REVIEW

Low vitamin D levels and prognosis in a COVID-19 pediatric population: a systematic review

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Abstract

We aim to study the relationship between vitamin D level, risk and severity of Coronavirus disease of 2019 (COVID-19) infection in pediatric population through systematic review. We searched PubMed, CINAHL, EMBASE, Cochrane Library and Google Scholar from December 2019 to June 2021 for retrieving articles studying association between vitamin D deficiencies with COVID-19. Qualitative details were synthesized in evidence table and quantitative data was used for deriving pooled estimate through meta-analysis. After initial search of 2261 articles, eight eligible studies (two reviews) were included in the systematic review. Meta-analysis of the quantitative data (six studies) showed pooled prevalence of vitamin D deficiency as 45.91% (95% CI: 25.148–67.450). In infected pediatric patients, low levels of vitamin D increased the risk of severe disease (odds ratio–5.5; 95% CI: 1.560–19.515; $P = 0.008$). It was also found that children and adolescents having vitamin D deficiency had greater risk of COVID infection as compared to patients with normal vitamin D levels. Improvement in disease severity with vitamin D supplementation was also noted. The systematic review showed that almost half of the pediatric COVID patients suffer from vitamin D deficiency. It is also clear that the low level of vitamin D is associated with greater risk of infection and poorer outcome in pediatrics.

Introduction

The Coronavirus disease of 2019 (COVID-19)–a respiratory illness, was first reported in December 2019, in Wuhan, China and since then it has posed a threat for the health systems across the world. COVID-19, that affects everyone regardless of age, was found to be more severe in patients with low immunity and other underlying comorbidities such as hypertension and diabetes mellitus.[1,2] The RNA virus with a unique characteristic of antigenic shift has resulted in the inability to find a proper cure. Moreover, the development of the COVID-19 vaccine which has proved to be efficacious would take a long time to cover the whole population. In the case of pediatrics, the vaccine is still under the developmental phase with very few countries initiating vaccination of the population below the age of 18 years.

Given the dire circumstances, researchers have focused on other measures that can help prevent COVID-19 spread.

The role of macro and micronutrients in modulating the immune response in diseased and healthy individuals is known for a long. Vitamin D—a fat-soluble vitamin is known to exert a variety of biological effects including immunomodulatory effects and since the emergence of the pandemic, vitamin D is gathering attention from the scientific community.[3] A recent systematic review of RCTs showed that Vitamin D supplementation significantly reduces the risk of acute respiratory infection.[4] These studies laid the foundation of the theory that Vitamin D might have a role to play in COVID-19 susceptibility and disease severity. This was further strengthened with the emerging studies showing the poorer outcome of COVID-19 in patients with vitamin D deficiency.[5] A significant association

between vitamin D, sun exposure, COVID-19 outcomes and severity had also been reported in adults.[6–8] One of the recently published meta-analysis showed that vitamin D supplementation reduces the risk of ICU admission in adult COVID patients and it also has a potential impact on reducing the risk of mortality.[9] Although many studies have demonstrated vitamin D as a protective factor, controversies and heterogeneities exist in the literature showing the effect of vitamin D in the prevention and treatment of COVID-19, especially in the case of the younger population. With this systematic review, we aimed to estimate (i) prevalence of vitamin D deficiency in pediatric COVID patients, (ii) association between vitamin D deficiency and COVID-19 severity in pediatrics and (iii) the relationship between vitamin D supplementation and improvement in COVID-19 severity.

Materials and methods

A systematic review as a methodological approach using the framework provided by Arksey and Malley was adopted for the study.[10] For reporting of the review, Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) was used.

Search strategy

We searched five databases—PubMed, CINAHL, EMBASE, Cochrane Library and Google Scholar from December 2019 to June 2021. The search was conducted using index terms (e.g. MeSH and Entree terms): COVID-19, SARS-CoV-2, COVID-2019, 2019-nCOV, 2019 novel coronavirus infection, coronavirus disease-19, coronavirus disease 2019, severe acute respiratory syndrome coronavirus 2, novel coronavirus, vitamin D, vit D, vitamin D supplementation, children, infant, neonate, young, newborn, baby, babies, pediatric, pediatric and juvenile. These search terms were combined as search sets, using Boolean operators (AND, OR and NOT). Retrieved articles were evaluated using title and abstract and selected articles were further screened using full-text evaluation. Additionally, reference tracking of the searched articles was carried out to identify and other relevant articles, which were missed during the initial search. We excluded duplicate studies from the final search.

We included studies published in English in peer-reviewed journals that were conducted in children (age ≤18), and those reporting vitamin D status and COVID-19 infection in pediatric patients. Studies reporting the role of vitamin D supplementation in improving disease severity in children and adolescents were also included. We excluded studies including only adult (age >18 years) patients and not published in English. The process of inclusion and exclusion is described using the PRISMA flowchart (Moher, Liberati, Tetzlaff and Altman, 2009) (Figure 1).

The initial search yielded 2261 articles, of which, after elimination of duplicates and screening of their titles and abstracts and full-text evaluation eight studies were considered relevant to this review.

Data extraction

Two independent reviewers screened the title and abstracts and assigned unique identification numbers to all included articles. Key information from each screened article was extracted by two independent researchers and categorized in an evidence table using the following heads: author(s), title, country, population, study period, total cases, the status of vitamin D, the severity of COVID-19, vitamin D supplementation, outcomes of the study and general findings. Any discrepancy in the coding was resolved by consensus.

Data synthesis

Data from the eligible articles were abstracted into evidence tables. Consensus or variations related to relevant variables were reported and presented as descriptive summaries in the Result Section. A meta-analysis was performed for assessing pooled deficiency of vitamin D in pediatric patients of COVID-19. We used a random-effect/fixed-effect model (based on heterogeneity) to calculate pooled weighted proportions with the 95% confidence interval. Heterogeneity or between-study variance was assessed using Cochran's Q test ($P < 0.10$), and quantified using the I^2 statistics. $I^2 > 50\%$ and a $P < 0.05$ were considered substantial heterogeneity. All statistics of meta-analysis were performed using MedCalc (Windows) version 15.0 (MedCalc Software, Ostend, Belgium). Publication bias was assessed using Begg's test and Egger's test.

Results

The current systematic review synthesized evidence from eight articles having different study designs.[11–18] This included two review articles published from Romania and Italy, rest of the articles were either retrospective cohort or case series studies. Out of eight, six articles provided details of vitamin D levels in pediatric COVID patients and were included for quantitative assessment through meta-analysis. Two studies assessing the role of vitamin D levels in disease severity were also included in meta-analysis to derive cumulative odds of developing poorer outcomes in case of vitamin D deficiency.[11,18]

Characteristic details of the included studies are presented in Table 1. According to geographic location, studies were reported from various parts of Europe and America. The sample size of the population varied widely with the lowest reporting as 14 patients to the highest as 9 87 849 patients.[13,14] Half of the studies included both pediatric and adult populations and four studies presented data exclusively from patients aging <18 years. Though our search included details till June 2021, evidence synthesis included studies published from March 2020 to January 2021.

Key findings from each study were summarized and tabulated (Table 2). Levels of vitamin D in pediatric COVID patients were provided by six studies and a pooled prevalence of vitamin D deficiency was analysed. Meta-analysis of the quantitative data (six studies) showed a pooled prevalence of vitamin D deficiency as 45.91% (95% CI: 25.148–67.450; random effect model) (Figure 2). This meta-analysis showed higher heterogeneity ($P < 0.0001$) but a lack of significant publication bias. This heterogeneity was imparted due to a wider range of vitamin D deficiency reporting by various studies (range: 5.7–72.5%). Some of the studies have also pointed to an inverse relationship between vitamin D levels and COVID-19 infection risk, indicating higher odds of infection in individuals with vitamin D deficiency as compared to their counterparts having normal vitamin D levels.[13,17] Apart from increased risk of infection, meta-analysis also showed that in infected pediatric patients, low levels of vitamin D increases the risk of severe course of disease (Figure 3; odds ratio: 5.5; 95% CI : 1.560–19.515; $P = 0.008$). Though only two studies included in the quantitative analysis, there was a complete absence of heterogeneity ($I^2 = 0\%$). We further wanted to study the association in deficient and
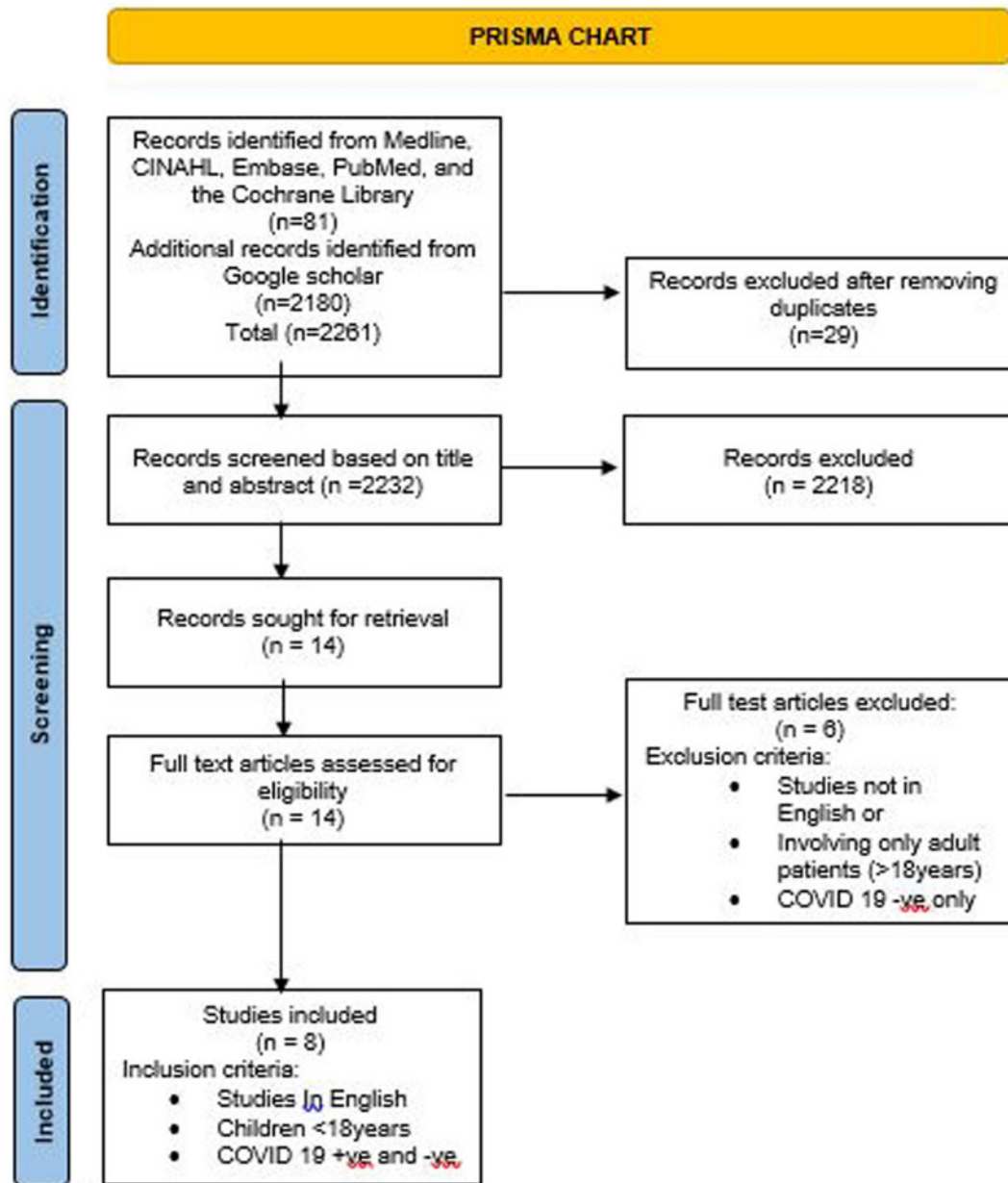
Figure 1. PRISMA chart of study selection.

insufficient groups, however due to non-availability of categorized data this cannot be explored.

Discussion

This global systematic review provides the most recent evidence synthesis addressing the relationship between vitamin D and COVID-19 in pediatric patients. It provided not only the quantitative estimate of vitamin D deficiency prevalence in children and adolescents infected with COVID-19, but also provided cumulative odds of developing severe disease in patients with low levels.

Vitamin D has been known for its protective role for ages, as it stimulates the production of antimicrobials in the epithelium of the respiratory tract and provides protection against respiratory tract infections.[19] Vitamin D regulates immune responses by reducing plasma cells, proinflammatory cytokine production and immunoglobulin release, thus increasing anti-inflammatory cytokine production.[20–23] Vitamin D also promotes the gene responsible for the expression of angiotensin-converting enzyme 2, which has an anti-inflammatory action.[24]

Our study noted that a considerable number of pediatric patients suffering from COVID-19 had low vitamin D levels. A study by Molla *et al.* assessed the importance of nutrition in the regulation of the immune system, and it was found that most of the pediatric COVID-19 patients were deficient in Vitamin D.[15] The pathology of COVID-19 provokes release of inflammatory mediators due to the complex interaction between the virus and the immune system. A greater emphasis is placed on vitamin D, as it has become increasingly clear that hyper inflammation is an important component of COVID-19.[25] Though

Table 1. Characteristic details of the studies included in the review

Sr. No	Author	Title	Country	Study type	Population	Study period	Total cases
1	Bayramoğlu et al.[11]	The association between vitamin D levels and the clinical severity and inflammation markers in pediatric COVID-19 patients: single-center experience from a pandemic hospital	Germany	Retrospective cohort study	Pediatric (1 to 18 years)	March and May 2020	356
2	Feketea et al.[12]	Vitamin D in Corona Virus Disease 2019 (COVID-19) Related Multisystem Inflammatory Syndrome in Children (MIS-C)	Romania	Mini review	Children and adults	up to 30th December 2020	Not provided
3	Katz et al..[13]	Increased risk for COVID-19 in patients with vitamin D deficiency	USA	Cross sectional study	Children and adults	Up to 30 June 2020	987849
4	Nadiger et al.[14]	Vitamin D Levels in Children With COVID-19 Admitted to the PICU	USA	Retrospective case series	Children	Jan 2021	14
5	Molla et al.[15]	Evaluation of nutritional status in pediatric patients diagnosed with Covid-19 infection	Turkey	Evaluation study	Pediatric (1 to 18 years)	May and 15 June 2020	49
6	Panfili et al.[16]	Possible role of vitamin D in Covid-19 infection in pediatric population	Italy	Short review	Children and adults	Not provided	Not provided
7	Söbü et al.[17]	Vitamin D levels of COVID-19 positive symptomatic pediatric cases	Turkey	Retrospective study	Pediatric	March to April 2020	112
8	Yilmaz and Sen[18]	Is vitamin deficiency a risk factor for COVID-19 in children?	Turkey	Retrospective study	Pediatric (1 to 18 years)	March 2020 and May 2020	85

evidence related to the effect of vitamin D on pediatric COVID is limited, in adult patients' numerous studies have documented its role. Raharusun et al., in their study conducted on adults, found deficient or insufficient levels of vitamin D in 47.3% of 780 patients diagnosed with COVID-19.[26] It was also found that vitamin D has a clear impact on disease severity and hence COVID associated mortality. As a result, there is a policy implication adopted by various regulatory bodies, where vitamin D supplementation has been recommended in deficient adults.

Studies included in the current review also assessed the effect of vitamin D deficiency on worsening of clinical outcomes such as increased days of stay in the intensive care unit and mortality. Two studies revealed an association between vitamin D deficiency and clinical severity, in addition to inflammation markers in COVID-19 pediatric patients. This association was

observed when there was a deficiency rather than an insufficiency in the study by Bayramoglu et al.[11] A six times higher chance of having a moderate to severe clinical course was demonstrated in Vitamin D deficient patients, using multivariate logistic regression analysis. A study by Yilmaz et al. recorded that 72.5% ($n = 29$) of the cases were vitamin D deficient or insufficient out of which 2 patients needed intensive care.[18] A negative correlation was found between vitamin D levels and fever symptoms. Patients with high fever had deficient or insufficient levels of Vitamin D. Although adequate studies are not available assessing the role of vitamin D and disease severity in pediatric patients, several studies have shown that children with insufficient or deficient levels of vitamin D are more susceptible to respiratory infections.[27] Raharusun et al., observed mortality in 49.1% and 46.7% of the patients with insufficient and deficient vitamin D levels, respectively, in contrast to only 4.1% mortality

Table 2. Key findings of the studies included in review

Sr. No.	Author	Key findings
1	Bayramoğlu *et al.*[11]	• There is an association between vitamin D deficiency and clinical severity in pediatric COVID-19 cases. • Vitamin D level was correlated positively with the lymphocyte count, and negatively with age, CRP and fibrinogen levels. • Vitamin D deficiency is an independent predictor of severe clinical outcome.
2	Feketea *et al.*[12]	• Role of vitamin D was evaluated as biomarker and nutritional supplement for MIS-C • Lower concentration of serum vitamin D may be significantly associated with neonatal pneumonia and poorer outcome • Supplementation of vitamin D might improve the outcome, though more studies are needed to substantiate this
3	Katz *et al.*[13]	• Patients with vitamin D deficiency were 4.6 times more likely to be positive for COVID-19 than patients with no deficiency ($P < 0.001$). • The association of low vitamin D level remains significant even after adjusting effect of race, periodontal disease, diabetes and obesity.
4	Nadiger *et al.*[14]	Majority of the pediatric patients who tested positive for COVID19 and in need of ICU treatment were obese, vitamin D deficient adolescents.
5	Molla *et al.*[15]	• Vitamin D deficiency was the most common vitamin deficiency among COVID-19 pediatric patients. • It is possible that vitamin D deficiency increases susceptibility to the infection.
6	Panfili *et al.* 2020[16]	• Vitamin D might have a role in prevention and control of COVID- 9 in both adults and pediatric population • Role of vitamin D in preventing or even treating the disease urgently needs to be further addressed especially in patients with deficiencies
7	Söbü *et al.*[17]	• Vitamin D levels were assessed between healthy and children with COVID-19 infection. • Median vitamin D was significantly (8.9 vs. 18.5 ng/ml; $P < 0.05$) lower in hospitalized COVID patients as compared to healthy control. • Age and gender did not differ among both the groups. • 93.3% of COVID positive patients were given Vitamin D supplementation and showed good outcome.
8	Yilmaz and Sen[18]	Children with COVID-19 had significantly lower vitamin D levels as compared to their control counterparts [13.14 μg/l (4.19–69.28) vs. 34.81 (3.8–77.42) μg/l; ($P < 0.001$)].

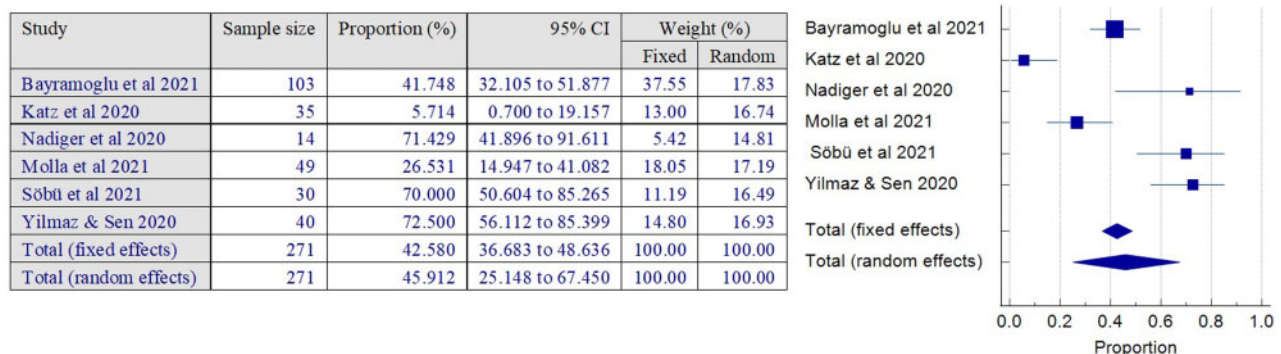| Study	Sample size	Proportion (%)	95% CI	Weight (%)	
				Fixed	Random
Bayramoglu et al 2021	103	41.748	32.105 to 51.877	37.55	17.83
Katz et al 2020	35	5.714	0.700 to 19.157	13.00	16.74
Nadiger et al 2020	14	71.429	41.896 to 91.611	5.42	14.81
Molla et al 2021	49	26.531	14.947 to 41.082	18.05	17.19
Söbü et al 2021	30	70.000	50.604 to 85.265	11.19	16.49
Yilmaz & Sen 2020	40	72.500	56.112 to 85.399	14.80	16.93
Total (fixed effects)	271	42.580	36.683 to 48.636	100.00	100.00
Total (random effects)	271	45.912	25.148 to 67.450	100.00	100.00

Figure 2. Forest plot of vitamin D deficiency (%) prevalence in pediatric COVID patients.

in patients with normal vitamin D levels.[26] Also previous studies found an inverse correlation between vitamin D level and pneumonia severity, increased risk of sepsis, CRP level and ARDS risk.[28–31]

Vitamin D is known as 'sunshine vitamin', as sunlight helps in the conversion of 7-dehydrocholesterol in the skin to cholecalciferol. It gets converted into 1,25(OH)D or calcitriol through hydroxylation in the liver and kidney. Vitamin D receptors

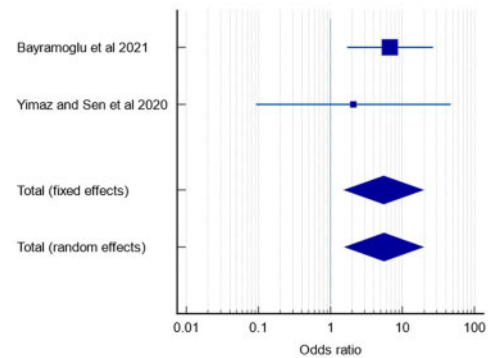| Study	Intervention	Controls	Odds ratio	95% CI	Z	P	Weight (%)	
							Fixed	Random
Bayramoglu et al 2021	24/43	3/19	6.737	1.708 to 26.570			83.74	83.74
Yimaz and Sen et al 2020	2/29	0/11	2.091	0.0929 to 47.043			16.26	16.26
Total (fixed effects)	26/72	3/30	5.517	1.560 to 19.515	2.649	0.008	100.00	100.00
Total (random effects)	26/72	3/30	5.569	1.587 to 19.549	2.681	0.007	100.00	100.00

Figure 3. Forest plot of association between low level of vitamin D and disease severity in pediatric COVID patients.

(VDR) are activated by 1,25 dihydroxy vitamin D.[32,33] Since sunlight alone cannot provide sufficient amounts of vitamin D to everyone, supplements are recommended. Vitamin D supplementation helps to decrease proinflammatory cytokines in the lung by the modulation of T lymphocyte activity two concerns remain regarding Vitamin D supplementation and disease outcome, first, the appropriate levels needed to produce an immunomodulatory effect is unknown. Second, the effects of supplementation may not be observed by administration of a single dose of vitamin D. Therefore, a study conducted in adults, they chose an arbitrary value of 25(OH)D levels >50 ng/ml to produce an immunomodulatory effect. It was observed, that a single dose administration of 540 000 IU of vitamin D3 increased the levels to >20 ng/ml and more than 38.2 ± 16.5 ng/ml at 1 week.[34] A recent meta-analysis, including 25 randomized controlled trial showed that the risk of developing acute respiratory tract infection could be reduced by the supplementation of Vitamin D weekly.[35] Though the present study provides evidence that COVID-19 severity has an association with vitamin D deficiency, more robust evidence through well-conducted randomized controlled trials are required to substantiate this further. Till the time findings emerge from more prospective studies, supplementation can be recommended in pediatric COVID patients especially in case of deficiency based on results of the current review.

Though the review provides some of the most useful information, it suffers from few inherent limitations. Due to limited and heterogeneously published literature, the effect of vitamin D supplementation on COVID-19 infectivity and severity could not be explored in pediatrics. Similarly, the influence of age, gender and other confounders on vitamin D deficiency and COVID outcome were also not studied due to the unavailability of primary studies.

Conclusion

The systematic review showed that almost half of the pediatric COVID patients suffer from vitamin D deficiency. It is also clear that the deficiency is associated with greater risk of infection and poor outcome in pediatrics. Vitamin D supplementation needs to be explored as a preventive prophylactic, for the prevention and management of COVID-19 in children and adolescents.

Conflict of interest. None declared.

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