Trends in the Diagnosis of Vitamin D Deficiency

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abstract

BACKGROUND: Vitamin D has attracted considerable interest in recent years, and health care providers have reported large increases in vitamin D test requests. However, rates of diagnosis of vitamin D deficiency in clinical practice have not been investigated. We examined trends in diagnosis of vitamin D deficiency in children in England over time, and by sociodemographic characteristics.

METHODS: Cohort study using primary care records of 711 788 children aged 0 to 17 years, from the Health Improvement Network database. Incidence rates for diagnosis of vitamin D deficiency were calculated per year between 2000 and 2014. Rate ratios exploring differences by age, sex, ethnicity, and social deprivation were estimated using multivariable Poisson regression.

RESULTS: The crude rate of vitamin D deficiency diagnosis increased from 3.14 per 100 000 person-years in 2000 (95% confidence interval [CI], 1.31–7.54) to 261 per 100 000 person-years in 2014 (95% CI, 241–281). After accounting for changes in demographic characteristics, a 15-fold (95% CI, 10–21) increase in diagnosis was seen between 2008 and 2014. Older age (≥10 years), nonwhite ethnicity, and social deprivation were independently associated with higher rates of diagnosis. In children aged <5 years, diagnosis rates were higher in boys than girls, whereas in children aged ≥10 they were higher in girls.

CONCLUSIONS: There has been a marked increase in diagnosis of vitamin D deficiency in children over the past decade. Future research should explore the drivers for this change in diagnostic behavior and the reasons prompting investigation of vitamin D status in clinical practice.

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Dr Basatemur conceptualized and designed the study, conducted the analysis, interpreted the data, drafted the initial manuscript, and wrote the final manuscript; Dr Sutcliffe contributed to the conception and design of the study, the interpretation of data, and critical revision of the manuscript; Drs Rait, Horsfall, and Marston contributed to the design of the study, the interpretation of data, and critical revision of the manuscript; and all authors approved the final version of the manuscript as submitted.

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WHAT'S KNOWN ON THIS SUBJECT: Vitamin D has attracted considerable interest in recent years, and health care providers have reported large increases in vitamin D test requests. However, trends in the diagnosis of vitamin D deficiency in clinical practice have not been investigated.

WHAT THIS STUDY ADDS: There has been a marked increase in testing and diagnosis of vitamin D deficiency among English children over the past decade (15-fold between 2008 and 2014). Older age, nonwhite ethnicity, and social deprivation were associated with higher rates of diagnosis.

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Vitamin D has attracted considerable clinical and academic interest over the past 2 decades. Regional studies and hospital case series in the United Kingdom, United States, and Australia have suggested an increase in numbers of children presenting with symptomatic complications of vitamin D deficiency (rickets and hypocalcemia).[1–3] Furthermore, a large body of observational research has stimulated debate regarding the postulated role of vitamin D in modifying the risk of developing various diseases beyond its established function in bone metabolism and calcium homeostasis.[4]

As vitamin D has attracted increasing attention, hospitals in Australia and the United Kingdom have reported a surge in test requests.[5,6] Annual primary care spending on vitamin D prescriptions in England increased from £28 million to £92 million between 2004 and 2014.[7,8] Given the high prevalence of biochemical vitamin D deficiency in the general population, and uncertainty that treatment of asymptomatic individuals leads to improved health outcomes, some authors have questioned whether the large growth in testing may result in unnecessary health care costs and potential overdiagnosis.[4,5,9] However, there has not been any empirical investigation of rates of diagnosis of vitamin D deficiency in clinical practice, and trends in testing and treatment have not been examined in children specifically. Using a large, population-based cohort of children in England, we determined longitudinal trends in rates of vitamin D deficiency diagnosis over the past 15 years, and explored differences by sociodemographic characteristics.

METHODS

Data Source

We conducted a dynamic (open) cohort study by using The Health Improvement Network (THIN) primary care database, which contains anonymized electronic health records of >11 million patients from 639 UK general practices. The THIN cohort is broadly representative of the UK population in terms of age, sex, prevalence of medical conditions, and mortality rates.[10] THIN includes data regarding medical diagnoses, laboratory test results, medication prescriptions, and sociodemographic characteristics. Diagnoses are recorded by using a hierarchical coding system called Read codes.[11] Diagnoses made in secondary care may be coded from discharge summaries and outpatient letters. A subset of THIN practices in England (n = 156) are linked to patient-level Hospital Episode Statistics (HES) data, available up to March 31, 2012. HES contains records of all hospital care episodes in England, although clinical diagnoses are recorded only for inpatient admissions. We used linked HES data to augment information regarding ethnicity.

Study Population

Children aged 0 to 17 years registered with a THIN practice linked to HES, at any point between January 1, 2000, and December 31, 2014, were included. Children with chronic renal disease, liver disease, or conditions associated with gastrointestinal malabsorption were excluded. The start of the observation period for each child was the latest of the date of practice registration (plus 3 months for children aged ≥1 year at registration), the date the practice met 2 predefined quality indicators for electronic data recording (acceptable mortality recording and acceptable computer usage),[12,13] and January 1, 2000. Diagnoses recorded shortly after patient registration can represent historical information transferred from medical records rather than incident events.[14] We observed greater recording of vitamin D deficiency diagnosis in the first 3 months after registration, therefore we excluded this period from observation for children aged ≥1 year at registration. The acceptable mortality recording and acceptable computer usage criteria identify periods of incomplete use of computerized systems in primary care (eg, following transition from paper records), and are described elsewhere.[12,13] Exit from the observation period for each individual was the earliest of the date they transferred to a different practice, the date the practice stopped contributing data to THIN, the midpoint of their 18th year after birth, the date they died, December 31, 2014, or the date of the earliest record meeting the case definition for diagnosis of vitamin D deficiency.

Outcome

Diagnosis of vitamin D deficiency was defined as a record of any 1 of the following criteria in the THIN medical record: (1) a Read code related to vitamin D deficiency or rickets; (2) prescription of vitamin D (calciferol) at a "treatment dose" (see later in this article); or (3) a serum 25-hydroxyvitamin D (25-OH-D) test result <25 nmol/L (<10 ng/mL). Read code lists were developed by using published guidelines.[15] General practitioners do not always record diagnoses by using Read codes, instead entering data as free text that is not routinely accessible.[16] The use of Read codes alone to identify cases can result in case underascertainment, therefore we also included prescription and test records in the case definition.

To capture prescriptions of cholecalciferol or ergocalciferol issued for the treatment of established deficiency, as opposed to prophylactic supplementation or maintenance therapy, we used the following dose thresholds: (1) ≥1500 U per day if age <6 months; (2) ≥3000 U per day if age 6 months

to 12 years; (3) ≥5000 U per day if age >12 years; (4) one-off (stoss) dose of ≥100 000 U at any age. These thresholds are higher than doses recommended for prophylaxis of between 400 and 1000 U per day,[17] and represent half of the British National Formulary for Children treatment doses (≥3000 U per day if age 1–6 months, ≥6000 U per day if age 6 months to 12 years, and ≥10 000 U per day if age >12 years).[18] A range of alternative dosage thresholds were explored by using sensitivity analyses. The threshold of <25 nmol/L for 25-OH-D tests represents deficiency in UK guidance.[17,19]

Sensitivity analysis was performed additionally including *International Classification of Diseases, 10th Revision* (ICD-10) codes for vitamin D deficiency and rickets from HES inpatient records in the case definition. This analysis was limited to follow-up to December 31, 2011.

Covariates

Socioeconomic position (SEP) was measured by using the 2004 Index of Multiple Deprivation (IMD), an area-level indicator available in national quintiles.[20] Recording of ethnicity in primary care databases is incomplete, but can be augmented by linkage with HES data.[21] Ethnicity was grouped into the 2001 UK Census 5-category classification (white, mixed, Asian, black, or other). As consistency of ethnicity recording is greater in primary care data than HES, ethnicity was assigned from THIN where available, and supplemented with HES data.[21] For individuals with multiple ethnicity categories recorded (0.3% of the cohort), the most frequently recorded category was used.

For children with missing ethnicity, maternal ethnicity was taken as a proxy measure for the child if available. Child-mother linkage was performed by using similar methods to previous THIN studies.[22,23] Children were linked to women sharing identical household identifiers with a pregnancy or delivery record in which the expected or recorded date of delivery was in proximity to the child's month of birth. Linked mothers were excluded if children matched to several women (0.3% of linked children), or >20 people shared the same household identifier (likely to represent an apartment block).

Statistical Analysis

Crude incidence rates were calculated for each year between 2000 and 2014. Differences in rates by sex, age group (<5, 5–9, 10–14, and 15–17 years), ethnicity, IMD, and calendar year were examined by using multivariable Poisson regression. Multivariable analysis was limited to follow-up between 2008 and 2014, due to small numbers of cases per year before 2008. Interactions between explanatory variables were examined, and interaction terms retained in the final model if their inclusion resulted in both a qualitative change in parameter rate ratios and a significant likelihood ratio test ($P < .05$). The multivariable model was run with and without inclusion of the general practice as a random effect to account for data clustering.

Missing data for ethnicity and IMD were handled by using complete cases in the main analysis, and by using multivariable multiple imputation for sensitivity analysis.[24] The imputation model included all variables in the substantive model, plus auxiliary variables coding geographical region, and the ethnicity and IMD distributions of practice patients and of individuals sharing identical household identifiers. Analyses were performed by using Stata 13.1 (Stata Corp, College Station, TX).

The THIN data collection was approved by the NHS South-East Multicentre Research Ethics Committee in 2003. This study was approved by CSD Medical Research's Scientific Review Committee.

RESULTS

The study cohort contained 711 788 children from 156 practices, of whom 2918 were diagnosed with vitamin D deficiency between 2000 and 2014. Median observation time was 3.9 years (interquartile range 1.5–8.0). Descriptive characteristics are shown in Table 1.

Analysis of time trends showed a marked increase in diagnosis of vitamin D deficiency after 2007 (Fig 1) (Supplemental Table 3). The crude incidence rate increased from 3.14 per 100 000 person-years at risk in 2000 (95% confidence interval [CI], 1.31–7.54) to 261 per 100 000 person-years at risk in 2014 (95% CI, 241–281). After accounting for temporal changes in sociodemographic factors, a 15-fold increase in diagnosis (95% CI, 10–21-fold) was seen between 2008 and 2014 (Table 2).

Supplemental Fig 2 shows the overlap between cases identified from diagnosis codes, prescription records, and 25-OH-D test records. Results did not differ substantially in sensitivity analyses using alternative dosage thresholds for calciferol prescriptions (Supplemental Fig 3), or addition of ICD-10 diagnosis codes from HES inpatient records (Supplemental Fig 4), in the case definition.

In multivariable analysis, older age, nonwhite ethnicity, and socioeconomic deprivation were associated with higher rates of vitamin D deficiency diagnosis (Table 2). There was an interaction between sex and age; among children aged ≥10 years, diagnosis rates were higher in girls, whereas among children aged <5 years, they were higher in boys (Supplemental Fig 5). No sex difference was seen in

children aged 5 to 9 years. Although the magnitude of the effects of ethnicity and SEP were attenuated after accounting for clustering by practice, they remained strongly associated with the outcome (Table 2). There was a moderate proportion of missing data for ethnicity (12.7%) and IMD (8.3%). The results of analyses by using multiple imputation were similar to the main analyses using complete cases (Supplemental Table 4).

TABLE 1 Descriptive Characteristics of the Study Cohort (n = 711 788)

Characteristic	Value
Age at entry to follow-up, y, median (IQR)	4.1 (0.40–10.5)
Sex, *n* (%)	
Boys	366 378 (51.5)
Girls	345 410 (48.5)
Ethnicity, *n* (%)[a]	
White	491 962 (69.1)
Asian or Asian British	34 521 (4.9)
Black or black British	24 797 (3.5)
Mixed	15 558 (2.2)
Chinese or other ethnic group	13 443 (1.9)
Missing	131 507 (18.5)
IMD quintile, *n* (%)	
1 (least deprived)	158 866 (22.3)
2	134 765 (18.9)
3	138 264 (19.4)
4	136 498 (19.2)
5 (most deprived)	95 656 (13.4)
Missing	47 739 (6.7)

IQR, interquartile range.
[a] Ethnicity data were available from the child's THIN or HES record for 67.7% of the cohort, and maternal ethnicity was available as a proxy measure for 13.8%.

DISCUSSION

In this large representative cohort of English children, there was a 15-fold increase in the diagnosis of vitamin D deficiency between 2008 and 2013, after which rates plateaued. Sociodemographic factors independently associated with higher rates of diagnosis included nonwhite ethnicity, socioeconomic deprivation, older age, female sex in children aged ≥10 years, and male sex in children aged <5 years.

Comparison With Other Studies

To the best of our knowledge, this is the first study to report national estimates for overall rates of diagnosis of vitamin D deficiency in clinical practice, in the United Kingdom or internationally. However, a number of studies have investigated the incidence of clinical complications of vitamin D deficiency in children. The annual incidence of symptomatic vitamin D deficiency presenting to pediatricians was reported to be 7.5 per 100 000 children aged 0 to 5 years in the West Midlands region of England, and between 2.2 and 2.9 per 100 000 children in New Zealand,[25] Denmark,[26] and Canada.[27] The annual incidence of hypocalcemic seizures secondary to vitamin D deficiency was 3.49 per million children age 0 to 15 years in the United Kingdom.[28]

Vitamin D deficiency was diagnosed considerably more frequently in

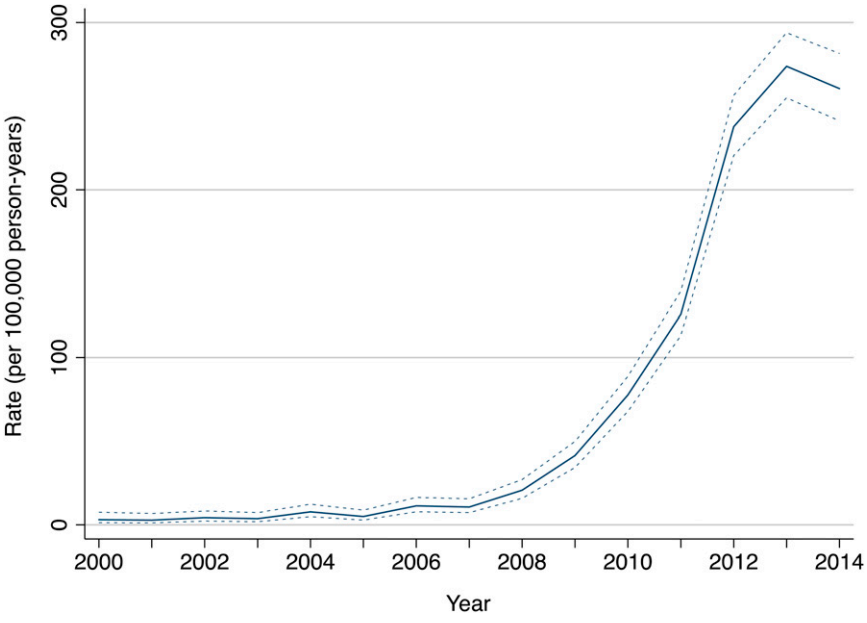

FIGURE 1
Time trends in the diagnosis of vitamin D deficiency in children, 2000 to 2014. Crude incidence rates are shown, with 95% confidence limits represented by the dashed lines.

Asian and black compared with white children, which was expected given that they have lower vitamin D levels and higher risk of symptomatic deficiency.[28–30] Diagnosis also was more frequent in children from deprived backgrounds. Low SEP is associated with suboptimal vitamin D status in children independent of ethnicity, and with reduced use of vitamin D supplements.[31–33] The magnitude of the effects of ethnicity and SEP were attenuated after accounting for clustering by practice. One explanation for this observation is that the sociodemographic characteristics of a practice population may have contextual effects on clinicians' diagnostic behavior, separate from the influence

of individual patients' characteristics. General practitioners working in practices with more deprived and ethnically diverse populations may be more likely to test for vitamin D deficiency even in low-risk patients, because of increased awareness of the condition. Possible explanations for greater diagnosis in older compared with younger children may include more frequent presentation to health care services with chronic pain or other medically unexplained symptoms,[34,35] and higher thresholds for requesting vitamin D tests in younger children in primary care due to the practical challenges of phlebotomy. Among older children, factors contributing to higher diagnosis rates in girls compared with boys may include higher overall primary care consultation rates,[36] and the influence of cultural dress in some communities.

Strengths and Limitations

Study strengths include the large sample size, and use of a prospectively collected database of health care records representative of real-life clinical practice. As the THIN cohort has a similar age and sex distribution to the general population, our results should be broadly generalizable to England as a whole. However, it is somewhat overrepresentative of individuals from more affluent areas,[10] therefore the observed diagnosis rates may underestimate true national rates to an extent. The inclusion of vitamin D prescriptions and tests in the case definition allowed identification of children in whom the diagnosis was not recorded by using Read codes, helping to minimize case underascertainment. However, some cases still may have been missed, for example children who were diagnosed and received their full course of treatment in secondary care, if the diagnosis was not subsequently entered into the primary care record from hospital correspondence. Missing data for ethnicity were minimized by using linked HES data, and taking maternal ethnicity as a proxy measure where the child's ethnicity was not available. However, the risk of misclassification will be greater where maternal ethnicity was used. Although there was a moderate proportion of missing data for ethnicity and IMD, complete case analysis and multiple imputation gave very similar results, suggesting that missing data did not substantially influence the findings under the missing at random assumption.[24] Data were not available regarding other factors, such as BMI, that are associated with vitamin D status and may influence testing in clinical practice.

TABLE 2 Associations Between Sociodemographic Factors and Diagnosis of Vitamin D Deficiency (n = 414 182)

Characteristic		Single-level Model		Multilevel Model	
		Adjusted IRR[a] (95% CI)	P[b]	Adjusted IRR[a] (95% CI)	P[b]
Sex, stratified by age group, y			<.001		<.001
0–4	Boys	1		1	
	Girls	0.73 (0.57–0.93)		0.72 (0.57–0.92)	
5–9	Boys	1		1	
	Girls	1.06 (0.87–1.29)		1.04 (0.86–1.27)	
10–14	Boys	1		1	
	Girls	1.97 (1.71–2.27)		1.97 (1.71–2.27)	
15–17	Boys	1		1	
	Girls	2.60 (2.18–3.11)		2.65 (2.21–3.16)	
Age group, y, stratified by sex			<.001		<.001
Boys	0–4	1		1	
	5–9	1.22 (0.99–1.50)		1.20 (0.98–1.48)	
	10–14	2.22 (1.83–2.70)		2.19 (1.80–2.65)	
	15–17	2.39 (1.93–2.96)		2.36 (1.90–2.93)	
Girls	0–4	1		1	
	5–9	1.77 (1.41–2.23)		1.73 (1.37–2.18)	
	10–14	6.00 (4.91–7.34)		5.95 (4.86–7.27)	
	15–17	8.52 (6.93–10.5)		8.61 (7.00–10.6)	
Ethnicity[c]			<.001		<.001
White		1		1	
Asian or Asian British		22.4 (20.1–24.9)		7.98 (6.98–9.13)	
Black or black British		14.2 (12.5–16.2)		5.47 (4.70–6.37)	
Mixed		5.64 (4.52–7.03)		2.99 (2.38–3.76)	
Chinese or other ethnic group		8.91 (7.38–10.8)		3.63 (2.96–4.45)	
IMD quintile			<.001		<.001
1 (least deprived)		1		1	
2		1.98 (1.63–2.41)		1.34 (1.07–1.67)	
3		2.40 (2.00–2.88)		1.41 (1.12–1.77)	
4		2.67 (2.23–3.20)		1.63 (1.29–2.05)	
5 (most deprived)		3.54 (2.96–4.24)		1.96 (1.52–2.53)	
Calendar year			<.001		<.001
2008		1		1	
2009		2.20 (1.45–3.35)		2.19 (1.44–3.34)	
2010		3.87 (2.62–5.71)		3.66 (2.48–5.40)	
2011		6.61 (4.55–9.60)		6.28 (4.32–9.12)	
2012		12.7 (8.83–18.2)		12.1 (8.43–17.4)	
2013		14.7 (10.2–21.1)		14.1 (9.85–20.3)	
2014		14.7 (10.2–21.2)		15.7 (10.9–22.6)	

Results of multivariable Poisson regression models of rates of incident diagnosis of vitamin D deficiency. Missing data are handled using complete case analysis. IRR, incidence rate ratio.

[a] Adjusted for all variables listed in the table, including an interaction term between age and sex (likelihood ratio test for interaction $P < .001$). The multilevel model additionally included the general practice as a random effect.

[b] P values from likelihood ratio tests comparing nested models.

[c] Ethnicity data were taken from the child's THIN or HES record for 84.6% of children. Maternal ethnicity was used as a proxy measure for the remaining 15.4%.

Clinical Implications

Given the magnitude of the increase in diagnosis of vitamin D

deficiency over a short period, it is unlikely to be explained by changes in population vitamin D levels, incidence of clinical complications of vitamin D deficiency, or population demographics. It is likely that the rise in testing and treatment has been driven by increased awareness and consideration of vitamin D deficiency among clinicians. There are several possible contributing factors for this: clinician education through the development of clinical guidelines and dissemination of Department of Health recommendations concerning vitamin D supplementation for high-risk groups,[37] and wide reporting in the lay media and medical literature of research suggesting a link between vitamin D status and numerous nonmusculoskeletal health outcomes.[38]

The data available did not permit exploration of the clinical indications prompting investigation of vitamin D status. We do not know how much the increase in diagnosis is being driven by improved recognition of children with clinical features consistent with symptomatic vitamin D deficiency, or by testing in other clinical situations (for example, screening of asymptomatic children, or testing prompted by the presence of nonmusculoskeletal diseases that have been linked to vitamin D deficiency, such as diabetes, atopic disorders, and infectious diseases). Sharp increases in vitamin D test requests in adults have been reported in Australia and the United Kingdom over the past decade.[5,6] The introduction of a defined set of clinical criteria permitting 25-OH-D testing in Alberta, Canada, in 2015 resulted in a 92% reduction in the number of tests ordered, and annual cost savings of almost US$4 million.[39] This suggests that, before the intervention, most vitamin D tests in adults were performed in individuals without specific clinical features or risk factors for deficiency. Further studies are required to explore the reasons for investigation of vitamin D status in children in clinical practice.

Biochemical vitamin D deficiency, as defined by current guidelines, has a high prevalence in the general population, and testing in any patient group is likely to identify a significant proportion of abnormal results.[4] Although the benefits of treatment with pharmacological doses of vitamin D are clear in children with symptomatic deficiency, there is no evidence that testing and treating asymptomatic individuals results in improved health outcomes compared with prophylaxis with low-dose supplements.[4,40] Although numerous observational studies have reported associations between low serum 25-OH-D levels and increased risk of various nonmusculoskeletal diseases, their results are subject to reverse causality, confounding and bias, and findings from randomized controlled trials are generally null or inconsistent.[5,40–42] The UK Scientific Advisory Committee on Nutrition, US Institute of Medicine, and European Society for Pediatric Gastroenterology, Hepatology, and Nutrition have concluded that there is insufficient evidence of a causative role for vitamin D deficiency in the etiology of nonmusculoskeletal health outcomes.[40,43,44] Furthermore, there is limited evidence that optimizing vitamin D status is beneficial for the management of these conditions once they have developed, for example in improving glycemic control in diabetes or reducing disease severity in asthma.[45,46]

The UK National Institute for Health and Care Excellence, US Endocrine Society, and European Society for Pediatric Endocrinology recommend that vitamin D status should not be checked as a routine screening test,[47–49] a position supported by the Choosing Wisely campaigns in North America and Australia.[50–52] Shaw and Mughal[4] proposed a set of clinical indications for the measurement of 25-OH-D in children that relate to symptoms and signs directly attributable to vitamin D deficiency, biochemical or radiologic evidence of metabolic bone disease, or the presence of disorders that can interfere with vitamin D metabolism. Testing outside of this context requires careful consideration of whether vitamin D deficiency is related to the child's presentation or is a coincidental finding. The interpretation of 25-OH-D results is further complicated by the inconsistency of commonly used laboratory assays and the limited evidence base underpinning the threshold values used to define deficiency.[40,43,44,53] At the population level, unnecessary testing can result in avoidable costs from the tests themselves and from prescription of pharmacological doses of vitamin D. From a public health perspective, resources may be better used if directed toward improving the currently low uptake of inexpensive vitamin D supplements, recommended by the UK Scientific Advisory Committee on Nutrition and the American Academy of Pediatrics for the prevention of deficiency, by pregnant women and young children,[54,55] particularly among high-risk ethnic groups.[48,56]

CONCLUSIONS

There has been a marked increase in the testing and diagnosis of vitamin D deficiency in children in England over the past decade. Future research should explore the drivers for this change in clinicians' diagnostic behavior, and the reasons prompting investigation of vitamin D status in clinical practice.

ABBREVIATIONS

25-OH-D: 25-hydroxyvitamin D
CI: confidence interval
HES: Hospital Episode Statistics
ICD-10: *International Classification of Diseases, 10th Revision*
IMD: Index of multiple deprivation
SEP: socioeconomic position
THIN: The Health Improvement Network

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