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Vitamin D insufficiency in infants with increased risk of developing type 1 diabetes: a secondary analysis of the POInT Study

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ABSTRACT

Background Vitamin D insufficiency (VDI) may be a factor in the development of type 1 diabetes (T1D). The aim of this study is to investigate the presence and persistence of VDI in a large cohort of infants with increased risk of developing T1D, in light of the differences in local supplementation guidelines.

Methods In the POInT Study, a multicentre primary prevention study between February 2018 and March 2021 in Germany, Poland, Belgium, England and Sweden, including infants aged 4–7 months at high genetic risk of developing β-cell autoantibodies, vitamin D levels were analysed at each study visit from inclusion (4–7 months) until 3 years, with an interval of 2 months (first three visits) or 4–6 months (visits 4–8). The protocol actively promotes vitamin D sufficiency to optimise immune tolerance. VDI was defined as a concentration below 30 ng/mL and was treated according to local guidelines of participating centres. Recovery from VDI was defined as a concentration above or equal to 30 ng/mL on the subsequent visit after VDI.

Results 1050 infants were included, of which 5937 vitamin D levels were available for analyses. VDI was observed in 1464 (24.7%) visits and 507 (46.1%) of these were not resolved at the next visit. The risk of having VDI was independently associated with season (higher in winter), weight (higher with increased weight), age (higher with increased age) and country (higher in England). The risk of not recovering from VDI was independently associated with the season of the previously determined VDI, which was higher if VDI was identified in winter.

Conclusions VDI is frequent in infants with increased risk of developing T1D. Treatment guidelines for VDI do not seem effective. Increasing supplementation dosages in this patient population seems warranted, especially during winter, and increasing dosages more aggressively after VDI should be considered.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Vitamin D supplementation guidelines for infants and children differ greatly per country.
⇒ The association between vitamin D insufficiency and type 1 diabetes is well established, although a causative role in type 1 diabetes development remains to be proven.
⇒ In the POInT Study, including children with an increased genetic risk of developing type 1 diabetes, vitamin D levels are systematically analysed, and parents are counselled to adjust supplementation doses accordingly to avoid vitamin D insufficiency.

WHAT THIS STUDY ADDS

⇒ Vitamin D insufficiency is frequent and persistent in infants and children with an increased genetic risk of developing type 1 diabetes, despite systematic counselling.
⇒ Even with large increments in supplementation dose after vitamin D insufficiency, vitamin D intoxication is extremely rare in the study population.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Adaptation of the guidelines in terms of standard dose of vitamin D supplementation, as well as dose increments after vitamin D insufficiency, should be considered in this population.
⇒ Factors such as season and body mass index for age could be taken into account when treating vitamin D insufficiency in this group of children with increased type 1 diabetes risk.

INTRODUCTION

Vitamin D can be obtained from ultraviolet (UV)B-dependent endogenous production, from the diet and from supplements.[1] When UVB hits the skin, it leads to the production of pre-vitamin D, which is an unstable intermediate thermally converted into vitamin D_3. Vitamin D may also be obtained to a lesser extent from the diet or from vitamin D supplements. Importantly, both synthesised and dietary-obtained vitamin D is an inactive

prohormone and both 25-hydroxylation and 1α-hydroxylation are required for activation. The 25-hydroxylation occurs in the liver and 25-OH-vitamin D reflects the nutritional vitamin D status. The next step to obtain active vitamin D is 1α-hydroxylation in the kidneys.[2]

There is controversy about the level of adequacy of vitamin D. The Endocrine Society defines deficiency as 25-(OH)D_3 levels less than 20 ng/mL (50 nmol/L) and vitamin D insufficiency (VDI) as levels 21–29 ng/mL (52–72 nmol/L).[3] The Institute of Medicine defines deficiency as 25-(OH)D_3 levels less than 12 ng/mL (30 nmol/L) and insufficiency as levels 12–20 ng/mL (30–50 nmol/L).[4] A recent French expert consensus paper recommends a 25(OH)D level >20 ng/mL (50 nmol/L) in children to prevent rickets and a 25(OH)D level >30 ng/mL (75 nmol/L) to avoid any mineralisation defects.[5] However, these cut-offs have been defined based on associations with bone metabolism, with markers such as parathyroid hormone and bone fracture risk,[6 7] whereas much higher vitamin D levels are needed to influence the immune effects of vitamin D in animal studies.[2 8] Low levels of vitamin D are common, as a study in 6275 American children and adolescents aged 1–21 years showed that 61% were 25-(OH)D_3 insufficient (15–29 ng/mL) and 9% deficient (<15 ng/mL).[9] When treating VDI, there is a risk of reaching a vitamin D intoxication with concentrations of more than 150 ng/mL (374 nmol/L), which can lead to hypercalcaemia and an imbalance in the regulation of bone metabolism.[1]

There is also controversy and discussion about the correct supplementation regime. The Endocrine Society recommends the following for vitamin D intake: 400–1000 IU, 600–1000 IU and 1500–2000 IU daily for children under 1 year, children 1–18 years and all adults, respectively, to treat and prevent vitamin D deficiency.[10] The expert consensus paper recommends supplementing healthy children 0–18 years of age with a minimum of 400 IU and a maximum of 800 IU of vitamin D per day.[5]

The importance of vitamin D in the regulation of both the innate and adaptive immune system was demonstrated by the discovery of the presence of VDR expression in almost all cells of the immune system.[2 11] Essentially, adequate levels of vitamin D result in a shift in the immune status towards a more tolerogenic status.[12] This makes vitamin D an appealing immune modulator in the treatment of immune-mediated diseases. Epidemiological data showed an association between 25-(OH)D_3 deficiency and the incidence of type 1 diabetes (T1D),[13 14] but that VDI is a causal factor in T1D development remains unproven.[15 16]

Studies in animal models of autoimmune diseases showed that restoring serum 25-(OH)D_3 levels using high doses of vitamin D metabolites or analogues could alter the course of autoimmune diseases like T1D, multiple sclerosis or rheumatoid arthritis.[17] In humans, the European Diabetes Centre's EURODIAB Study showed a significant decrease in T1D diagnosis in children receiving vitamin D supplementation,[18] while other studies indicated that maternal vitamin D supplementation during pregnancy did not reduce the risk of T1D in the offspring.[19 20] In a recent study of 395 children with T1D between 3 and 18 years old without vitamin D supplementation, 64% were vitamin D insufficient.[21]

The goal of this subanalysis of the Primary Oral Insulin Trial (POInT Study) was to investigate the presence of VDI and the evolution of these insufficiencies over time, and to analyse the effect of country-specific supplementation guidelines and participant characteristics.

METHODS

The POInT Study, a multicentre primary prevention study that aims to induce immune tolerance to β-cell autoantigens through regular exposure to oral insulin, also aimed for vitamin D sufficiency to optimise the immune response, and therefore, vitamin D levels were repeatedly measured (registered as NCT03364868 on ClinicalTrials.gov). All infants aged 4–7 months with a high genetic risk of developing β-cell autoantibodies were eligible for inclusion and were recruited in the seven participating centres: Munich, Hanover and Dresden (Germany), Warsaw (Poland), Malmö (Sweden), Oxford (England) and Leuven (Belgium). Exclusion criteria were concomitant disease or treatment that may interfere with the assessments, any condition that could be associated with poor compliance or may jeopardise the infant's safe participation, diagnosis of diabetes at the time of recruitment or participation in another clinical trial.[22] For this secondary analysis, visits without a vitamin D measurement were excluded. Patients were not involved in the study design but in the prioritisation of the research question of T1D prevention. Patients support recruitment through dissemination and participation in press conferences. The participating families previously assessed the burden of the intervention in a prior pilot prevention trial.[22 23]

25-OH-vitamin D levels were analysed at the local laboratory of the participating centres at each study visit from the age of 4–7 months until 3 years of age, with an interval of 2 months (for the first three visits) or 4–6 months (from visit 4 to 8). VDI was defined as a vitamin D concentration below 30 ng/mL. Study nurses and physicians at each site were notified via email by the centralised study software if vitamin D values were too low. VDI was then subsequently treated according to the local guidelines of the participating centres, which is shown in table 1. Parents were instructed to continue the same supplementation dose if they were not contacted after the study visit, as they were not actively informed when vitamin D levels were sufficient. Recovery from VDI was defined as a concentration above or equal to 30 ng/mL, the subsequent visit after VDI.

Multivariable logistic regression analysis, adjusted for season (January–March as winter, April–June as spring, July–September as summer, October–December as autumn), sex, history of T1D in a first-degree relative,

Table 1 Overview of local vitamin D supplementation guidelines per participating centre

	Standard dosage <1 year	Standard dosage >1 year
Germany	500 IU/day	500 IU/day
Belgium	400 IU/day	400 IU/day
England	400 IU/day	400 IU/day
Poland	400–600 IU/day	600–1000 IU/day
Sweden	400 IU/day	400 IU/day
	If vitamin D <30 µg/L <1 year	**If vitamin D <30 µg/L >1 year**
Germany	Plus 500 IU increase	Plus 1000 IU increase
Belgium	Plus 66 IU increase	Plus 66 IU increase
England	Plus 600 IU increase	Plus 600 IU increase
Poland	Plus 300–600 IU increase	Plus 500–1000 IU increase
Sweden	Plus 400–800 IU increase	Plus 400–2800 IU increase

age, weight, height and country, was used to assess independent associations with the risk of VDI and the chance of recovery from VDI. Effect sizes are reported as ORs and 95% CIs. Statistical analyses were performed with JMP Pro V.14.0.0 (SAS Institute, Cary, North Carolina, USA). Statistical significance was set at a p value of <0.05.

RESULTS

In total, 1050 children were included, of which 5937 vitamin D levels were available for analyses. Baseline characteristics of these participants are shown in table 2.

Figure 1 represents the distribution of the vitamin D levels per country. The number of patients and the available vitamin D levels per visit per country are illustrated in online supplemental figure 1A,B. Of the 5937 measured vitamin D levels, 1464 (24.7%) were below 30 ng/mL and defined as VDI. The number of children who had at least one VDI at any time point was 667 out of the 1050 (63.5%). Of the 1464 measured VDIs, 592 (53.9%) insufficiencies rose above the threshold of 30 ng/mL at the next visit, whereas 507 insufficiencies (46.1%) were not resolved at the next visit. Of the 592 recovered insufficiencies, 33 (5.6%) were in the excess range above 50 ng/mL, and none were in the toxic range above 150 ng/mL. In this subgroup of the 592 recovered insufficiencies, there was no difference between the participating countries in normal or excess ranges (p=0.66). 4476 out of the total of 5937 measurements were defined as vitamin D sufficiency (75.3%), and 686 of them (15.3%) were classified as a VDI on the next visit.

Risk of having a VDI

In multivariable logistic regression, the risk of having VDI was independently associated with the season, weight, age and country (table 3). The risk of VDI was higher in winter as compared with all other seasons, and lower in summer as compared with all other seasons. Also, for every kilogram increase in body weight and for every year increase in age, the risk of VDI increased. Finally, the risk of having VDI was higher in England as compared with Germany (OR 1.42 (1.06 to 1.90), p=0.01), Poland (OR 1.69 (1.24 to 2.31), p=0.0009) and Belgium (OR 1.43 (1.00 to 2.03), p=0.04). The risk was lower in Poland as compared with Germany (OR 0.83 (0.71 to 0.99), p=0.03) and Sweden (OR 0.79 (0.65 to 0.99), p=0.03). There was no independent association between height, sex or a first-degree relative with T1D and the risk of VDI. The repeated measurements analysis (table 4), which corrects for multiple measurements of vitamin D of the same child, shows similar results for season, age and body weight. However, the effect of country largely disappears, which indicates that this effect is probably mostly driven by children who have persistent insufficiencies.

Table 2 Baseline characteristics of the participants

	Participants N=1050
Male sex, N (%)	527 (50.3)
Age (months) at visit 1, median (IQR)	5.9 (5.2–6.5)
Weight (kg) at visit 1, median (IQR)	7.8 (7.1–8.4)
Height (cm) at visit 1, median (IQR)	68 (66–69)
Positive history of T1DM in first-degree relatives, N (%)	556 (53.0)
Vitamin D level (ng/mL) of all visits combined, median (IQR)	36 (30–43)
Vitamin D level (ng/mL) of all visits combined, mean (SD)	37 (11)
Vitamin D toxic levels (>150 ng/mL) of all visits combined, N (%)	1 (0.02)
Country, N (%)	
Germany	504 (48.0)
Belgium	80 (7.6)
England	51 (4.9)
Poland	242 (23.0)
Sweden	173 (16.5)
Participants with vitamin D level available on each visit, N (%)	
Visit 1	965 (91.9)
Visit 2	957 (91.1)
Visit 3	937 (89.2)
Visit 4	930 (88.6)
Visit 5	811 (77.2)
Visit 6	641 (61.0)
Visit 7	443 (42.2)
Visit 8	253 (24.1)

T1DM, type 1 diabetes mellitus.

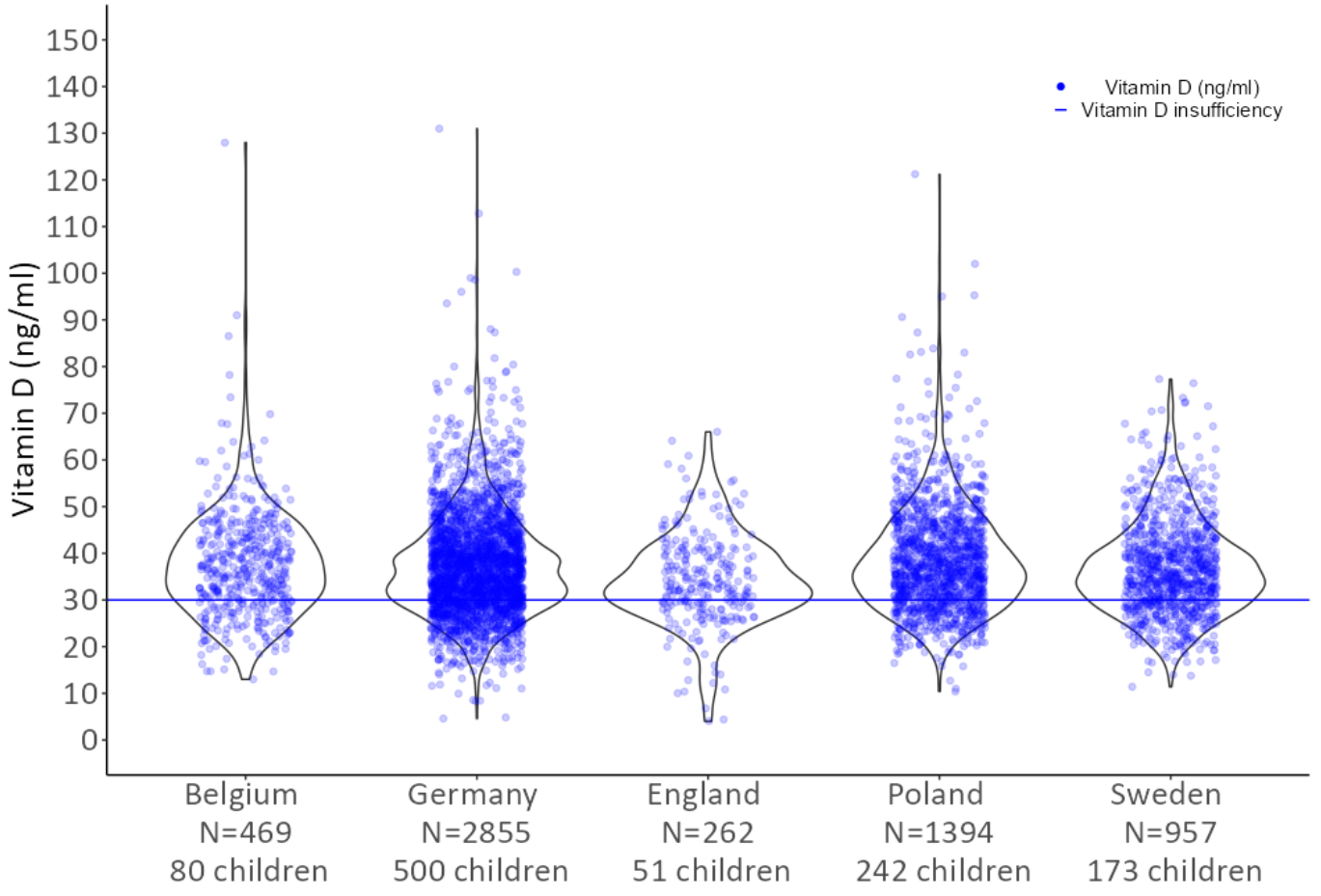

Figure 1 Violin plots of the vitamin D levels per country. The kernel density estimation visualises the distribution of the data. Each blue dot represents a single vitamin D level.

Risk of not recovering from a VDI

The risk of not recovering from VDI was independently associated with the season of the previously determined VDI (table 5). If the VDI was identified in winter, the risk of not recovering was higher as compared with insufficiencies identified in spring or summer. Insufficiencies identified in summertime had higher chances of recovery than the insufficiencies in autumn or spring. None of the other available variables was associated with the risk of not recovering from VDI.

DISCUSSION

This study covers a large sample size of almost 6000 analysed 25-OH-vitamin D levels in 1050 infants and children between the age of 4 months and 3 years with an increased genetic risk of developing β-cell autoantigens, in five European countries. One-fourth of the measured values were defined as at least a VDI, and almost half of these insufficiencies were not resolved by the next visit. The risk of having a VDI increased in winter, with higher age and body weight, and in England. A risk factor for not recovering from a VDI was if the VDI was measured in wintertime.

Since VDI is associated with T1D and might play a role in the pathogenesis,[24] and since VDI is associated with rickets, muscle weakness and other chronic diseases,[25] its prevalence and its persistence after dose increments in this population of infants with a confirmed increased genetic risk of developing T1D are unexpected. However, in a substudy of the TRIGR Study, investigating the effect of an extensively hydrolysed formula on the incidence of T1D,[16] the mean vitamin D levels at baseline in infants (until 18 months) with an increased genetic risk of T1D with and without autoantibodies were 26.2 ng/mL and 26.9 ng/mL, respectively.[26] The mean vitamin D levels during follow-up in our study are significantly higher (37 ng/mL), which might be explained by the regularity of the blood analyses, the close follow-up and emphasis on the importance of compliance towards the parents. However, despite this systemic counselling, the prevalence of VDI was still 25%, which is comparable with the prevalence of VDI in healthy infants: depending on the geographical population that was examined, the prevalence of a VDI is ranging from 19.3% to 40%.[27–29] Moreover, although recommendations on increasing the vitamin D supplementation when necessary were also systematically made,

Table 3 Multivariable logistic regression analysis of the risk of a vitamin D insufficiency

	OR (95% CI)	P value
Season		<0.0001
Summer vs winter	0.42 (0.35 to 0.50)	<0.0001
Autumn vs winter	0.67 (0.56 to 0.80)	<0.0001
Spring vs winter	0.77 (0.65 to 0.91)	0.002
Weight		
Per kg increase	1.09 (1.03 to 1.16)	0.002
Height		
Per cm increase	0.99 (0.97 to 1.01)	0.56
Age		
Per year increase	1.03 (1.01 to 1.05)	0.003
Country		0.008
England vs Germany	1.42 (1.06 to 1.90)	0.01
Poland vs Germany	0.84 (0.71 to 0.99)	0.03
Belgium vs Germany	1.00 (0.78 to 1.27)	0.96
Sweden vs Germany	1.05 (0.87 to 1.26)	0.60
Gender		
Male vs female	1.03 (0.91 to 1.17)	0.58
First-degree relative (FDR) with T1DM		
FDR vs no FDR	1.03 (0.90 to 1.17)	0.60

T1DM, type 1 diabetes mellitus.

Table 4 Repeated measurements analysis of the risk of a vitamin D insufficiency

	OR (95% CI)	P value
Season		<0.0001
Summer vs winter	0.38 (0.31 to 0.47)	<0.0001
Autumn vs winter	0.64 (0.52 to 0.78)	<0.0001
Spring vs winter	0.54 (0.45 to 0.65)	0.006
Weight		
Per kg increase	1.11 (1.03 to 1.20)	0.008
Height		
Per cm increase	0.99 (0.97 to 1.02)	0.61
Age		
Per year increase	1.03 (1.01 to 1.06)	0.009
Country		0.06
England vs Germany	1.53 (1.00 to 2.34)	0.05
Poland vs Germany	0.80 (0.63 to 1.01)	0.06
Belgium vs Germany	1.00 (0.71 to 1.43)	0.99
Sweden vs Germany	1.04 (0.79 to 1.35)	0.79
Gender		
Male vs female	1.04 (0.87 to 1.26)	0.64
First-degree relative (FDR) with T1DM		
FDR vs no FDR	1.03 (0.86 to 1.25)	0.71

T1DM, type 1 diabetes mellitus.

Table 5 Multivariable logistic regression analysis of the risk of not recovering from a vitamin D insufficiency (VDI)

	OR (95% CI)	P value
Season of the first VDI measured		<0.0001
Summer vs winter	0.37 (0.26 to 0.54)	<0.0001
Autumn vs winter	0.67 (0.44 to 1.03)	0.06
Spring vs winter	0.65 (0.46 to 0.93)	0.01
Weight		
Per kg increase	1.04 (0.91 to 1.18)	0.52
Height		
Per cm increase	1.00 (0.95 to 1.05)	0.85
Age		
Per year increase	0.99 (0.95 to 1.03)	0.66
Country		0.65
Gender		
Male vs female	1.03 (0.79 to 1.33)	0.81
First-degree relative (FDR) with T1DM		
FDR vs no FDR	0.96 (0.74 to 1.25)	0.79

T1DM, type 1 diabetes mellitus.

almost half of the insufficiencies were not resolved at the next study visit. Remarkably, having a first-degree family member with T1D, which was the case in more than half of the children, and which could potentially influence adherence, did not affect the risk of a VDI or of a VDI recovery.

Taking into account the results of the multivariable analysis, we can speculate on how to improve the clinical approach in these patients to avoid VDI and to resolve their insufficiency faster. First, as the supplementation guidelines differ between the participating countries, and as a country such as Poland with a higher range and maximum of supplementation guidelines is independently associated with a lower risk of a VDI, it seems warranted to increase the supplementation dosage. Only 1 of nearly 6000 vitamin D levels reached toxic levels (>150 ng/mL). Moreover, although not decreasing the risk of VDI recurrences, the largest range of increasing supplementation dosages after insufficiency in the local guidelines in our study was in Sweden (depending on the severity of insufficiency: 400–800 IU/day for infants younger than 1 year of age, 400–2800 IU/day for older children). Therefore, it seems safe to increase the supplementation dosages in countries where they are low in comparison with Sweden. Next, systematically increasing the dosage in wintertime should be considered in these children. Conversely, more practically challenging is increasing supplementation dosages with increased weight or body mass index for age. A recent randomised controlled trial showed that daily 6000 IU vitamin D supplementation in obese children was safe and sufficient to reach vitamin D sufficiency.[30] Increasing

more aggressively in obese children could be taken into account when increasing dosages in these children does not resolve a previously identified vitamin D deficit.

Finally, the strategy of increasing the dosage, which differed extensively between countries, when a VDI was measured, did not contribute to the risk of not resolving the VDI. However, as almost half of the insufficiencies were not resolved after increasing the dose, increasing more aggressively in wintertime seems warranted, as this was the only independent contributor to the risk of not recovering. As shown in a recent randomised controlled trial in children and adolescents with newly diagnosed T1D, even very high dosages of adjunctive ergocalciferol supplementation in high dosage (50 000 IU weekly) was safe and did not lead to toxic levels.[31]

Limitations in this study include the lack of data available on the actual administered dose of vitamin D supplementation by the parents. The use of diaries or other measures of adherence could have improved the analysis. Additionally, quantification of the 25-OH-vitamin D levels was not centralised but was performed by the local laboratories of the participating centres. Since all local laboratories are certified, we believe that the risks of this affecting the results are minimal. The strengths of the study include the multicentre design, as well as the large cohort of more than 1000 infants with increased risk of T1D without missing data for the included variables, of which nearly 6000 vitamin D levels were available for analysis.

CONCLUSION

Despite the established health benefits of having sufficient levels of vitamin D and our emphasis to parents on the importance of adequate supplementation, VDI is frequent in infants and young children with increased risk of developing T1D, as seen in children not selected on high-genetic T1D risk. The insufficiency remains unresolved very often, even after using treatment dosages. Increasing supplementation dosages in this patient population seems warranted, especially during wintertime. When VDI is detected, increasing dosages more aggressively should be considered.

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Contributors AJ, VV, CW, A-GZ, ML, HEL, OK, TvdB, EEB, M-LZ, AH, MO, AS and KC were responsible for collection of the patients' data. AJ and AW performed the statistical analyses. AJ, MW and KC wrote the manuscript. VV, CW, A-GZ, ML, HEL, OK, TvdB, EEB, M-L Z, AH, MO, AS, RB and JAT revised the manuscript. KC is guarantor of this study.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not required.

Ethics approval This study involves human participants and was approved by the local ethical committees and regulatory authorities of the Technische Universität München, Medical Faculty (326/17 Af), the Medical University of Warsaw (Instytucie Matki I Dziecka w Warszawie) (199/2017), the UK Health Research Authority (18/SC/0019), Onderzoek UZ/KU Leuven (S60711) and the Regionala etikprövningsnämnden i Lund (2017/918). Participants gave informed consent to participate in the study before taking part.

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Data availability statement Data are available upon reasonable request. The data that support the findings of this study are available on request from the GPPAD-Coordinating Centre.

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