Association of Vitamin E Intake at Early Childhood with Alanine Aminotransferase Levels at Mid-Childhood

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ABSTRACT (275 words max)

The extent to which vitamin E (alpha-tocopherol) intake early in childhood is associated with alanine aminotransferase (ALT) level later in childhood is unknown. The objective of this research is to test the hypothesis that higher alpha-tocopherol intake during early childhood is associated with lower odds of elevated ALT levels during mid-childhood, and to examine how body mass index (BMI) influences these relationships. We studied 528 children in Project Viva. Mothers reported child dietary intake at early childhood visits (median 3.1 years) using a validated food frequency questionnaire. At mid-childhood (median 7.6 years), we collected child blood and anthropometric data. The main outcome was elevated sex-specific mid-childhood ALT level (≥ 22.1 units/liter for females and ≥ 25.8 units/liter for males). In multivariable logistic regression models, we assessed the association of energy-adjusted alpha-tocopherol intake with ALT levels, adjusting for child age, sex, race/ethnicity, diet, and age-adjusted, sex-specific BMIz at mid-childhood. Among children in this study, 48% were female, 63% were non-Hispanic white, 19% were non-Hispanic black, and 4% Hispanic/Latino. Mean alpha-tocopherol intake was 3.7±1.0 mg/day (range 1.4-9.2) at early childhood. At mid-childhood, mean BMIz was 0.41±1.0 units and 22% had an elevated ALT level. In multivariable-adjusted logistic regression models, children with higher early childhood vitamin E intake had lower odds of elevated mid-childhood ALT [adjusted odds ratio (AOR) 0.62 (95% CI: 0.39-0.99)] for quartiles 2-4 compared with the lowest quartile of intake. Findings persisted after accounting for early childhood diet [0.62 (0.36, 1.08)] and were strengthened after additionally accounting for mid-childhood BMIz [0.56 (0.32, 0.99)].

Conclusion: In this cohort, higher early childhood intake of alpha-tocopherol was associated with lower odds of elevated mid-childhood ALT level.

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease in children, and the prevalence of pediatric NAFLD has increased rapidly over the past two decades.(1, 2) The term NAFLD encompasses a variety of disease phenotypes including simple steatosis, steatohepatitis, and fibrosis; the hallmark of each is hepatic steatosis (fat infiltration of liver cells) without alternative causes.(3) An estimated 40% of children with overweight (sex-specific body mass index [BMI] $\geq 85^{th}$ and $<95^{th}$ percentile for age) and obesity (BMI $\geq 95^{th}$ percentile), and around one in ten children age 2-19 years of all weight categories, have NAFLD.(2, 4, 5) In cross-sectional pediatric studies, older age, race/ethnicity, and male sex are risk factors.(4, 6-8) Long-term complications may include cirrhosis and hepatocellular carcinoma, and NAFLD has emerged as the most rapidly growing cause of hepatocellular carcinoma requiring liver transplant among adults in the United States.(9)

Expert committees have recommend use of serum alanine aminotransferase (ALT) levels to screen for NAFLD among at-risk children.(10, 11) In adults of all BMI categories, continuous increases in serum ALT levels are associated with hepatocellular carcinoma risk, type 2 diabetes risk, and mortality.(12) Among children ages 12-19 years, thresholds for serum ALT >25.8 units/liter for males and >22.1 for females show 80-92% sensitivity and 79-85% specificity to detect pediatric NAFLD, and have been used in epidemiologic studies to estimate prevalence of NAFLD.(2, 13) Given the high proportion of adolescents with elevated plasma ALT levels,(2) early and mid-childhood could be key windows of opportunity to prevent rising ALT levels. Moreover, identifying protective factors against elevated ALT levels could inform future interventions to prevent pediatric NAFLD. Yet, little information exists on etiologies of elevated ALT levels during childhood.

Vitamin E is a prime candidate for protection against development of NAFLD because its anti-oxidant properties may combat lipotoxic effects of free fatty acids and metabolites, which play a role in hepatocellular damage. Among children and adolescents with biopsy-proven steatohepatitis, higher intake of the alpha-tocopherol isoform of vitamin E had a cross-sectional correlation with lower degree of steatosis and alpha-tocopherol supplementation improved histologic outcomes in a randomized-controlled trial.(2, 14) Identifying the prospective association of alpha-tocopherol intake during early childhood with later ALT levels could inform future efforts to prevent liver damage in children.

The overall goal of this research was to prospectively examine the relationship of alpha-tocopherol intake during early childhood with subsequent ALT levels, and to ascertain the extent to which mid-childhood adiposity mediates this relationship. We hypothesized that higher intake of alpha-tocopherol during early childhood would be associated with lower odds of elevated ALT levels later in childhood, and that this relationship would operate independent of child age- and sex-specific BMI (BMI z-score).

METHODS

Study Design and Participants

We studied children in Project Viva, an ongoing prospective pre-birth cohort study. Pregnant women were recruited from Atrius Harvard Vanguard Medical Associates, a multi-specialty group practice in eastern Massachusetts. Study recruitment and retention details are described elsewhere.(15) Mothers gave written informed consent at enrollment in pregnancy and at in-

person visits in early (median age 3.1 years) and mid-childhood (median child age 7.6 years), and children gave verbal assent at mid-childhood. The institutional review board of Harvard Pilgrim Health Care approved all study protocols.

Of the 2128 live singleton births in the cohort, 1708 remained enrolled and thus were eligible for a mid-childhood study visit and 1116 attended an in-person visit between age 6 and 10 years. Of those, 635 had blood available for ALT analysis; 534 of those had information on early childhood dietary intake; and 528 had information on BMI z-score at mid-childhood and form the study population for this analysis. Characteristics of the study sample of 528 were similar to the 588 who attended a mid-childhood visit but did not have blood available for ALT analysis in terms of maternal age and pre-pregnancy BMI; child sex; and BMI z-score at mid-childhood (data not shown). However, compared to children with mid-childhood visits not included in this analysis, children in our study sample had slightly lower mean age at early (38.3 ± 2.7 versus 39.1 ± 4.9 months) and mid-childhood (94.2 ± 8.9 versus 97.7 ± 11.5 months) visits.

Measurements

Main Exposure: Early childhood alpha-tocopherol intake. Vitamin E intake measured as alpha-tocopherol during early childhood was the main exposure. At early childhood visits, parents reported children's dietary intake by completing a semi-quantitative food frequency questionnaire that was validated for use in pre-school aged children, including for measurement of alpha-tocopherol intake.(16) Questions assessed usual frequency of intake of specific food and drink. We calculated nutrient intakes using the Harvard nutrient composition database, which is based primarily on U.S. Department of Agriculture information, and it is continually

supplemented by other published sources.(17-19) We estimated energy-adjusted total daily alpha-tocopherol intake from foods using the nutrient residual method. We categorized alpha-tocopherol intake during early childhood into quartiles based on the sample of children with available alpha-tocopherol intake information. We defined insufficient alpha-tocopherol intake based on age-specific recommended daily allowance (RDA) for alpha-tocopherol.(20) The current RDA for natural alpha-tocopherol is 6 mg for children age 1-3 years, and 7 mg for children age 4-8 years. However, because self-reported insufficient alpha-tocopherol intake has high prevalence nationally,(20) we additionally defined low alpha-tocopherol intake as the lowest quartile (< 2.98 mg/day).

Main Outcome: Mid-childhood ALT level. We collected blood samples from children at the mid-childhood visit. Samples were processed within 24 hours and frozen at -80° C until the time of analysis. We measured concentration of ALT by enzymatic assay on the Roche P Modular system using Roche reagents (Roche Diagnostics, Indianapolis, IN). This assay is approved by the Food and Drug Administration for clinical use and standardized across centers. The lowest detection limit of this assay is 4 U/L and the day-to-day imprecision values at concentrations of 42, 55 and 130 U/L are 4.4, 3.7 and 3.3%, respectively. We classified elevated ALT levels as ≥ 25.8 units/liter for males and ≥ 22.1 for females.(2, 13)

Covariates. At recruitment during pregnancy, we collected information including maternal age, education, parity and pre-pregnancy weight and height; and paternal weight and height. Child sex was documented at delivery. At early childhood, we collected information about marital status; household income; and child race/ethnicity. We also collected data on diet and physical

activity factors at early childhood that could act as confounders of the relationship between alpha-tocopherol intake and ALT level. As described above for alpha-tocopherol intake, mothers provided information on child diet using a semi-quantitative validated food frequency questionnaire. Based on existing literature on dietary factors that could be related to NAFLD in children,(21, 22) we estimated daily intakes of fruit and vegetable; sugar-sweetened beverages; total energy intake in calories; and energy-adjusted total fat, carbohydrates, protein, saturated fat, polyunsaturated fat, fructose, vitamin D, and vitamin C intake using the nutrient residual method.(16) Mothers reported child moderate-to-vigorous daily physical activity at early childhood.(23)

Potential intermediates. We examined mid-childhood BMI z-score as a potential intermediate of the relationship between alpha-tocopherol intake. We measured height and weight of children using a calibrated stadiometer (Shorr Productions, Olney, MD) and scale (Seca model 881, Seca corporation, Hanover, MD). We calculated age- and sex-specific BMI z-scores using CDC 2000 growth reference data.(24) Research assistants followed standardized techniques for measurements and participated in in-service training to ensure measurement validity (IJ Shorr, Shorr Productions, Olney, MD).(25) Inter- and intra-rater measurement errors were within published reference ranges for all measurements.(26)

Statistical Analysis

We first examined the bivariate relationships of alpha-tocopherol intake with other covariates and the main outcome. We used logistic regression models to assess the effect of low alpha-tocopherol intake at early childhood with high ALT level at mid-childhood. We also examined

the relationship between each quartile of alpha-tocopherol intake and ALT outcomes. In multivariable models, we included only those covariates that were of *a priori* interest based on prior literature. The covariate-adjusted model included child age, sex, and race/ethnicity. In subsequent models, we additionally adjusted for individual dietary factors that had a statistically-significant correlation (p-value > 0.01) with vitamin E intake at early childhood and could therefore act as confounders of the association between alpha-tocopherol and ALT level. The diet-adjusted model included fruit, vegetable, energy-adjusted saturated fat, energy-adjusted polyunsaturated fat, fructose, vitamin D, and vitamin C intake at early childhood. To account for the potential intermediate of BMI z-score at mid-childhood, we additionally adjusted the covariate-adjusted and the diet-adjusted models for mid-childhood BMI z-score.

Because ALT levels differ between males and females, we also investigated whether child sex modified the effect estimate of early childhood alpha-tocopherol intake and mid-childhood elevated ALT level. We conducted all of the analyses using SAS version 9.4 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Table 1 shows family and child characteristics of the 528 children included in our analyses. 48% were female, 63% were non-Hispanic white, 19% were non-Hispanic black, 4% Hispanic/Latino, and 2% were Asian. At early childhood, fruit and vegetable intake; and energy-adjusted saturated fat, polyunsaturated fat, fructose, vitamin D, and vitamin C intake were correlated with vitamin E intake (p-value < 0.001). Sugar-sweetened beverage intake, calories, total fat, carbohydrate, and

protein intake were not correlated with alpha-tocopherol intake at early childhood. (Data not shown)

Table 2 shows total energy and energy-adjusted alpha-tocopherol intake during early childhood by mid-childhood ALT category. At mid-childhood, 22% of children had elevated ALT levels. Children with high mid-childhood ALT levels had similar maternal-reported early childhood mean total energy intake as those with normal mid-childhood ALT levels.

In Table 3, we present results from logistic regression models testing our first hypothesis of the effects of early childhood alpha-tocopherol intake on mid-childhood ALT levels. In unadjusted models, compared to children with the lowest quartile of alpha-tocopherol intake, those with higher alpha-tocopherol intake (quartiles 2-4) had lower odds of elevated ALT level [odds ratio (OR) 0.65 (95% CI: 0.41, 1.02)]. After adjusting for *a priori* confounders, these findings persisted [OR 0.62 (0.39, 0.99)]. In models examining quartiles of alpha-tocopherol intake, children in the 3rd quartile of alpha-tocopherol intake had lower odds of elevated ALT at mid-childhood compared to those with the lowest quartile of intake in unadjusted [OR 0.48 (0.27, 0.88)] and child-adjusted models [OR 0.43 (0.23,0.80)]. We also found lower odds of ALT elevation among children in the 2nd and 4th quartiles of alpha-tocopherol intake compared to those with the lowest quartile of intake, but confidence intervals were wide and included the null. We did not find any modification of the effect of alpha-tocopherol intake and ALT elevation by child sex (p-interaction > 0.1 for all models).

We then examined the extent to which dietary factors correlated with alpha-tocopherol intake at early childhood accounted for the relationship between alpha-tocopherol intake and ALT elevation. In models adjusted for child age, sex, race/ethnicity, and individual dietary factors, we found that adjusting for vegetable, polyunsaturated fat, or vitamin D intake slightly attenuated the relationship between alpha-tocopherol intake at early childhood and elevated ALT at mid-childhood (Figure 1). After adjusting for fruit, saturated fat, fructose, or vitamin C intake, the association of higher alpha-tocopherol intake at early childhood with lower odds of elevated ALT at mid-childhood persisted. In the diet-adjusted model, children with higher vitamin E intake (quartiles 2-4) had similar odds of elevated ALT level as in the covariate-adjusted model, but confidence intervals widened and crossed the null. In models examining the association of each quartile of alpha-tocopherol intake with elevated ALT level, findings were similar to the covariate-adjusted model.

We next investigated our hypothesis that the relationship between early childhood alpha-tocopherol intake and elevated ALT level at mid-childhood would be independent of mid-childhood adiposity. Mid-childhood BMI z-score was highest in the 2nd and 3rd quartiles of early childhood alpha-tocopherol intake (Table 1). We did not find a correlation between early childhood alpha-tocopherol intake and mid-childhood BMI z-score (Spearman $r = 0.06$, $p = 0.15$), but BMI z-score had a cross-sectional correlation with ALT at mid-childhood (Spearman $r = 0.21$, $p < 0.001$). After adjusting our models of early childhood alpha-tocopherol intake and mid-childhood elevated ALT for mid-childhood BMI z-score, we found lower odds ratios with narrower confidence intervals for models comparing 2nd-4th quartiles to the lowest quartile of intake [OR 0.55 (0.34, 0.89)]. In models comparing individual quartiles to the lowest quartile of

alpha-tocopherol intake, adjusting for BMI z-score resulted in strengthening of associations of alpha-tocopherol quartile with ALT elevation (e.g. among children in the 3rd vs. 1st quartile of intake [OR 0.37 (0.20, 0.69)]).

In our final model adjusting for covariates, early childhood diet, and mid-childhood BMI z-score, findings persisted but confidence intervals widened in models comparing 2nd-4th quartiles [OR 0.56 (0.32, 0.99)] to the lowest quartile, as well as in models comparing individual quartiles to the lowest quartile of alpha-tocopherol intake.

DISCUSSION

In this prospective cohort study, children with higher alpha-tocopherol intake during early childhood had lower likelihood of elevated ALT levels at mid-childhood. Overall, the relationship between higher alpha-tocopherol intake and lower odds of elevated ALT persisted after accounting for demographic and dietary confounders. Accounting for mid-childhood BMI z-score strengthened the relationship between higher alpha-tocopherol intake at early childhood and lower odds of ALT elevation at mid-childhood. Taken together, these findings suggest that appropriate levels of alpha-tocopherol intake could promote liver health later in childhood, and that this relationship is not mediated by an effect of alpha-tocopherol intake on BMI.

Our study is the first of which we are aware to demonstrate a link between early childhood dietary risk factors and later childhood liver health. We prospectively examined a modifiable risk factor for elevated plasma ALT levels during mid-childhood. Plasma or serum ALT levels are used to screen for pediatric NAFLD, a prevalent childhood obesity complication. Although little

information on the natural history of NAFLD in children exists, fibrosis/cirrhosis and end-stage liver disease can occur even in childhood. Thus, identifying alpha-tocopherol as an early childhood protective factor against later elevation of ALT levels suggests that future interventions to study approaches to prevent development and progression of pediatric NAFLD should take early childhood alpha-tocopherol consumption into account. National data shows that >90% of the US population under-consumes alpha-tocopherol, leading to the classification of vitamin E as a shortfall nutrient by the 2015 Dietary Guidelines Advisory Committee.(27) Given the high prevalence of both inadequate vitamin E consumption and NAFLD, our findings are relevant to the general US population.

Lower alpha-tocopherol intake is a plausible risk factor for elevated ALT levels and NAFLD. Substantial evidence shows a link between intake of the fat-soluble antioxidant vitamin E and severity of NAFLD in children with biopsy-proven steatohepatitis. In a cross-sectional study of children with biopsy-proven steatohepatitis, intake of alpha-tocopherol was inversely related to steatosis grade.(21) In the multi-center, placebo-controlled Treatment of Nonalcoholic Fatty Liver Disease in Children (TONIC) trial, children with established NAFLD who received vitamin E as alpha-tocopherol 400 IU twice daily had improvement in histological outcomes after 96 weeks, but did not have a statistically significant improvement in ALT levels compared to the placebo group.(28) In the Pioglitazone vs. Vitamin E vs. Placebo in Non-alcoholic Steatohepatitis (PIVENS) randomized-controlled trial, vitamin E supplementation improved ALT levels among adults regardless of whether they lost, gained, or maintained stable weight.(29) Thus, our results extend the existing literature showing alpha-tocopherol treatment

effect in established NAFLD to suggest that alpha-tocopherol intake early in childhood could have a protective role against liver injury later in childhood.

We hypothesized that the association between alpha-tocopherol intake and ALT would be independent of BMI z-score. In a recent adult clinical trial, presence of metabolic syndrome lowered the bioavailability of alpha-tocopherol after ingestion of doses compatible with the RDA, suggesting that higher oxidative stress and inflammation increases alpha-tocopherol requirements.(30) However, in our study, we found no relationship between early childhood alpha-tocopherol intake and mid-childhood BMI z-score. Children with overweight or obesity are more likely to have elevated ALT levels than children with a healthy weight, and we did find a relationship between mid-childhood BMI z-score and ALT level. Adjusting for mid-childhood BMI z-score resulted in further reduction of odds of ALT elevation among children with higher alpha-tocopherol intake, suggesting that the beneficial effects of early childhood alpha-tocopherol intake were not mediated by mid-childhood BMI z-score.

In the TONIC trial, children received 400 IU, or 180 milligrams, of alpha-tocopherol twice daily. Our study sample had early childhood alpha-tocopherol intake, measured as α-tocopherol, ranging from 1.4 – 9.2 milligrams, substantially below the supplemental amounts in the TONIC trial. Also, Vitamin E is present in foods that are more often consumed by those with healthful diets, such as wheat germ, almonds, spinach, and broccoli, as well as cooking oils,(27) and less often by young children. We included alpha-tocopherol intake from diet and supplements in our calculations, but cannot distinguish the contribution of various foods or supplements to alpha-tocopherol intake.

Strengths of our study include the prospective nature of the design and its evaluation of a modifiable risk factor during a life course period that is important to prevention of pediatric NAFLD. However, we also note some limitations. Because this is a population-based cohort, we did not have liver imaging or liver tissue available for analysis, which limits our ability to determine grade and stage of liver disease. However, in clinical guidelines, ALT levels are the recommended test for NAFLD screening and substantial evidence shows that higher ALT levels are linked to morbidity and mortality, supporting the importance of ALT levels as a health outcome. Second, we estimated vitamin E intake based on parental report of child diet, which could be prone to over or underestimation. Finally, we had small sample sizes of Asian and Hispanic children. Because these racial/ethnic groups are more likely to have NAFLD compared to non-Hispanic white or black children,(2) our effect estimates may underestimate the association alpha-tocopherol intake with circulating ALT levels.

In summary, we found that higher intake of the alpha-tocopherol isoform of vitamin E during early childhood was associated with lower odds of elevated ALT level during mid-childhood. Our findings suggest that modifiable risk factors, specifically intake of vitamin E, should be considered in future interventions to identify approaches to prevent pediatric NAFLD.

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Table 1. Parent and child characteristics according to early childhood vitamin E (alpha-tocopherol) intake. Data from 528 mother-child pairs.

	Overall	Early Childhood Vitamin E (alpha-Tocopherol) Intake Quartile			
		1	2	3	4
N	**528**	**132**	**131**	**133**	**132**
Family/Household characteristic					
Maternal age, mean ± SD, y	32.2 ± 5.3	32.1 ± 5.0	31.8 ± 5.2	32.0 ± 5.2	32.7 ± 5.9
Education, college graduate, n,%	366 (69)	95 (72)	90 (69)	95 (71)	86 (65)
Parity, multipara, n, %	299 (57)	73 (55)	72 (55)	76 (57)	78 (59)
Marital status, married/cohabiting, n, %	472 (89)	121 (92)	118 (90)	117 (88)	116 (88)
Annual household income at early childhood, n, %					
<$40,000/y	84 (16)	14(11)	19 (14)	27 (20)	24 (18)
$40-70,000/y	106 (20)	26 (20)	28 (21)	22 (16)	30 (23)
>$70,000/y	327 (63)	89 (69)	80 (63)	83 (63)	75 (58)
Maternal pre-pregnancy BMI, mean ± SD, kg/m^2	24.8 ± 5.2	24.4 ± 5.0	24.6 ± 4.7	25.1 ± 5.4	25.0 ± 5.5
Paternal pre-pregnancy BMI, mean ± SD, kg/m^2	26.4 ± 3.7	26.7 ± 3.8	26.6 ± 3.5	26.4 ± 3.9	25.0 ± 5.4
Child					
Girl, n, %	254 (48)	55 (42)	61 (47)	74 (56)	64 (48)
Age early childhood vitamin E (alpha-tocopherol) intake measurement, mean ± SD, mo	38.3 ± 2.6	37.8 ± 1.8	37.9 ± 2.2	38.6±2.6	38.8±3.6

Age mid-childhood blood draw, mean ± SD, mo	94.2 (8.9)	94.4 (9.1)	92.6 (7.9)	95.6 (10.0)	94.0 (8.4)
BMI z-score, mid-childhood, mean ± SD	0.41 ± 1.0	0.24±0.8	0.51±1.0	0.54±1.0	0.37±1.1
BMI category, mid-childhood, n, %					
<5th percentile	12 (2.3)	1 (0.8)	4 (3.1)	1 (0.8)	6 (4.5)
5th to <85th percentile	371 (70.3)	107 (81.1)	87 (66.4)	91 (68.4)	86 (65.2)
85th to <95th percentile	74 (14.0)	17 (12.9)	16 (12.2)	17 (12.8)	24 (18.2)
≥95th percentile	71 (13.4)	7 (5.3)	24 (18.3)	24 (18.0)	16 (12.1)
Race/ethnicity, n, %					
Asian	13 (2)	4 (3)	4 (3)	3 (2)	2 (2)
Hispanic	21 (4)	6 (5)	7 (5)	5 (4)	3 (2)
White, non-Hispanic	332 (63)	93 (70)	80 (61)	84 (63)	75 (57)
Black, non-Hispanic	98 (19)	14 (11)	24 (18)	24 (18)	36 (27)
Other/More than 1 race	64 (12)	15 (11)	16 (12)	17 (13)	16 (12)

[a]All estimates of vitamin E (alpha-tocopherol) intake were adjusted for total energy intake using the nutrient residual method.

Table 2. Energy-adjusted vitamin E (alpha-tocopherol) intake during early childhood according to mid-childhood plasma ALT levels. Data from 528 mother-child pairs.

	Overall (N=528)	**Children with normal ALT level[a] (N=411)**	**Children with high ALT level (N=117)**
Early Childhood Nutrient Intake		Mean ± SD or N (%)	
Total energy, mean ± SD, kcal	1871 ± 539	1885 ± 548	1822 ± 506
Vitamin E (alpha-tocopherol)[b] , mean ± SD, mg	3.7 ± 1.0	3.7 ± 1.0	3.6 ± 1.0
Vitamin E (alpha-tocopherol)[b], mg, n (%), quartiles			
Q1 (< 3.0)	132 (25.0)	95 (23.1)	37 (31.6)
Q2 (3.0 to < 3.6)	131 (24.8)	100 (24.3)	31 (26.5)
Q3 (3.6 to < 4.2)	133 (25.2)	112 (27.2)	21 (18.0)
Q4 (≥ 4.2)	132 (25.0)	104 (25.3)	28 (23.9)

[a] Normal ALT defined as < 22.1 units per liter for females and < 25.8 units per liter for males

[b] All estimates of vitamin E (alpha-tocopherol) intake were adjusted for total energy intake using the nutrient residual method.

Table 3. Multivariable regression models for association of energy-adjusted vitamin E (alpha-tocopherol) intake during early childhood with elevation in ALT levels at mid-childhood. Data from 528 children in Project Viva.

	Unadjusted	Covariate-adjusted Model[a]	Diet-adjusted Model[b]	BMIz-adjusted Model[c]	Diet and BMIz-adjusted Model[d]
			OR (95% CI)		
Early Childhood Vitamin E (alpha-tocopherol) Intake					
Low Vitamin E (alpha-tocopherol) Intake					
1st quartile	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
2nd-4th quartiles	0.65 (0.41, 1.02)	**0.62 (0.39, 0.99)**	0.62 (0.36, 1.08)	**0.55 (0.34, 0.89)**	**0.56 (0.32, 0.99)**
Quartiles of Vitamin E (alpha-tocopherol) Intake					
1st quartile	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
2nd quartile	0.80 (0.46, 1.38)	0.80 (0.46, 1.41)	0.82 (0.45, 1.50)	0.70 (0.39, 1.24)	0.74 (0.40, 1.37)
3rd quartile	**0.48 (0.26, 0.88)**	**0.43 (0.23, 0.80)**	**0.40 (0.20, 0.80)**	**0.37 (0.20, 0.69)**	**0.35 (0.17, 0.72)**
4th quartile	0.69 (0.39, 1.22)	0.67 (0.38, 1.20)	0.66 (0.28, 1.55)	0.63 (0.35, 1.14)	0.67 (0.28, 1.58)

Bold indicates statistically significant values where the 95% CI does not cross the null.

[a]Covariate-adjusted model: Adjusted for child sex, race/ethnicity, and age at time of mid-childhood visit

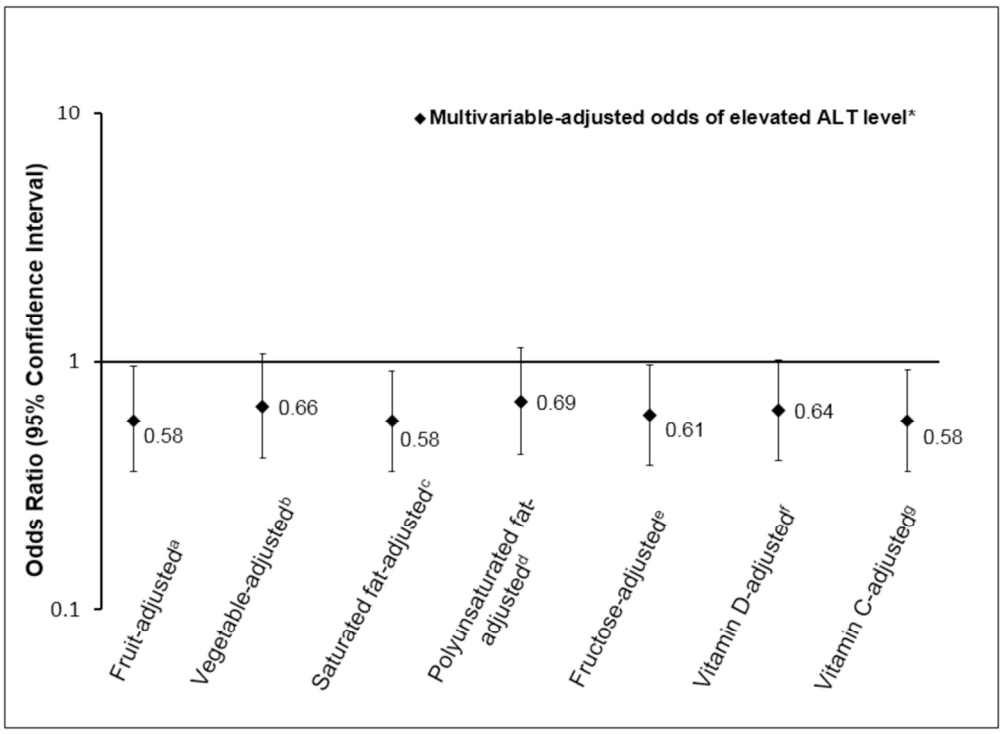
[b]Diet-adjusted model: Covariate-adjusted model additionally adjusted for fruit and vegetable intake; and energy-adjusted saturated fat, polyunsaturated fat, fructose, vitamin D, and vitamin C at early childhood visit

[c]BMIz-adjusted model: Covariate-adjusted model additionally adjusted for child BMI z-score at mid-childhood visit

[d]Diet and BMIz-adjusted Model: Diet-adjusted model additionally adjusted for BMI z-score at mid-childhood visit

FIGURE LEGEND

Figure 1. Association of energy-adjusted alpha-tocopherol intake during early childhood with elevation in alanine aminotransferase levels at mid-childhood adjusted for specified food groups and nutrients. Data from 528 children in Project Viva.



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