group	Study group	Control group	Study group	Control group
Abhari *et al.*[37] (2019)	Iran (Hospital)	Cross-sectional	46 children with adenoid hypertrophy grade 3/4 and OME	43 children with adenoid hypertrophy grade 3 and 4 without OME	5.8 (2.1)	NA	24.7 (13.1)	22.9 (12.2)
Abu-Elnasr *et al.*[35] (2015)	Egypt (Hospital)	Case-control	40 preschool children with OME	40 age- and sex-matched children	3.8 (0.5)	3.8 (0.6)	15 (9)	28 (9)
Akcan *et al.*[33] (2018)	Turkey (Hospital)	Case-control	174 children with bilateral OME.	80 children who underwent circumcision or inguinal hernia repair operations without OME	5.1 (2.1)	4.70 (2.08)	18.98 (10.60)	28.07 (14.10)
Asghari *et al.*[34] (2017)	Iran (Hospital)	Cross-sectional	32 children with OME who underwent adenotonsillectomy	42 children without OME who underwent adenotonsill -ectomy	5.4 (1.5)	5.46 (1.31)	9.79 (4.36)	13.61 (6.33)
Hosseini *et al.*[38] (2016)	Iran (Hospital)	Case-control	40 children with OME and candidates for adenotonsillectomy	80 matched children	5.7 (2.6)	7.2 (2.2)	26.1 (14.6)	29.5 (17.9)
Mohammed *et al.*[39] (2021)	Egypt (Hospital)	Case-control	20 children with bilateral OME	20 matched children	3.8 (2.2)	5.3 (3.1)	17.02 (8.49)	25.85 (8.94)
Nabil *et al.*[40] (2022)	Egypt (Hospital)	Case-control	50 children with adenotonsillar hypertrophy and OME without resolution after 3 months of watchful waiting	50 healthy children who underwent routine hearing check-up.	4.5 (0.8)	5.4 (1.1)	16.0 (6.1)	15.7 (5.3)
Walker *et al.*[36] (2017)	New Zealand (Community)	Case-control	178 children aged 3-4 years old diagnosed with OME, who had been referred for tympanostomy tube placement	179 randomly selected healthy children recruited from primary care practices.	4.0 (0.6)	4.11 (0.55)	28.67 (8.89)	29.67 (10.64)

Exposure [serum 25(OH)D]		Adjusted confounding factors	Outcomes (OME)			
Timing of masurement	Measurement methods of serum 25(OH)D level		Diagnostic criteria	Assessment time	Cut-off, ng/mL	Outcomes (vit D deficient *vs.* vit D non-deficient); event, n
NA	ELISA by spectro-photometry	NA	Tympanometry type B and C	NA	<15	8 (19) *vs.* 24 (82)
NA	ELISA	NA	Otoscopic examination and tympanometry type B	Prior to surgery	<30	35 (51) *vs.* 5 (29)
3 months post-OME diagnosis	NA	NA	Otoscopic examination and tympanogram type B or C	Prior to surgery	≤15	68 (88) *vs.* 106 (166)
Perioperative (during surgery)	ELISA by spectrophotometry with Diaplas Kit (ELISA reader, USA)	NA	Otoscopic examination and tympanometry type B	NA	<20	23 (38) *vs.* 9 (36)
Perioperative (on the day of surgery)	ELISA	NA	Evidence of middle ear exudate and tympanometry type B or C2	Prior to surgery	<15	8 (19) *vs.* 24 (82)
NA	ELISA	NA	History taking, otoscopic examination, audiologic evaluation	NA	<10	8 (11) *vs.*. 12 (29)
1 week prior to surgical intervention	Electro chemiluminescence immunoassay (ECLIA) technique	NA	History taking, otoscopic examination, audiologic evaluation, tympanometry type B	NA	≤20	37 (76) *vs.* 13 (24)
NA	LC-MS/MS	Age, sex, ethnicity, tobacco smoke exposure, duration of breastfeeding, and season of blood sampling, and NZDep	NA	Prior to surgery	per +10	0.86 (95%CI 0.77 to 0.97)

Table 2. Risk of bias assessment of the included studies

Study ID	1	2	3	4	5	6	7	8	9	10
Cross-sectional studies*										
Abhari *et al.*[37]	+	+	+	+	+	+	+	+		
Asghari *et al.*[34]	+	+	+	+	+	-	+	-		
Case Control studies**										
Akcan *et al.*[33]	+	+	+	+	+	?	?	+	+	+
Abu-Elnasr *et al.*[35]	+	+	+	+	+	+	+	+	+	+
Hosseini *et al.*[38]	+	+	+	+	+	?	?	+	+	-
Nabil *et al.*[40]	+	+	+	+	+	+	+	+	?	+
Mohammed *et al.*[39]	+	+	+	+	+	-	-	+	?	+
Walker *et al.*[36]	+	+	+	+	+	+	+	?	+	+

***Questions in risk of bias for cross-sectional studies**

1. Were the criteria for inclusion in the sample clearly defined?
2. Were the study subjects and the setting described in detail?
3. Was the exposure measured in a valid and reliable way?
4. Were objective, standard criteria used for measurement of the condition?
5. Were confounding factors identified?
6. Were strategies to deal with confounding factors stated?
7. Were the outcomes measured in a valid and reliable way?
8. Was appropriate statistical analysis used?

****Questions in risk of bias for case control studies**

1. Were the groups comparable other than the presence of disease in cases or the absence of disease in controls?
2. Were cases and controls matched appropriately?
3. Were the same criteria used for identification of cases and controls?
4. Was exposure measured in a standard, valid and reliable way?
5. Was exposure measured in the same way for cases and controls?
6. Were confounding factors identified?
7. Were strategies to deal with confounding factors stated?
8. Were outcomes assessed in a standard, valid and reliable way for cases and controls?
9. Was the exposure period of interest long enough to be meaningful?
10. Was appropriate statistical analysis used?

-=low risk; ?=unclear risk; +=high risk

Conflict of interest

None declared.

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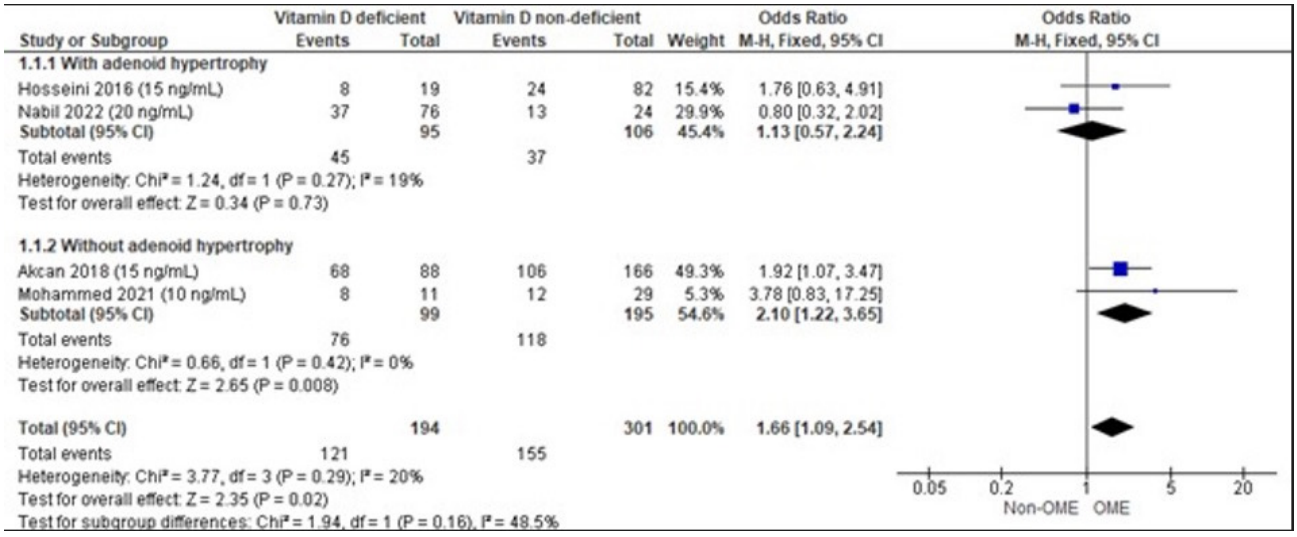

Figure 2. Forest plot of four studies on the odds of OME in children with vitamin D deficiency

Table 3. Summary of findings assessed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework[18]

Outcomes	Anticipated absolute effects (95%CI)		OR (95%CI)	No. of participants (cases vs. controls); no. of observational studies)	Certainty of the evidence (GRADE)
	Odds with normal vitamin D	Odds with vitamin D deficiency			
OME	515 per 1,000	638 per 1000 (536 to 729)	1.66 (1.09 to 2.54)	194 *vs.* 301 (4 studies)	⨁◯◯◯ VERY LOW[a,b,c]
OME with adenoid hypertrophy	349 per 1,000	377 per 1000 (234 to 546)	1.13 (0.57 to 2.24)	95 *vs.* 106 (2 studies)	⨁◯◯◯ VERY LOW[a,b,c]
OME without adenoid hypertrophy	605 per 1,000	763 per 1000 (652 to 848)	2.10 (1.22 to 3.65)	99 *vs.* 195 (2 studies)	⨁◯◯◯ VERY LOW[a,b,c]

[a]Initial quality of a body of evidence was at low certainty due to observational study design; [b]downgraded one level due to study limitations (both studies did not identify confounding factors nor stated strategies to deal with confounding factor); [c]downgraded one level due to imprecision (wide confidence interval due to small sample size)

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