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ORIGINAL ARTICLE

Both youth and long-term vitamin D status is associated with risk of type 2 diabetes mellitus in adulthood: a cohort study

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ABSTRACT

Objectives: To determine whether vitamin D status in childhood and adolescence (herein collectively referred to as youth) and the long-term status from youth to adulthood is associated with risk of developing type 2 diabetes mellitus (T2DM) and impaired fasting glucose (IFG) in adulthood.

Materials and methods: This was a 31-year follow-up study of 2300 participants aged 3–18 years. Multinomial logistic regression was used to assess the association of both (a) baseline 25-hydroxyvitamin D (25OHD) levels and (b) the mean of baseline and the latest follow-up 25OHD levels (continuous variable and quartiles) with incident T2DM and IFG (cut-off = 5.6 mmol/L) in adult life.

Results: High serum 25OHD levels in youth and also mean values from youth to adulthood were associated with reduced risk of developing T2DM in adulthood (odds ratio, 95% confidence interval= 0.73, 0.57–0.95 and 0.65, 0.51–0.84, respectively, for each SD increment in 25OHD). Compared to Q1, a dose-dependent negative association was observed across other quartiles of youth 25OHD, while the strongest association was found in the Q3 for the mean 25OHD levels. Neither youth nor the mean 25OHD was associated with IFG.

Conclusions: High serum 25OHD levels in youth, and from child to adult life, were associated with a reduced risk of developing T2DM in adulthood.

KEY MESSAGES

- High serum 25OHD levels in youth, and between youth and adulthood, were associated with a lower risk of T2DM in adulthood.
- Each SD (15.2 nmol/L) increment in youth serum 25OHD levels was associated with a 26% reduction in odds for T2DM, which was independent of a number of confounding variables and other risk factors for T2DM. A similar magnitude of association was observed for the long-term 25OHD levels between youth and adulthood.
- These findings suggest a potentially simple and cost-effective strategy for reducing adulthood risk of T2DM starting in an earlier stage of life – improving and maintaining vitamin D status throughout youth and early adulthood.

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25-hydroxyvitamin D; type 2 diabetes mellitus; impaired fasting glucose; youth

Introduction

More than 400 million adults suffer from type 2 diabetes mellitus (T2DM) worldwide and this number is expected to increase substantially over the next several decades [1]. Of note, children and young adults represent an emerging group with a remarkable increase in incident T2DM [2–4], which is estimated to worsen with the current epidemic of obesity [5]. Moreover, young adults with T2DM appear at greatest risk of developing overt cardiovascular at an earlier life

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stage [6]. Despite these findings, current strategies to reduce the risk of T2DM have been largely unsuccessful, with the majority of research focused on identifying and improving risk factors in adulthood.

Many conventional risk factors for T2DM (e.g. obesity) that develop in childhood have been shown to increase the risk of T2DM in adulthood [7–12], suggesting promising benefits of preventing adult T2DM by improving these risk factors at an early stage of life. In addition to these well-known risk factors, low vitamin D status has also been associated with increased risk of T2DM in adults, though its causal role is unclear [13,14]. Moreover, suboptimal vitamin D status in childhood has been associated with higher insulin resistance [15], which is an independent risk factor for T2DM in adulthood [11]. However, it remains untested if low vitamin D status in childhood, and across childhood to early adulthood, is associated with an increased risk of T2DM in adulthood.

Therefore, this study aimed to examine the association between serum 25-hydroxyvitamin D (25OHD) status in childhood and adolescence (herein collectively referred to as youth), as well as the long-term status from youth to adulthood, and the incidence of T2DM and impaired fasting glucose (IFG) in adulthood using data from the Cardiovascular Risk in Young Finns Study.

Materials and methods

The Cardiovascular Risk in Young Finns Study is a multi-centre population-based follow-up study of cardiovascular risk factors in Finland [16]. In 1980 (baseline), 3596 participants aged 3–18 years (3, 6, 9, 12, 15 and 18 years old) were randomly selected from the national register of the study areas. They were followed up in 2001, 2007 and 2011, when 2283, 2204 and 2060 (aged 34–50 years) participants were re-examined, respectively. Participants who had type 1 diabetes ($n = 20$) or were pregnant at each follow-up visits ($n = 91$) were excluded from all analyses. The current analyses used data from 2300 participants who had complete risk factor data from baseline, with adult T2DM data available from the 2001, 2007 and 2011 surveys. All participants gave written informed consent, and local ethics committees approved the study.

Definition of T2DM and IFG

Participants were classified as having T2DM if, at any of the follow-up visits (2001, 2007 and 2011), their fasting plasma glucose value was $\geq$7 mmol/L (126 mg/dl) or if they reported having been given a T2DM diagnosis by a physician [10]. Moreover, participants whose HbA1c was $\geq$6.5% (48 mmol/mol) at the 2011 follow-up or who reported taking glucose-lowering medication at the 2007 or 2011 follow-up were classified as having T2DM. Finally, T2DM diagnoses were obtained from the National Social Insurance Institution Drug Reimbursement Registry. Fasting plasma glucose concentration was determined by the enzymatic hexokinase method (Glucose Olympus System Reagent, Olympus, Dublin, Ireland). IFG was defined as having a fasting plasma glucose $\geq$5.6 but $\leq$6.9 mmol/L by the latest available measurement [17].

Serum 25OHD

Youth 25OHD levels were measured in 2010 using serum samples taken in 1980 and stored at $-20\,^{\circ}$C [18]. Serum 25OHD levels were remeasured using serum samples taken in 2001 (1094 measured by 2003 and the rest during 2011) and 2007 (measured in 2008) (stored at $-70\,^{\circ}$C). Serum 25OHD levels were analysed by radioimmunoassay (DiaSorin Inc., Stillwater, MN) for all time points. The limit of detection was 3.8 nmol/L. The interassay coefficient of variation was 8.5% ($n = 128$) and 8.8% ($n = 113$) at the level of 35.7 and 135.3 nmol/L, respectively.

Other measurements at baseline

Height and weight were measured, and body mass index (BMI) calculated as weight/height (kg/m^2) (also measured in 2001, 2007 and 2011). Other baseline variables were: *blood pressure* was measured from the brachial artery while seated after a 5-min rest using a standard mercury sphygmomanometer. An ultrasound device was used to measure blood pressure of participants aged 3 years. At least three readings to the nearest even number of millimeters of mercury were performed with mean calculated for analyses. For *serum lipid* levels, venous blood samples were drawn after an overnight fast [16]. Serum insulin was measured with an immunoassay method. Information on *diet* was obtained with a short 19-item non-quantitative food frequency questionnaire. In 12- to 18 years old, information on *smoking* habits was collected during a medical examination in a solitary room. Smoking was defined as regular cigarette smoking on a weekly basis (or more often). Those aged younger than 12 years were considered not smoking. The frequency and intensity of physical activity were asked and a physical activity index was calculated as previously described [19]. The physical activity index was

calculated by summing up different variables concerning exercise habits, including intensity, frequency of exercise, athletic club (frequency of participating in training at an athletic club), athletic competitions (whether participated in club, district or national level competitions), leisure time (usual activities during spare time: indoors, mostly indoors and mostly outdoors) and sports participation. Two different types of physical activity questionnaires were used. For participants aged 3 and 6 years, a parent-completed questionnaire was used, and for children aged 9–18 years self-completed questionnaires were used. This measure has been shown to be reliable and valid [20]. Age-standardized physical activity indices were calculated. Questionnaires were used to obtain data on parents' history of T2DM and years of their parental education.

Other measurements in adulthood (years 2001, 2007 and 2011)

Physical activity was assessed by standardized questionnaire. The metabolic equivalent index (MET index) was calculated as described previously [21]. Smoking and educational status was assessed using a questionnaire. Participants who smoked daily were considered as smokers. Educational status was based on participant's highest degree (grammar school, college or vocational school and university degree). In the 48-h recall, dietary interviewers, all trained dietitians, collected information on foods and beverages consumed by participants during the 2 days prior to the interview. The latest available measures for these variables were used as their adulthood values.

Statistical analyses

Mean (SD) and number (%) were used, as appropriate, to describe variables. Difference in baseline characteristics between participants with and without T2DM in adulthood was tested using analysis of variance or chi-square test as appropriate. Adulthood BMI was defined as the latest available measures in 2001, 2007 and 2011, and missing data were imputed using baseline age, gender and BMI as predictors ($n = 25$). The mean 25OHD levels between youth and adulthood were calculated using data from 1980 and 2007 (25OHD levels in 2001 were used when data were missing in 2007). When 25OHD levels were missing in both 2001 and 2007, adulthood 25OHD levels were imputed using baseline 25OHD, age, gender and adulthood BMI ($n = 119$).

Univariable and multivariable multinomial logistic regression models were used to estimate the odds ratio (OR) and 95% confidence interval (CI) of adult T2DM and IFG (normal fasting glucose as referent outcome group, <5.6 mmol/L) according to baseline 25OHD and the mean value between youth and adulthood. We specified 25OHD levels as either a continuous or categorical variable. The categorical variable was based on quartile of the distribution within our cohort at baseline or between youth and adulthood: Q1 = 12–41 and 15–44; Q2 = 42–51 and 44.5–52.4; Q3 = 52–62 and 52.5–62; Q4 = 63–122 and 62.5–124 nmol/L, respectively. We used quartile 1 as the reference category in our analyses given the range of values contained in this group is more relevant to the general definition of vitamin D deficiency. We selected potential confounders based on the biological plausibility of an association of a factor with both the outcome and the exposure of interest (e.g. consumption of vegetables at baseline and adult month of blood taken). Age, sex, BMI and month of blood draw at baseline were included in all models. Other factors were retained in the final model when the estimated effect size of serum 25OHD for T2DM changed by more than 10%. Finally, age, sex, BMI, month of blood taken, parental history of diabetes, and consumption of fruits were included as confounders. Analyses were initially performed by not adjusting for any confounders (Model 1), adjusting for the factors retained in the confounder selection (Model 2), and then additionally adjusting for consumption of vegetables, physical activity, smoking, systolic blood pressure, high-density lipoprotein cholesterol (HDL-C), triglycerides, insulin and parental years of education (Model 3). Finally, we additionally adjusted for adult BMI (Model 4).

Interactions between baseline and mean 25OHD, sex and baseline age (25OHD × sex and 25OHD × age) were tested in regression models. As there were no significant interactions between 25OHD, sex and baseline age irrespective of adjustment for confounders, data were not stratified by sex or baseline age. Potential non-linear association between serum 25OHD and risk of T2DM and IFG was assessed by comparing the change in goodness of fit when a squared term of 25OHD was added to the completely adjusted model.

We performed sensitivity analyses by running all multinomial logistic regressions again using an alternate cut-off of 6.1 mmol/L to define IFG.

All statistical analyses were performed using STATA version 12 (Stata Corporation, College Station, TX). A two-tailed p value $<.05$ was considered statistically significant.

Results

Table 1 shows baseline (1980) characteristics, mean 25OHD levels between youth and adulthood and adult characteristics of participants by status of T2DM and IFG in adulthood. During the follow-up period of 31 years, 94 (4.1%) and 473 (20.5%) participants developed T2DM and IFG, respectively. Compared with the normal fasting glucose (NFG) group, participants who developed T2DM or IFG were older, had higher BMI, systolic blood pressure, fasting insulin, triglycerides, and had low serum 25OHD levels, HDL-C levels and frequency of fruit consumption. They were also more likely to be current smokers and had higher adult BMI but lower mean 25OHD between youth and adulthood. Participants who had T2DM but not IFG were more likely to have a family history of diabetes and to have parents who completed less years at school (Table 1). The IFG group had higher physical activity levels but was less likely to be female than the NFG and T2DM groups. In adulthood, participants who developed T2DM or IFG had higher BMI, lower physical activity level and were more likely to be current smokers, but had similar educational status and consumption of fruits and vegetables. Baseline characteristics of participants by quarters of youth 25OHD are also presented in Supplemental Table 1.

Table 2 shows the OR and 95% CI for the association of 25OHD levels in youth, and the mean 25OHD between youth and adulthood, with adult T2DM and IFG. In unadjusted analysis, 25OHD levels in both youth and mean 25OHD were negatively associated with the risk of T2DM in adulthood (Table 2). After adjustment for confounders (age, sex, BMI, month of blood taken, parental history of diabetes and consumption of fruits), these associations were reduced but remained statistically significant. The associations remained similar after a further adjustment of known risk factors for T2DM. After further adjustment for adult BMI, these associations remained similar for youth 25OHD but were attenuated somewhat for

Table 1. Participants' youth (in 1980) and adulthood characteristics by NFG, IFG and T2DM status in adulthood.

	NFG ($n = 1733$)	IFG[a] ($n = 473$)	T2DM ($n = 94$)
Youth			
Age (years)	10.1 (5.0)	11.4 (4.8)	13.1 (4.8)
Female, *n* (%)	1012 (58)	150 (32)	47 (50)
BMI (kg/m^2)	17.6 (3.0)	18.1 (3.0)	20.4 (4.0)
25OHD (nmol/L)	52.0 (15.2)	51.9 (15.6)	45.8 (14.2)
Study month, *n* (%)			
September	104 (6)	29 (6)	7 (8)
October	1014 (59)	295 (62)	65 (69)
November	562 (32)	136 (29)	20 (21)
December	53 (3)	13 (3)	2 (2)
Physical activity index (*z*-score)	−0.02 (0.99)	0.15 (1.04)	−0.03 (0.93)
Systolic blood pressure (mmHg)	112 (12)	114 (12)	118 (14)
Fasting insulin (mU/L)	9.2 (5.7)	10.0 (5.8)	12.4 (6.4)
Triglycerides (mmol/L)	0.66 (0.30)	0.66 (0.29)	0.79 (0.46)
HDL-C (mmol/L)	1.57 (0.31)	1.55 (0.30)	1.49 (0.31)
Parental history of diabetes, *n* (%)	33 (2)	10 (2)	6 (6)
Fruit consumption (>6 times/week), *n* (%)	1404 (81)	381 (81)	65 (69)
Vegetable consumption (>6 times/week), *n* (%)	591 (34)	159 (34)	29 (31)
Smokers, *n* (%)	85 (5)	36 (8)	13 (14)
Parental years attended at school	10.0 (3.3)	9.9 (2.9)	9.1 (3.1)
Adulthood[b]			
Age (years)	41.1 (5.0)	42.4 (4.8)	44.1 (4.8)
BMI (kg/m^2)	25.5 (4.6)	28.0 (4.7)	32.2 (6.1)
25OHD (nmol/L)	56.3 (19.8)	55.1 (18.1)	49.0 (16.8)
Physical activity index	9.1 (1.9)	8.7 (1.8)	8.4 (1.6)
Smokers, *n* (%)	299 (17)	111 (24)	22 (29)
Educational status			
Grammar school	225 (14)	68 (16)	16 (20)
College or vocational school	717 (46)	212 (49)	42 (53)
University degree	616 (40)	149 (35)	22 (27)
Fasting glucose (mmol/L)	5.08 (0.34)	5.96 (0.28)	7.06 (2.39)
Fasting insulin (mU/L)	7.9 (8.5)	12.4 (10.5)	21.8 (21.1)
Fruit consumption (g/day)	196 (207)	175 (190)	194 (164)
Vegetable consumption (g/day)	274 (187)	261 (187)	298 (180)
Mean 25OHD (nmol/L)[c]	54.2 (13.8)	53.5 (12.9)	47.4 (12.8)

NFG: normal fasting glucose; IFG: impaired fasting glucose; T2DM: type 2 diabetes mellitus; BMI: body mass index; 25OHD: 25-hydroxyvitamin D; HDL-C: high-density lipoprotein cholesterol.

[a]IFG cut-off is 5.6 mmol/L.

[b]All variables used data from the latest available values in adulthood (from 2001, 2007 and 2011), and the number of participants are 1767 for fruit and vegetable consumption and ranged from 2067 to 2300 for other variables.

[c]See "Statistical analyses" section in the text for how this was calculated.

Data are mean (SD) for continuous variable and number (%) for categorical variables.

Table 2. The association between continuous youth and the mean of youth and adulthood 25OHD levels, T2DM and IFG in adulthood.

	n	Childhood serum 25OHD levels Odds ratio (95% CI)[a]	Mean of childhood and adulthood serum 25OHD levels Odds ratio (95% CI)[b]
Model 1			
NFG	1733	Reference	Reference
IFG	473	1.00 (0.89–1.10)	0.95 (0.86–1.06)
T2DM	94	**0.64 (0.51–0.81)**	**0.57 (0.45–0.72)**
Model 2			
NFG	1733	Reference	Reference
IFG	473	1.05 (0.93–1.18)	1.00 (0.90–1.12)
T2DM	94	**0.71 (0.55–0.91)**	**0.63 (0.50–0.81)**
Model 3			
NFG	1733	Reference	Reference
IFG	473	1.04 (0.93–1.18)	1.00 (0.89–1.12)
T2DM	94	**0.73 (0.57–0.95)**	**0.65 (0.51–0.84)**
Model 4			
NFG	1733	Reference	Reference
IFG	473	1.05 (0.93–1.19)	1.06 (0.94–1.19)
T2DM	94	**0.74 (0.56–0.97)**	**0.73 (0.56–0.95)**

NFG: normal fasting glucose; IFG: impaired fasting glucose (cut-off 5.6 mmol/L); T2DM: type 2 diabetes mellitus; 25OHD: 25-hydroxyvitamin D.
[a]Odds ratio for every SD (15.2 nmol/L) increase in childhood serum 25OHD levels.
[b]Odds ratio for every SD (13.6 nmol/L) increase in the mean of childhood and adulthood serum 25OHD levels. Missing data of adult 25OHD were imputed for 119 participants.
Bold values denote statistical significance, $p < .05$.
Model 1: unadjusted; Model 2: adjusted for age, sex, body mass index, month of blood taken, parental history of diabetes and fruit consumption; Model 3: model 2 + physical activity, smoking, systolic blood pressure, high-density lipoprotein cholesterol, triglycerides, insulin, vegetable consumption, socioeconomic status (the parental length of time spent in education). Model 4: model 3 + adult body mass index (missing data of adult body mass index were imputed for 25 participants).

Table 3. Odds ratio of T2DM and IFG in adulthood by quarters of youth 25OHD levels.

	Quartile 1 (n= 587)	Quartile 2 (n= 602)	Quartile 3 (n= 565)	Quartile 4 (n= 546)	p for trend
25OHD, mean (range) (nmol/L)	33 (12–41)	46 (42–51)	57 (52–62)	72 (63–122)	–
NFG, *n* (%)[a]	432 (73.6)	453 (75.2)	428 (75.8)	420 (76.9)	–
IFG, *n* (%)	116 (19.8)	125 (20.8)	120 (21.2)	112 (20.5)	–
Model 1	Reference	1.03 (0.77–1.37)	1.04 (0.78–1.39)	0.99 (0.74–1.33)	.99
Model 2	Reference	1.08 (0.80–1.46)	1.11 (0.81–1.51)	1.16 (0.83–1.60)	.39
Model 3	Reference	1.09 (0.80–1.47)	1.11 (0.81–1.53)	1.15 (0.83–1.61)	.40
Model 4	Reference	1.10 (0.81–1.50)	1.11 (0.81–1.54)	1.18 (0.84–1.66)	.37
T2DM, *n* (%)	39 (6.6)	24 (4.0)	17 (3.0)	14 (2.6)	–
Model 1	Reference	**0.59 (0.35–0.99)**	**0.44 (0.25–0.79)**	**0.37 (0.20–0.69)**	<.001
Model 2	Reference	0.71 (0.41–1.24)	0.54 (0.29–1.01)[b]	**0.49 (0.25–0.97)**	.02
Model 3	Reference	0.73 (0.42–1.28)	0.58 (0.31–1.11)[b]	0.52 (0.26–1.04)[b]	.04
Model 4	Reference	0.78 (0.44–1.38)	0.62 (0.32–1.21)	0.54 (0.26–1.11)[b]	.07

Values are odds ratio (95% confidence interval) unless otherwise stated.
NFG: normal fasting glucose; IFG: impaired fasting glucose (cut-off 5.6 mmol/L); T2DM: type 2 diabetes mellitus; 25OHD: 25-hydroxyvitamin D.
[a]Reference group for the outcome comparison.
[b]$p < .1$. Bold values denote statistical significance, $p < .05$.
Model 1: unadjusted; Model 2: adjusted for age, sex, body mass index, month of blood taken, parental history of diabetes and fruit consumption; Model 3: model 2 + physical activity, smoking, systolic blood pressure, high-density lipoprotein cholesterol, triglycerides, insulin, vegetable consumption, socioeconomic status (the parental length of time spent in education). Model 4: model 3 + adult body mass index (missing data of adult body mass index were imputed for 25 participants).

mean 25OHD. However, both associations remained statistically significant. Adding a squared term for 25OHD did not significantly improve the goodness of fit of the model (likelihood-ratio test, $p > .44$ for IFG and T2DM for both youth and the mean 25OHD), suggesting a linear association between 25OHD and risk of T2DM and IFG.

Tables 3 and 4 show the OR of T2DM and IFG in adulthood by quartile of youth and the mean 25OHD. Compared to the lowest quartile, a negative dose-dependent effect was observed with increasing 25OHD levels associated with a lower risk of T2DM while the strongest association was found in the Q3 for the mean 25OHD (P for trend = 0.001). These associations were attenuated after further adjustment for adult BMI but remained significant for mean 25OHD and marginally significant for youth 25OHD. Neither youth nor the mean 25OHD was associated with risk of IFG in adulthood (Tables 2–4). All multinomial logistic regression results remained similar in sensitivity

Table 4. Odds ratio of T2DM and IFG in adulthood by quarters of the mean of youth and adulthood 25OHD levels.

	Quartile 1 (n= 574)	Quartile 2 (n= 548)	Quartile 3 (n= 598)	Quartile 4 (n= 580)	p for trend
25OHD, mean (range) (nmol/L)	39 (15–44)	48.5 (44.5–52.4)	56.5 (52.5–62)	69 (62.5–124)	–
NFG, n (%)[a]	413 (72.0)	418 (76.3)	452 (75.6)	450 (77.6)	–
IFG, n (%)	120 (20.9)	104 (19.0)	133 (22.2)	116 (20.0)	–
Model 1	Reference	0.86 (0.64–1.15)	1.01 (0.76–1.34)	0.89 (0.67–1.18)	.68
Model 2	Reference	0.88 (0.65–1.20)	1.00 (0.75–1.34)	1.01 (0.75–1.37)	.75
Model 3	Reference	0.87 (0.64–1.19)	1.00 (0.75–1.35)	1.00 (0.74–1.36)	.78
Model 4	Reference	0.91 (0.66–1.25)	1.09 (0.80–1.48)	1.14 (0.83–1.57)	.26
T2DM, n (%)	41 (7.1)	26 (4.7)	13 (2.2)	14 (2.4)	–
Model 1	Reference	0.63 (0.38–1.04)[b]	**0.29 (0.15–0.55)**	**0.31 (0.17–0.58)**	<.001
Model 2	Reference	0.69 (0.41–1.18)	**0.33 (0.17–0.64)**	**0.41 (0.21–0.77)**	<.001
Model 3	Reference	0.70 (0.41–1.20)	**0.35 (0.18–0.69)**	**0.43 (0.22–0.82)**	.001
Model 4	Reference	0.80 (0.46–1.40)	**0.41 (0.20–0.81)**	0.55 (0.28–1.09)[b]	.02

NFG: normal fasting glucose; T2DM: type 2 diabetes mellitus; IFG: impaired fasting glucose (cut-off 5.6 mmol/L); 25OHD: 25-hydroxyvitamin D.
Values are odds ratio (95% confidence interval) unless otherwise stated. Missing data of adult 25OHD were imputed for 119 participants.
[a]Reference group for the outcome comparison.
[b]$p < 0.1$. Bold values denote statistical significance, $p < .05$.
Model 1: unadjusted; Model 2: adjusted for age, sex, body mass index, month of blood taken, parental history of diabetes and fruit consumption; Model 3: model 2 + physical activity, smoking, systolic blood pressure, high-density lipoprotein cholesterol, triglycerides, insulin, vegetable consumption, socioeconomic status (the parental length of time spent in education). Model 4: model 3 + adult body mass index (missing data of adult body mass index were imputed for 25 participants).

analyses by using 6.1 mmol/L as cut-off for IFG, except that the associations by quartiles of mean 25OHD were stronger and the P for trend became statistically significant (Supplemental Tables 2–4).

Discussion

The association between vitamin D and risk of developing T2DM has been investigated in adults but remains unknown between child and adult life. Our data, from a multi-centre population-based cohort with 31 years of follow-up, provide the first evidence that high youth 25OHD levels (as well as long-term 25OHD status between youth and adulthood) were associated with a lower risk of T2DM in adulthood. Each 15.2 nmol/L increment in youth serum 25OHD was associated with a 26% reduction in the odds of developing T2DM, which was independent of a number of confounding variables and other risk factors for T2DM (e.g. BMI). A similar magnitude of association was observed for long-term 25OHD status between youth and adulthood. These findings may have important clinical and public health implications as they suggest a potentially simple and cost-effective strategy for reducing adulthood risk of T2DM starting in an earlier stage of life and having a long-term maintenance. However, these findings need to be confirmed by more longitudinal studies and the causality need to be confirmed before making any recommendations of supplementing vitamin D in youth in order to reduce the risk of T2DM in adulthood.

Although the mechanism under which vitamin D may play a role in T2DM is currently unclear, it has been suggested that vitamin D may be associated with pancreatic beta-cell function and insulin secretion and sensitivity [22–25]. For instance, it has been shown that mice whose vitamin D receptors in pancreatic beta cells were removed had a reduction in maximum serum insulin levels of approximately 60% when blood glucose was elevated after oral or subcutaneous glucose loading compared with wild-type mice [24]. Human studies have also demonstrated low vitamin D status to be associated with decreased insulin sensitivity and increased insulin resistance [22,23,25]. Moreover, one potential explanation for our findings may be that a low serum 25OHD concentration is a marker of obesity, which is a known risk factor for T2DM. However, the associations between 25OHD and T2DM remained, though the effect sizes somewhat reduced, after we further adjusted for BMI in adulthood, suggesting a role of vitamin D independent of obesity.

The effect size of this study is of clinical importance. Compared with those in the lowest quartile of youth 25OHD, participants in the second, third and fourth quartiles of 25OHD had a 22, 38 and 46% lower odds, respectively, of developing T2DM, independent of many well-known risk factors, such as BMI, physical activity, serum insulin, systolic blood pressure and family history of diabetes. The effect sizes were largely comparable for the mean 25OHD between youth and adulthood, except for the third quartile, which was even greater (59% lower odds). In addition, we did not observe a threshold above which the association between 25OHD and risk of T2DM plateaued, suggesting an additional benefit of increased 25OHD levels.

Studies in adults have drawn conflicting conclusions on the association between vitamin D status and the risk of T2DM [13,14,26,27], particularly with regard to causality. A recent study of 31,040 white Danes aged

20–100 years demonstrated that in conventional analysis, participants who had a 20 nmol/L reduction in plasma 25OHD concentration was associated with an increased risk of T2DM (OR = 1.16, 95% CI: 1.08–1.25) [13]. In Mendelian randomization analysis that replaced 25OHD levels with genetic instrumental variables, the causal relationship was confirmed as determined by genetic variation in DHCR7 (related to endogenous production) (OR = 1.51, 95% CI: 0.98–2.33 for each 20 nmol/L reduction in 25OHD) but not CYP2R1 (related to liver conversion) (OR = 1.02, 95% CI: 0.75–1.37). However, the findings for DHCR7 needs to be replicated by independent data. In contrast, although another recent study showed a pooled relative risk (RR) of 1.21 (95% CI: 1.16–1.27) by meta-analysing 22 prospective observational studies (8492 cases and 89,698 non-cases) [14], a causal relationship was not confirmed in the Mendelian randomization analysis (OR = 1.01, 95% CI: 0.75–1.36 for each 25 nmol/L reduction in genetically determined 25OHD levels). However, these findings in adults may not be applicable in children as there are potential life course variations in the association between genetic variants and health outcomes. For example, it has been shown that the associations between gene variants, weight, BMI [28], and lipid level [29] varied across the life course, strengthening during childhood but weakening with increasing adult age.

A meta-analysis of 35 randomized controlled trials (RCTs) showed that vitamin D supplementation did not improve glucose homeostasis or prevent T2DM [26]. However, the majority of included studies were short-term (only four studies ≥2 years), had small sample size and moderate heterogeneity, which limit the conclusions. The only available prospective data in children, of which we are aware, is a birth cohort of 10,366 children who were followed up for 31 years, demonstrating that participants who had regular or irregular vitamin D supplementation had a lower risk of developing type 1 diabetes compared with those who did not receive supplementation (RR = 0.12, 95% CI: 0.03–0.51 and 0.16, 0.04–0.74 for regular and irregular supplementation, respectively) [30]. Nevertheless, direct evidence from RCTs with a long-term follow-up and larger sample size is needed to confirm our findings in children.

Surprisingly, neither youth 25OHD, nor the mean 25OHD from child to adult life, were associated with risk of developing IFG in adulthood. The potential mechanism for the different associations for IFG and T2DM is unclear. However, this may suggest the role of vitamin D in glycemic control is dependent on the glucose level, which is more effective in those at higher risk of developing T2DM. Indeed, data from controlled trials of vitamin D and/or calcium supplementation suggest that combined vitamin D and calcium supplementation may help prevent T2DM among those with IFG but not normal glucose tolerance [31].

The most important strength of this unique cohort study is its very long-term follow-up, which allows us to examine the association between youth vitamin D status and incidence of clinically diagnosed T2DM in adulthood. As with all studies, there are however some potential limitations. First, misclassification might exist in the type of T2DM as it has been shown that approximately 10% of typical T2DM of all ages is accounted for by latent autoimmune diabetes [32], for which we are not able to exclude from our analysis. Although the exact impact of this issue is unknown, it is possible that the association between vitamin D status and T2DM has been underestimated as it has been observed that vitamin D intake was associated with insulin resistance in patients with T2DM but not latent autoimmune diabetes [33]. Second, the 25OHD levels were analysed from serum samples that had been collected in 1980 and stored for 30 years in −20 °C, which may be inaccurate and erroneously low. However, this is unlikely to have introduced a systematic bias. Third, our results may be limited to Caucasians and may not be generalizable to other race/ethnic groups. Fourth, there were participants from the original study lost to follow-up but we have also previously shown that the follow-up cohort is representative of the original sample [34], though participants lost to follow-up had slightly lower 25OHD levels than those who were not (50.4 vs. 51.7 nmol/L, $p = .01$), suggesting our estimates may underestimate the true association between 25OHD and risk of T2DM. Finally, as we have discussed, causality cannot be inferred from our observational data. For example, although the measure of physical activity has been shown to be reliable and valid [20], our adjustment for physical activity might not exclude the possibility of residual confounding. Therefore, our results should be interpreted with caution before being confirmed.

In conclusion, high serum 25OHD status both in youth, and its long-term maintenance between youth and adulthood, was associated with a lower risk of developing T2DM in adulthood among Finnish children and adolescents aged 3–18 years old. This finding should be confirmed by other longitudinal studies and the causality needs to be confirmed in Mendelian randomization studies and RCTs of vitamin D supplementation.

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Disclosure statement

The authors declare that they have no conflict of interest to disclose.

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