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Patterns and Determinants of Micronutrient Dietary Biomarkers and Their Associations with Dietary Intakes in Young Children

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A B S T R A C T

Background: Circulating dietary biomarkers are not direct proxies for intake, as the biomarkers re ect not only food and supplement consumption but also nutrient absorption, metabolism, and tissue distribution. Therefore, along with nutrient intake, several other upstream factors can impact dietary biomarker concentrations, including demographic, medical history, and genetic factors.

Objectives: The aim of this study was to explore the dietary and nondietary determinants of circulating levels of vitamins A, C, D, and E among children aged 6 mo–4 y.

Methods: Plasma retinol, -carotene, ascorbic acid, 25(OH)D, α-tocopherol, and γ-tocopherol were measured in 2887 samples from 1490 children enrolled in The Environmental Determinants of Diabetes in the Young study. Dietary intake was assessed with 3-d food records. Associations of genetic and environmental factors with biomarker concentrations were examined using multivariable linear regression models with random intercepts.

Results: All biomarkers except retinol were positively associated with intake of the same nutrient. Inverse associations were identified between recent gastrointestinal infection and -carotene, ascorbic acid, and α-tocopherol, whereas recent respiratory infection was associated inversely with plasma retinol. Several genetic determinants of biomarker status were identified, validating previously reported findings. For some genetic and environmental exposures, we found evidence of statistical interaction with same-nutrient intake, indicating that the association between intake and biomarker concentration is dependent on the level or status of these other exposures. For example, the association between -carotene intake and concentration is weaker among children with a recent respiratory infection.

Conclusions: Our findings suggest that nondietary exposures including childhood infections can alter micronutrient metabolism. This summary of micronutrient determinants will facilitate improved design of future analyses exploring the role of diet in childhood chronic disease etiology through a better understanding of relevant potential confounders and mediators of the diet–outcome relationships.

Keywords: dietary biomarkers, nutrient intake, food group intake, breastfeeding, probiotics, anthropometric measurements, longitudinal, nested case-control, children, gene-environment interaction

Abbreviations: CDC, Centers for Disease Control and Prevention; CI, confidence interval; CV, coefficient of variation; FDR, first degree relative; HLA, human leukocyte antigen; HPLC, high-performance liquid chromatography; LDP, long distance protocol; NCC, nested case-control; QC, quality control; SD, standard deviation; SNP, single nucleotide polymorphism; TEDDY, The Environmental Determinants of Diabetes in the Young.

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Introduction

Circulating dietary biomarkers in nutritional epidemiology are used as complementary indicators of dietary adequacy, alongside self-reported dietary intake. Dietary biomarker measures, compared with intake measures such as food records or food frequency questionnaires, are often cited as having a lower risk for measurement error [1]. However, circulating biomarkers are not direct proxies for intake, as the biomarkers re ect not only food and supplement consumption but also nutrient absorption, metabolism, and tissue distribution [2]. The biological processes in uencing biomarker concentrations are often complex, being driven by homeostatic mechanisms [3]. It is important to establish the determinants of these biomarkers, both dietary and nondietary, in order to identify potential confounders or effect modifiers that could disguise their role in the etiological processes of disease development.

Several upstream exposures other than nutrient intake can impact dietary biomarker concentrations, including demographic, medical history, and genetic factors. The substantial impact of in ammatory response to infection on micronutrient status is well-established [4], and chronic in ammation from obesity may also alter vitamin levels. Other chronic conditions such as celiac disease may also in uence nutrient status through inadequate intake or poor absorption [5]. Children exposed to second-hand smoke have been shown to have low concentrations of antioxidants including vitamin C, vitamin E, and carotenoids [6]. The contribution of genetics is demonstrated by the strong heritability of nutrient status, with water-soluble and fat-soluble nutrient status heritability ranging from 56 to 59 and 30 to 70 , respectively [7]. Single nucleotide polymorphisms (SNPs) may also affect dietary preferences through intolerances or aversions, which indirectly in uence biomarker status [2]. Along with the direct impact of dietary intake on biomarker status of the same nutrient, prior research suggests that diet may also indirectly in uence micronutrient status via alterations to the microbiome [8,9], altered absorption dependent on the food matrix [10], and synergistic interactions between nutrients with overlapping metabolic pathways [11,12]. Despite the existing evidence for contributions of both dietary and nondietary factors in micronutrient status, causal pathways have been difficult to illuminate because it is often unclear to what extent these factors act independently of each other.

Micronutrient biomarkers analyzed in The Environmental Determinants of Diabetes in the Young (TEDDY) study (vitamins A, C, D, and E) were selected based on having biologically plausible roles in the development of islet autoimmunity or type 1 diabetes. Ascorbic acid (vitamin C) and 25(OH)D (vitamin D) concentrations have both been previously shown in the TEDDY study to be inversely associated with a risk of islet autoimmunity [13,14], and 25(OH)D concentration in infancy was shown to have a U-shaped association with celiac disease autoimmunity [15]. There are several other known physiological functions of these nutrients including the role of vitamin A in immunity, growth, and development, vitamin C in connective tissue development, vitamin D in bone mineralization, and the antioxidative role of vitamin E [10,16].

The aims of this study were to examine the longitudinal patterns and explore the dietary and nondietary determinants of circulating concentrations of vitamins A, C, D, and E among young children genetically at risk of type 1 diabetes and explore potential effect modification of the association between nutrient intake and biomarker status by environmental exposures. Exposures of interest included intake of nutrients, breastmilk, infant formula, and other food groups, demographic factors, weight and height, celiac disease status, acute infections and antibiotic use, probiotic use, and parental smoking status.

Methods

Study design

TEDDY is a multinational observational birth cohort study that enrolled children genetically high risk for type 1 diabetes in the United States (Colorado, Georgia and Florida, and Washington state), Finland, Germany, and Sweden from 2004 to 2010 [17–19]. Written informed consent was obtained for all participants from a parent or primary caretaker, for genetic screening and for participation in continued follow-up. TEDDY is approved by local Institutional Review Boards and monitored by an External Advisory Board. Samples were collected as part of a nested case-control (NCC) study within the TEDDY study. Cases with islet autoimmunity or type 1 diabetes were identified, and 3 controls were matched to each case for a total of 1843 children [20]. Inverse probability of selection weighting (for selection into the NCC study) was used for all analyses, so the presented results are representative of the full TEDDY cohort. At each study visit, parents reported chronic disease diagnoses and acute illnesses that had occurred since the previous visit, and staff translated these reports into International Classification of Diseases (ICD-10) codes (www.who.int/classifications/icd/en/). Parents also reported all medications started since the time of the previous visit as well as the reason for medication use and the frequency or duration of use. Use of dietary supplements and medications containing probiotics were likewise reported. Height and weight were measured at each visit, and z-scores were calculated using the Centers for Disease Control and Prevention (CDC) growth chart. Parents reported if they smoked cigarettes, cigars, or pipes either in the household or in the car during pregnancy (mother only) and again at the 9 mo visit (both parents).

Dietary data collection and analysis

Dietary intake was assessed with 3-d food records completed during the same study visit windows as the biomarker blood draws (median difference of 4 d from the first day of the food record to the blood draw). TEDDY families recorded the child s food and supplement consumption, following detailed instructions and examples from TEDDY staff. Families were asked to conduct food records on 3 consecutive days (2 weekdays and 1 weekend day; 7 of food records include nonconsecutive days). Country-specific food composition databases were used to quantify nutrient intake, individual foods were categorized into groups (for example, cereals, fruits, and berries) and the daily averages were calculated for nutrients and food groups. Energy, nutrients, and food groups have been harmonized for comparability across the 4 TEDDY countries, with the exception of fiber, which could not be harmonized for Germany [21,22].

Sample collection

Plasma samples were collected in the years 2004 through 2012 at age 6 mo and annually from 1 y to 4 y of age, up to the

endpoint age for cases and the endpoint age of the matched case for controls. Children living far away from the nearest TEDDY study center followed the long-distance sample collection protocol, in which blood samples were collected by the child s pediatrician and transported to a TEDDY study center within 24 h. Samples were aliquoted into dedicated, barcoded (Symnol LS 2208), and color-coded cryovials as determined by the type of analyses to be performed [23]. Preservatives were added at the initial collection stage to enhance the stability of the analyte. For example, cryovials used for plasma samples designated for ascorbic acid analysis contained 0.2 mL of 5 trichloroacetic acid and 200 mg disodium EDTA/L. The blood samples were then shipped frozen to the NIDDK Repository and immediately stored at –80°C. Quality control (QC) plasma samples that appeared identical to actual subject samples were incorporated into the overall sample management in a blinded manner to determine intra-assay variability.

Laboratory measurements

All dietary biomarker measurements were performed at the Department of Government Services (Biomarkers laboratory), Finnish Institute for Health and Welfare. Storage time from sample collection to laboratory analysis ranged from a mean of 58 mo (range 13–100) for 25(OH)D to a mean of 68 mo (range 25–113) for ascorbic acid.

Ascorbic acid was determined by a modification of a previously published method, by ion-paired, reversed-phase, high-performance liquid chromatography (HPLC) using electrochemical detection [24]. Isoascorbic acid was used as an internal standard for the quantification of ascorbic acid. 25(OH)D concentrations were measured using the ARCHITECT 25-OH vitamin D chemiluminescent microparticle immunoassay, which has been shown to have excellent agreement with liquid chromatography-tandem mass spectrometry [25]. Plasma tocopherols, carotenoids and retinol were analyzed by a modification of a previously published method [26] by first precipitating proteins with ethanol, followed by extraction with hexane and HPLC. α-tocopherol and γ-tocopherol were analyzed by reversed-phase HPLC and uorescence detection. Trans-- -carotene and retinol were determined by reversed-phase HPLC with multiwavelength detection. The cholesterol assay (Abbott Laboratories) was used to analyze cholesterol enzymatically, using the ARCHITECT ci8200 analyzer. Intra-assay precision [coefficient of variation (CV)] of the methods was 4.6 –5.6 for ascorbic acid, α-tocopherol, γ-tocopherol, -carotene, and retinol, 2.8 for 25(OH)D, and 0.6 for cholesterol, for control samples used for validation of the method. Inter-assay precision (CV) of QC samples included in each batch during analysis of case-control samples were as follows: ascorbic acid (9.9 ± 0.8), 25(OH)D (4.0 ± 0.5), α-tocopherol (9.2 ± 3.1), γ-tocopherol (6.0 ± 0.2), -carotene (6.0 ± 2.4), retinol (7.3 ± 0.8), and cholesterol (1.40 ± 0.03) [mean ± standard deviation (SD)].

Statistical analysis of the QC sample values indicated there was no significant batch effect on any of the analytes. To achieve the best possible accuracy, the values of calibrators were compared with reference standards. Certified reference materials were purchased from NIST. For standardizing measurements and for ensuring analytical reliability, the laboratory took part in external quality assessment programs. For 25(OH)D, the laboratory participated in DEQAS and in Labquality programs. For cholesterol, the laboratory participated in the Lipid Standardization Program organized by the CDC and Labquality. For fat-soluble vitamins, ascorbic acid, and carotenoids, the laboratory participated in Micronutrients Measurement Quality Assurance Program arranged by NIST.

SNP genotyping and imputation

SNPs were genotyped using the ImmunoChip and/or the T1DExomeChip (a custom genotyping array with >90,000 custom content SNPs added to the Infinium CoreExome-24 v.1.1 BeadChip) at the Center for Public Health Genomics at the University of Virginia. QC measures involved excluding individuals with a low call rate (95) or discordance with reported sex, and SNPs with a low call rate (95), deviating from Hardy–Weinberg equilibrium in controls with the European ancestry, or with concordance 99 in duplicates, as described previously [27]. Genome-wide association study (GWAS) imputation analysis was conducted using the Trans-Omics for Precision Medicine (TOPMed) freeze 8 reference panel (built from 97,256 deeply sequenced human genomes containing >308.1 million genetic variants), the 1000 Genomes, and a subset of the TEDDY subjects ($n = 1119$) with the whole-genome sequencing data as reference panels. MetaMinimac2 was used to combine genotype data imputed against these 3 reference panels. For imputed genotype data, we retained rare variants with minor allele frequency >0.5 in unrelated controls with European ancestry and with imputation quality $R^2 > 0.50$.

Statistical analyses

Samples were excluded from analyses if any of the 6 dietary biomarkers were not available or if food record data or anthropometric data was not collected for the child at the same age. Samples from children in the United States and Finland were more likely to be included than those from Germany or Sweden (P 0.001). Outcomes were the standardized, log base 2 transformed, circulating concentrations of vitamin A (retinol and -carotene), vitamin C (ascorbic acid), vitamin D (25(OH)D), and vitamin E (α-tocopherol and γ-tocopherol). Key exposures for the 6 biomarkers, respectively, were dietary intake of retinol, -carotene, vitamin C, vitamin D, and the same variable for vitamin E (α-tocopherol equivalents) for both tocopherols [all intakes were log base 2 transformed and then centered and standardized (mean = 0, SD = 1)]. Biomarker concentration distributions within the included population were summarized by visit, country, and biological sex. Relationships across biomarkers were quantified with Pearson correlation coefficients. Longitudinal trends within each biomarker were also summarized with Pearson correlation coefficients between samples from during infancy (6 mo) and after infancy (24 mo).

Associations between selected exposures and biomarker concentrations were assessed by multivariable linear regression analyses for each biomarker outcome with random intercepts to account for the correlation of biomarker measurements from the same child. Three categories of exposures were included, with mutual adjustment for the exposures within each category. The first model for each outcome regressed the biomarker concentration on dietary intake of the same and other nutrients, selected a priori for each nutrient separately based on a literature review. Associations for the same-nutrient intakes are from the first model

set because this re ects typical dietary habits in which no 1 nutrient is consumed in isolation; however, additional models were analyzed without adjusting for intake of other nutrients. The second model set included intake of key food groups (original units of g/d were log base 2 transformed, centered, and standardized): cereals, fruits and berries, vegetables, meats, fish and seafood, milk and milk products, fats, juices, infant formula (any or none), and breastmilk (any or none). The third model set included the exposures of weight (continuous; *z*-score), height (continuous; *z*-score), celiac disease status (healthy, past celiac disease diagnosis, celiac disease diagnosis within the next year), gastrointestinal infection within 14 d before blood draw (yes or no), respiratory infection within 14 d before blood draw (yes or no), antibiotic use during the same month of age as the blood draw (yes or no), ongoing probiotic use (yes or no), and parent smoking status (≥1 parent smokes; yes or no). The third model for vitamin D also included season of blood draw (continuous; time in months from the nearest occurrence of September 1st). We additionally examined the associations between dietary biomarkers and human leukocyte antigen (HLA) genotype (any DR3 compared with no DR3) and SNPs, with each SNP assessed individually. Included SNPs were those identified as having a significant association with circulating biomarker concentration in the most recent available GWAS studies for each nutrient [28–35]. A total of 5 SNPs were included for retinol, 2 for -carotene, 10 for ascorbic acid, 87 for 25(OH)D, 7 for α-tocopherol, and 3 for γ-tocopherol. All models were adjusted for same-nutrient intake, biological sex (male or female), age (restricted cubic splines with knots at the 10th, 50th, and 90th percentiles), clinical center (Colorado, Georgia, Washington, Finland, Germany, and Sweden), NCC study and case status, type 1 diabetes first degree relative status (a matching factor for the NCC study), and long distance protocol status. Sensitivity analyses were conducted excluding supplement users, and separately, excluding visits with a food record shorter than 3 d. Additionally, variance in ation factors were checked to assess potential multicollinearity.

All exposures were additionally assessed as potential effect modifiers of the association between dietary intake and biomarker concentration, with an interaction term between the exposure and dietary intake. Main effects of exposures were not adjusted for multiple comparisons because all covariates were selected a priori; however, the interaction analyses were of an exploratory nature, and therefore, *P* values from interactions terms were adjusted using the false discover rate control method. We additionally examined the determinants of the ratio of α-tocopherol to γ-tocopherol, following the same procedure as outlined for the raw biomarkers.

Data management was conducted using SAS 9.4 (SAS Institute), and analyses were performed using R version 4.3.1 [36] with multilevel models fit using the package lme4 [37].

Results

A total of 2887 plasma samples were collected from 1490 children (Supplemental Figure 1) with a median of 2 time points per child. The majority of samples were drawn at 6 mo (1005 samples) and 12 mo (912 samples) of age (Supplemental Table 1). Biomarker distributions stratified by country and by sex are shown in Supplemental Tables 2 and 3, and distributions of exposure variables are shown in Supplemental Table 4.

Longitudinal biomarker trends

Median retinol and -carotene both peaked at age 12 mo, whereas ascorbic acid trended downward with age, 25(OH)D peaked at age 24 mo, α-tocopherol reached its nadir at age 24 mo, and γ-tocopherol appeared to increase with age (Figure 1). Trends varied by country, particularly for 25(OH)D, which increased with age in the United States and Finland but decreased with age in Germany and Sweden (Supplemental Figure 2). Nonlinear trends for age were confirmed with likelihood ratio test model comparisons, in which models with restricted cubic splines for age were a significantly better fit than those without splines for all biomarkers.

Correlations between and within biomarkers

The strongest correlation among biomarkers was between α-tocopherol and γ-tocopherol {Pearson s correlation $r = 0.43$ [95 confidence interval (CI)]: 0.35, 0.50) at age 12 mo; Figure 2}. In contrast, the correlation was weak [$r = 0.06$ (95 CI: –0.03, 0.14)] between circulating retinol and -carotene, a retinol precursor. A moderate correlation was seen between α-tocopherol and both -carotene [$r = 0.22$ 95 CI: 0.14, 0.31)] and ascorbic acid [$r = 0.21$ (95 CI: 0.14, 0.28)].

Correlations within each biomarker across ages (6 mo compared with 24 mo) showed the weakest correlation for ascorbic acid [$r = 0.15$ (95 CI: 0.002, 0.30)] and the strongest correlation for γ-tocopherol [$r = 0.42$ (0.23, 0.62)]. Other within-biomarker correlations were retinol $r = 0.20$ (95 CI: 0.03, 0.36), -carotene $r = 0.38$ (95 CI: 0.25, 0.51), 25(OH)D $r = 0.24$ (95 CI: 0.10, 0.38), and α-tocopherol $r = 0.18$ (95 CI: 0.04, 0.32).

Dietary determinants of biomarkers

All biomarkers except retinol were positively associated with intake of the same nutrient after adjusting for the intake of other nutrients (Table 1). Associations were similar or stronger without adjustment for other nutrients (Supplemental Table 5). The strongest associations between other nutrients and biomarkers, after adjustment for same-nutrient intake, were between PUFA and 25(OH)D (SD: 0.25, 95 CI: 0.18, 0.31), and fiber and -carotene (SD: 0.22, 95 CI: 0.18, 0.26). There was also a notable inverse association between energy intake and vitamin D concentration (SD: –0.30, 95 CI: –0.36, –0.23). Associations of food group intakes with biomarkers adjusted for same-nutrient intake tended to be weak; nonetheless, every biomarker was significantly associated with the intake of at least one food group (Table 2). The strongest food group association was between vegetable intake and -carotene concentration (SD: 0.22, 95 CI: 0.18, 0.26). The intake of any infant formula and any breastmilk had opposite directions of association with retinol concentration [infant formula: 0.16 (95 CI: 0.06, 0.26); breastmilk: –0.35 (95 CI: –0.45, –0.25)] and with γ-tocopherol concentration [infant formula: 0.14 (95 CI: 0.05, 0.24); breastmilk: –0.34 (95 CI: –0.43, –0.24)]. There were no notable differences after excluding supplement users or after excluding visits with food records shorter than 3 d.

We found evidence of statistical interaction (false discover rate adjusted for multiple comparisons) between several exposures with dietary same-nutrient intake on biomarker concentration. -carotene and γ-tocopherol had the highest number of significant interactions, whereas we did not find any evidence of

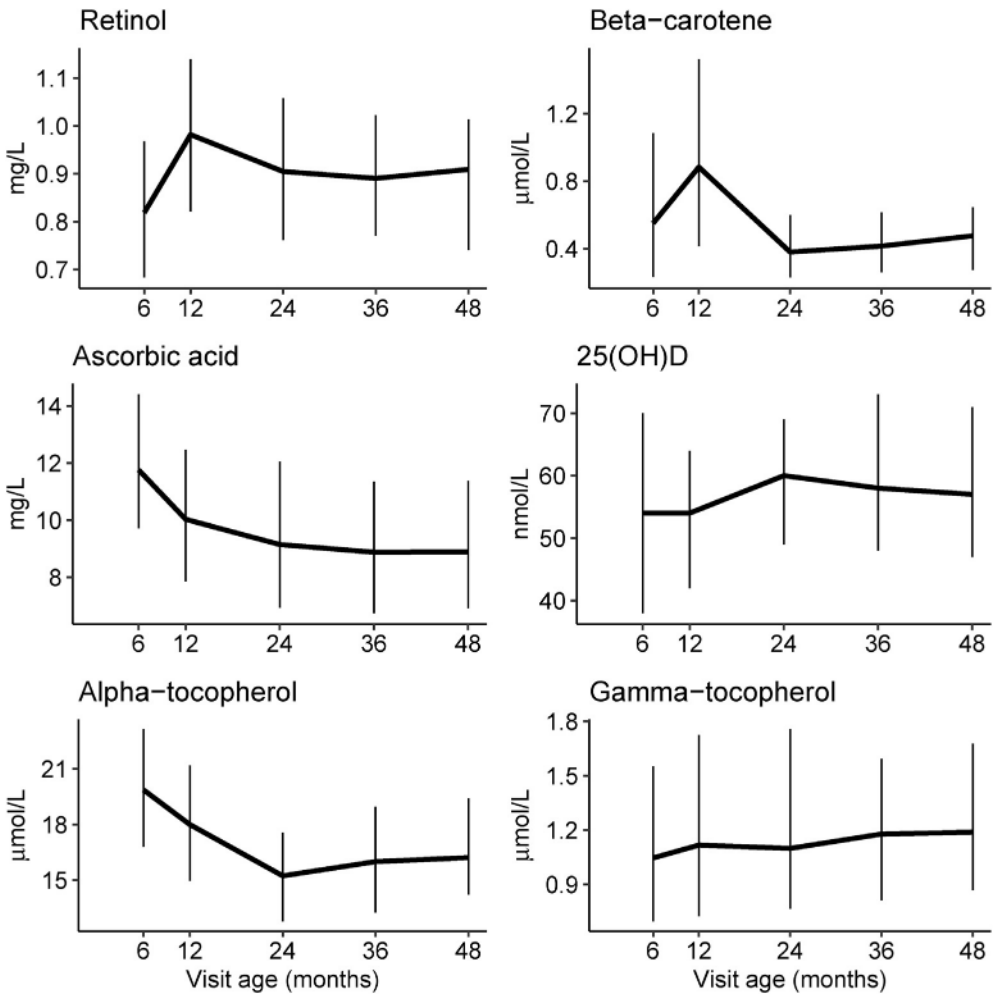

FIGURE 1 Median and interquartile range plasma concentration of 6 dietary biomarkers by age, in the TEDDY study. Samples sizes differ by age: 6 mo $N = 1005$, 12 mo $N = 912$, 24 mo $N = 533$, 36 mo $N = 292$, and 48 mo $N = 145$.

interactions for ascorbic acid (Figure 3). There was, for example, a negative interaction between respiratory infection and -carotene, indicating a weaker association between intake and circulating concentration for children with a recent respiratory infection. We also investigated determinants of the ratio of α-tocopherol to γ-tocopherol and found an inverse association with PUFA intake (SD: –0.14, 95 CI: –0.21, –0.06).

Because fiber intake data from Germany was not able to be harmonized with the other TEDDY countries, we checked for interactions between fiber intake and clinical center (reference = Colorado). There was a significant interaction for Washington in the retinol model, for Finland in the -carotene model, for Finland and Germany in the ascorbic acid model, for Germany and Sweden in the 25(OH)D model, for Washington and Sweden in the α-tocopherol model, and for Germany and Sweden in the γ-tocopherol model.

Nondietary determinants of biomarkers

Strong associations were seen in the comparison of European clinical centers compared with Colorado, in particular, for ascorbic acid and γ-tocopherol, with lower concentrations at the European centers (Table 3). Inverse associations were identified between recent gastrointestinal infection and -carotene (–0.32, 95 CI: –0.50, –0.14), ascorbic acid (–0.38, 95 CI: –0.60, –0.15), and α-tocopherol (–0.27, –0.45, –0.10). In contrast, recent respiratory infection was inversely associated with retinol (–0.40, 95 CI: –0.48, –0.32), as was antibiotic use (–0.16, 95 CI: –0.29, –0.04).

Previously identified SNPs associated with biomarker concentrations that were confirmed in our analysis are listed in Table 4 (the complete list of SNP associations is presented in Supplemental Table 6). Additionally, there was statistical evidence that the association between dietary intake and biomarker concentration was modified by 21 SNPs for vitamin D (listed in Supplemental Material), 2 SNPs for ascorbic acid (rs117885456 and rs56738967), 1 SNP for α-tocopherol (rs12272004), 1 SNP for γ-tocopherol (rs4238001), and 2 for -carotene (HLA DR3 and rs6564851).

Discussion

Our study in 1490 children in the TEDDY cohort, ≤4 y of age, describes the distributions and correlations of 6 dietary biomarkers and their associations with dietary and nondietary exposures. We observed positive associations between intake and plasma concentrations of all nutrients except retinol, and nonlinear associations with age. We found an inverse association between retinol and respiratory (but not gastrointestinal)

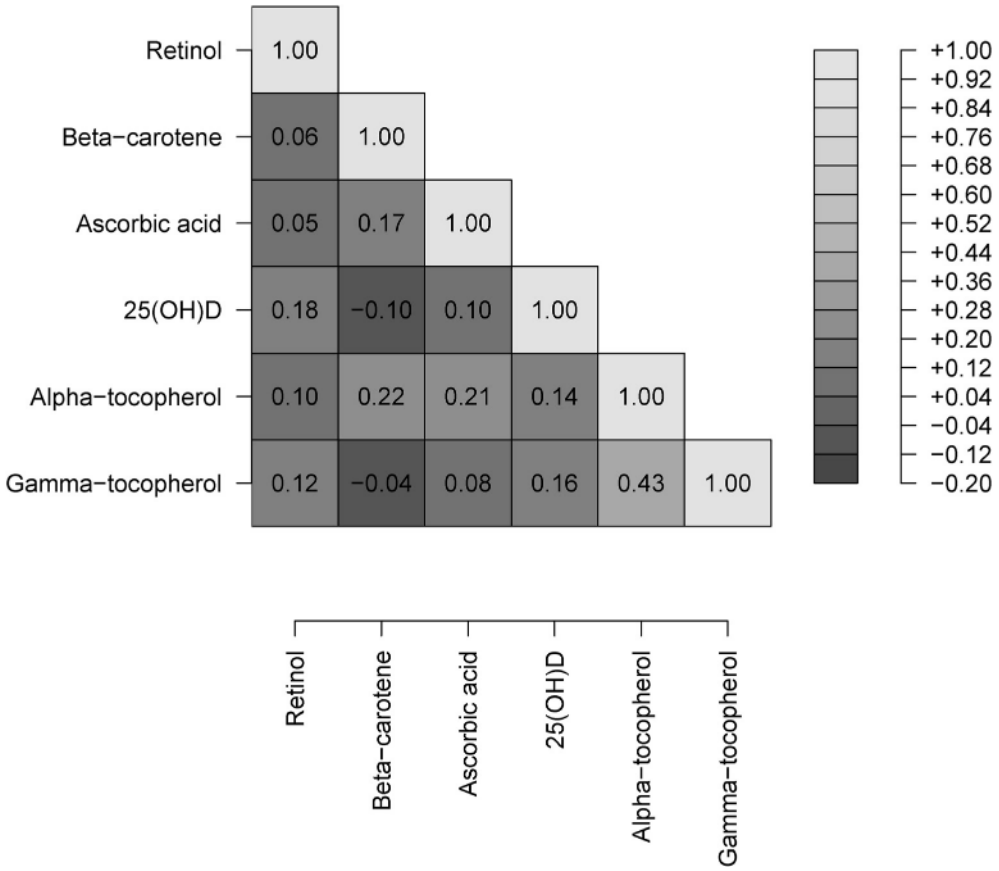

FIGURE 2 Pearson correlation coefficients between dietary biomarkers from the 12-mo visit. Among 912 samples from the TEDDY study.

TABLE 1
Associations between nutrient intake and biomarker concentrations in 2887 samples collected from 1490 children in the TEDDY study

	Retinol	-carotene	Ascorbic acid	25(OH)D	α-tocopherol	γ-tocopherol
Retinol	–0.02 (–0.06, 0.02)					
-carotene		0.35 (0.32, 0.38)				
Vitamin C			0.32 (0.28, 0.36)			
Vitamin D				0.35 (0.31, 0.39)		
Vitamin E					0.17 (0.13, 0.21)	0.12 (0.07, 0.16)
Iron	0.10 (0.05, 0.16)	0.14 (0.10, 0.18)	0.00 (–0.05, 0.04)	0.04 (0.00, 0.08)	0.10 (0.06, 0.15)	0.20 (0.15, 0.25)
Fiber	0.08 (0.03, 0.13)	0.22 (0.18, 0.26)	0.02 (–0.03, 0.06)	0.03 (–0.01, 0.07)	0.00 (–0.03, 0.04)	–0.01 (–0.05, 0.04)
PUFA	–0.10 (–0.17, –0.03)	–0.03 (–0.09, 0.02)		0.25 (0.18, 0.31)	0.08 (0.02, 0.14)	0.18 (0.11, 0.26)
Zinc	0.21 (0.15, 0.27)	–0.08 (–0.13, –0.03)				
Calcium				0.13 (0.08, 0.18)		
Energy	0.00 (–0.07, 0.07)	–0.09 (–0.14, –0.04)	–0.16 (–0.21, –0.10)	–0.30 (–0.36, –0.23)	–0.13 (–0.18, –0.08)	–0.13 (–0.18, –0.07)

Abbreviations: FDR, first degree relative; LDP, long distance protocol; NCC, nested case-control; TEDDY, The Environmental Determinants of Diabetes in the Young.

Each column contains results from 1 linear regression model with random intercepts, mutually adjusted for all covariates listed in the table rows and NCC cohort and case status, FDR status, LDP status, sex, age, clinical center, season (25(OH)D only), and plasma cholesterol (-carotene and tocopherols only).

Coefficients (95 confidence intervals) indicate the estimated change in log biomarker concentration (in standard deviation units) associated with a 1 standard deviation increase in the log intake of the nutrient. Nutrients for each model were selected a priori based on a literature review.

infections, and inverse associations between weight and several nutrient concentrations. Strong associations were identified for breastmilk and infant formula intake with several biomarkers. Some exposures that were not found to be associated with the biomarkers did modify the association between same-nutrient intake and biomarker concentration, for example, respiratory infection and -carotene.

We observed associations between SNPs and biomarker concentrations, and were able to validate some, but not all, previous findings. A low sample size likely contributes to the null results; however, there could also be true heterogeneity between this cohort of young children who are genetically at high risk for type 1 diabetes compared with adults or those with a different genetic background. We found an interaction between DR3 and

TABLE 2
Associations between food group intakes and biomarker concentrations in 2887 samples collected from 1490 children in the TEDDY study

	Retinol	-Carotene	Ascorbic acid	25(OH)D	α-Tocopherol	γ-Tocopherol
Intake of the respective nutrient	–0.01 (–0.05, 0.03)	0.27 (0.24, 0.30)	0.31 (0.27, 0.35)	0.35 (0.31, 0.39)	0.21 (0.18, 0.24)	0.17 (0.13, 0.20)
Cereals	0.03 (–0.04, 0.09)	0.04 (0.00, 0.09)	–0.02 (–0.08, 0.04)	–0.08 (–0.13, –0.03)	0.08 (0.03, 0.12)	0.08 (0.02, 0.13)
Fruits and berries	–0.01 (–0.05, 0.04)	0.10 (0.07, 0.13)	0.05 (0.00, 0.09)	–0.03 (–0.07, 0.00)	–0.01 (–0.04, 0.03)	0.00 (–0.04, 0.04)
Vegetables	0.07 (0.03, 0.12)	0.22 (0.18, 0.26)	–0.01 (–0.06, 0.03)	0.03 (–0.01, 0.07)	–0.02 (–0.06, 0.01)	–0.06 (–0.10, –0.02)
Meats	–0.01 (–0.06, 0.04)	0.04 (0.00, 0.07)	0.01 (–0.04, 0.06)	–0.01 (–0.05, 0.03)	–0.05 (–0.09, –0.02)	0.01 (–0.04, 0.05)
Fish and seafood	–0.01 (–0.05, 0.03)	0.01 (–0.01, 0.04)	–0.02 (–0.06, 0.02)	–0.03 (–0.06, 0.01)	0.00 (–0.03, 0.03)	0.01 (–0.02, 0.04)
Milk and milk products	0.09 (0.05, 0.14)	0.08 (0.04, 0.11)	–0.07 (–0.12, –0.02)	0.09 (0.05, 0.14)	–0.01 (–0.05, 0.02)	0.06 (0.02, 0.11)
Fats	0.10 (0.04, 0.16)	0.03 (–0.01, 0.08)	0.02 (–0.05, 0.08)	0.10 (0.04, 0.15)	–0.03 (–0.08, 0.02)	0.07 (0.02, 0.13)
Juices	0.02 (–0.02, 0.06)	0.06 (0.03, 0.10)	–0.01 (–0.05, 0.04)	–0.01 (–0.05, 0.02)	0.02 (–0.01, 0.06)	0.00 (–0.04, 0.03)
Any infant formula	0.16 (0.06, 0.26)	0.05 (–0.02, 0.13)	0.21 (0.10, 0.31)	0.08 (0.00, 0.17)	0.26 (0.18, 0.34)	0.14 (0.05, 0.24)
Any breastmilk	–0.35 (–0.45, –0.25)	0.01 (–0.06, 0.09)	0.12 (0.02, 0.23)	–0.21 (–0.30, –0.12)	0.05 (–0.03, 0.13)	–0.34 (–0.43, –0.24)

Abbreviations: FDR, first degree relative; LDP, long distance protocol; NCC, nested case-control; TEDDY, The Environmental Determinants of Diabetes in the Young.

Each column contains results from 1 linear regression model with random intercepts, mutually adjusted for all covariates listed in the table rows and NCC cohort and case status, FDR status, LDP status, sex, age, clinical center, energy intake, season (25(OH)D only), and plasma cholesterol (-carotene and tocopherols only).

Coefficients (95 confidence intervals) indicate the estimated change in log biomarker concentration (in standard deviation units) associated with a 1 standard deviation increase in the log intake of the nutrient or food group. The first row is intake of the same nutrient as the respective biomarker. For example, a 1 standard deviation increase in the log transformed intake of -carotene is associated with a 0.27 standard deviation increase in log transformed circulating -carotene concentration. Infant formula and breastmilk are dichotomous (any compared with none).

-carotene; however, because DR3 is usually inherited as part of an extended haplotype encompassing HLA class I, class II, and class III genes, we cannot determine which gene within this region directly affects -carotene metabolism.

A previous study from Colorado in a similar population of children at increased risk for type 1 diabetes examined determinants of circulating micronutrients [38]. In agreement with our findings, they showed higher vitamin D concentration in warmer compared with cooler months, and a positive association between same-nutrient intake and circulating concentration for most nutrients. In contrast to our results, they found an association between environmental smoke exposure and -carotene but not retinol. Differences in which covariates were adjusted for and the slightly older age range (9 mo–8 y) of their population may partially explain the discrepant findings. A Finnish study, also enrolling children at risk for type 1 diabetes, reported consistent findings for -carotene, with serum concentration higher at age 1 y than that at age 2 or 3, and a strong association between vegetable intake and -carotene circulating concentration [39]. A 2022 systematic review reported use of circulating concentrations of retinol, -carotene, ascorbic acid, and α-tocopherol as markers of fruit and vegetable intake in children, with variability in the reported relative strength of associations for individual fruits and vegetables [40]. Their findings suggest that a more detailed assessment of food groups may be beneficial to further explore the relationship between food intake and dietary biomarkers. In contrast to our findings, prior studies in populations of United States and British children and adolescents have shown a positive association between retinol intake and its circulating concentration [41–43].

There are several mechanisms through which the diet can impact micronutrient status, including a possible role for nutrients that shape the microbiome including fiber and iron, via altered nutrient absorption [8]. Similarly, antibiotic medications and probiotic supplement use may in uence biomarkers through their effect on the microbiome [9]. The food matrix may be in uential through its impact on nutrient bioavailability and absorption. For example, the bioavailability of -carotene is higher from fruit compared with vegetable sources [10], and fat-soluble nutrients (including vitamins A, D, and E) are absorbed more efficiently when consumed together with fats [10]. The bioavailability of vitamin E varies by form, being higher for α-tocopherol than γ-tocopherol [11]. There are synergistic and antagonistic interactions across nutrients, often a re ection of their overlapping metabolic pathways. For example, high doses of α-tocopherol intake have been shown to deplete plasma γ-tocopherol concentration, and the overall requirement for vitamin E is dependent on the amount of PUFA intake [11, 44]. Other examples include the negative impact of zinc deficiency on vitamin A status markers because of their coordinated metabolic roles, and potential changes in retinol metabolism by -carotene metabolites through a competitive binding to retinoid receptors [10,12]. Differences in associations between micronutrient status with breastmilk compared with infant formula consumption could be explained by modification of the gastrointestinal tract by bioactive compounds in breastmilk [45].

Care must be taken in searching for potential causal associations between exposures and biomarker concentrations. Feedback mechanisms of endogenous regulatory processes designed to maintain concentration of vital nutrients obscure these relationships. The association between body size and nutrient status is particularly challenging to study because there is a circular causal pathway, in which obesity in uences biomarker concentration and also deficiency of several micronutrients may increase obesity through altered macronutrient metabolism [46]. Furthermore, circulating concentration of fat-soluble nutrients may not be an accurate representation of true nutrient status in obese patients because of substantial nutrient reserves in adipose tissue [46]. Similarly, the distribution of several nutrients is altered in a state of in ammation, and therefore, the

Modifying factor	Retinol	Beta-carotene	Ascorbic acid	25(OH)D	Alpha-tocopherol	Gamma-tocopherol
Male						
Georgia (vs Colorado)				-		
Washington (vs Colorado)					+	+
Finland (vs Colorado)		+		-		
Germany (vs Colorado)		+				
Sweden (vs Colorado)						-
Weight z-score					+	
Height z-score					+	
Celiac disease						
Celiac disease within 1 year						
Gastrointestinal infection						
Respiratory infection		-				
Antibiotic use						
Probiotic use						
Parent smokes	+				+	
Cereals		+				-
Fruits and berries		+				-
Vegetables		+				
Meats	+	+		-		-
Fish and seafood						-
Milk and milk products		-				-
Fats		+				-
Juices		+				-
Any infant formula	-	-				
Any breastmilk		+				+
Iron intake	-	-			+	
Fiber intake		+		-		
PUFA intake		-			+	
Zinc intake		-				
Calcium intake						

FIGURE 3 Interactions between dietary intake of a nutrient and potential modifying factors in relation to circulating biomarker concentration in the TEDDY study. False discovery rate adjusted *P* values from interaction terms are summarized as positive interaction, negative interaction, or no interaction. Gray cells indicate interactions that were not tested because these factors were not identified as potential determinants based on a literature review. TEDDY, The Environmental Determinants of Diabetes in the Young.

validity of plasma measurements as a measure of overall nutrient status may be weaker in patients with heightened levels of in ammation.

There were several strengths in the present study, including the use of a standard protocol for sample collection and exposure data collection across all clinical centers, and harmonized dietary intake data across the 4 countries. The TEDDY study is a uniquely rich resource with a span of different data types (plasma samples, diet, genetics, and clinical data) available for the same population across multiple timepoints. Most previous studies on the determinants of dietary biomarkers have focused on adult populations, and findings from these studies cannot always be extrapolated to juvenile populations because many physiological processes vary across age groups. Therefore, our study of children aged 6 mo–4 y is valuable for understanding the utility of dietary biomarkers in epidemiological studies for childhood diseases.

Limitations of our study include having a largely European-descent population, so results may not be generalizable to other ethnic groups. Additionally, children were not fasting at

TABLE 3
Demographic and medical history determinants of dietary biomarker concentrations in 2887 samples collected from 1490 children in the TEDDY study

	Retinol	-Carotene	Ascorbic acid	25(OH)D	α-Tocopherol	γ-Tocopherol
Intake of the respective nutrient (1 SD)	0.04 (0.01, 0.08)	0.44 (0.41, 0.47)	0.30 (0.26, 0.34)	0.42 (0.38, 0.45)	0.23 (0.21, 0.26)	0.26 (0.22, 0.29)
Male	–0.04 (–0.13, 0.05)	0.06 (–0.01, 0.13)	0.00 (–0.09, 0.08)	0.01 (–0.07, 0.09)	–0.15 (–0.22, –0.08)	–0.10 (–0.18, –0.02)
Georgia (vs. Colorado)	0.24 (0.05, 0.44)	0.14 (–0.02, 0.29)	0.10 (–0.07, 0.28)	0.18 (0.00, 0.35)	0.10 (–0.05, 0.25)	0.22 (0.05, 0.40)
Washington (vs. Colorado)	–0.12 (–0.30, 0.06)	0.10 (–0.04, 0.25)	–0.08 (–0.24, 0.07)	0.12 (–0.04, 0.29)	–0.01 (–0.15, 0.13)	–0.14 (–0.31, 0.02)
Finland (vs. Colorado)	–0.19 (–0.33, –0.05)	0.60 (0.49, 0.72)	–0.56 (–0.69, –0.43)	–0.84 (–0.97, –0.71)	–0.18 (–0.29, –0.07)	–1.09 (–1.23, –0.96)
Germany (vs. Colorado)	–0.44 (–0.76, –0.12)	0.35 (0.10, 0.60)	–0.51 (–0.82, –0.20)	–0.02 (–0.30, 0.26)	0.20 (–0.05, 0.44)	–1.08 (–1.37, –0.79)
Sweden (vs. Colorado)	–0.21 (–0.36, –0.06)	0.11 (0.00, 0.23)	–0.83 (–0.97, –0.70)	–0.22 (–0.35, –0.09)	0.02 (–0.10, 0.13)	–0.79 (–0.93, –0.66)
Weight z-score	0.04 (–0.02, 0.09)	–0.06 (–0.10, –0.02)	–0.05 (–0.10, 0.00)	–0.09 (–0.14, –0.04)	–0.05 (–0.09, –0.01)	0.01 (–0.04, 0.06)
Height z-score	–0.01 (–0.07, 0.04)	0.01 (–0.03, 0.05)	0.00 (–0.05, 0.05)	0.05 (0.01, 0.10)	–0.05 (–0.09, 0.00)	–0.08 (–0.13, –0.03)
Celiac disease	0.65 (0.09, 1.20)	–0.43 (–0.86, 0.01)	0.22 (–0.34, 0.79)	0.25 (–0.23, 0.73)	0.08 (–0.35, 0.50)	0.00 (–0.50, 0.50)
Celiac within the next year	–0.14 (–0.66, 0.38)	–0.46 (–0.86, –0.05)	–0.42 (–0.94, 0.11)	–0.17 (–0.62, 0.27)	0.34 (–0.06, 0.73)	–0.14 (–0.61, 0.33)
Gastrointestinal infection[1]	–0.14 (–0.36, 0.09)	–0.32 (–0.50, –0.14)	–0.38 (–0.60, –0.15)	0.17 (–0.02, 0.36)	–0.27 (–0.45, –0.10)	–0.10 (–0.31, 0.10)
Respiratory infection[1]	–0.40 (–0.48, –0.32)	–0.05 (–0.11, 0.01)	–0.08 (–0.16, 0.00)	–0.07 (–0.13, 0.00)	0.05 (–0.01, 0.11)	–0.02 (–0.09, 0.06)
Antibiotic use[2]	–0.16 (–0.29, –0.04)	0.02 (–0.08, 0.12)	–0.02 (–0.14, 0.11)	0.10 (–0.01, 0.20)	0.01 (–0.09, 0.10)	0.00 (–0.12, 0.11)
Probiotics use	–0.04 (–0.20, 0.11)	–0.09 (–0.21, 0.03)	0.15 (0.00, 0.30)	0.05 (–0.09, 0.18)	0.07 (–0.04, 0.19)	–0.12 (–0.26, 0.02)
Parent smokes	0.14 (0.03, 0.26)	–0.03 (–0.12, 0.06)	0.02 (–0.09, 0.13)	0.01 (–0.10, 0.11)	–0.03 (–0.12, 0.06)	0.10 (0.00, 0.21)
Season (time from Sep 1; per mo)				–0.11 (–0.13, —0.10)		

Abbreviations: FDR, first degree relative; LDP, long distance protocol; NCC, nested case-control; SD, standard deviation; TEDDY, The Environmental Determinants of Diabetes in the Young.
Coefficients (95 confidence intervals) indicate the estimated change in log biomarker concentration (in SD units) associated with a 1-unit change in the exposure. The first row is intake of the same nutrient as the respective biomarker.
Each column contains results from 1 linear regression model with random intercepts, mutually adjusted for all covariates listed in the table rows and NCC cohort and case status, FDR status, LDP status, age, and plasma cholesterol (-carotene and tocopherols only).
[1] Within 14 d before the date of blood draw, based on parent report.
[2] Taken during the same month of age as blood draw.

TABLE 4
SNPs significantly associated (P 0.05) with dietary biomarker concentration in the TEDDY study

Biomarker	Gene	SNP	Minor allele	SD change in biomarker concentration (95 CI)	P value
Retinol	FFAR4	rs10882272	G	–0.11 (–0.18, –0.05)	0.001
	RBP4	rs10882283	C	–0.14 (–0.21, –0.07)	0.001
-Carotene		rs6564851	G	0.19 (0.14, 0.24)	0.001
Ascorbic acid	BCAS3	rs9895661	G	–0.08 (–0.15, –0.01)	0.028
	SLC23A1	rs33972313	A	–0.49 (–0.67, –0.32)	0.001
25(OH)D		rs1065853	T	0.13 (0.02, 0.25)	0.025
		rs148514005	T	–0.97 (–1.47, –0.47)	0.001
		rs17765311	C	–0.09 (–0.15, –0.03)	0.003
		rs73015021	G	–0.11 (–0.21, –0.02)	0.015
	COPB1	rs571484036	G	1.46 (0.48, 2.44)	0.004
	CYP2R1	rs117576073	T	–0.33 (–0.56, –0.09)	0.006
	CYP2R1	rs117913124	A	–0.62 (–0.81, –0.44)	0.001
	GC	rs11723621	G	–0.24 (–0.30, –0.18)	0.001
	GC	rs560384646	C	–0.49 (–0.88, –0.10)	0.014
	PDE3B	rs10832289	T	–0.15 (–0.21, –0.09)	0.001
	PDE3B	rs188480917	G	–0.54 (–0.80, –0.28)	0.001
	PRKAR1A	rs2909218	T	0.08 (0.00, 0.15)	0.037
	PSMA1	rs554808052	A	–0.96 (–1.88, –0.04)	0.041
	PSMA1	rs577185477	C	–0.65 (–0.94, –0.37)	0.001
	SEC23A	rs8018720	G	0.08 (0.00, 0.16)	0.038
α-Tocopherol	CYP4F2	rs2108622	A	0.09 (0.03, 0.15)	0.002
γ-Tocopherol	SEC14L2	rs182488695	A	0.62 (0.02, 1.22)	0.042

Abbreviations: FDR, first degree relative; LDP, long distance protocol; NCC, nested case-control; SD, standard deviation; SNP, single nucleotide polymorphism; TEDDY, The Environmental Determinants of Diabetes in the Young.
Candidate SNPs were selected primarily from GWAS studies, with additional SNPs selected for retinol, -carotene, and the tocopherols.
Adjusted for same-nutrient intake, NCC cohort and case status, FDR status, LDP status, age, energy intake, season (25(OH)D only), and plasma cholesterol (-carotene and tocopherols only).

the time of blood sample collection, and samples were not always drawn at the same time of day. We were reliant on parent-reported information for most exposure data including dietary intake and respiratory and gastrointestinal infections. In future analyses, it may be possible to incorporate virome data or in- ammatory biomarkers as alternative measures of infection and acute in ammation. This would allow investigation of subclinical infections, which have been shown to impact micronutrient status [4], as well as further exploration of mechanisms underlying the divergent associations for gastrointestinal compared with respiratory infections. Although we do have measured weight and height, body fat percentage was not measured at the visits included in the present analysis; therefore, the role of obesity as a determinant of biomarker concentrations is obscured. Fiber intake data was not able to be harmonized for Germany; therefore, we checked for interactions between fiber intake and clinical center. Our results showed interactions for centers other than just Germany, so although we cannot rule out bias from unharmonized intake data, there is likely also true heterogeneity for the associations of fiber and biomarker concentrations by location.

We identified several notable determinants of dietary biomarker concentration, and modifiers of the intake-biomarker relationship, including gastrointestinal and respiratory infections, and intake of breastmilk and infant formula. Our findings will facilitate improved design of future analyses exploring the role of diet in childhood chronic disease etiology through a better understanding of relevant potential confounders and mediators of the diet–outcome relationships. In addition to frequently collected demographic information, it may be necessary to consider incorporating records of acute and chronic health conditions, anthropometric measurements, and genetic data in future investigations on the relationship between diet and health.

Author contributions

The authors responsibilities were as follows – JLC: designed research, performed statistical analysis, wrote paper, had primary responsibility for final content; JY: designed research, wrote paper; LH: designed research; PA: conducted research; KL: designed research; HMP: conducted research; CAA: designed research; UU: designed research, wrote paper; JMN: designed research; SMV: designed research; IE: designed research, conducted research; and all authors have read and approved the final manuscript.

Con ict of interest

All authors report no con ict of interest.

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Data availability

Data from The Environmental Determinants of Diabetes in the Young (https://doi.org/10.58020/y3jk-x087) reported here will be made available for request at the NIDDK Central Repository (NIDDK-CR) website, Resources for Research (R4R), https://repository.niddk.nih.gov/.

Appendix A Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tjnut.2024.10.001.

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