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RAPID COMMUNICATIONS
CVD risk factors

Childhood 25-hydroxy-vitamin D levels predict early cardiovascular outcomes in adulthood: the Cardiovascular Risk in Young Finns Study

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Observational studies among adults have suggested that low serum vitamin D levels are related to increased cardiovascular events.[1] We have previously shown that low childhood vitamin D levels associate with increased adult carotid artery intima-media thickness,[2] a phenotype strongly associated with conventional risk factors. However, whether low vitamin D levels in childhood predict adult-onset cardiovascular events is unknown. Therefore, we describe the relationship between low childhood vitamin D levels and adult-onset atherosclerotic cardiovascular disease (ASCVD) events.

Subjects ($n = 3516$) were participants of the prospective cardiovascular risk in Young Finns study with serum concentrations of 25-hydroxy (OH) vitamin D measured in 2010 from stored frozen samples collected in 1980 when aged 3–18 years.[2] Conventional childhood risk factors such as body mass index (BMI), LDL cholesterol, HDL cholesterol, triglycerides, systolic blood pressure, consumptions of fruits, vegetables and fish, physical activity, socioeconomic status, and smoking were measured.[2] Linkages to national registries covering all Finnish citizens, including the Care Register for Health Care and the National Death Index, were used to ascertain ASCVD outcomes.[3] The Cox proportional hazard model was used to analyse the associations of varying cut points of low childhood 25-OH-vitamin D levels and adult ASCVD events, adjusted for age, sex, and childhood risk factors. There was no apparent sex * childhood vitamin D interaction ($P = 0.22$ for interaction term). Analyses were performed using SAS software version 9.4. Statistical significance was inferred at a two-tailed P-value of <0.05. All participants and/or their legal guardians gave written informed consent, and the study was conducted in compliance with the Declaration of Helsinki and approved by the Joint Commission on Ethics of the University of Turku and the Turku University Central Hospital.

The baseline age of the participants was 10.5 ± 5.0 years, and 50.9% of the participants were females. In childhood, mean BMI was 17.9 ± 3.1 kg/m^2, and mean 25-OH-vitamin D concentration was 51.3 ±

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Table 1 Hazard ratios and 95% confidence intervals for cardiovascular events in adulthood among individuals with low childhood 25-hydroxy-vitamin D levels according to different cut points

Cut-point level vitamin D (nmol/L) in 1980	Model A ($n = 3516$)		Model B ($n = 3194$)	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
31[a] ($n = 299$[b], 8.5% percentile point)	2.09 (1.25–3.50)	0.005	2.07 (1.15–3.73)	0.016
33 ($n = 385$, 10.9%)	1.77 (1.07–2.93)	0.025	1.76 (1.00–3.11)	0.049
35 ($n = 481$, 13.7%)	2.07 (1.30–3.29)	0.002	2.19 (1.30–3.69)	0.003
37 ($n = 610$, 17.3%)	1.77 (1.13–2.78)	0.013	1.84 (1.10–3.05)	0.019
39 ($n = 725$, 20.6%)	1.50 (0.96–2.34)	0.076	1.51 (0.91–2.49)	0.111
41 ($n = 879$, 25.0%)	1.49 (0.97–2.30)	0.069	1.50 (0.92–2.44)	0.104
43 ($n = 1058$, 30.1%)	1.36 (0.89–2.08)	0.152	1.36 (0.85–2.19)	0.201

Results are from Cox's regression analyses. Model A: Adjusted with age and sex. Model B: Adjusted with age, sex, and childhood measures of body mass index, LDL cholesterol, HDL cholesterol, triglycerides, systolic blood pressure, diet (fruit consumption, vegetable consumption, fish consumption), physical activity, smoking, parental school years, and study month.
[a]All different cut points for vitamin D (i.e. 31, 33, 35, 37, 39, 41, and 43 nmol/L) were utilized in separate models.
[b]*n*-values and percentages indicate those individuals meeting each cut point in Model A.

15.4 nmol/L. By 2018, 95 individuals (2.7%) had been diagnosed with ≥1 ASCVD event.[4] The median age at first ASCVD events was 47 years (range 31–56 years).[3] *Table 1* (Model A) shows baseline age- and sex-adjusted hazard ratios for adulthood ASCVD events according to different childhood 25-OH-vitamin D level cut points. Significant associations were found using cut points of 37, 35, 33, and 31 nmol/L. The results were similar in a multivariable model further adjusted for multiple conventional childhood factors (*Table 1*, Model B). These findings remained essentially similar after propensity score matching, adjustment for adult vitamin D levels or when using vitamin D deficiency (i.e. <30 nmol/L) as a cut point (data not shown).

The current study demonstrates that low 25-OH-vitamin D levels in childhood associate with adult-onset ASCVD events, even after adjustment for conventional childhood risk factors. Observational data among adults have previously shown that individuals with low vitamin D levels have an increased risk of cardiovascular events and mortality.[1] Recently, a prospective analysis of the Alpha Omega Cohort study (69 ± 5.6 years and 78% males), over a 14-year follow-up, demonstrated that vitamin D plays an independent and combined role with physical activity in secondary prevention of CVD risk and all-cause mortality in post-myocardial infarction patients.[5] However, the causal nature of such associations remains debated, as randomized trials and meta-analysis of the effects of vitamin D supplementation have not demonstrated a significant reduction in cardiovascular risk with increases in serum vitamin D.[6] One explanation is that the effects of vitamin D on cardiovascular risk may operate earlier in the life course.

In our analysis, over nearly four decades of follow-up, we showed that 25-OH-vitamin levels below 37 nmol/L in childhood were associated with adult-onset ASCVD events in analyses adjusted with multiple potential confounders. From a clinical perspective, our findings suggest that suboptimal vitamin D levels in childhood could be a risk marker for adult ASCVD. This is consistent with current dietary recommendations supporting the use of supplemental vitamin D during childhood, and US guidelines suggesting optimal vitamin D levels in childhood being ≥50 nmol/L.[7] However, despite of the contemporary supplement recommendations during our cohort follow-up, nearly one-fifth of our young study subjects did not reach vitamin D level cut point > 37 nmol/L, which suggests further need for optimization of vitamin D supplementation also in the paediatric population.

There are several potential pathophysiological mechanisms linking low childhood vitamin D with adult atherosclerosis. The vitamin D receptor is expressed in cells throughout the vascular system, and many of these are able to convert 25-OH-vitamin D to calcitriol, the active form of vitamin D. Calcitriol reduces inflammation, regulates the renin–angiotensin–aldosterone system, and inhibits proliferation of vascular smooth muscle,[8] and in addition, vitamin D supplementation has been associated with slower epigenetic aging.[9]

The strengths of this study include the large, randomly selected cohort prospectively followed from childhood, the availability of childhood 25-OH-vitamin D levels, extensive data on other factors associated with atherosclerosis, and the system by which ASCVD events are ascertained in Finland. However, the potential for measurement error in baseline 25-OH-vitamin D levels is a limitation; we analysed childhood 25-OH-vitamin D from serum samples that had been collected in 1980 and stored for 30 years in −20°C. Thus, it is possible that the levels of 25-OH-vitamin D from stored samples may be inaccurate and erroneously low, although this would not have introduced a systematic bias,[3] and vitamin D is considered stable under long-term storage.[10] Our ethnically homogenous study population may limit the generalizability of our findings to Caucasian/White European subjects. We also recognize that the association does neither directly report causality. In addition, the study subjects within our cohort are still relatively young, and many participants have not yet reached the age at which ASCVD incidence sharply increases (typically >60–70 years of age), which warrants the need for continual follow-up studies when ASCVD events accumulate gradually. We had neither recorded bone metabolism disorders, calcium or phosphorus levels at baseline.

In summary, our data suggest that low 25-OH-vitamin D levels in childhood are related to higher future risk for early-onset ASCVD. The results may thus have implications in future prevention of ASCVD, and easy and cost-beneficial CVD risk mitigation via supporting optimized 25-OH-vitamin D supplementation during childhood.

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Author contributions

All authors contributed to the conception, design, or acquisition of the work. J.N., T.T.L., M.J., and O.R. contributed to the analysis and interpretation of data for the work. J.N. and T.T.L. drafted the manuscript. J.N., T.T.L., M.J., and O.R. critically revised the manuscript. All gave final approval and agreed to be accountable for important intellectual content of work ensuring integrity and accuracy.

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Conflict of interest: none declared.

Data availability

The dataset supporting the conclusions of this article was obtained from the Cardiovascular Risk in YFS after submission and approval of our study plan by the YFS coordinators. The YFS dataset comprises health-related participant data, and their use is therefore restricted under the regulations on professional secrecy (Act on the Openness of Government Activities, 612/1999) and on sensitive personal data (Personal Data Act, 523/1999, implementing the EU Q9 data protection directive 95/46/EC). Due to these legal restrictions, the data from this study cannot be stored in public repositories or otherwise made publicly available. However, data access may be permitted on a case-by-case basis upon request only. Data sharing outside the group is performed in collaboration with the YFS group and requires a data-sharing agreement. Investigators can submit an expression of interest to the chairman of the publication committee (Prof. Mika Kähönen, Tampere University, Finland).

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