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ORIGINAL ARTICLE

Prevalence of obesity was related to HLA-DQ in 2–4-year-old children at genetic risk for type 1 diabetes

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OBJECTIVES: Body size is postulated to modulate type 1 diabetes as either a trigger of islet autoimmunity or an accelerator to clinical onset after seroconversion. As overweight and obesity continue to rise among children, the aim of this study was to determine whether human leukocyte antigen DQ (HLA-DQ) genotypes may be related to body size among children genetically at risk for type 1 diabetes.
METHODS: Repeated measures of weight and height were collected from 5969 children 2–4 years of age enrolled in The Environmental Determinants of Diabetes in the Young prospective study. Overweight and obesity was determined by the International Obesity Task Force cutoff values that correspond to body mass index (BMI) of 25 and 30 kg m^{-2} at age 18.
RESULTS: The average BMI was comparable across specific HLA genotypes at every age point. The proportion of overweight was not different by HLA, but percent obesity varied by age with a decreasing trend among DQ2/8 carriers (P for trend = 0.0315). A multivariable regression model suggested DQ2/2 was associated with higher obesity risk at age 4 (odds ratio, 2.41; 95% confidence interval, 1.21–4.80) after adjusting for the development of islet autoantibody and/or type 1 diabetes.
CONCLUSIONS: The HLA-DQ2/2 genotype may predispose to obesity among 2–4-year-old children with genetic risk for type 1 diabetes.

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Keywords: body mass index; HLA genotype; type 1 diabetes; pediatric; autoantibodies

INTRODUCTION

Type 1 diabetes is a multifactorial chronic disease that mostly but not exclusively manifests before 25 years.[1] The human leukocyte antigen (HLA) class II immune recognition molecules, as indicators of genetic risk, are of particular importance as they are found to explain more than 50% of familial clustering in type 1 diabetes risk[2] with certain HLA haplotypes, such as DQA1*0301-B1*0302 (DQ8) and A1*0501-B1*0201 (DQ2) positively associated with type 1 diabetes.[3] In recent decades, a global increase in the incidence of type 1 diabetes has been reported[4–9] and a younger age at onset was also noted in multiple studies.[10–12] It is unlikely that these phenomena are attributable to changes in genetic susceptibility because population prevalence of high-risk HLA genotypes for type 1 diabetes has not risen over time.[13,14] Environmental factors are postulated to modify disease pathogenesis; in particular body mass index (BMI) has been hypothesized to be an accelerator in the development of type 1 diabetes.[15,16] It has been reported in several studies that the increase in type 1 diabetes incidence rate may be correlated with an increase of childhood obesity in the population.[17–20] In Finland, positive associations between weight and the risk of type 1 diabetes were seen in children below the age of 15 years.[17] In Sweden,

susceptibility for childhood type 1 diabetes was associated with the A1*05:01-B1*02:01/A1*05:01-B1*02:01 (DQ2/2) genotype and an increased BMI.[18] A report from a Mediterranean pediatric cohort further suggested a positive association between the age at diagnosis of type 1 diabetes and BMI score adjusted for age and gender.[20] In the United States, the prevalence of overweight (defined as ⩾ 85th percentile for BMI for age and gender) among children newly diagnosed with type 1 diabetes increased from 12.6% during 1979–1989 to 36.8% during 1990–1998.[19] Among the Pediatric Diabetes Consortium participants who were diagnosed with type 1 diabetes between 2009 and 2011, 21% were overweight or obese at the time of diagnosis.[21]

As both HLA class II genotypes and body size were found to be related to type 1 diabetes risk, it is of interest to examine the association between these two factors and investigate the role of HLA genotypes in physical growth. To our knowledge there is a paucity of investigations of the very young age group with respect to body size, weight, length and the HLA-associated risk for islet autoimmunity and the subsequent onset of type 1 diabetes. The Better Diabetes Diagnosis study group reported a negative association between HLA risk level and BMI; however, their data were from newly diagnosed type 1 diabetes children aged 0–18

years.[18] Larsson et al.[22] examined HLA genotypes and physical growth before type 1 diabetes diagnosis among the Diabetes Prediction in Skåne study participants and reported increased linear growth, but not BMI, was associated with this disease independent of HLA genotypes between 0–18 months of age. It was, therefore, important to examine BMI in the entire group of The Environmental Determinants of Diabetes in the Young (TEDDY) children as they have a documented higher risk of developing islet autoimmunity. The objective of this analysis was to assess the prevalence of overweight and obesity by specific HLA genotypes associated with increased risk for type 1 diabetes.

SUBJECTS AND METHODS

TEDDY is a prospective cohort study funded by the National Institutes of Health with the primary goal to identify environmental causes of type 1 diabetes. It includes six clinical research centers—three in the United States: Colorado, Georgia/Florida, Washington and three in Europe: Finland, Germany and Sweden. Newborn children were screened for type 1 diabetes risk HLA genotypes either in the cord blood or on heel sticks within 3 months after birth.[23] If a child was determined to have increased genetic risk, the family was contacted by a TEDDY nurse and invited to participate in a 15-year-follow-up study before the child reached 4.5 months of age. Detailed study design and methods have been previously published.[23,24] Written informed consents were obtained for all study participants from a parent or primary caretaker, separately, for genetic screening and participation in prospective follow-up. The study was approved by local Institutional Review Boards and is monitored by an External Advisory Board formed by the National Institutes of Health.

Questionnaire data

Subject information, including date of birth, gender, whether the subject had first-degree relatives (FDR) with type 1 diabetes, birth weight and length and number of fetuses in the pregnancy (singleton, twin, triplet and so on), were collected by questionnaire at the time of HLA typing or at the first clinic visit when the infant was 3 months of age. The FDR status was considered positive if the child had a biological relative (mother, father or sibling) with type 1 diabetes. In the United States, subjects also identified their race/ethnicity using the USA census questions. Maternal factors, including maternal age, prepregnancy weight and height, presence of pregestational diabetes (type 1 or type 2) or gestational diabetes, gestational age and gestational weight gain were collected by questionnaire at the same time. A subject is required to withdraw from the study after he or she is diagnosed with type 1 diabetes. The date of diagnosis was reported by the caretaker.

Weight and height

Body weight was measured in kilograms using an electronic scale calibrated monthly. From the age of 2 years, height was measured to the nearest 0.1 cm using a wall-mounted stadiometer. For subjects who could not attend a clinical visit, anthropometric data were copied from their pediatricians' records collected around the visit date. BMI was calculated using measured weight divided by measured height in meters squared. Overweight and obesity status was determined by the International Obesity Task Force cutoff values, which were derived from averaged centile curves that pass through BMI of 25 kg m^{-2} for overweight and 30 kg m^{-2} for obesity.[25]

HLA typing and antibody testing

Detailed description of HLA typing and antibody testing has been published previously.[26] In brief, a total of 424 788 newborns were screened for HLA-DR, DQ genotypes associated with type 1 diabetes.[24] Blood samples of newborn children were obtained in the maternity clinics either as cord blood or dry blood spots. HLA genotypes were determined using either a genotyping system with an asymmetric PCR and subsequent hybridization of allele-specific probes for HLA-DQA1, DQB1 and DRB1 as described[27] using DELFIA reagents (Perkin-Elmer, Waltham, MA, USA) or in a dot blot hybridization assay as detailed elsewhere.[28]

Newborns with no FDR with type 1 diabetes were eligible for the study if they had one of the following four HLA genotypes:

(1) DR3/4 = DR4-DQA1*030X-DQB1*0302 (or *0304)/DR3-DQA1*0501-DQB1*0201 (abbreviated as DQ8/2);

(2) DR4/4 = DR4-DQA1*030X-DQB1*0302 (or *0304)/DR4-DQA1*030X-DQB1*0302(or *0304) (abbreviated as DQ8/8);

(3) DR3/3 = DR3-DQA1*0501-DQB1*0201/DR3-DQA1*0501-DQB1*0201 (abbreviated as DQ2/2); and

(4) DR4/8 = DR4-DQA1*030X-DQB1*0302 (or *0304)/DR8-DQA1*0401-DQB1*0402 (abbreviated as DQ8/X where X is not DR3-DQA1*0501-DQB1*0201 or DR4-DQA1*030X-DQB1*0302(*0304)).

Infants who had a FDR with type 1 diabetes were eligible for enrollment if they had any of the above four HLA genotypes or one of the additional genotypes:

(5) DR4-DQA1*030X-DQB1*0302 (or *0304)/DR4-DQA1*030X-DQB1*020X (abbreviated as DQ8/X where X is not DR3-DQA1*0501-DQB1*0201 or DR4-DQA1*030X-DQB1*0302(*0304));

(6) DR4-DQA1*030X-DQB1*0302 (or *0304)/DR1(not DR10)-DQA1*0101-DQB1*0501 (abbreviated as DQ8/X where X is not DR3-DQA1*0501-DQB1*0201 or DR4-DQA1*030X-DQB1*0302(*0304));

(7) DR4-DQA1*030X-DQB1*0302 (or *0304)/DR13-DQA1*0102-DQB1*0604 (abbreviated as DQ8/X where X is not DR3-DQA1*0501-DQB1*0201 or DR4-DQA1*030X-DQB1*0302(*0304)); and

(8) DR4-DQA1*030X-DQB1*0302/DR4-DQA1*030X-DQB1*0304 (abbreviated as DQ8/X where X is not DR3-DQA1*0501-DQB1*0201 or DR4-DQA1*030X-DQB1*0302(*0304));

(9) DR4-DQA1*030X-DQB1*0302 (or *0304)/DR9-DQA1*030X-DQB1*0303 (abbreviated as DQ8/X where X is not DR3-DQA1*0501-DQB1*0201 or DR4-DQA1*030X-DQB1*0302(*0304)); and

(10) DR3-DQA1*0501-DQB1*0201/DR9-DQA1*030X-DQB1*0303 (abbreviated as DQ2/X where X is not DR3-DQA1*0501-DQB1*0201 or DR4-DQA1*030X-DQB1*0302(*0304)).

These additional HLA genotypes were present in only 276 (3%) of the TEDDY subjects who were included in the current analyses. Newborns carrying the DR4 subtype DRB1*0403 were excluded if they had no FDR with type 1 diabetes.

Islet autoantibodies to insulin (IAA), glutamic acid decarboxylase 65 or insulinoma antigen-2 were measured by radiobinding assays in both central autoantibody laboratories, one located in the United States and one in Europe.[24] All positive islet autoantibodies and 5% of negative samples were retested in the other laboratory and deemed confirmed if concordant. Persistent confirmed islet autoantibody was defined as confirmed positive IAA, glutamic acid decarboxylase 65 or insulinoma antigen-2 on at least two consecutive study visits.

Transglutaminase antibody testing was carried out annually in all children starting at 24 months of age to screen for celiac disease. The testing was completed with the assessment of tissue transglutaminase autoantibodies (TGA) using radiobinding assays analyzed at the Bristol Laboratory (University of Bristol, UK) for the European sites and the Barbara Davis Center Laboratory (Aurora, CO, USA) for the USA sites. At the Barbara Davis Center , the radiobinding assays uses anti-IgA agarose to capture IgA-TGA; whereas, in Bristol a mixture of both anti-IgA agarose and protein A sepharose is used to assess both IgA-TGA and IgG-TGA. The discrepancy in methods does not impact detection of autoantibodies as the two IgA-TGA assays have proven highly concordant in previous TGA workshops.[29]

TEDDY enrolled 8677 subjects between 2004 and 2010. After excluding those whose HLA genotypes do not meet TEDDY's criteria (n = 113), who were not followed for 2 or more years (n = 2378), who did not have repeated weight and height measurements collected at study clinics (n = 195) and too few subjects with HLA genotype DQ2/X to draw inference (n = 22), 5969 subjects were included in this analysis as of March 2012.

Statistical analysis

Characteristics of subjects were summarized and compared as follows: Pearson's χ^2-tests or Fisher's exact test was used to analyze the categorical variables, namely subject's gender, country of residence, FDR, mother's diabetes status during pregnancy, and race/ethnicity (USA subjects only). Analysis of variance was used to analyze continuous variables, including gestational age, gestational weight gain, mother's BMI before pregnancy and subject's birth weight. The temporal trend of varying proportions of overweight and obesity within every HLA genotype was tested using the Cochran–Armitage Trend Test. Multivariable logistic regression models adjusted for the above factors were used to estimate the risk of being overweight or obese by comparing the proportion of subjects with HLA genotype DQ2/2, DQ8/8 and DQ8/X subjects against the proportion of subjects with the DQ2/8 genotype. A birth weight z-score was developed

Table 1. Characteristics of 5969 2–4-year-old children at genetic risk for type 1 diabetes

	DQ2/8	DQ8/8	DQ2/2	DQ8/X	
	(n = 2341)	(n = 1180)	(n = 1241)	(n = 1207)	P
Participant					
Sex (male/female)	1195/1146	593/587	676/565	617/590	0.1477
Age (months)	55.8 (17.2)	55.7 (17.2)	55.1 (16.9)	55.6 (17.0)	0.7167
Country					
United States (n = 2314)	923 (40.0%)	473 (20.4%)	556 (24.0%)	362 (15.6%)	< 0.0001
Finland (n = 1374)	465 (33.8%)	222 (16.2%)	205 (14.9%)	482 (35.1%)	
Germany (n = 357)	141 (39.5%)	64 (17.9%)	71 (19.9%)	81 (22.77%)	
Sweden (n = 1924)	812 (42.2%)	421 (21.9%)	409 (21.3%)	282 (14.6%)	
Having FDR with type 1 diabetes					
Yes (n = 675)	212 (31.4%)	112 (16.6%)	99 (14.7%)	252 (37.3%)	< 0.0001
No (n = 5294)	2129 (40.2%)	1068 (20.2%)	1142 (21.6%)	955 (18.0%)	
Birth weight (g)	3516.2 (554.3)	3510.4 (530.5)	3500.6 (546.8)	3506.5 (550.4)	0.8742
Maternal					
Diabetes during pregnancy					
Type 1 (n = 235)	71 (30.2%)	41 (17.4%)	26 (11.1%)	97 (41.3%)	< 0.0001
Type 2 (n = 16)	3 (18.7%)	4 (25.0%)	5 (31.3%)	4 (25.0%)	
GDM (n = 330)	137 (41.5%)	63 (19.1%)	59 (17.9%)	71 (21.5%)	
None (n = 5203)	2064 (39.6%)	1039 (20.0%)	1111 (21.4%)	989 (19.0%)	
Prepregnancy BMI	24.7 (5.1)	24.7 (5.1)	25.2 (5.7)	24.8 (5.3)	0.0759
Gestational age (weeks)	39.6 (1.6)	39.5 (1.5)	39.4 (1.7)	39.5 (1.7)	0.0539
Gestational weight gain (kg)	14.9 (6.0)	14.5 (6.5)	14.9 (6.4)	14.1 (6.2)	0.0051

Abbreviations: FDR, first-degree relatives; GDM, gestational diabetes mellitus. Data are *n* (%) or means (s.d.). All percentages are by row.

to adjust for country, gender, mother's height, gestational age and birth type. We repeated all univariate analyses by including and excluding subjects who developed islet autoantibody, type 1 diabetes and/or TGA and found no change in results to account for the possibility that individuals with type 1 diabetes might have different height/weight than the general population at the time of diagnosis[18,21] and that the presence of islet antibody and/or TGA may or may not affect growth trajectory.[30] The logistic regression models were then adjusted for autoimmunity and disease diagnosis. All tests for significance were two-tailed with a significance level of 0.05. Analysis was performed using the Statistical Analysis System Software (Version 9.3, SAS Institute, Cary, NC, USA).

RESULTS

Among the 5969 eligible subjects shown in Table 1, overall distribution of high-risk genotypes was 39.2% for DQ2/8, 19.8% for DQ8/8, 20.8% for DQ2/2 and 20.1% for DQ8/X. DQ2/8 was the most common high-risk genotype in every TEDDY country except in Finland, where DQ8/X was most common with DR4-DQA1*030X-DQB1*0302(or *0304)/DR8-DQA1*0401-DQB1*0402 being the predominant genotype. A larger proportion of subjects (n = 5294) without FDR carried DQ2/8 (40.2%), whereas FDR subjects (n = 675) carried DQ8/X more frequently (37.3%; P < 0.0001). The distribution of high-risk genotypes did not differ by the gender of the subject.

Gestational weight gain among the TEDDY mothers differed significantly when examined by their children's HLA genotypes (P < 0.01); however, our previous report indicated TEDDY subjects had comparable birth weight (data not shown).[31] The average BMI at each cross-sectional assessment point between ages 2 and 4 was not statistically different and followed a normal pattern of decline with increasing age (Figure 1). According to the International Obesity Task Force cutoff values, 12.1, 12.2, 11.1, 11.7 and 12.0% of subjects at 2, 2.5, 3, 3.5 and 4 years were overweight but not obese. The lowest prevalence, 10.4%, was seen in 3-year-old subjects with DQ8/X genotype and the highest prevalence, 13.3%,
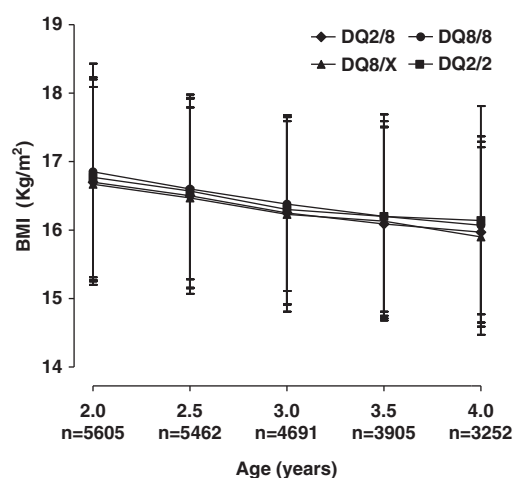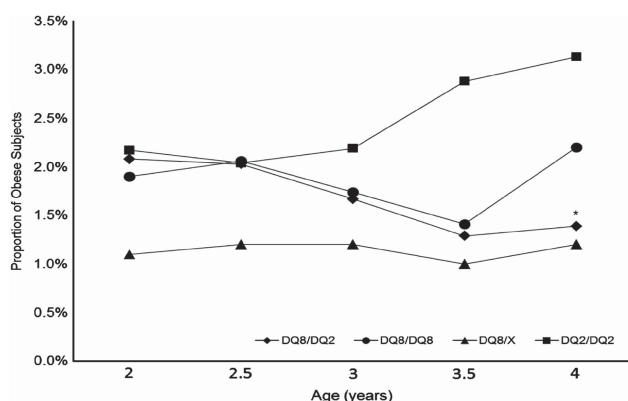

Figure 1. Cross-sectional comparison of body mass index by age and type 1 diabetes high-risk HLA genotypes among 5969 2–4-year-old children genetically at risk for type 1 diabetes.

was seen in 2.5-year-old children with the DQ2/2 genotype. The overall proportion of obese subjects was 1.9, 1.9, 1.7, 1.6 and 1.9% at 2, 2.5, 3, 3.5 and 4 years, respectively. Univariate analysis indicated that the proportion of overweight was not significantly different by age, HLA genotypes or country of residence, but a decreasing trend of obesity was also observed among those that carried the DQ2/8 genotype (P for trend = 0.0315, Figure 2).

Race/ethnicity comparison was conducted only among USA participants due to data availability. The prevalence of overweight and obesity did not differ by HLA genotypes in USA Non-Hispanic White and Hispanic subjects in univariate analysis except that the obesity rate declined from 3.2% (age 2) to 1.7% (age 4) in

Figure 2. Prevalence of obesity among 5969 2–4-year-old children genetically at risk for type 1 diabetes by age and by type 1 diabetes high-risk HLA genotypes. The asterisk denotes a significant declining trend in obesity within the DQ 2/8 genotype (*P* = 0.0315).

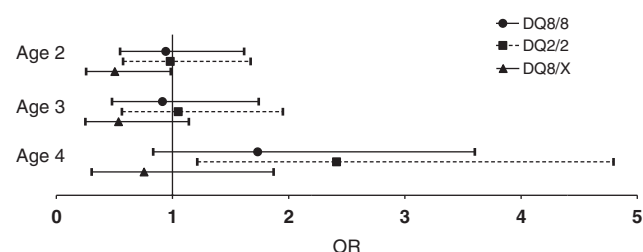|	2	2.5	3	3.5	4
DQ2/8 (n)	2213	2165	1857	1547	1291
DQ8/8 (n)	1105	1067	918	782	636
DQ8/X (n)	1136	1100	956	776	655
DQ2/2 (n)	1151	1130	960	800	670
Total (n)	5605	5462	4691	3905	3252

Figure 3. Association between obesity and HLA-DQ genotypes among 5969 2–4-year-old children genetically at risk for type 1 diabetes. Reference group = DQ2/8. Birth weight *z*-score was created to adjust for country, sex, mother's height, gestational age and the number of fetuses in the pregnancy (singleton, twin, triplet and so on). The development of persistent confirmed islet autoantibody and type 1 diabetes diagnosis was also adjusted for in the logistic regression model.

the Non-Hispanic White DQ2/8 group (*P* = 0.032) and peaked at 6.3% (age 3) compared with 3.3% at age 2 and 3.3% at age 4 (*P* < 0.0001) in the Hispanic DQ2/8 group.

Children carrying the DQ2/2 genotypes were independently associated with significantly higher risk of obesity at age 4 (*n* = 3 252, odds ratio (OR) = 2.41, 95% confidence interval (CI) = 1.21–4.80) after adjusting for mother's prepregnancy BMI, birth weight *z*-score and the development of type 1 diabetes or persistent confirmed islet autoantibody (Figure 3). In the meanwhile, mother's prepregnancy BMI was associated with risk of obesity between age 2 and 4 with an adjusted OR of 1.05 (95% CI 1.01–1.08) at age 2 (*n* = 5605), OR 1.10 (95% CI 1.06–1.13) at age 3 (*n* = 4691) and 1.09 (95% CI 1.06–1.13) at age 4 (*n* = 3252).

DISCUSSION

In this international study of 2–4-year-old children who are at increased genetic risk for type 1 diabetes, we report two major findings. First, a trend of continuously declining obesity was seen among DQ2/8 children (*P* = 0.0315) compared with other genotype groups. Second, the DQ2/2 genotype was independently associated with higher risk of obesity at age 4 (OR = 2.21, 95% CI = 1.12–4.33) after adjusting for maternal BMI before pregnancy, a widely acknowledged factor that influences body size.

The first finding that HLA-DQ8/2 genotype being associated with decreasing prevalence of obesity as the subjects aged was consistent with the result reported by Carlsson *et al.*,[18] which indicated that the frequency of high-risk HLA genotypes declined with increasing BMI. Taking into account that children with HLA DQ8/2 genotype tend to develop type 1 diabetes at a younger age,[32–34] it is reasonable to hypothesize that carriers of DQ8/2 may have a more progressive disease progress and/or a more rapid loss of insulin production, which would lead to a classic diabetes symptom—weight loss.

The second observation that genotype DQ2/2 was associated with higher risk of obesity suggested that individuals with this genotype may be more susceptible to become obese during physical development and their BMI may mediate their likelihood of developing type 1 diabetes imposed by genotype. Such a mediation may be realized by some cytokines secreted by adipocytes (for example, interleukin-6) affecting the risk of islet

autoimmunity through a direct effect on the function of autoimmunity suppression T regulatory cells,[35] or by other cytokines influencing beta cell function.[36] In addition, increase in adiposity was found to contribute to prepubertal insulin resistance.[37] All of the above factors may account for the reported correlation between higher prevalence of childhood obesity in the population and elevated type 1 diabetes incidence rate.[17–19] Another possible contributor to the relationship between DQ2/2 and higher risk of obesity observed in the TEDDY sample might be the role HLA genotype has in the pathogenesis of celiac disease. Class II HLA-DQA1 and HLA-DQ81 loci are strong genetic components of celiac disease with approximately 90% of celiac subjects having HLA-DQ2 heterodimers.[38]

The major findings in this paper were observed in more than 5000 children from four different countries in which the proportion of overweight children ranged from 10.4–13.3% and the proportion of obese children varied from 1.0–3.1% across four high-risk HLA genotypes and five age points. Within each TEDDY country, the prevalence of overweight and obesity was lower than the country-specific data from similar study cohorts.[39–41] Compared with national data from the age-comparable general population in the United States, the prevalence of overweight and obesity among the TEDDY USA cohort was lower than the estimates from the 2007–2008 National Health and Nutrition Examination Survey, which noted 21.2% of 2–5-year-old children were overweight and 10.4% of the same group were obese.[39] The Pediatric Diabetes Consortium study also observed that newly diagnosed type 1 diabetes patients had lower BMI than the general population after adjusting for age and gender.[21] TEDDY Swedish participants had an overweight rate of 16.8% and an obesity rate of 1.9%, which were lower than the rates in another pediatric cohort from the same region in Sweden.[40] The TEDDY subjects in Finland also had lower proportion of obesity (0.92% at age 2 and 0.75% at age 4) compared with the observations from a Finnish population without diabetes.[41] The lower prevalence in TEDDY may be attributed to the different genetic background between the TEDDY cohort and general public. Parental awareness of their children's disease risk might also have caused the TEDDY parents to follow health recommendations more closely, which in turn, might have resulted in lower BMI. An examination among multiple birth cohorts from a same area indicated longer breast feeding duration and reduced energy and dietary fat intake might have contributed to a decreasing trend for overweight at two years of age.[42]

In conclusion, HLA-DQ genotype was found to be associated with risk of obesity early in life when controlling for country, gender, birth weight, mother's height, maternal prepregnancy weight, gestational age and number of fetuses in the pregnancy. Effect of HLA-DQ genotype on developing type 1 diabetes may be

mediated by BMI as individuals carrying different genotypes may have different susceptibility to obesity. Longitudinal examinations of BMI as the TEDDY cohort ages will be valuable to verify findings in this study and to evaluate whether age and adiposity rebound affect the relationship between HLA genotypes and BMI. Data collected from similar populations such as the Diabetes Prediction in Skåne study and the Diabetes Autoimmunity Study in the Young study could also be used to test the findings. Investigation of the relationship between growth velocity and HLA genotypes will further shed light on alternative mediators in the development of type 1 diabetes.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

JY and KV researched data, contributed to discussion, wrote the manuscript and reviewed and edited the manuscript. AL contributed to discussion, reviewed and edited the manuscript. UMU, KFL, RV, CW, HEL, MR, JXS, AGZ, OGS, WAH, BA, and JPK reviewed the manuscript. JY is the guarantor of this work and, as such, had full access to all the data in the study and takes final responsibility for the decision to submit for publication.

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