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Timing of Complementary Food Introduction and Age at Diagnosis of Type 1 Diabetes: the SEARCH Nutrition Ancillary STUDY (SNAS)

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Abstract

The association between timing of complementary food introduction and age at diagnosis of type 1 diabetes was investigated among 1077 children in the SEARCH for Diabetes in Youth study. Age at diagnosis was 5-month earlier for children introduced to sugar-sweetened beverages (SSB) in the first 12 months of life compared to those who were not (9.0 ± 0.2 vs. 9.5 ± 0.1; p=0.02), independent of HLA-risk status. Analyses stratified by HLA-risk status found that children with a high risk HLA genotype had an earlier age at diagnosis if they were introduced to fruit juice in the first year of life (mean age of diagnosis=9.3 ± 0.1, 9.1 ± 0.1 and 9.6 ± 0.2 for introduction at ≤ 6

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Contribution statement

T.L Crume made substantial contributions to the conception and design, analysis and interpretation of the data; drafting and revising of the article.

J. Crandell made substantial contributions to the conception and design, analysis and interpretation of the data, reviewed article.

J.M. Norris made substantial contributions to the conception and design, interpretation of the data, reviewed article.

D. Dabelea made substantial contributions to the conception and design, interpretation of the data, reviewed article.

M.T. Fangman made substantial contributions to the conception and design, analysis and interpretation of the data, reviewed article.

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E.J. Mayer-Davis made substantial contributions to the conception and design, analysis and interpretation of the data, revising the article for intellectual content, final approval of version to be published.

Conflicts of Interest

The authors report no competing financial interests in relation to this work.

months, between 7 and 11 months, and ≤12 months, respectively; p=0.04). Introduction of SSB in the first year of life may accelerate onset of type 1 diabetes independent of HLA-risk status.

Keywords

infant diet; type 1 diabetes; autoimmunity; islet autoantibodies; age factors; diabetes mellitus genetics; genetic susceptibility to disease; HLA-DQ antigens; disease progression

INTRODUCTION

Type 1 diabetes mellitus is one of the leading chronic diseases of childhood, affecting 1.54 youth per 1,000 in the U.S. according to the SEARCH for Diabetes in Youth study (1). The autoimmunity that precedes type 1 diabetes can appear in the first year of life suggesting that early environmental exposures may trigger the disease process (2). An increasing body of evidence suggests that type and timing of complementary food introduction may play a role in the etiology (3). Early infant diet patterns may lead to accelerated childhood growth, beta-cell overload and accelerated failure of beta cells in the face of an autoimmune attack, especially among genetically predisposed individuals, resulting in an earlier at onset of type 1 diabetes (4;5). We tested the hypothesis that timing of introduction of selected types of complementary foods and beverages was associated with earlier age at diagnosis of type 1 diabetes using data collected by SEARCH Nutrition Ancillary Study (SNAS).

RESEARCH DESIGN AND METHODS

SNAS is an ancillary study to SEARCH that retrospectively collected infant diet history among youth diagnosed with type 1 diabetes between 2002 and 2005. SEARCH is a multicenter population-based ascertainment of youth < 20 years of age with newly diagnosed (incident) non-gestational diabetes recruited from four geographically defined populations throughout the United States. A detailed description of the SEARCH study methods has been published elsewhere (6). Fasting blood samples at the baseline SEARCH visit were analyzed for two diabetes autoantibodies (DA): glutamic acid decarboxylase-65 (GAD65) and insulinoma- associated-2 (IA-2) using a standardized protocol. In addition, Human Leukocyte Antigen class II genotyping (HLA DR-DQ) was performed with a PCR-based sequence-specific oligonucleotype 1 diabetes probe system. Genetic susceptibility to autoimmunity was categorized based on recommendations by the Type 1 Diabetes Genetic Consortium (7).

The SNAS study asked mothers or primary guardians of SEARCH participants to complete a questionnaire that asked about breastfeeding duration and timing of introduction of various beverages and foods common in the infant diet (19 total items). Respondents were asked the age of the child in months when the listed food or beverage was introduced on a regular basis, defined as “at least once per week” with an additional option of “not given regularly in the first year”. The study was approved by the local Institutional Review Board(s) and complied with the Health Insurance Portability and Accountability Act.

Subjects for this analysis included youth in the SNAS study diagnosed with type 1 diabetes and positive for at least one DA (GAD65 or IA-2). The relationship between age at introduction and age at diagnosis was modeled using linear regression, adjusted for sex, race/ethnicity, total household income, birth year, breastfeeding (never, 1 day through 5months, ≥ 6 months), HLA risk status, and exposure to maternal diabetes *in utero*. Subsequently, an interaction term was added to the full model to test for potential effect modification by HLA risk group (high risk vs. low risk).

RESULTS

There were 1,077 participants in the SEARCH/ SNAS study. The mean age at diagnosis of type 1 diabetes was 9.4 ± 3.9 years, average time between diagnosis of diabetes and administration of the SNAS questionnaire was 5.4 ± 1.4 years and average age of child at the SNAS visit was 11.3 ± 4.2 years. Seventy-seven percent of participants were non-Hispanic white, 11% were Hispanic, 9% were black and 3% were of other race and non-Hispanic ethnicity. Forty-three percent of respondents reported breastfeeding for ≥ 6 months, 30% for 1 day to 5 months, and 27% reported that the child never received breast milk. Overall, 32% had high risk or susceptible HLA genotypes.

The modeled average age at diagnosis by age at introduction of each food and beverage grouping from the full model is presented in **Table 1**. Timing of introduction of the majority of foods and beverages were not associated with age at diagnosis of type 1 diabetes. The exception was introduction of sugar-sweetened beverages (SSBs) (excluding juice) in the first 12 months of life which was associated with a 5-month earlier age at diagnosis (p=0.02), independent of a HLA risk status. **Table 2** displays the mean age at diagnosis by timing of complementary food introduction, according to HLA risk. Among those with a high risk/susceptible HLA, introduction of fruit juice in the first year of life was associated with a younger age at diagnosis compared with those not introduced (p=0.04).

DISCUSSION

In this large, diverse cohort of youth with type 1 diabetes, most dietary exposures were not associated with an earlier age at diagnosis with the exception of SSB consumption in the first year of life. Among those with high risk/susceptible HLA genotype, introduction of fruit juice in the first 12 months of life was associated with a younger age at diagnosis, suggesting that early exposure to SSBs may accelerate the onset of type 1 diabetes, independent of HLA-risk status and early exposure to juice may speed onset among youth who are genetically predisposed to type 1 diabetes.

Biologic plausibility of our results are offered “overload hypothesis” (4), which suggests that environmental exposures may overstimulate beta cells, thus accelerating their autoimmune-mediated destruction. Increased insulin demand due to chronic exposure to high sugar intake and SSBs consumption has been reported in children (8), though no studies that we are aware of have assessed their role in the infant diet in a type 1 diabetes cohort. A high intake of carbohydrates, especially sucrose and disaccharides the year before diabetes diagnosis has been associated with increased type 1 diabetes risk, independent of

total energy intake (9). The major limitation of our study is the reliance on maternal recall 11.3 ± 4.2 years prior, however the validity of surrogate recall of food groups up to 43 years prior has been reported to be acceptable in the Fels Longitudinal Study(10).

CONCLUSIONS

Findings from our observational study suggests that introduction of SSB in the first year of life may accelerate onset of type 1 diabetes, independent of HLA-risk status and among youth with susceptible HLA genotypes, early introduction of juice may speed onset.

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Abbreviations

SEARCH	SEARCH for Diabetes in Youth Study
SNAS	SEARCH Nutrition Ancillary Study
DA	diabetes autoantibody
GADA	Glutamic acid decarboxylase-65 autoantibody
IA-2A	insulinoma-associated-2 autoantibody
SSB	Sugar-sweetened beverages

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Table 1

Mean age at diagnosis of type 1 diabetes by timing of introduction of complementary foods into the infant diet on a regular basis (at least once per week).

	Predicted mean age at diagnosis (years) ± SE (N=1,077)				
Age at introduction (months)	**<3m**	**3-6m**	**7-11m**	**12m or more**	**P-value**
Any solid food	9.41 ± 0.15	9.42 ± 0.08	9.38 ± 0.14		0.95
Vegetables excluding potatoes	9.50 ± 0.08		9.31 ± 0.1	9.31 ± 0.18	0.08
Cereal	9.39 ± 0.16	9.4 ± 0.08	9.32 ± 0.13	9.74 ± 0.22	0.38
Gluten	9.43 ± 0.23	9.45 ± 0.09	9.36 ± 0.09	9.49 ± 0.14	0.73
Fruit excluding juice	9.46 ± 0.08		9.34 ± 0.1	9.27 ± 0.16	0.29
Potatoes and rice	9.36 ± 0.17	9.43 ± 0.08	9.43 ± 0.13	9.38 ± 0.21	0.96
Meat including fish	9.42 ± 0.11		9.39 ± 0.09	9.47 ± 0.11	0.74
All dairy including formula	9.45 ± 0.09	9.41 ± 0.11	9.29 ± 0.11	9.49 ± 0.12	0.42
Dairy excluding formula	9.44 ± 0.11		9.42 ± 0.09	9.42 ± 0.09	0.97
Fruit juice	9.43 ± 0.09		9.32 ± 0.1	9.49 ± 0.11	0.29
Sweetened beverage excluding juice	9.04 ± 0.18			9.45 ± 0.08	0.02

Least-squares predicted means from model adjusted for sex, race, education, income, birth year, breastfeeding (never, 1-5m vs. ≥6m), HLA risk status (low risk/protective vs. high risk/susceptible) and in utero maternal DM exposure.

Note: cell size less than 30 were collapsed with the adjoining cell to improve precision.

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Table 2

Model-estimated mean age at diagnosis of type 1 diabetes for windows of introduction of complementary foods, for youth with moderate and high HLA risk genotypes.

	Low Risk/Protective HLA (estimated mean age at diagnosis ± SE) (N=684)					High Risk/ Susceptible HLA (estimated mean age at diagnosis ± SE) (N=316)					
Age at introduction (months)	**<3m**	**3-6m**	**7-11m**	**≥ 12m**	**p-value**	**<3m**	**3-6m**	**7-11m**	**≥ 12m**	**p-value**	**Overall P for interaction†**
Any solid food	9.40 ± 0.17	9.45 ± 0.08	9.40 ± 0.16		0.9	9.44 ± 0.25	9.33 ± 0.11	9.32 ± 0.21		0.9	0.86
Vegetables excluding potatoes	9.55 ± 0.09		9.30 ± 0.11	9.30 ± 0.2	0.05	9.39 ± 0.12		9.33 ± 0.15	9.35 ± 0.34	0.9	0.6
Cereal	9.33 ± 0.18	9.43 ± 0.08	9.37 ± 0.15	9.77 ± 0.26	0.5	9.54 ± 0.28	9.31 ± 0.11	9.21 ± 0.21	9.67 ± 0.38	0.6	0.8
Fruit excluding juice	9.51 ± 0.09		9.34 ± 0.11	9.26 ± 0.18	0.3	9.33 ± 0.12		9.35 ± 0.15	9.36 ± 0.32	0.7	0.5
Gluten	9.58 ± 0.27	9.53 ± 0.1	9.34 ± 0.1	9.51 ± 0.16	0.2	9.07 ± 0.43	9.29 ± 0.13	9.42 ± 0.14	9.45 ± 0.24	1.0	0.3
Potatoes and rice	9.28 ± 0.19	9.47 ± 0.09	9.5 ± 0.15	9.34 ± 0.23	0.7	9.57 ± 0.3	9.34 ± 0.11	9.27 ± 0.21	9.59 ± 0.45	0.8	0.5
Meat including fish	9.48 ± 0.12		9.45 ± 0.09	9.40 ± 0.12	0.9	9.26 ± 0.17		9.27 ± 0.12	9.66 ± 0.17	0.09	0.1
All dairy including formula	9.47 ± 0.1	9.52 ± 0.12	9.3 ± 0.13	9.44 ± 0.14	0.4	9.39 ± 0.15	9.12 ± 0.18	9.26 ± 0.17	9.52 ± 0.18	0.3	0.3
Dairy excluding formula	9.50 ± 0.12		9.47 ± 0.1	9.41 ± 0.1	0.8	9.29 ± 0.19		9.3 ± 0.13	9.41 ± 0.13	0.7	0.6
Fruit juice	9.47 ± 0.1		9.39 ± 0.11	9.39 ± 0.13	0.7	9.3 ± 0.13		9.13 ± 0.16	9.63 ± 0.16	0.04	0.09
Sweetened bvg excluding juice	9.15 ± 0.21			9.48 ± 0.08	0.1	8.74 ± 0.35			9.41 ± 0.11	0.06	0.4

Adjusted for sex, race, education, income, birth year, breastfeeding, HLA risk status and in utero maternal DM exposure

Note: cell size less than 30 were collapsed with the adjoining cell to improve precision.

† Heterogeneity of effect between age at diagnosis and age at introduction by HLA genotype category was tested in the model with an interaction term.