European Journal of Clinical Nutrition (2018) 72:1700–1708
https://doi.org/10.1038/s41430-018-0157-3

ARTICLE

Minerals, trace elements, Vit. D and bone health

Familial clustering of vitamin D deficiency via shared environment: The Korean National Health and Nutrition Examination Survey 2008–2012

Namki Hong[1,2] · Young Ki Lee[1] · Yumie Rhee[1]

Received: 4 February 2018 / Revised: 23 February 2018 / Accepted: 28 February 2018 / Published online: 18 April 2018

Abstract

Background/objectives Familial correlation of serum 25-hydroxyvitamin D concentration (25(OH)D) was reported in twin- or parent-offspring studies. However, data on relative contribution of environmental factors on familial clustering of 25(OH)D in extended families are limited.

Subjects/methods We performed cross-sectional study using data from the Korean National Health and Nutrition Examination Survey (KNHANES) 2008–2012. Familial correlations of 25(OH)D were estimated in 28,551 subjects from 10,882 families. The variance component method was used to assess the relative contribution of additive genetic or environmental contributions to the variation in 25(OH)D level. Logistic regression models with interaction term were built to evaluate the differential influence of parental vitamin D status on the adolescents and adults offspring.

Results Mean serum 25(OH)D concentration of subjects was 44.6 nmol/L (vitamin D insufficiency (30–50 nmol/L), 51%; vitamin D deficiency (< 30 nmol/L), 17%). Familial clustering explained 40% of the total variation in 25(OH)D. In the variance component model, 4%, 39%, and 57% of the variation in serum 25(OH)D level was attributed to additive genetic, common shared environmental, and individual environmental factors, respectively. The odds of vitamin D deficiency in offspring with both parents with vitamin D deficiency compared with those with both parents with sufficient vitamin D levels was greater in adolescents (< 19 years) than in adults (≥ 19 years) (odds ratio = 41.1 vs. 12.5; p for interaction = 0.03).

Conclusions We found a familial clustering of vitamin D deficiency in a large family-based cohort. Parental influence on vitamin D status of offspring was greater in adolescents than in adults.

Introduction

Vitamin D deficiency is a well-established modifiable risk factor for the progression of osteoporosis and fragility fractures [1]. Moreover, recent studies have reported that low vitamin D level is associated with a wide range of non-communicable diseases such as diabetes, heart failure, hypertension, obesity, autoimmune diseases, infertility, and cancer [2–7]. As vitamin D deficiency is often asymptomatic, establishing an efficient strategy to identify individuals at risk of vitamin D deficiency would have clinical impact, particularly in a population with prevalent low vitamin D levels [8].

Both genetic and environmental factors are known to influence vitamin D status. Heritability of serum 25-hydroxyvitamin D (25(OH)D) level was reported from twin studies, although the range varied significantly between about 20% and 70% [9–12]. Candidate gene studies and genome-wide association studies have identified susceptibility genes such as *GC*, *CYP2R1*, *CYP24A1*, and *DHCR7* in large population cohorts [13]. Meanwhile, several environmental factors including obesity, low sunlight exposure, and dietary pattern have been identified as potent modifiers of circulating 25(OH)D levels in humans,

These authors contributed equally: Namki Hong, Young Ki Lee.

Electronic supplementary material The online version of this article (https://doi.org/10.1038/s41430-018-0157-3) contains supplementary material, which is available to authorized users.

✉ Yumie Rhee
yumie@yuhs.ac

[1] Department of Internal Medicine, Severance Hospital, Endocrine Research Institute, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul, Republic of Korea

[2] Graduate School, Yonsei University College of Medicine, Seoul, Republic of Korea

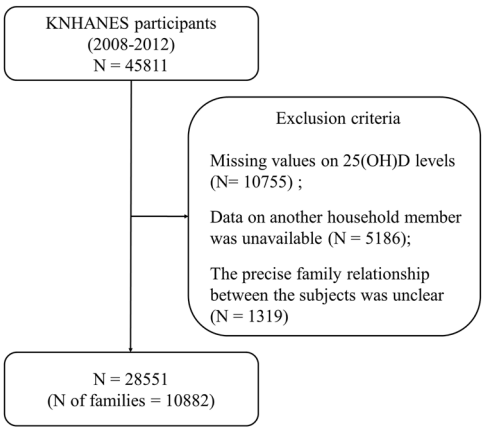

Fig. 1 Flow chart of study population selection, and inclusion and exclusion criteria

particularly in vulnerable populations such as adolescents and the elderly. Thus, if vitamin D deficiency is identified in a member of the family, other family members in the same household might also be at risk for low vitamin D status. The risk might differ between family relations according to the relative contribution of shared environment and genetic components. Previous studies based on community-dwelling populations suggested significant familial association of vitamin D status between parents and children or adolescent offspring across different ethnicities [14–16]. However, there are limited data on the association of vitamin D status between other important family relations, such as spouses. Furthermore, the relative contribution of common shared environmental factors and genetic determinants on circulating 25(OH)D level remains controversial in previous family-based studies, which were mainly performed in Western populations [17–20].

In this study, we aimed to assess the relative contribution of additive genetic and environmental components on serum 25(OH)D level by the variance components method in a nationwide family-based cohort. Further, we evaluated the association of vitamin D status of the index individual with prevalent vitamin D deficiency of each family member, including spouse, offspring, sibling, and grand-offspring. The additive effects of paternal and maternal vitamin D status on offspring according to the age of offspring were also investigated.

Methods

Study subjects

This study was based on data from the Korean National Health and Nutrition Examination Survey (KNHANES) (IV-2, 3, and V), conducted from 2008 to 2012. The KNHANES is a nationwide cross-sectional survey performed by the Division of Chronic Disease Surveillance, Korea Centers for Disease Control and Prevention (CDC), which assessed the health, nutritional status, and socioeconomic status of the non-institutionalized civilian population of South Korea. Subjects were selected using a stratified multistage clustered probability sampling design. A total of 56,846 individuals were sampled and 45,811 of them participated in the survey (Fig. 1). Laboratory tests were performed for individuals aged 10 years or older, and serum 25(OH)D was measured in 35,056 subjects. Family relationships between household members were retrieved from the raw data. Families, including at least two family members with serum 25(OH)D measurements and whose family relationships could be accurately identified were selected for the study. After the selection process, a total of 28,551 subjects from 10,882 families were included in our study. Detailed information on family structures are as follows: 9644 subjects from 4822 families comprised husband and wife, 304 subjects from 148 families consisting of siblings only, 14,852 subjects from 4849 families with both parents and offsprings, 1506 subjects from 470 families with parents, offsprings, and spouses of offsprings altogether, 471 subjects from 178 families with grandparents and grand-offsprings, and 1774 subjects from 415 families comprising all three generations. As the primary sampling unit of the KNHANES was a household, we assumed that all family members in this study lived together. This study was approved by the Institutional Review Board of Korea CDC and Prevention (No. 2008-04EXP-01-C, 2009-01CON-03-2C, 2010-02CON-21-C, 2011-02CON-06-C, and 2012-01EXP-01-2C) and all study participants provided written informed consent.

Measurement of serum vitamin D

Approximately 15 mL of blood samples from individual subjects were collected during the survey. The blood samples were properly processed, immediately refrigerated in the mobile examination centers, and transported in cold storage to the testing facility. Serum 25(OH)D level was measured using a gamma counter (1470 Wizard, Perkin-Elmer, Finland) with a radioimmune assay kit (DiaSorin, Stillwater, Minnesota, USA). The Institute of Medicine (IOM) and the Endocrine Society defined vitamin D deficiency as having serum 25(OH)D levels < 30 nmol/L and < 50 nmol/L, respectively [21–24]. In this study, for the main analysis, serum vitamin D status was categorized as follows according to IOM definition: deficiency (serum 25(OH)D < 30 nmol/L); insufficiency (serum 25(OH)D between 30 and 49 nmol/L), and sufficiency (serum 25(OH)D ≥ 50 nmol/L). Sensitivity analysis according to the Endocrine Society definition (sufficiency: serum 25(OH)D ≥ 75; insufficiency: serum 25(OH)D between 50 and 74 nmol/L; deficiency:

serum 25(OH)D <50 nmol/L) was performed to test the robustness of findings [22–24].

Assessment of familial clustering, heritability and shared environmental influences

To estimate how much of the overall variation of serum 25 (OH)D level is simply explained by familial clustering, intraclass correlation (ICC) was calculated from the multilevel linear mixed model with family as a random variable as follows: ICC = between-family SD^2/(between-family SD^2 + within-family SD^2). To estimate the relative contributions of genetic (heritability in a narrow sense) and shared environmental influences on potential clustering of serum 25(OH)D concentrations among family members, we applied the variance components method using the Sequential Oligogenic Linkage Analysis Routines (SOLAR-Eclipse) software package version 8.1.1 (http://solar-eclipse-genetics.org/index.html) [25]. The phenotypic variance (σ^2_p) of serum 25(OH)D levels was divided into three factors: additive genetic components (A, the total sum of the additive effects of genes that influence the serum 25 (OH)D levels), common environmental components (C, the influences of environmental factors shared by family members, such as similar diet patterns and family outing activities), and unique environmental components (E, the influences of individual environmental factors different among family members, such as differences regarding clothing, sunscreen use, and vitamin supplements use). Initially, the full ACE model was fit to the data and then compared with the three nested submodels AE, CE, or E. The statistical significance of each component A or C was assessed by testing the deterioration of the model fit in the submodels where each element was removed from the fully specified ACE model, using standard likelihood ratio tests. If specific components A or C could be removed from a full model without significant deterioration of the model fit, simpler models that contain only essential components were assumed to be superior, according to the principle of parsimony. Another statistic, Akaike's information criterion (AIC; $\chi^2 - 2 \times$ degrees of freedom), was also used to determine the best fitting model [26]. Serum 25(OH)D was analyzed as a continuous variable for estimating heritability with adjustment for age and sex, and estimates of variance components A, C, and E were described as estimates ± SEs.

Statistical analyses

Data were presented as mean ± SD and number (%) for continuous and categorical variables, respectively. Partial correlation coefficients for serum 25(OH)D level were estimated in spouse–spouse, parent–offspring, sibling–sibling, and grandparent–grand-offspring pairs, by calculating Pearson's correlation coefficients of residuals from linear regressions of 25(OH)D on age and sex [27]. Serum 25(OH)D was assumed to have normal distribution. To assess the odds of vitamin D deficiency in other family members (a spouse, an offspring, a sibling, or a grand-offspring) according to the vitamin D status of a particular family member (an index family member), a multiple logistic regression model was built in each type of family relation (spouse–spouse, parent–offspring, sibling–sibling, or grandparents–offspring). When the power and a was set at 0.9 and 0.05 (one-sided), respectively, 886 subjects would be needed to detect an odds ratio (ORs) of 1.8 for an individual with vitamin D deficiency, which was lower than minimum number of subjects ($n = 1002$) in subgroup analysis. To assess the additive effect of paternal and maternal vitamin D status on their offspring, ORs for vitamin D deficiency in offspring according to vitamin D status of both parents were evaluated in a subset of 3407 families with available serum 25(OH)D measurements of father, mother, and at least one of their offspring. Also, mean serum 25 (OH)D levels in offspring was compared according to vitamin D status of parents using analysis of variance with unequal variances (Welch's test) with Bonferroni correction. All tests were two-sided and a value of $p < 0.05$ was considered statistically significant. All statistical analyses were performed using STATA 14.0 (Stata Corp., College Station, TX, USA).

Results

Baseline characteristics

A total of 28,551 subjects from 10,882 families were analyzed (Table 1). The mean age of the study subjects was 43

Table 1 Baseline characteristics of study population ($N = 28,551$)

Characteristics	Value
Age, years	43 ± 19
Male sex	13,343 (47)
Serum 25(OH)D, nmol/L	45 ± 16
Vitamin D status	
Sufficiency (≥ 50 nmol/L)	9076 (32)
Insufficiency (30–49 nmol/L)	14,441 (51)
Deficiency (< 30 nmol/L)	5034 (17)
Body mass index, kg/m^2	23 ± 4
Residential area	
Urban	22,490 (79)
Rural	6053 (21)

25(OH)D 25-hydroxyvitamin D. Values are presented as mean ± SD or number (%)

Table 2 Correlations of 25(OH)D level in family relations

Family relations	Pair count	Estimated correlation coefficient	*P*-value
Spouses	8710	0.41 (0.39–0.43)	< 0.001
Parent–offspring	13,420	0.38 (0.36–0.39)	< 0.001
Father–son	2891	0.41 (0.38–0.44)	< 0.001
Mother–son	4242	0.36 (0.34–0.39)	< 0.001
Father–daughter	2663	0.35 (0.31–0.38)	< 0.001
Mother–daughter	3624	0.39 (0.36–0.42)	< 0.001
Sibling	2590	0.51 (0.47–0.53)	< 0.001
Grandparents–offspring	1002	0.28 (0.22–0.33)	< 0.001

25(OH)D, 25-hydroxyvitamin D.

years and 47% were male. The mean serum 25(OH)D concentration was 45 nmol/L and vitamin D insufficiency and deficiency were found in 51% and 17% of the study subjects, respectively. Only 5% of the study subjects had serum 25(OH)D levels > 75 nmol/L. Most of the subjects (72%) had body mass index within the normal range (< 25 kg/m^2).

Correlation of serum 25(OH)D level among family members

In the overall study population, familial clustering accounted for 40% of the total variation in serum 25(OH)D level (ICC 0.40, between-family SD 3.91, within-family SD 4.79). Table 2 shows the estimated correlation coefficient for serum 25(OH)D level for each pair of relations within the family. The correlation coefficients between spouses (who did not share genetic component) and between siblings were estimated to be 0.41 (95% confidence interval (CI): 0.39–0.43) and 0.51 (95% CI: 0.47–0.53), and estimated correlation coefficients between parent and offspring varied from 0.35 (father and daughter) to 0.41 (father and son). The correlation between grandparents and grandoffspring (0.28, 95% CI: 0.22–0.33) was positive but relatively weak.

Relative contribution of genetic and environmental influences

To estimate the relative contribution of genetic and environmental influences for determining serum 25(OH)D level, we first built the ACE model with all three components and then tested that model against nested submodels AE, CE, and E (Table 3). In the ACE model, additive genetic components (A) and common environmental components (C) explained 4% and 39% of the variation in 25(OH)D levels, respectively. The remaining 57% was explained by unique individual environmental influences different among family members (E). Removal of A or C components from the ACE model significantly worsened the model fit ($p = 0.02$ and $p < 0.001$, respectively), indicating ACE model is optimal. The model selection by AIC also yielded the same result. To evaluate the influence of seasonal variation on the result, we performed additional subgroup analyses of 5581 subjects for whom the seasonal information at the time of 25(OH)D measurements was available. In all seasons, the CE model was selected as the best fitting model. Shared environments (C) consistently accounted for variations in 25(OH)D levels of up to 24%, 41%, 33%, and 33% in spring, summer, autumn, and winter, respectively.

Risk of vitamin D deficiency according to vitamin D status of an index family member

The ORs for the presence of vitamin D deficiency in family members according to the vitamin D status of an index family member are presented in Fig. 2. Vitamin D insufficiency or deficiency of index family member was associated with increased odds of vitamin D deficiency in other family members in a dose–response manner. For example, if a man or a woman was diagnosed with vitamin D insufficiency or deficiency, his/her spouse would have 3.0- to 8.7-fold increased odds of having vitamin D deficiency compared with those who have spouses with sufficient vitamin D levels. A consistent association was observed across each family relationship including spouse–spouse, parent–offspring, sibling–sibling, and grandparent–grandoffspring pairs. The results were consistent when vitamin D status was defined using the Endocrine Society threshold (Supplementary Figure 2).

Additive effect of parental vitamin D status on offspring

A total of 3407 families with complete data of 25(OH)D measurements in both parents and at least one offspring (3407 mothers, 3407 fathers, and 5059 offspring) were analyzed to evaluate the additive effect of maternal and paternal vitamin D status on offspring. In Fig. 3, the ORs for the presence of vitamin D deficiency in offspring were plotted against nine combinations of paternal and maternal vitamin D statuses. The prevalence of vitamin D deficiency varied among groups from 8% in offspring of both parents with sufficient vitamin D level to 58% in offspring with both parents with vitamin D deficiency. The ORs for vitamin D deficiency in offspring were additively increased as the vitamin D status of father and mother deteriorated (Fig. 3a). When both parents had vitamin D deficiency, the odds for the presence of vitamin D deficiency in offspring was 20.2-fold higher than the reference group with both parents with sufficient vitamin D levels (OR 20.2, 95% CI:

Table 3 Relative contribution of genetic and environmental influences on individual serum 25(OH)D levels

Model	A	C	E	−2 Log-likelihood statistics	χ^2	Δdf	AIC[a]	*P*-value[b]
ACE	**0.04 ± 0.02**	**0.39 ± 0.01**	**0.57 ± 0.02**	128,803				
AE	0.62 ± 0.01		0.38 ± 0.01	130,613	1810	1	1808	<0.001
CE		0.40 ± 0.01	0.60 ± 0.01	128,807	4	1	2	0.02
E			1.00	132,445	3642	2	3638	<0.001

A additive genetic components, *AIC* Akaike's information criterion, *C* common environmental components, *df* degrees of freedom, *E* unique environmental components, *25(OH)D* 25-hydroxyvitamin D

[a] Models with the lowest AIC were preferred, and the reference model (ACE model) was the best model, because all AIC values of AE, CE, and E models were larger than zero. [b] *P*-values were obtained from a likelihood ratio test of the AE, CE, or E model compared with the ACE model. Significant *P* value ($p < 0.05$) indicates that the excluded components did have a significant role in explaining the data. Estimates were described as mean ± SEs. The best fitting model is in boldface

13.5–30.0, $p < 0.001$). When offsprings were further grouped into adolescents (younger than 19 years) and adults (19 years or older), the ORs for vitamin D deficiency increased more steeply in adolescent offspring in association with parental vitamin D status compared with adult offspring. It was more evident in offspring with both parents with vitamin D deficiency (Fig. 3b, c; OR = 41.1 in adolescents and 12.5 in adults, $p < 0.001$ respectively; p for interaction = 0.03), suggesting potential differences in the magnitude of shared environmental influences in the household between adolescents and adults groups. When serum 25(OH)D level was compared as continuous variable (Supplementary Figure 1), offspring with both parents with vitamin D deficiency had lower mean 25(OH)D level (30 nmol/L) compared with the reference group (52 nmol/L, $p < 0.001$), which was consistent with the results from the categorical outcomes. Similar results were found when vitamin D deficiency was defined as < 50 nmol/L according to Endocrine Society cutpoint (Supplementary Figure 3).

Discussion

Our study investigated the familial correlations, the relative contribution of additive genetic components and common shared environmental factors, and additive effect of parental vitamin D status on offspring in a nationwide survey comprising 10,882 families. About 40% of the total variation in 25(OH)D levels among the study participants was explained by familial clustering. Using the variance components model, we found that additive genetic components and common shared environment among family members explained 4% and 39% of the variation in serum 25(OH)D level, respectively. Within the family, a positive correlation was observed not only between members sharing genetic information (parent–offspring or grandparent–grand-offspring) but also between members who do not share genetic information (spouse pair). The identification of vitamin D insufficiency or deficiency in an index member of the family was associated with higher odds of the presence of vitamin D deficiency in family members including their spouse. An additive increase in the risk of vitamin D deficiency in offspring was observed according to a combination of paternal and maternal low vitamin D status, particularly in adolescents.

As previously reported, vitamin D insufficiency and deficiency were prevalent in this Korean nationwide cohort [28]. The mean value of serum 25(OH)D level in the study participants was 45 nmol/L, which was relatively lower than the reported mean value of 25(OH)D from nationally representative cohorts from the United States (NHANES 2001–2006, 55 nmol/L) and Canada (CHMS 2007–2009, 68 nmol/L) [29, 30]. In a study of 200 families performed in Denmark, 27% (up to 40% when confined to children aged 4–17 years) of the total variation in serum 25(OH)D level was attributed to familial clustering [14]. In our study, familial clustering explained 40% of the total variation in serum 25(OH)D level, which was similar to the value reported from the Danish families [14]. A positive correlation of vitamin D level was found in all pairs of family relations, and the OR for having vitamin D deficiency in each family member increased in a dose–response manner according to the vitamin D status of the index family member. In line with these findings, a strong familial association of bone mineral density between parents and offspring was also reported from the KNHANES [27]. Given the direct influence of vitamin D status on bone metabolism, it is conceivable that the familial association of bone mineral density might be at least partly attributable to the vitamin D clustering observed in our study, although further studies are needed to confirm this hypothesis [1].

Environmental factors such as diet, outdoor physical activity, dress patterns, and the season are well known to affect vitamin D status [9, 14, 20]. According to family-based studies, there is a strong tendency for family members to share similar lifestyles or behavioral habits including

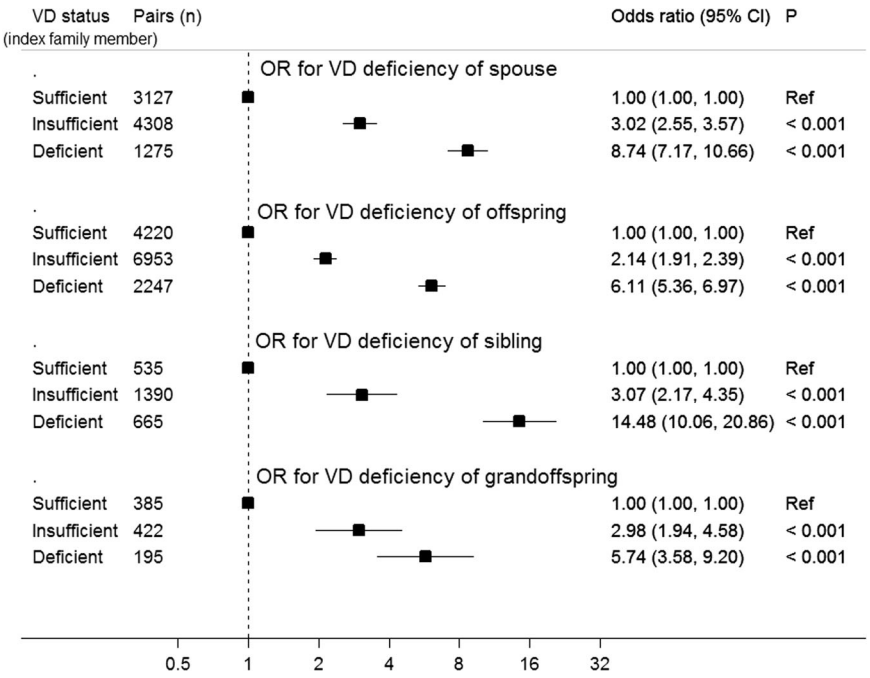

Fig. 2 Age- and sex-adjusted odds ratios (ORs) for vitamin D deficiency (serum 25(OH)D levels < 30 nmol/L) in family members according to vitamin D status of index subjects. ORs are presented with their respective 95% confidence intervals

milk consumption, smoking, the pattern of alcohol intake, and physical activity, which is called "familial resemblance." [15, 31, 32] In our study, shared environmental factors explained about 39.1% of the total variation in serum 25(OH)D level, second to unique individual environmental factors. Interestingly, a moderately positive correlation between serum 25(OH)D was also observed between spouse pairs who did not share genetic information, supporting the substantial role of shared environmental factors. A previous study of 95 families also reported a modestly positive correlation between spouse pairs, followed by parent-offspring pairs [17]. Assortative mating (i.e., correlation of vitamin D at the time of mating) could be another explanation for the positive correlation between spouse pairs, although the effect of shared environmental factors was significant in the variance component model in this study [17]. Heritability and influence of shared environmental factors might vary by season. A study of White, male twins showed that environmental conditions predominated over genetic factors in summer, whereas 25(OH)D level was heritable during the winter season only [9]. In the subgroup analysis, we also found a similar pattern that the proportion of the variation explained by shared environmental factors peaked during the summer up to 41%, and gradually decreased across the fall and winter, and reached trough level (24%) during spring. As analysis regarding seasonal variation was performed in a subset of the population with available data, decreased sample size could be one explanation for the attenuated statistical significance of additive genetic components in each season.

The genetic influence in the total variation in 25(OH)D levels from the previous twin- and family-based studies showed discordant results, varying from about 0% to 80% [9–12, 14, 17–20, 33, 34]. In our study, the contribution of additive genetic components in the total variation in 25(OH)D levels was statistically significant but relatively small (3.7%) compared with previous reports. This difference might be at least partly explained by differences in study design and population demographics of the study participants. Twin studies are known to tend to report a higher heritability, in part due to the accentuated environmental similarity in monozygotic twins than dizygotic twins [35]. Given that most of the previous studies were performed in the Western population, ethnicity might affect the degree of genetic influence on vitamin D status [36]. We analyzed extended familial relations including spouses and grandparents and grand-offspring pairs in this study, which might influence the proportion of 25(OH)D variance explained by the additive genetic components. Genetic predictors of vitamin D status from genome-wide association studies in Caucasians explained about 1–9% of the total variation in serum 25(OH)D level [13, 19, 37]. An intriguing finding was that in a large genome-wide association study, high genotype score conferred about a two-fold increase in the risk of vitamin D insufficiency (defined as 25(OH)D < 50 nmol/L or < 75 nmol/L), whereas high genotype score was associated with a 1.4-fold increased risk of threshold using < 25 nmol/L [13]. This might suggest the potential contribution of environmental factors to the severe vitamin D deficiency, although further studies are needed to validate these findings.

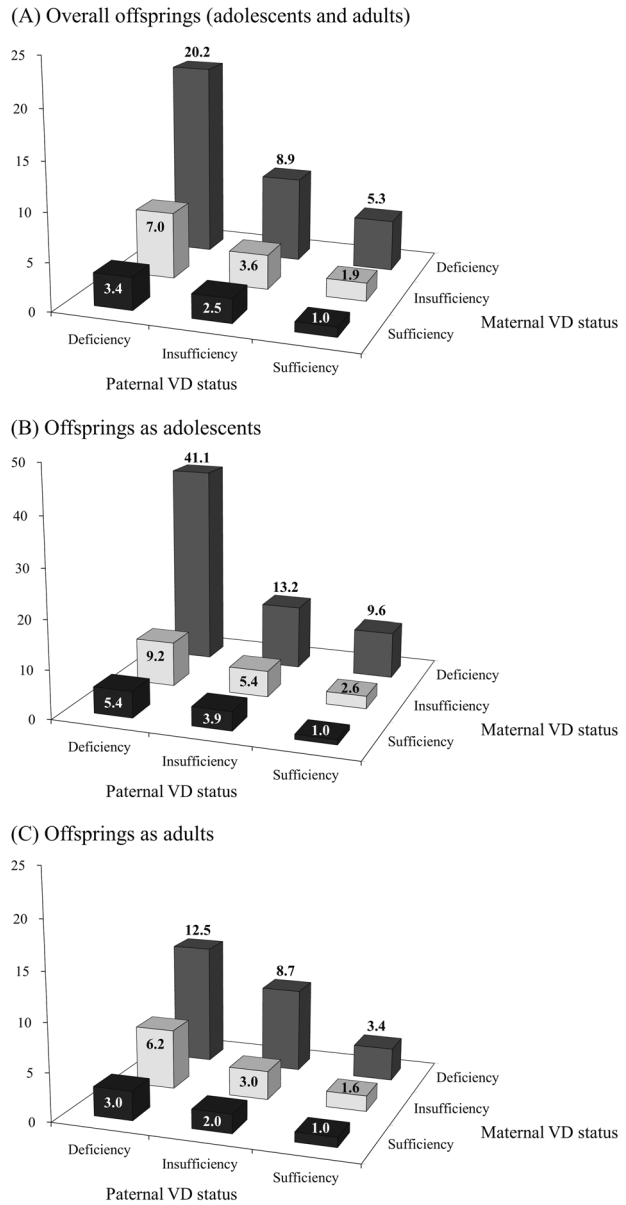

Fig. 3 Odds ratios (ORs) for vitamin D deficiency (serum 25(OH)D levels < 30 nmol/L) **a** in all offspring, **b** in adolescent (age between 10 and 18 years) offspring, and **c** in adult (age 19 years or more) offspring according to the vitamin D status of parents after adjustment for age and sex of offspring ($p < 0.05$ in all cases). The effect of parental vitamin D status on vitamin D deficiency in their offspring was greater among adolescent offspring compared with adult offspring (OR = 41.1, 95% CI: 21.2–79.3 in adolescents vs. OR = 12.5, 95% CI: 6.8–22.8 in adult offspring; p for interaction = 0.03)

We observed that the OR for vitamin D deficiency was additively increased according to the combination of paternal and maternal low vitamin D status, suggesting a synergistic effect of both genetic and environmental factors. Of note, low vitamin D status of parents had greater impact on adolescent offspring (younger than 19 years) than adults (19 years or older). Adolescents are more likely to share similar activities and dietary habits than adults within a family, suggesting the possible greater influence of shared environment of a family on adolescents. Given the benefit of vitamin D supplement in adolescents at risk of low vitamin D status, familial screening for adolescent offspring of patients with low vitamin D level would be one strategy to facilitate intervention on adolescents with vitamin D deficiency [38]. Whether any interventions to correct parental vitamin D would improve the vitamin D status of offspring, particularly adolescents, needs to be further investigated.

Our study has some limitations. Inference of causality could not be made due to the cross-sectional design of the study. As the food composition database used in the KNHANES did not include vitamin D, vitamin D intakes via foods or supplements could not be assessed. Geographic latitude data were not available on an individual level, although the study population was selected from a relatively narrow range of 34° N to 38° N. Furthermore, no significant influence of latitude on 25(OH)D concentration was observed in a twin study population from latitude 21° to 49° N, except in one living at 61° N [9]. As all of our study participants were Asian, our results might not be generalizable to different races or ethnic groups. Although radioimmunoassay is a widely used method for measurement of serum (25(OH)D) concentration, limited accuracy and reproducibility of this method has been recognized largely due to immunoassay cross-reactivity and lack of reference methods [39]. Further studies with liquid chromatography tandem mass spectrometry method might provide more specific determination of serum 25(OH)D level.

In conclusion, we found strong familial association of vitamin D deficiency in a large, nationally representative family cohort in a vitamin D deficiency-prevalent area. Family-based screening for vitamin D deficiency in patients with low vitamin D status might have clinical implications as a preemptive strategy for identifying individuals, adolescents in particular, at the risk of poor bone health.

Acknowledgements NH, YKL, and YR designed research. NH and YKL conducted research and analyzed data. NH, YKL, and YR wrote the paper. YR had primary responsibility for final content. All authors read and approved the final manuscript. This study was not funded by any industrial, commercial, or governmental sources.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Dawson-Hughes B, Bischoff-Ferrari HA. Therapy of osteoporosis with calcium and vitamin D. J Bone Miner Res. 2007;22(Suppl 2): V59–63. https://doi.org/10.1359/jbmr.07s209

2. Holick MF. Vitamin D deficiency. N Engl J Med. 2007;357:266–81. https://doi.org/10.1056/NEJMra070553
3. Muscogiuri G. New light on an old vitamin: The role of the sunshine vitamin D in chronic disease. Rev Endocr Metab Disord. 2017;18:145–7. https://doi.org/10.1007/s11154-017-9427-y
4. Savastano S, Barrea L, Savanelli MC, Nappi F, Di Somma C, Orio F, et al. Low vitamin D status and obesity: Role of nutritionist. Rev Endocr Metab Disord. 2017;18:215–25. https://doi.org/10.1007/s11154-017-9410-7
5. Muscogiuri G, Altieri B, de Angelis C, Palomba S, Pivonello R, Colao A, et al. Shedding new light on female fertility: The role of vitamin D. Rev Endocr Metab Disord. 2017;18:273–83. https://doi.org/10.1007/s11154-017-9407-2
6. Ullah MI, Koch CA, Tamanna S, Rouf S, Shamsuddin L. Vitamin D deficiency and the risk of preeclampsia and eclampsia in Bangladesh. Horm Metab Res. 2013;45:682–7. https://doi.org/10.1055/s-0033-1345199
7. Ullah MI, Uwaifo GI, Nicholas WC, Koch CA. Does vitamin d deficiency cause hypertension? Current evidence from clinical studies and potential mechanisms. Int J Endocrinol. 2010;2010:579640. https://doi.org/10.1155/2010/579640
8. Holick MF. The vitamin D deficiency pandemic: approaches for diagnosis, treatment and prevention. Rev Endocr Metab Disord. 2017;18:153–65. https://doi.org/10.1007/s11154-017-9424-1
9. Karohl C, Su S, Kumari M, Tangpricha V, Veledar E, Vaccarino V, et al. Heritability and seasonal variability of vitamin D concentrations in male twins. Am J Clin Nutr. 2010;92:1393–8. https://doi.org/10.3945/ajcn.2010.30176
10. Snellman G, Melhus H, Gedeborg R, Olofsson S, Wolk A, Pedersen NL, et al. Seasonal genetic influence on serum 25-hydroxyvitamin D levels: a twin study. PLoS ONE. 2009;4:e7747. https://doi.org/10.1371/journal.pone.0007747
11. Arguelles LM, Langman CB, Ariza AJ, Ali FN, Dilley K, Price H, et al. Heritability and environmental factors affecting vitamin D status in rural Chinese adolescent twins. J Clin Endocrinol Metab. 2009;94:3273–81. https://doi.org/10.1210/jc.2008-1532
12. Hunter D, De Lange M, Snieder H, MacGregor AJ, Swaminathan R, Thakker RV, et al. Genetic contribution to bone metabolism, calcium excretion, and vitamin D and parathyroid hormone regulation. J Bone Miner Res. 2001;16:371–8. https://doi.org/10.1359/jbmr.2001.16.2.371
13. Wang TJ, Zhang F, Richards JB, Kestenbaum B, van Meurs JB, Berry D, et al. Common genetic determinants of vitamin D insufficiency: a genome-wide association study. Lancet. 2010;376:180–8. https://doi.org/10.1016/s0140-6736(10)60588-0
14. Madsen KH, Rasmussen LB, Mejborn H, Andersen EW, Molgaard C, Nissen J, et al. Vitamin D status and its determinants in children and adults among families in late summer in Denmark. Br J Nutr. 2014;112:776–84. https://doi.org/10.1017/S0007114514001263
15. Park SI, Rhee Y, Lim JS, Park S, Kang SW, Lee MS, et al. Right adrenal venography findings correlated with C-arm CT for selection during C-arm CT-assisted adrenal vein sampling in primary aldosteronism. Cardiovasc Interv Radiol. 2014;37:1469–75. https://doi.org/10.1007/s00270-013-0820-y
16. Robinson SL, Ramirez-Zea M, Roman AV, Villamor E. Nine Mesoamerican Countries Metabolic Syndrome Study G. Correlates and family aggregation of vitamin D concentrations in school-aged children and their parents in nine Mesoamerican countries. Public Health Nutr. 2017;20:2754–65. https://doi.org/10.1017/S1368980017001616
17. Livshits G, Karasik D, Seibel MJ. Statistical genetic analysis of plasma levels of vitamin D: familial study. Ann Hum Genet. 1999;63:429–39.
18. Hansen JG, Tang W, Hootman KC, Brannon PM, Houston DK, Kritchevsky SB, et al. Genetic and environmental factors are associated with serum 25-hydroxyvitamin D concentrations in older African Americans. J Nutr. 2015;145:799–805. https://doi.org/10.3945/jn.114.202093
19. Hiraki LT, Major JM, Chen C, Cornelis MC, Hunter DJ, Rimm EB, et al. Exploring the genetic architecture of circulating 25-hydroxyvitamin D. Genet Epidemiol. 2013;37:92–8. https://doi.org/10.1002/gepi.21694
20. Fohner AE, Wang Z, Yracheta J, O'Brien DM, Hopkins SE, Black J, et al. Genetics, Diet, and Season Are Associated with Serum 25-Hydroxycholecalciferol Concentration in a Yup'ik Study Population from Southwestern Alaska. J Nutr. 2016;146:318–25. https://doi.org/10.3945/jn.115.223388
21. Del Valle HB, Yaktine AL, Taylor CL, Ross AC. Dietary reference intakes for calcium and vitamin D. Washington DC: National Academies Press, Institute of Medicine; 2011.
22. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011;96:1911–30. https://doi.org/10.1210/jc.2011-0385
23. Pludowski P, Holick MF, Pilz S, Wagner CL, Hollis BW, Grant WB, et al. Vitamin D effects on musculoskeletal health, immunity, autoimmunity, cardiovascular disease, cancer, fertility, pregnancy, dementia and mortality-a review of recent evidence. Autoimmun Rev. 2013;12:976–89. https://doi.org/10.1016/j.autrev.2013.02.004
24. Pludowski P, Holick MF, Grant WB, Konstantynowicz J, Mascarenhas MR, Haq A, et al. Vitamin D supplementation guidelines. J Steroid Biochem Mol Biol. 2018;175:125–35. https://doi.org/10.1016/j.jsbmb.2017.01.021
25. Almasy L, Blangero J. Multipoint quantitative-trait linkage analysis in general pedigrees. Am J Hum Genet. 1998;62:1198–211. https://doi.org/10.1086/301844
26. Akaike H. Factor analysis and AIC. Psychometrika. 1987;52:317–32.
27. Choi HS, Park JH, Kim SH, Shin S, Park MJ. Strong familial association of bone mineral density between parents and offspring: KNHANES 2008-2011. Osteoporos Int. 2017;28:955–64. https://doi.org/10.1007/s00198-016-3806-1
28. Choi HS, Oh HJ, Choi H, Choi WH, Kim JG, Kim KM, et al. Vitamin D insufficiency in Korea--a greater threat to younger generation: the Korea National Health and Nutrition Examination Survey (KNHANES) 2008. J Clin Endocrinol Metab. 2011;96:643–51. https://doi.org/10.1210/jc.2010-2133
29. Ganji V, Zhang X, Tangpricha V. Serum 25-hydroxyvitamin D concentrations and prevalence estimates of hypovitaminosis D in the U.S. population based on assay-adjusted data. J Nutr. 2012;142:498–507. https://doi.org/10.3945/jn.111.151977
30. Langlois K, Greene-Finestone L, Little J, Hidiroglou N, Whiting S. Vitamin D status of Canadians as measured in the 2007 to 2009 Canadian Health Measures Survey. Health Rep. 2010;21:47–55.
31. Perusse L, Leblanc C, Bouchard C. Familial resemblance in lifestyle components: results from the Canada Fitness Survey. Can J Public Health. 1988;79:201–5.
32. Bogl LH, Silventoinen K, Hebestreit A, Intemann T, Williams G, Michels N et al. Familial resemblance in dietary intakes of children, adolescents, and parents: does dietary quality play a role? Nutrients. 2017;9. https://doi.org/10.3390/nu9080892.
33. Shea MK, Benjamin EJ, Dupuis J, Massaro JM, Jacques PF, D'Agostino RB Sr., et al. Genetic and non-genetic correlates of vitamins K and D. Eur J Clin Nutr. 2009;63:458–64. https://doi.org/10.1038/sj.ejcn.1602959
34. Orton SM, Morris AP, Herrera BM, Ramagopalan SV, Lincoln MR, Chao MJ, et al. Evidence for genetic regulation of vitamin D status in twins with multiple sclerosis. Am J Clin Nutr. 2008;88:441–7.
35. Griffiths AJF MJ, Suzuki DT. An Introduction to Genetic Analysis. 7th ed. New York: W. H. Freeman; 2000.

36. Yao S, Hong CC, Bandera EV, Zhu Q, Liu S, Cheng TD, et al. Demographic, lifestyle, and genetic determinants of circulating concentrations of 25-hydroxyvitamin D and vitamin D-binding protein in African American and European American women. Am J Clin Nutr. 2017;105:1362–71. https://doi.org/10.3945/ajcn.116.143248
37. Ahn J, Yu K, Stolzenberg-Solomon R, Simon KC, McCullough ML, Gallicchio L, et al. Genome-wide association study of circulating vitamin D levels. Hum Mol Genet. 2010;19:2739–45. https://doi.org/10.1093/hmg/ddq155
38. Sacheck JM, Van Rompay MI, Chomitz VR, Economos CD, Eliasziw M, Goodman E, et al. Impact of three doses of vitamin D3 on serum 25(OH)D deficiency and insufficiency in at-risk schoolchildren. J Clin Endocrinol Metab. 2017. https://doi.org/10.1210/jc.2017-01179
39. van den Ouweland JM, Vogeser M, Bacher S. Vitamin D and metabolites measurement by tandem mass spectrometry. Rev Endocr Metab Disord. 2013;14:159–84. https://doi.org/10.1007/s11154-013-9241-0