

Trends in the Diagnosis of Vitamin D Deficiency

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Short title: Trends in the Diagnosis of Vitamin D Deficiency

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Abbreviations:

25-OH-D: 25-hydroxyvitamin D
ACU: acceptable computer usage
AMR: acceptable mortality recording
CI: confidence interval
HES: Hospital Episode Statistics
IMD: Index of multiple deprivation
PYAR: person-years at risk
SACN: Scientific Advisory Committee on Nutrition
SEP: socioeconomic position
THIN: The Health Improvement Network
UK: United Kingdom
US: United States

What's Known on This Subject:

Vitamin D has attracted considerable interest in recent years, and healthcare 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 the testing and diagnosis of vitamin D deficiency in children in England over the last decade (15-fold between 2008-2014). Older age, non-white ethnicity, and social deprivation were associated with higher rates of diagnosis.

Table of Contents Summary:

Analysis of UK primary care data reveals a marked increase in the testing and diagnosis of vitamin D deficiency in children over the last decade.

Contributors' Statement:

Dr Basatemur conceptualized and designed the study, conducted the analysis, interpreted the data, drafted the initial manuscript, and wrote the final manuscript.

Professor 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.

All authors approved the final version of the manuscript as submitted.

Abstract:

Background

Vitamin D has attracted considerable interest in recent years, and healthcare 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 the diagnosis of vitamin D deficiency in children in England over time, and by sociodemographic characteristics.

Methods

Cohort study using primary care electronic health records held in The Health Improvement Network database. 711 788 children aged 0-17 years were included. Incidence rates for diagnosis of vitamin D deficiency were calculated in each year between 2000-2014. 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 fold) increase in diagnosis was seen between 2008-2014. Older age (≥ 10 years), non-white 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, whilst in children aged ≥ 10 they were higher in girls.

Conclusions

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

Introduction

Vitamin D has attracted considerable clinical and academic interest over the last two decades. Regional studies and hospital case series in the United Kingdom (UK), United States (US), and Australia have suggested an increase in numbers of children presenting with symptomatic complications of vitamin D deficiency (rickets and hypocalcaemia).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 UK have reported a surge in test requests.^{5,6} Primary care spending on vitamin D prescriptions in England increased from £28 million to £92 million between 2004-2014.^{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 over-diagnosis.^{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 socio-demographic characteristics.

Methods

Data Source

We conducted a dynamic (open) cohort study using The Health Improvement Network (THIN) primary care database, which contains anonymised 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 socio-demographic characteristics. Diagnoses are recorded 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 31st March 2012. HES contains records of all hospital care episodes in England, although clinical diagnoses are only recorded for inpatient admissions. We used linked HES data to augment information regarding ethnicity.

Study Population

Children aged 0-17 years registered with a THIN practice linked to HES, at any point between 1st January 2000 and 31st December 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 two pre-defined quality indicators for electronic data recording (acceptable mortality recording [AMR] and acceptable computer usage [ACU]),^{12,13} and 1st January 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 AMR and ACU criteria identify periods of incomplete use of computerised systems in primary care (e.g. 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 mid-point of their 18th year after birth, the date they died, 31st December 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 one 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 below); or (3) a serum 25-hydroxyvitamin D (25-OH-D) test result < 25 nmol/L (< 10 ng/ml). Read code lists were developed using published guidelines.¹⁵ GPs do not always record diagnoses using Read codes, instead entering data as free text which is not routinely accessible.¹⁶ Using Read codes alone to identify cases can result in case under-ascertainment, therefore we also included prescription and test records in the case definition.

In order to capture prescriptions of colecalciferol 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 units/day if age < 6 months; (2) ≥ 3000 units/day if age 6 months to 12 years; (3) ≥ 5000 units/day if age > 12 years; (4) one-off (stoss)

dose of $\geq 100\,000$ units at any age. These thresholds are higher than doses recommended for prophylaxis of between 400-1000 units/day,¹⁷ and represent half of the British National Formulary for Children treatment doses (≥ 3000 units/day if age 1-6 months, ≥ 6000 units/day if age 6 months to 12 years, and $\geq 10\,000$ units/day if age >12 years).¹⁸ A range of alternative dosage thresholds were explored 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 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 31st December 2011.

Covariates

Socioeconomic position (SEP) was measured 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 using similar methods to previous THIN studies.^{22,23} Children were linked to women sharing identical household identifiers with

a pregnancy or delivery record where 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 a block of flats).

Statistical Analysis

Crude incidence rates were calculated for each year between 2000-2014. Differences in rates by sex, age group (<5, 5-9, 10-14, and 15-17 years), ethnicity, IMD, and calendar year were examined using multivariable Poisson regression. Multivariable analysis was limited to follow-up between 2008-2014, 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 ($p < 0.05$). 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 was handled using complete cases in the main analysis, and 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 using Stata 13.1 (StataCorp, 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 2000-2014. 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 (Figure 1, and Supplemental Table 3). The crude incidence rate increased from 3.14 per 100 000 person-years at risk (PYAR) in 2000 (95% confidence interval [CI]: 1.31-7.54) to 261 per 100 000 PYAR in 2014 (95% CI: 241-281). After accounting for temporal changes in socio-demographic factors, a 15-fold increase in diagnosis (95% CI: 10-21 fold) was seen between 2008-2014 (Table 2).

Supplemental Figure 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 Figure 3), or addition of ICD-10 diagnosis codes from HES inpatient records (Supplemental Figure 4), in the case definition.

In multivariable analysis older age, non-white 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, whilst among children aged < 5 years they were higher in boys (Supplemental Figure 5). No sex difference was seen in children aged 5-9 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 using multiple imputation were very similar to the main analyses using complete cases (Supplemental Table 4).

Discussion

In this large representative cohort of English children, there was a 15-fold increase in the diagnosis of vitamin D deficiency between 2008-2013, after which rates plateaued. Socio-demographic factors independently associated with higher rates of diagnosis included non-white 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 UK 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 paediatricians was reported to be 7.5 per 100 000 children aged 0-5 years in the

West Midlands region of England, and between 2.2 to 2.9 per 100,000 children in New Zealand,²⁵ Denmark,²⁶ and Canada.²⁷ The annual incidence of hypocalcaemic seizures secondary to vitamin D deficiency was 3.49 per million children age 0-15 years in the UK.²⁸

Vitamin D deficiency was diagnosed considerably more frequently in Asian and black compared to white children, which was expected given that they have lower vitamin D levels and higher risk of symptomatic deficiency.²⁸⁻³⁰ Diagnosis was also 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 socio-demographic characteristics of a practice population may have contextual effects on clinicians' diagnostic behaviour, separate from the influence of individual patients' characteristics. GPs 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 to younger children may include more frequent presentation to healthcare 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 to 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 healthcare 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 generalisable to England as a whole. However, it is somewhat over-representative 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 where the diagnosis was not recorded using Read codes, helping to minimise case under-ascertainment. However, some cases may still 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 was minimised by utilising 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 was not available regarding other factors, such as body mass index, that are associated with vitamin D status and may influence testing in clinical practice.

Clinical Implications

Given the magnitude of the increase in diagnosis of vitamin D deficiency over a short period of time, it is very 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 non-musculoskeletal 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 non-musculoskeletal 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 UK over the last 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 4 million US dollars.³⁹ This suggests that, prior to the intervention, the majority of 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 Whilst 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 to prophylaxis with low-dose supplements.^{4,40} Whilst numerous observational studies have reported associations between low serum 25-OH-D levels and increased risk of various non-musculoskeletal diseases, their results are subject to reverse causality, confounding and bias, and findings from RCTs are generally null or inconsistent.^{5,40–42} The UK Scientific Advisory Committee on Nutrition (SACN), 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 aetiology of non-musculoskeletal health outcomes.^{40,43,44} Furthermore, there is limited evidence that optimising vitamin D status is beneficial for the management of these conditions once they have developed, for example in improving glycaemic 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 Paediatric 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 proposed a set of clinical indications for the measurement of 25-OH-D in children, which relate to symptoms and signs directly attributable to vitamin D deficiency, biochemical or radiological evidence of metabolic bone disease, or the presence of disorders that can interfere with vitamin D metabolism.⁴ 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 towards improving the currently low uptake of inexpensive vitamin D supplements, recommended by SACN 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 last decade. Future research should explore the drivers for this change in clinicians' diagnostic behaviour, and the reasons prompting investigation of vitamin D status in clinical practice.

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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.

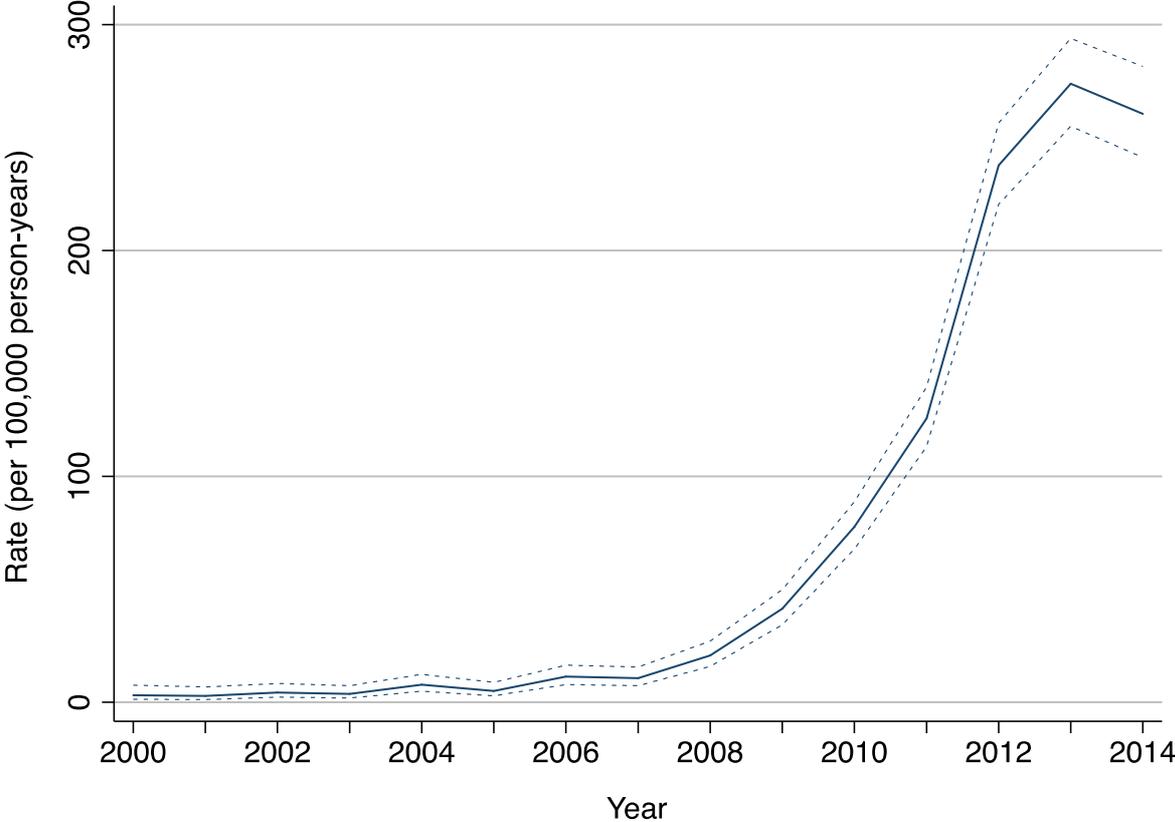


TABLE 1 Descriptive Characteristics of the Study Cohort (n=711 788)

Characteristic	Value
Age at entry to follow-up, years, median (IQR)	4.1 (0.40-10.5)
Sex, n (%)	
Male	366 378 (51.5)
Female	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)
Index of multiple deprivation 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%.

TABLE 2 Associations Between Socio-Demographic Factors and Diagnosis of Vitamin D Deficiency (n=414 182)^a

Characteristic	Single-level Model		Multilevel Model	
	Adjusted IRR ^b (95% CI)	P value ^c	Adjusted IRR ^b (95% CI)	P value ^c
Sex, stratified by age group				<0.001
0-4 years:	Male	1	1	
	Female	0.73 (0.57-0.93)	0.72 (0.57-0.92)	
5-9 years:	Male	1	1	
	Female	1.06 (0.87-1.29)	1.04 (0.86-1.27)	
10-14 years:	Male	1	1	
	Female	1.97 (1.71-2.27)	1.97 (1.71- 2.27)	
15-17 years:	Male	1	1	
	Female	2.60 (2.18-3.11)	2.65 (2.21-3.16)	
Age group, stratified by sex				<0.001
Males	0-4 years	1	1	
	5-9 years	1.22 (0.99-1.50)	1.20 (0.98-1.48)	
	10-14 years	2.22 (1.83-2.70)	2.19 (1.80-2.65)	
	15-17 years	2.39 (1.93-2.96)	2.36 (1.90-2.93)	
Females:	0-4 years	1	1	
	5-9 years	1.77 (1.41-2.23)	1.73 (1.37-2.18)	
	10-14 years	6.00 (4.91-7.34)	5.95 (4.86-7.27)	
	15-17 years	8.52 (6.93-10.5)	8.61 (7.00-10.6)	
Ethnicity ^d				<0.001
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				<0.001
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				<0.001
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)	

CI, confidence interval; IMD, Index of Multiple Deprivation; IRR, incidence rate ratio.

^a Results of multivariable Poisson regression models of rates of incident diagnosis of vitamin D deficiency. Missing data is handled using complete cases analysis.

^b Adjusted for all variables listed in the table, including an interaction term between age and sex (likelihood ratio test for interaction p value<0.001). The multilevel model additionally included the general practice as a random effect.

^c P values from likelihood ratio tests comparing nested models.

^d Ethnicity data was 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%.

SUPPLEMENTAL TABLE 3 Crude incidence rates for the diagnosis of vitamin D deficiency in children, by year between 2000 and 2014.

Year	Number of Children Diagnosed with Vitamin D Deficiency	Person Years at Risk (PYAR)	Rate per 100 000 PYAR (95% CI)
2000	5	159 318	3.14 (1.31-7.54)
2001	5	177 945	2.81 (1.17-6.75)
2002	9	208 386	4.32 (2.25-8.30)
2003	8	219 036	3.65 (1.83-7.30)
2004	18	231 690	7.77 (4.89-12.3)
2005	12	240 543	4.99 (2.83-8.78)
2006	28	247 374	11.3 (7.82-16.4)
2007	27	253 053	10.7 (7.32-15.6)
2008	54	260 812	20.7 (15.9-27.0)
2009	110	266 102	41.3 (34.3-49.8)
2010	212	273 217	77.6 (67.8-88.8)
2011	351	279 387	126 (113-139)
2012	673	283 111	238 (220-256)
2013	761	277 985	274 (255-293)
2014	645	247 604	261 (241-281)

CI, confidence interval

SUPPLEMENTAL TABLE 4 Associations between socio-demographic factors and diagnosis of vitamin D deficiency, with missing data handled using multiple imputation (n=511 868).^a

Characteristic	Single-level Model		Multilevel Model	
	Adjusted IRR ^b (95% CI)	P value ^c	Adjusted IRR ^b (95% CI)	P value ^c
Sex, stratified by age group				<0.001
0-4 years:	Male	1	1	
	Female	0.78 (0.64-0.97)	0.78 (0.63-0.96)	
5-9 years:	Male	1	1	
	Female	1.18 (1.00-1.41)	1.18 (1.00-1.40)	
10-14 years:	Male	1	1	
	Female	1.98 (1.75-2.24)	1.99 (1.76-2.25)	
15-17 years:	Male	1	1	
	Female	2.57 (2.20-3.00)	2.63 (2.25-3.06)	
Age group, stratified by sex				<0.001
Males	0-4 years	1	1	
	5-9 years	1.28 (1.07-1.54)	1.26 (1.05-1.52)	
	10-14 years	2.30 (1.94-2.72)	2.26 (1.90-2.67)	
	15-17 years	2.39 (1.98-2.89)	2.37 (1.96-2.87)	
Females:	0-4 years	1	1	
	5-9 years	1.94 (1.60-2.26)	1.92 (1.58-2.33)	
	10-14 years	5.81 (4.89-6.91)	5.77 (4.85-6.86)	
	15-17 years	7.82 (6.54-9.36)	8.00 (6.68-9.56)	
Ethnicity ^d				<0.001
White		1	1	
Asian or Asian British		21.8 (19.8-24.0)	7.14 (6.31-8.07)	
Black or Black British		15.3 (13.6-17.1)	5.42 (4.74-6.20)	
Mixed		5.85 (4.80-7.14)	2.97 (2.42-3.65)	
Chinese or other ethnic group		8.56 (7.18-10.2)	3.41 (2.82-4.13)	
IMD quintile ^e				<0.001
1 (least deprived)		1	1	
2		2.01 (1.67-2.42)	1.33 (1.08-1.65)	
3		2.48 (2.08-2.95)	1.47 (1.18-1.83)	
4		2.94 (2.48-3.49)	1.70 (1.36-2.13)	
5 (most deprived)		4.51 (3.82-5.32)	1.94 (1.52-2.48)	
Calendar year				<0.001
2008		1	1	
2009		1.95 (1.41-2.71)	1.95 (1.40-2.70)	
2010		3.54 (2.62-4.78)	3.34 (2.47-4.51)	
2011		5.63 (4.21-7.51)	5.34 (4.00-7.13)	
2012		10.4 (7.87-13.8)	9.95 (7.52-13.2)	
2013		11.8 (8.93-15.6)	11.4 (8.63-15.1)	
2014		12.2 (9.21-16.1)	12.9 (9.70-17.0)	

CI, confidence interval; IMD, Index of Multiple Deprivation; IRR, incidence rate ratio.

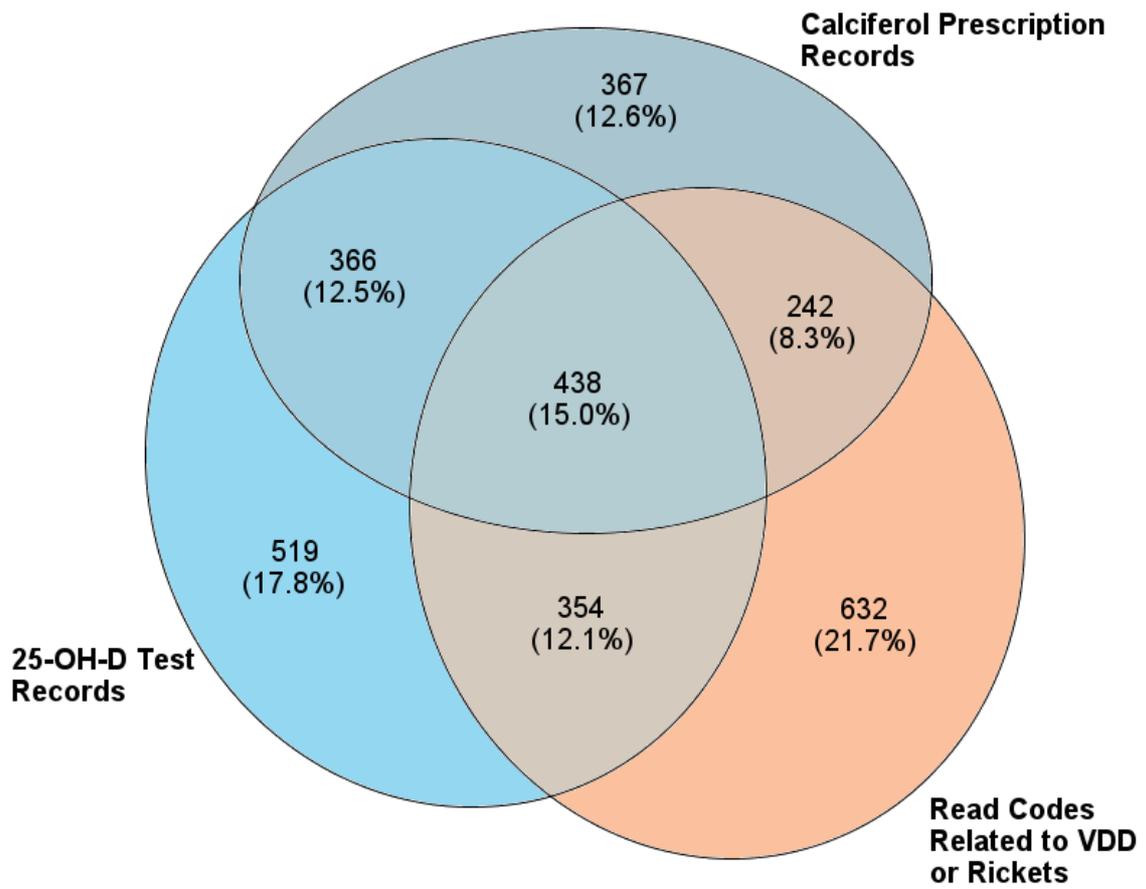
^a Results of multivariable Poisson regression models of rates of incident diagnosis of vitamin D deficiency. Missing data is handled using multivariable multiple imputation using chained equations.

^b Adjusted for all variables listed in the table, including an interaction term between age and sex (likelihood ratio test for interaction p value<0.001). The multilevel model additionally included the general practice as a random effect.

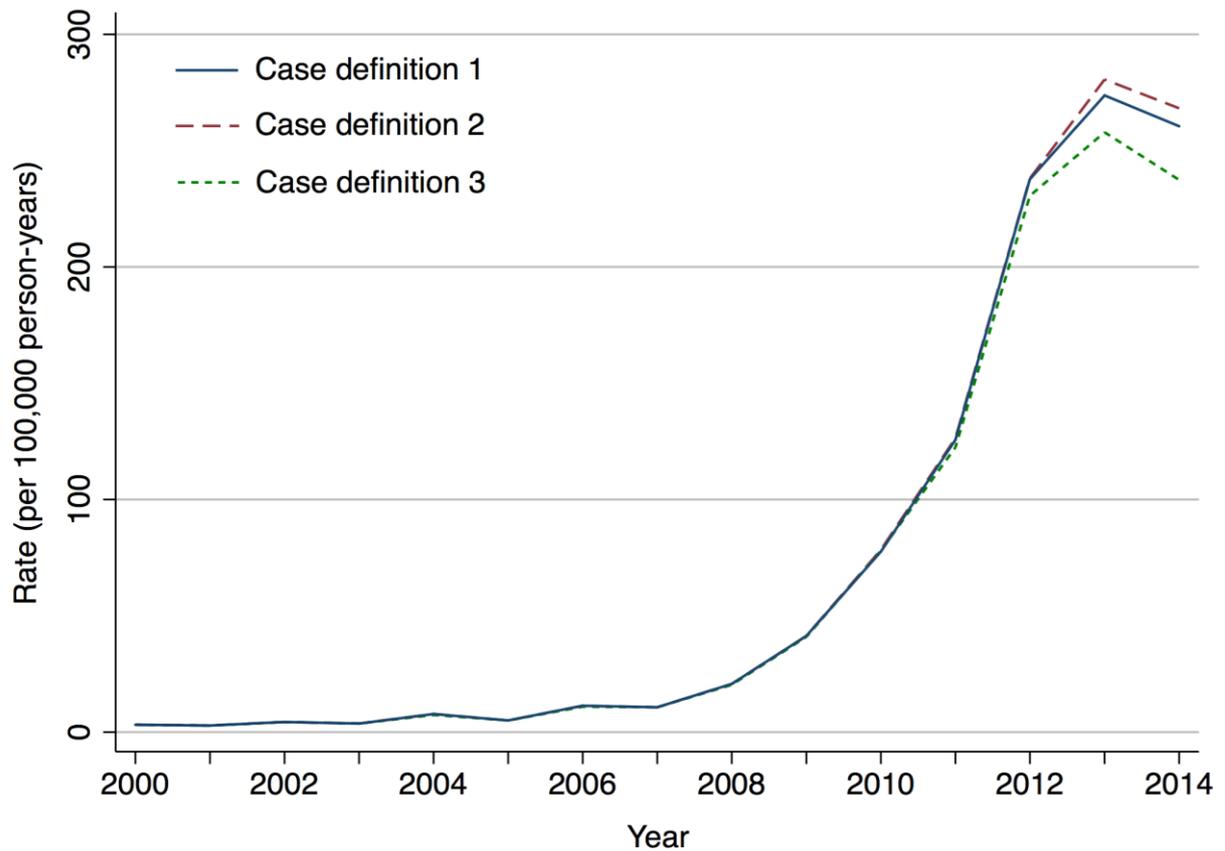
^c P values from likelihood ratio tests comparing nested models.

^d Ethnicity data was available from the child's THIN or HES record for 73.4% of children, from maternal ethnicity as a proxy measure for 13.9%, and was imputed for the remaining 12.7%.

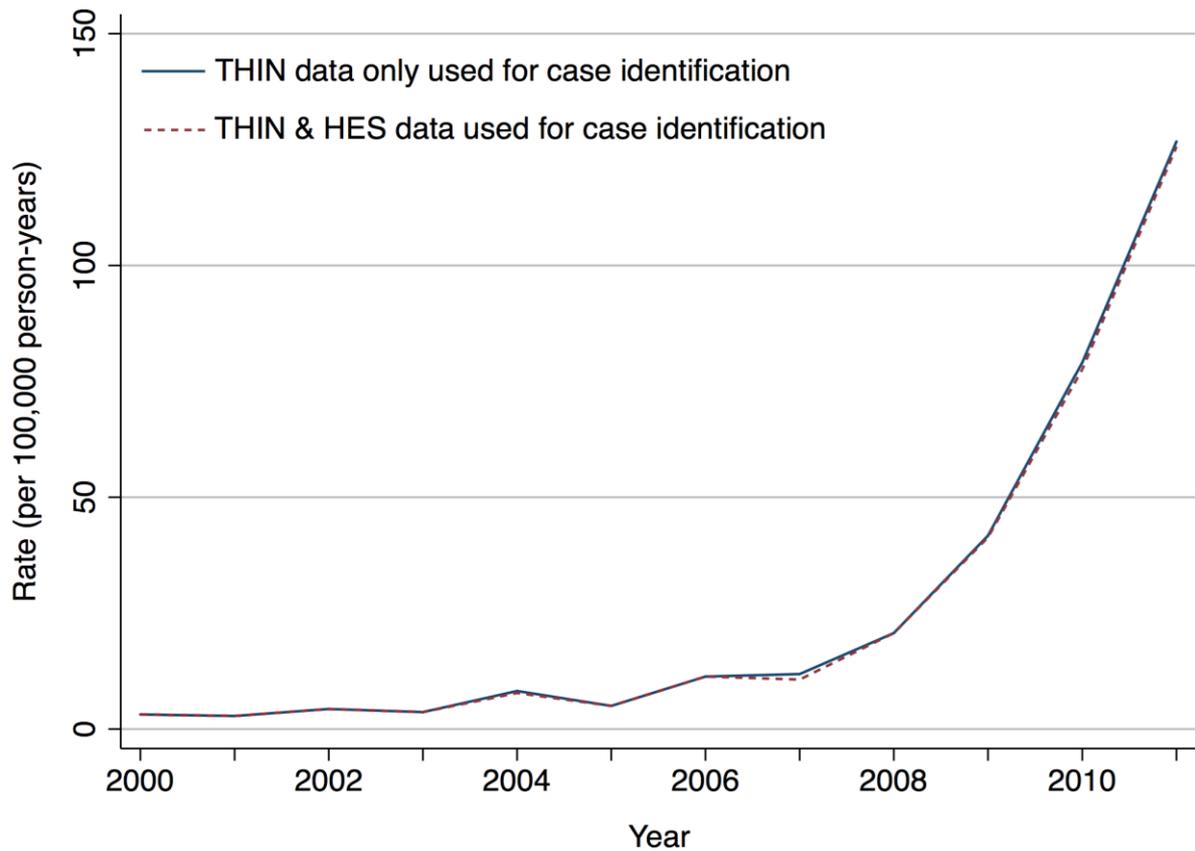
^e IMD was available from the THIN record for 91.7% of children, and was imputed for 8.3%.



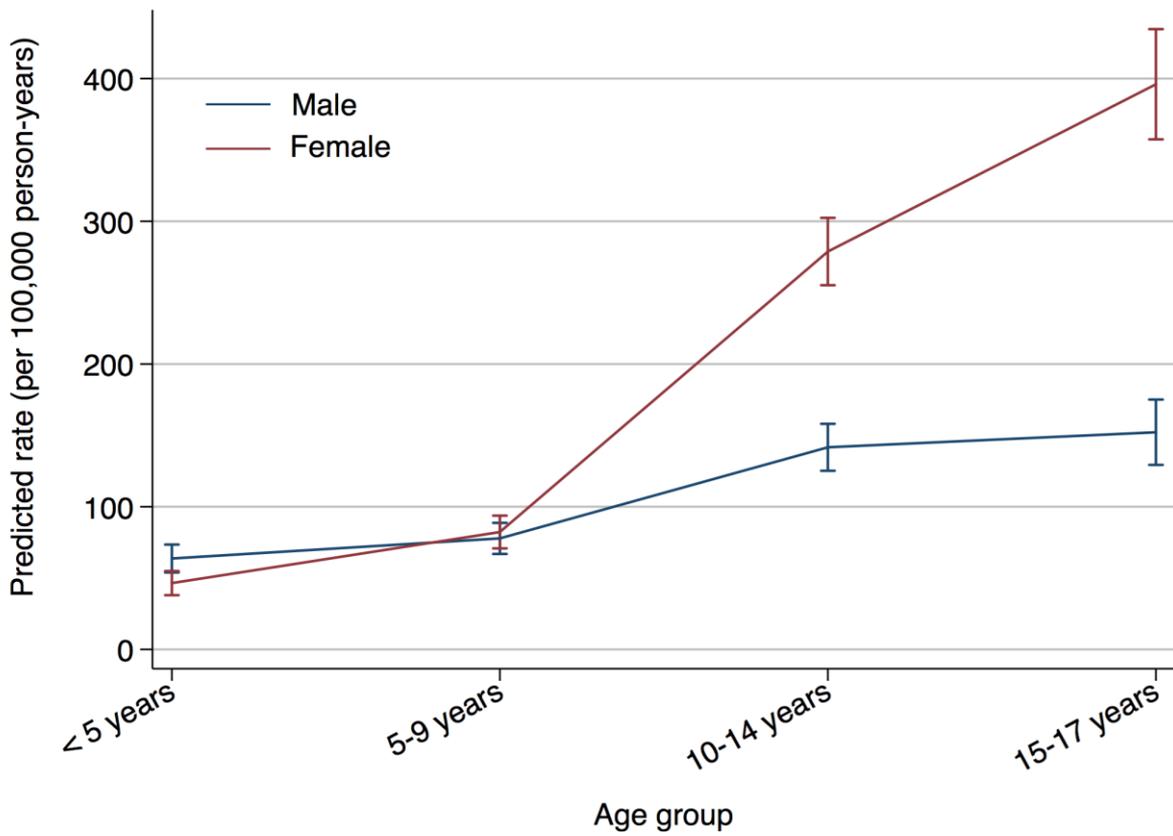
SUPPLEMENTAL FIGURE 2 Overlap between sources of case identification. VDD indicates vitamin D deficiency. Figures represent numbers (percentages). n=2918



SUPPLEMENTAL FIGURE 3 Time trends in the diagnosis of vitamin D deficiency in children, using different dosage thresholds for calciferol prescription in the case definition. Crude incidence rates are shown, between 2000 and 2014. Case definition 1 is that used in the main analysis, in which the calciferol dosage thresholds are as follows: ≥ 1500 units/day if age < 6 months, ≥ 3000 units/day if age 6 months to 12 years, ≥ 5000 units/day if age > 12 years, or one-off (stoss) dose of $\geq 100\,000$ units at any age. In case definition 2 the dosage thresholds are: ≥ 1000 units/day if age < 6 months, ≥ 2000 units/day if age 6 months to 12 years, ≥ 3000 units/day if age > 12 years, or one-off dose of $\geq 100\,000$ units at any age. In case definition 3 the dosage thresholds are: ≥ 3000 units/day if age < 6 months, ≥ 6000 units/day if age 6 months to 12 years, $\geq 10\,000$ units/day if age > 12 years, or one-off dose of $\geq 100\,000$ units at any age.



SUPPLEMENTAL FIGURE 4 Time trends in the diagnosis of vitamin D deficiency in children, with and without the inclusion of ICD-10 codes related to vitamin D deficiency or rickets from HES admitted patient care records in the case definition. Crude incidence rates are shown. THIN indicates The Health Improvement Network, HES indicates Hospital Episode Statistics, and ICD-10 indicates The International Classification of Diseases 10th Revision. The analysis was limited to follow-up between 2000 and 2011, as linked HES data is only available up to 31st March 2012.



SUPPLEMENTAL FIGURE 5 Adjusted predicted incidence rates for the diagnosis of vitamin D deficiency in children across categories of age, showing an interaction with sex. Predicted margins were derived from a multivariable Poisson regression model at average values for the remaining covariates (ethnicity, Index of Multiple Deprivation, and calendar year). The vertical bars represent 95% confidence intervals.