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Maternal Dietary Supplement Use and Development of Islet Autoimmunity in the offspring: the TEDDY Study

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Abstract

Objective: We investigated the association between maternal use of vitamin D and omega-3 fatty acids (n-3 FAs) supplements during pregnancy and risk of islet autoimmunity (IA) in the offspring.

Methods: The Environmental Determinants of Diabetes in the Young (TEDDY) Study is prospectively following 8676 children with increased genetic risk for type 1 diabetes in Finland, Germany, Sweden, and the US. Blood samples were collected every 3 months between 3 and 48 months of age then every 6 months thereafter to determine persistent IA. Duration, frequency, and supplement dose during pregnancy were recalled by mothers at 3–4 months postpartum. Cumulative intakes of supplemental vitamin D and n-3 FAs were analyzed as continuous or binary

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Conflict of Interest

The authors declare no conflict of interest.

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variables. We applied time-to-event analysis to study the association between maternal supplement use and IA, adjusting for country, HLA DR-DQ genotype, family history of type 1 diabetes and sex. Secondary outcomes included IAA or GADA as the first appearing autoantibody.

Results: As of February 2018, there were 747 (9.0%) children with IA. Vitamin D supplement intake during pregnancy (any vs none) was not associated with risk for IA (hazard ratio (HR) 1.11; 95% CI 0.94, 1.31); neither was cumulative vitamin D supplement intake. Supplemental n-3 FA intake was similarly not associated with IA risk (HR: 1.19, 95% CI 0.98, 1.45). Similar lack of association was observed for either IAA or GADA as the first appearing autoantibody.

Conclusions: The TEDDY cohort showed no evidence of benefit regarding IA risk for vitamin D or n-3 FA supplementation during pregnancy.

Keywords

dietary supplements; vitamin D; omega-3 fatty acids; pregnancy; islet autoimmunity

Introduction

Vitamin D and omega-3 fatty acid (n-3 FA) intakes from either food or supplements have been hypothesized to be potentially protective against islet autoimmunity (IA) and progression to type 1 diabetes (T1D). Because T1D can be diagnosed during infancy and early childhood, both genetics and environmental factors affecting the fetal environment may play a role in the development of early IA and T1D in young children (1). Maternal supplement use may provide a significant source of n-3 FA and/or vitamin D especially if the maternal diet does not contain significant quantities of dietary sources like fatty fish, fortified dairy products, and flax seeds.

Vitamin D plays a role in immune regulation. B cells, T cells, and other immune cells contain vitamin D receptors, and some cells of the immune system are also able to convert the inactive vitamin D precursor to the active form. The immune system is therefore able to respond to circulating active vitamin D as well as synthesize it (2) . Vitamin D may decrease the antigen-presenting cells that stimulate T cells to proliferate, thereby increasing immunological tolerance. Vitamin D deficiency in infancy and early childhood may trigger an autoimmune response in susceptible individuals by inhibiting immunologic tolerance (3). A meta-analysis of five European case-control studies concluded that vitamin D supplementation in infancy did offer protection against type 1 diabetes compared to no supplementation (4). The TEDDY Study found higher plasma vitamin D associated with a decreased risk of IA, primarily in children carrying a specific variant of the VDR gene(5).

Sufficient maternal vitamin D status, influenced by both food and supplement intake, is necessary for neonates to be born with adult-normal 25(OH)D concentrations (6) and may affect an infant’s risk for an autoimmune response. The ABIS Study in Sweden found Vitamin D supplement use by pregnant mothers did reduce risk for IA in offspring at 1 year of age, but had no effect on IA at 2.5 years of age (7) and later reported no association between maternal supplementation and T1D in offspring (8). The DAISY Study in the US showed benefit of food but not supplement sources of vitamin D in pregnant mom’s diets on

offspring IA (9). Conversely, a Finnish study found no association between maternal consumption of vitamin D from food and supplements during pregnancy and autoimmunity or T1D in offspring (10).

Moreover, maternal serum 25 (OH)D levels from late in pregnancy have been associated with reduced risk for T1D (11) while those from another study drawn in the first trimester have not (12).

Omega-3 fatty acids (n-3 FA) may also be protective against the development of islet autoimmunity. Wei et al. (13) have hypothesized that decreasing the n-6 to n-3 ratio in the body may impact insulin secretion by reducing the n-6 initiated pro-inflammatory cascade thereby protecting beta cells. Supplementation of n-3 FA may affect the n-3 to n-6 ratio enough to reduce risk of IA by reducing inflammation. Cod liver oil supplements, which contain both vitamin D and n-3 FA, when taken during pregnancy have been associated with reduced risk of IA in subjects in Norway (14). Conversely, another Norwegian study measured serum eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) status during pregnancy but did not find an association with decreased risk of T1D in the offspring (15).

The aim of this study was to examine the association between maternal dietary vitamin D and omega-3 fatty acid supplementation during pregnancy and development of islet autoimmunity in the offspring.

Methods

The Environmental Determinants of Diabetes in the Young (TEDDY) is a prospective cohort study funded by the National Institutes of Health with the primary goal to identify environmental causes of T1D. It includes six clinical research centers - three in the United States: Colorado, Georgia/Florida, Washington and three in Europe: Finland, Germany, and Sweden. Detailed study design and methods have been previously published (16) (17). The TEDDY study is conducted according to guidelines laid down by the Declaration of Helsinki and all procedures involving human subjects were approved by local ethics boards or Institutional Review Boards. Written informed consents were obtained for all study participants from a parent or primary caretaker, separately, for genetic screening at birth and participation in prospective follow-up. Screening and follow-up are monitored by an External Advisory Board of the National Institutes of Health.

Between September 2004-February 2010, a total of 424,788 newborn infants were screened for type 1 diabetes-associated HLA genotypes. The initial screening identified 21,589 eligible infants, of whom 8,676 were enrolled in the follow-up study before age 4.5 months.

Infants from the general population (GP), with no first-degree relative with type 1 diabetes, were eligible if they had any one of the following HLA-DR-DQ genotypes:

DRB1*04-DQA1*03-DQB1*03:02/DRB1*03-DQA1*05-DQB1*02:01 (DR3/4),

DRB1*04-DQA1*03-DQB1*03:02/DRB1*04-DQA1*03-DQB1*03:02 (DR4/4),

DRB1*04-DQA1*03-DQB1*03:02/DRB1*08-DQA1*04-DQB1*04:02 (DR4/8) and

DRB1*03-DQA1*05-DQB1*02:01/DRB1*03-DQA1*05-DQB1*02:01 (DR3/3).

Infants with a first-degree relative (FDR) with T1D were eligible with any above genotype or with:

DRB1*04-DQA1*03-DQB1*03:02/DRB1*04- DQA1*03-DQB1*02:02 (DR4/4b),

DRB1*04-DQA1*03-DQB1*03:02/DRB1*01- DQA1*01-DQB1*05:01 (DR4/1),

DRB1*04-DQA1*03-DQB1*03:02/DRB1*13-DQA1*01-DQB1*06:04 (DR4/13),

DRB1*04-DQA1*03-DQB1*03:02/DRB1*09- DQA1*03-DQB1*03:03 (DR4/9), and

DRB1*03-DQA1*05-DQB1*02:01/DRB1*09- DQA1*03-DQB1*03:03 (DR3/9).

For brevity, the extended haplotypes above will be referred to in this paper by their DR-based abbreviations shown at the end of each line.

Blood samples to test autoantibody status were drawn quarterly starting at 3 months old during the first four years and biannually thereafter. Three autoantibodies against glutamic acid decarboxylase (GADA), insulin (IAA), and insulinoma antigen-2 (IA-2A) were tested. Methods for testing samples for autoantibody positivity are described more thoroughly elsewhere (18). An individual was considered autoantibody positive when a blood sample was confirmed positive at two labs. Our primary outcome, persistent islet autoimmunity (IA), was defined as confirmed positive autoantibodies to IAA, GADA, or IA-2A in at least two consecutive samples. We also examined secondary outcomes of IAA only or GADA only as the first appearing autoantibody (IAA-first IA and GADA-first IA, respectively). Previously published studies in TEDDY have showed a relationship between the order of autoantibody appearance and risk of T1D.(19–22)

The infant screening form completed by the family at birth provided basic demographic information and family history of diabetes. This information was verified within the infant's first year of life in another questionnaire. Mothers reported prenatal details such as medications, smoking habits, education level attained in addition to dietary supplement use, both dose and duration, through self-administered questionnaire at 3.0–4.5 months postpartum. Trained interviewers reviewed questionnaires for completeness and detail at the first TEDDY visit. Interviewers obtained quantities of both vitamin D2 and D3 and n-3 fatty acids from the package from both single vitamin and multivitamin supplements. The fatty acids included in the analysis were total n-3, DHA, and EPA, the latter two being the most commonly supplemented single n-3 fatty acids. The cumulative intake of vitamin D and n-3 FA from supplements during pregnancy was calculated by summing the reported intake over the entire pregnancy. Extreme cumulative intake values (i.e., greater than the minimum of the four country-specific 99th percentiles of the intake values) were excluded. TEDDY has previously reported some concordance between national recommendations and the prevalence of prenatal vitamin D and n-3 FA supplement use among TEDDY mothers.(23) In 2008, new Swedish and German guidelines recommended that mothers to take

200mg/day DHA if they did not regularly consume fish. Consumption of n-3 FA supplements increased in all countries during TEDDY screening, with the highest proportion of fatty acid users found in Germany (32%). The prevalence of vitamin D supplement use was relatively stable throughout screening (65%). The highest proportion of vitamin D supplement users was in the US (81%), where the prenatal multivitamin all mothers are counseled to consume generally contains vitamin D.(23) Parents reported education level on a 10-category scale that was subsequently aggregated into two categories: basic primary and higher education, in order for the variable to be comparable across countries. Basic primary education is defined as primary school through trade school. Alcohol consumption was recorded as “yes” if any alcohol was consumed during any trimester in pregnancy.

Children whose HLA genotype was ineligible (n=120), whose autoantibody was indeterminate (n=54), with no information about maternal supplement use (n=140) or with no information about cumulative intake for vitamin D (n=87) or n-3 FA (n=15) from supplements were excluded, leaving 8,260 children for this maternal supplement analysis.

Statistical Analyses

Characteristics of those who developed IA, IAA as the first appearing autoantibody, GADA as the first appearing autoantibody and those who did not develop IA are presented for descriptive purposes.

Cox proportional hazards (PH) models were performed to examine the cumulative intake of vitamin D and n-3 FA from supplements during pregnancy related to the time-dependent risk of IA, the risk of IAA as the first appearing autoantibody, and the risk of GADA as the first appearing autoantibody. The magnitudes of the associations were described by hazard ratios (HR) with 95% confidence intervals (CI). HLA-DR-DQ genotype, family history of type 1 diabetes, sex, and country (as a strata) were adjusted in the Cox PH models. Cox PH analysis with additional adjustment for factors previously identified in TEDDY (24–28) (probiotic introduced before 28 days vs other, type of infant formula during the first 3 months, weight at 12 months, T1D-related SNPs [rs2476601 in PTPN22, rs2816316 in RGS1, rs2292239 in ERBB3, rs3184504 in SH2B3, rs4948088 in COBL, rs1004446 in INS, rs1270876 in CLEC16A, rs10517086] and two SNPs in complement genes [rs1143678 and rs4597342 in ITGAM]) were also performed as sensitivity analyses.

The cumulative intake of vitamin D and n-3 FA from supplements during pregnancy variable was incorporated into the Cox model in two ways: 1. Cumulative intake categorized as binary (0, or >0), i.e., supplement users or non-users. 2. Cumulative intake of nutrient as a continuous variable among supplement users. Considering the use of vitamin D supplements is relatively high (64%), an additional analysis was conducted by categorizing vitamin D use into three levels: (none, low (< median intake among users), or high (≥ median intake among users)). Analyses were performed using Statistical Analysis Software (Version 9.4, SAS Institute, Cary NC, USA).

Results

As of February, 2018, the median (IQR) follow-up time for the 8,260 children was 103 (38–126) months. There were 747 (9.0%) children with persistent confirmed islet autoimmunity (IA), with 279 (3.4%) children having IAA only as the first appearing autoantibody (IAA-first IA) and 325 (3.9%) children having GADA only as the first appearing (GADA-first IA) autoantibody. The median (IQR) age at onset of persistent confirmed IA was 35 (18–70) months.

In this study, 5,283 (64.0%) of the mothers reported vitamin D supplementation during pregnancy and the median (IQR) intake was 2,030 (1,050–2,800) mcg. A total of 1338 (16.2%) mothers reported n-3 FA supplementation during pregnancy and the median (IQR) intake was 61.6 (33.0 – 92.4) g. The characteristics of the children and details of the mother's intake of vitamin D and n-3 FA supplementation during pregnancy by the children's status of IA (IA negative, any IA, IAA-first IA and GADA-first IA) are presented in Table 1.

Adjusting for HLA-DR-DQ genotype, family history of type 1 diabetes, sex, and country (as a strata), intake of vitamin D via supplements (any vs none) was not associated with the risk of IA (HR 1.11; 95% CI 0.94, 1.31), IAA-first IA (HR 1.24; 95% CI 0.94, 1.62) or GADA-first IA (HR 1.01; 95% CI 0.79, 1.29) (Table 2). Additionally, there was no association between low or high maternal cumulative intake of vitamin D supplements during pregnancy and the risk of IA, IAA-first IA or GADA-first IA, compared with no intake. Intake of vitamin D via supplements (any vs. none) was examined for potential interaction with HLA-DR-DQ genotype, family history of type 1 diabetes, sex, and country, on the risk of IA, IAA-first IA and GADA-first IA. No significant interactions were detected.

Adjusting for HLA-DR-DQ genotype, family history of type 1 diabetes, sex, and country (as a strata), intake of n-3 FA supplements (any vs none) was not associated with the risk of IA (HR 1.19; 95% CI 0.98, 1.45), IAA-first IA (HR 1.22; 95% CI 0.89, 1.68) or GADA-first IA (HR 1.27; 95% CI 0.95, 1.70) (table 2), nor did the analysis of the cumulative n-3 FA acid intake indicate a significant association with the risk of IA, IAA-first IA or GADA-first IA. Again, no significant interactions between the n-3 FA supplement use and the other covariates in relation to IA, IAA-first IA or GADA-first IA were detected. The sensitivity analyses with additional adjustment for the risk factors for IA previously identified in TEDDY revealed similar results (data not shown).

Discussion

In this study, we investigated the association between mothers' use of vitamin D and n-3 FA supplements during pregnancy and risk for islet autoimmunity. Some previous studies have found limited associations between maternal dietary supplement use and reduced risk of IA or T1D. A study in Sweden found that Vitamin D supplementation in pregnancy subsequently decreased IA in the offspring at 1 year of age, but this is a time when IA have usually not yet developed, and by age 2.5 years, the protective effect of maternal vitamin D supplementation on childhood IA was not seen (6). Another study found that cod liver oil

supplementation of the mother protected the offspring from T1D, but this represents combined supplementation with both vitamin D and n-3 FA and it is unclear which nutrient is responsible or whether both were required (7, 14). Our current results from the TEDDY Study are consistent with multiple studies that have not found an effect of maternal vitamin D supplementation (8–10), maternal fatty acid levels (14) or maternal fatty acid intake (28) on T1D risk in the child. Recently, large studies utilizing the extensive data from the Danish National Register and Norwegian Mother and Child Cohort Study have examined the effect of both vitamin D status throughout pregnancy and neonatal status of the infant and found no association with type 1 diabetes.(29, 30) Maternal supplementation of vitamin D, DHA, and EPA was not associated with T1D risk in both countries.(30)

There have been varied results when studying children as opposed to in utero (maternal) exposure. The TEDDY study (with European and US children) has shown a relationship between child vitamin D levels and risk of islet autoimmunity(5). A US cohort has shown an association between child n-3 FA intake from food, n-3 FAs in the erythrocyte membrane, and a reduced risk of IA (31) but no association with progression from IA to T1D (32). According to these studies, the benefit of n-3 FA may be in the inhibition of IA seroconversion. More recently, the DAISY Study has shown a reduced risk for IA in children who consume alpha-linoleic acid (ALA) rich foods and supplements and have a specific genetic variant in fatty acid desaturation (33).

The main strength of this study is the large sample size and short period of time that passed from pregnancy to recording of supplement usage data. Infants were on average 3 months old when we asked mothers to recall pregnancy data for TEDDY.

The study was limited by a lack of dietary data on food sources of vitamin D and n-3 FA in the maternal diet. However, supplements contribute significantly to overall nutrient intake, especially when food sources are low. A study of US National Health and Nutrition Examination Surveys (NHANES) 2009–2012 food intake data revealed that 93% of the population surveyed consumed below the EAR (estimated average requirement) for vitamin D (10 mcg/day).(34) In a study of dairy fortification in Finland, mean dietary intake of vitamin D in women increased from 3 mcg/day to 18 mcg/day when the national fortification recommendation was doubled in 2010.(35) The TEDDY Study did not collect maternal food records because the participants were not contacted and recruited until the high-risk infants were identified at birth. For this same reason, we do not have any measures of maternal vitamin D or n-3 FA levels during pregnancy. It is possible that supplements which remedy a deficiency may show a more protective effect than supplements taken by mothers with adequate nutrient status. A study of Finnish mothers suggests that it is possible that vitamin D insufficiency during pregnancy may be more problematic with some maternal vitamin D receptor variants (36).

In conclusion, the present study does not find any association between maternal Vitamin D nor n-3 fatty acid supplement use and increased risk for IA. This result is the same whether looking at any supplement use vs. none, or for both a low and higher dose of vitamin D. Nevertheless, TEDDY will continue to investigate effect of other aspects of the in utero environment on the risk for islet autoimmunity and type 1 diabetes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Lindehammer SR, Fex M, Maziarz M, Hanson I, Marsal K, Lernmark A. Early-pregnancy cytokines in mothers to children developing multiple, persistent islet autoimmunities, type 1 diabetes, or both before 7 years of age. American Journal of Reproductive Immunology. 2011;66:495–503. [PubMed: 21749548]
2. Altieri B, Muscogiuri G, Barrea L, Mathieu C, Vallone CV, Mascitelli L, et al. Does vitamin D play a role in autoimmune endocrine disorders? A proof of concept. Reviews in Endocrine and Metabolic Disorders. 2017;18(3):335–346. [PubMed: 28070798]
3. Antico A, Tampoia M, Tozzoli R, Bizzaro N. Can supplementation with vitamin D reduce the risk or modify the course of autoimmune disease? A systematic review of the literature. Autoimmunity Reviews. 2012;12:127–36. [PubMed: 22776787]
4. Zipitis CS, Akobeng AK. Vitamin D supplementation in early childhood and risk of type 1 diabetes: a systematic review and meta-analysis. Archives of Disease in Childhood. 2008;93:512–7. [PubMed: 18339654]
5. Norris JM, Lee HS, Frederiksen B, Erlund I, Uusitalo U, Yang J, et al. Plasma 25-Hydroxyvitamin D Concentration and Risk of Islet Autoimmunity. Diabetes. 2018;67(1):146–54. [PubMed: 29061729]
6. Kovacs CS. Vitamin D in pregnancy and lactation: maternal, fetal, and neonatal outcomes from human and animal studies. American Journal of Clinical Nutrition. 2008;88(suppl):520S–8S. [PubMed: 18689394]
7. Brekke HK, Ludvigsson J. Vitamin D supplementation and diabetes-related autoimmunity in the ABIS study. Pediatr Diabetes. 2007;8(1):11–4. [PubMed: 17341286]
8. Granfors M, Augustin H, Ludvigsson J, Brekke HK. No association between use of multivitamin supplement containing vitamin D during pregnancy and risk of Type 1 Diabetes in the child. Pediatr Diabetes. 2016;17(7):525–30. [PubMed: 26552946]
9. Fronczak CM, Barón AE, Chase HP, Ross C, Brady HL, Hoffman M, et al. In utero dietary exposures and risk of islet autoimmunity in children. Diabetes Care. 2003;26(12):3237–42. [PubMed: 14633808]
10. Marjamäki L, Niinistö S, Kenward MG, Uusitalo L, Uusitalo U, Ovaskainen ML, et al. Maternal intake of vitamin D during pregnancy and risk of advanced beta cell autoimmunity and type 1 diabetes in offspring. Diabetologia. 2010;53(8):1599–607. [PubMed: 20369220]
11. Sørensen IM, Joner G, Jenum PA, Eskild A, Torjesen PA, Stene LC. Maternal serum levels of 25-hydroxy-vitamin D during pregnancy and risk of type 1 diabetes in the offspring. Diabetes. 2012;61(1):175–8. [PubMed: 22124461]
12. Miettinen ME, Reinert L, Kinnunen L, Harjutsalo V, Koskela P, Surcel HM, et al. Serum 25-hydroxyvitamin D level during early pregnancy and type 1 diabetes risk in the offspring. Diabetologia. 2012;55(5):1291–4. [PubMed: 22270224]

13. Wei D, Li J, Shen M, Jia W, Chen N, Chen T, et al. Cellular production on n-3 PUFAs and reduction of n-6-to-n-3 ratios in the pancreatic B-cells and islets enhance insulin secretion and confer protection against cytokine-induced cell death. Diabetes. 2010;59:471–8. [PubMed: 19933995]
14. Stene LC, Ulriksen J, Magnus P, Joner G. Use of cod liver oil during pregnancy associated with lower risk of Type I diabetes in the offspring. Diabetologia. 2000;43(9):1093–8. [PubMed: 11043854]
15. Sørensen IM, Joner G, Jenum PA, Eskild A, Stene LC. Serum long chain n-3 fatty acids (EPA and DHA) in the pregnant mother are independent of risk of type 1 diabetes in the offspring. Diabetes Metab Res Rev. 2012;28(5):431–8. [PubMed: 22396195]
16. Hagopian WA, Lernmark A, Rewers MJ, Simell OG, She JX, Ziegler AG, et al. TEDDY--The Environmental Determinants of Diabetes in the Young: an observational clinical trial. Ann N Y Acad Sci. 2006;1079:320–6. [PubMed: 17130573]
17. Group TS. The Environmental Determinants of Diabetes in the Young (TEDDY) study: study design. Pediatr Diabetes. 2007;8(5):286–98. [PubMed: 17850472]
18. Vehik K, Fiske SW, Logan CA, Agardh D, Cilio CM, Hagopian W, et al. Methods, quality control and specimen management in an international multicentre investigation of type 1 diabetes: TEDDY. Diabetes Metab Res Rev. 2013;29(7):557–67. [PubMed: 23674484]
19. Krischer JP, Lynch KF, Schatz DA, Ilonen J, Lernmark Å, Hagopian WA, et al. The 6 year incidence of diabetes-associated autoantibodies in genetically at-risk children: the TEDDY study. Diabetologia. 2015;58(5):980–7. [PubMed: 25660258]
20. Krischer JP, Lynch KF, Lernmark Å, Hagopian WA, Rewers MJ, She JX, et al. Genetic and Environmental Interactions Modify the Risk of Diabetes-Related Autoimmunity by 6 Years of Age: The TEDDY Study. Diabetes Care. 2017;40(9):1194–202. [PubMed: 28646072]
21. Krischer JP, Liu X, Lernmark Å, Hagopian WA, Rewers MJ, She JX, et al. The Influence of Type 1 Diabetes Genetic Susceptibility Regions, Age, Sex, and Family History on the Progression From Multiple Autoantibodies to Type 1 Diabetes: A TEDDY Study Report. Diabetes. 2017;66(12): 3122–9. [PubMed: 28903990]
22. Lynch KF, Lee HS, Törn C, Vehik K, Krischer JP, Larsson HE, et al. Gestational respiratory infections interacting with offspring HLA and CTLA-4 modifies incident β-cell autoantibodies. J Autoimmun. 2018;86:93–103. [PubMed: 28941965]
23. Aronsson CA, Vehik K, Yang J, Uusitalo U, Hay K, Joslowski G, et al. Use of dietary supplements in pregnant women in relation to sociodemographic factors - a report from The Environmental Determinants of Diabetes in the Young (TEDDY) study. Public Health Nutr. 2013;16(8):1390–402. [PubMed: 23452986]
24. Uusitalo U, Liu X, Yang J, Aronsson CA, Hummel S, Butterworth M, et al. Association of Early Exposure of Probiotics and Islet Autoimmunity in the TEDDY Study. JAMA pediatrics. 2016;170(1):20–8. [PubMed: 26552054]
25. Hummel S, Beyerlein A, Tamura R, Uusitalo U, Andrén Aronsson C, Yang J, et al. First Infant Formula Type and Risk of Islet Autoimmunity in The Environmental Determinants of Diabetes in the Young (TEDDY) Study. Diabetes Care. 2017;40(3):398–404. [PubMed: 28096222]
26. Elding Larsson H, Vehik K, Haller MJ, Liu X, Akolkar B, Hagopian W, et al. Growth and Risk for Islet Autoimmunity and Progression to Type 1 Diabetes in Early Childhood: The Environmental Determinants of Diabetes in the Young Study. Diabetes. 2016;65(7):1988–95. [PubMed: 26993064]
27. Törn C, Hadley D, Lee H-S, Hagopian W, Lernmark Å, Simell O, et al. Role of Type 1 Diabetes–Associated SNPs on Risk of Autoantibody Positivity in the TEDDY Study. Diabetes. 2015;64(5): 1818–29. [PubMed: 25422107]
28. Törn C, Liu X, Hagopian W, Lernmark Å, Simell O, Rewers M, et al. Complement gene variants in relation to autoantibodies to beta cell specific antigens and type 1 diabetes in the TEDDY Study. 2016;6:27887.
29. Jacobsen R, Thorsen SU, Cohen AS, Lundqvist M, Frederiksen P, Pipper CB, et al. Neonatal vitamin D status is not associated with later risk of type 1 diabetes: results from two large Danish population-based studies. Diabetologia. 2016;59(9):1871–81. [PubMed: 27241183]

30. Thorsen SU, Mårild K, Olsen SF, Holst KK, Tapia G, Granström C, et al. Lack of Association Between Maternal or Neonatal Vitamin D Status and Risk of Childhood Type 1 Diabetes: A Scandinavian Case-Cohort Study. Am J Epidemiol. 2018;187(6):1174–81. [PubMed: 29186303]

31. Norris JM, Yin X, Lamb MM, Barriga K, Seifert J, Hoffman M, et al. Omega-3 polyunsaturated fatty acid intake and islet autoimmunity in children at increased risk for type 1 diabetes. JAMA. 2007;298(12):1420–8. [PubMed: 17895458]

32. Miller MR, Yin X, Seifert J, Clare-Salzler M, Eisenbarth GS, Rewers M, et al. Erythrocyte membrane omega-3 fatty acid levels and omega-3 fatty acid intake are not associated with conversion to type 1 diabetes in children with islet autoimmunity: the Diabetes Autoimmunity Study in the Young (DAISY). Pediatr Diabetes. 2011;12(8):669–75. [PubMed: 21435137]

33. Norris JM, Kroehl M, Fingerlin TE, Frederiksen BN, Seifert J, Wong R, et al. Erythrocyte membrane docosapentaenoic acid levels are associated with islet autoimmunity: the Diabetes Autoimmunity Study in the Young. Diabetologia. 2014;57(2):295–304. [PubMed: 24240437]

34. Blumberg JB, Frei B, Fulgoni VL, Weaver CM, Zeisel SH. Contribution of Dietary Supplements to Nutritional Adequacy in Various Adult Age Groups. Nutrients. 2017;9(8):849.

35. Raulio S, Erlund I, Männistö S, Sarlio-Lähteenkorva S, Sundvall J, Tapanainen H, et al. Successful nutrition policy: improvement of vitamin D intake and status in Finnish adults over the last decade. Eur J Public Health. 2017;27(2):268–73. [PubMed: 28339536]

36. Miettinen ME, Smart MC, Kinnunen L, Mathews C, Harjutsalo V, Surcel HM, et al. Maternal VDR variants rather than 25-hydroxyvitamin D concentration during early pregnancy are associated with type 1 diabetes in the offspring. Diabetologia. 2015;58(10):2278–83. [PubMed: 26109216]

Table 1:

Characteristics of the Environmental Determinates of Diabetes in the Young (TEDDY) Study cohort

Characteristic		IA Negative N=7513	Any IA N=747	IAA first N=279	GADA first N=325
Country[4] N (%)	US	3275 (43.6)	250 (33.5)	84 (30.1)	126 (38.8)
	Finland	1543 (20.5)	183 (24.5)	88 (31.5)	60 (18.5)
	Germany	509 (6.8)	55 (7.4)	19 (6.8)	17 (5.2)
	Sweden	2186 (29.1)	259 (34.7)	88 (31.5)	122 (37.5)
First Degree Relative with T1D[4] N(%)	No	6756 (89.9)	602 (80.6)	220 (78.9)	269 (82.8)
	Yes	757 (10.1)	145 (19.4)	59 (21.1)	56 (17.2)
Sex[4] N(%)	Male	3776 (50.3)	412 (55.2)	159 (57.0)	173 (53.2)
	Female	3737 (49.7)	335 (44.8)	120 (43.0)	152 (46.8)
HLA Genotype[4]	DR3/4	2869 (38.2)	368 (49.3)	133 (47.7)	163 (50.2)
	DR4/4	1478 (19.7)	137 (18.3)	52 (18.6)	49 (15.1)
	DR4/8	1298 (17.3)	115 (15.4)	58 (20.8)	38 (11.7)
	DR3/3	1629 (21.7)	100 (13.4)	23 (8.2)	71 (21.8)
	FDR Specific[1]	239 (3.2)	27 (3.6)	13 (4.7)	4 (1.2)
Maternal Intake of Vit D	None	2716 (36.2)	261 (34.9)	90 (32.3)	116 (35.7)
	Low (<2030 mcg)	2378 (31.7)	253 (33.9)	105 (37.6)	95 (29.2)
	High (≥2030 mcg)	2419 (32.2)	233 (31.2)	84 (30.1)	114 (35.1)
Intake of Vit D (mcg) among users[2]	N	4643	473	184	202
	Median (Q1–Q3)	2000 (1050–2800)	1610 (1015–2800)	1400 (803–2800)	2100 (1103–2800)
	Mean (SD)	1912 (1094)	1882 (1135)	1770 (1192)	2009 (1076)
Maternal Intake of n-3 FA	None	6310 (84.0)	612 (81.9)	229 (82.1)	263 (80.9)
	Any	1203 (16.0)	135 (18.1)	50 (17.9)	62 (19.1)
Intake of n-3 FA (g) among users[3]	N	1156	127	49	56
	Median (Q1–Q3)	56(31–84)	62 (36–116)	56 (28–112)	78 (56–109)
	Mean (SD)	75(71)	89 (78)	83 (83)	93 (66)

[1] FDR-specific HLA-DR-DQ genotypes are DR4/4b, DR4/1, DR4/13, DR4/9, and DR3/9.

[2] 167 extreme intake values of Vitamin D (> 5600 mcg) were excluded.

[3]55 extreme intake values of n-3 FA (> 436 g) were excluded.

[4]Characteristics that were statistically significantly associated (p-value < 0.05) with the risk of islet autoimmunity (IA), IAA only as the first appearing autoantibody (IAA first) and GADA only as the first appearing autoantibody (GADA first).

Table 2:

Hazard ratios (HR), 95% confidence intervals (CI) and two-tailed p-values from Cox proportional hazards models[1] for the effects of Vitamin D and Omega-3 Fatty Acid intake from supplements during pregnancy on the risk of developing any islet autoimmunity (IA), IAA only as the first appearing autoantibody (IAA first) and GADA only as the first appearing autoantibody (GADA first). The Environmental Determinants of Diabetes in the Young (TEDDY)

Supplement		Any IA	IAA first	GADA first
		HR (95% Cl) p-value	HR (95% Cl) p-value	HR(95% Cl) p-value
Vitamin D				
Any or none (none as reference)	Any	1.11 (0.94, 1.31) 0.213	1.24 (0.94, 1.62) 0.217	1.01 (0.79, 1.29) 0.965
High (≥2030 mcg[2]) or Low (<2030 mcg) or none (none as reference)	Low (<2030 mcg)	1.08 (0.90, 1.29) 0.409	1.23(0.92,1.65) 0.164	0.91 (0.69,1.20) 0.507
	High (≥2030 mcg)	1.17(0.95, 1.43) 0.142	1.25 (0.89,1.75) 0.206	1.17 (0.86,1.58) 0.321
Cumulative intake	Per 1000 mcg increase	1.05 (0.96,1.15) 0.284	0.98 (0.84,1.14) 0.751	1.15 (1.00,1.32) 0.056
Omega-3 Fatty Acid				
Any or none (none as reference)	Any	1.19 (0.98,1.45) 0.076	1.22(0.89, 1.68) 0.219	1.27 (0.95, 1.70) 0.101
Cumulative intake	Per 100 g increase	1.18 (0.96,1.46) 0.121	1.03 (0.72,1.49) 0.854	1.24 (0.91,1.68) 0.170

[1] Adjusting for HLA-DR-DQ genotype, family history of T1D, sex, and country (as strata)

[2] Median of cumulative intake of Vitamin D by users throughout pregnancy is 2030 mcg.