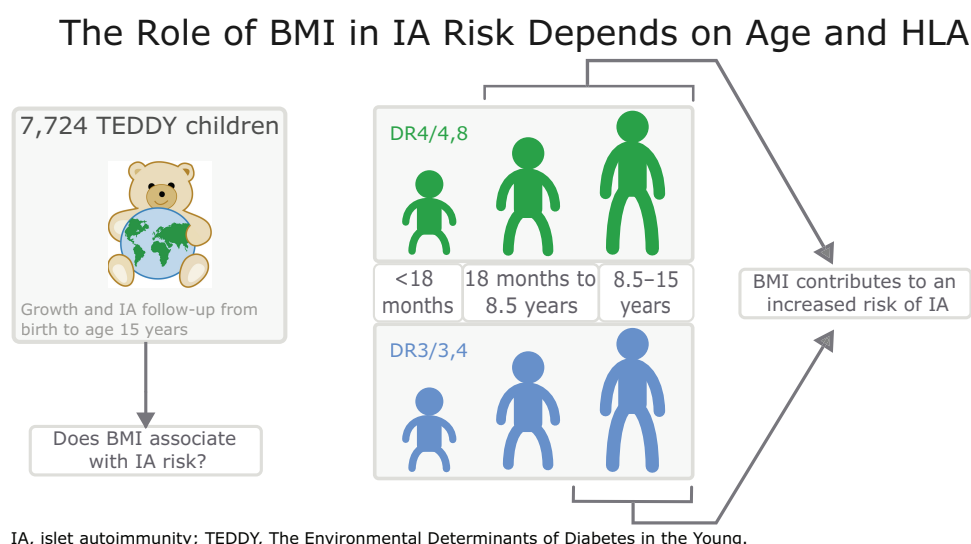


The Contribution of BMI to a Young Child's Risk of Islet Autoimmunity Is Dependent on HLA-DR4-DQ8 Without HLA-DR3-DQ2

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ARTICLE HIGHLIGHTS

- Why did we undertake this study?**

Age-related BMI trends coincide with age-related incidence of islet autoimmunity (IA). We studied whether a child's BMI correlates with IA risk during three distinct age periods.

- What is the specific question we wanted to answer?**

Does BMI correlate with the risk of IA and distinct first autoantibodies during infancy, early childhood, and puberty?

- What did we find?**

BMI z score did not correlate with infancy IA risk, whereas a high BMI z score correlated with IA risk during childhood and specifically for children carrying the HLA-DR4-DQ8 haplotype. During puberty, the correlation was not dependent on HLA.

- What are the implications of our findings?**

The association of BMI with IA risk after infancy and before puberty is dependent on HLA and not the first-appearing IA phenotype.



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OBJECTIVE

Childhood obesity may impact the risk of islet autoimmunity (IA). The trajectory of BMI through childhood resembles the early peak incidence of first-appearing autoantibodies against insulin (IAA-first) but not GAD65 (GADA-first). We studied whether a child's BMI can impact the age-related risk of first-appearing IA phenotypes.

RESEARCH DESIGN AND METHODS

We identified 7,724 children at risk for IA with at least three BMI measurements in The Environmental Determinants of Diabetes in the Young (TEDDY) study. We modeled the risk of IAA-first, GADA-first, and IA overall on a child's BMI z score and change in BMI during infancy (age 2 weeks to 1.5 years, $n = 7,724$), early childhood (age 1.5–8.5 years, $n = 6,396$), and puberty (age 8.5–15 years, $n = 4,732$) using joint modeling of longitudinal BMI and time-to-event IA.

RESULTS

An infant's BMI z score was not associated with IA risk before 18 months of age ($n = 185$, hazard ratio [HR] 1.03 [95% CI 0.88, 1.19]). In contrast, a child's BMI correlated with an increased risk of IA from 1.5 to 8.5 years of age ($n = 470$, HR 1.20 [95% CI 1.04, 1.32]) and from 8.5 to 15 years of age ($n = 209$, HR 1.27 [95% CI 1.09, 1.49]). No interactions with first-appearing IA phenotypes were observed. However, high BMI z score ($SD > 0.5$) from age 9 months increased the risk of IA in early childhood, specifically for children with HLA-DR4/4 or HLA-DR4/8 and not with HLA-DR3/3 or HLA-DR3/4 (HLA * BMI interaction, $P < 0.005$).

CONCLUSIONS

The contribution of BMI to risk of IA during early childhood is dependent on the HLA-DR-DQ genotype more so than the first-appearing IA phenotype.

Metabolic stress and adiposity may impact the risk of islet autoimmunity (IA) and type 1 diabetes (1). Infancy is characterized by 3.5 times faster weight gain than later childhood (2), which may increase both metabolic stress and adiposity, thereby increasing the risk of IA. Consistent with this hypothesis, the incidence curve of IA resembles the childhood BMI trajectory (3), which also defines three age periods with varying proportions of cases with the first autoantibodies against

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*A complete list of the TEDDY Study Group can be found in the supplementary material online.

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insulin (IAA-first) and GAD65 (GADA-first). Both BMI and the incidence of IA peak during infancy before age 18 months, the latter mostly explained by IAA-first cases. Thereafter, BMI declines until age 3–8.5 years (BMI rebound), when the incidence of IAA-first and GADA-first are comparable. After BMI rebound, BMI starts to increase again, and the incidence of IA is explained mainly by GADA-first cases (4). While BMI is typically not used in clinical practice during infancy (5), infancy BMI peak is a well-established marker of childhood obesity (6) and a risk factor for adolescent and adult cardiometabolic outcomes (7,8).

Prior studies have observed that BMI correlates with an increased risk of IA (3,9,10). However, these small studies could neither determine whether BMI contributes to the risk prediction of IA nor fully characterize the association by age and genetic background. Here, we make use of The Environmental Determinants of Diabetes in the Young (TEDDY) study and examine whether BMI during the three age phases of the BMI trajectory is associated with the risk of IA during each age period, by HLA or non-HLA IA risk genes, and specifically with age-related first-appearing IA phenotypes.

RESEARCH DESIGN AND METHODS

Participants

TEDDY is a prospective cohort study funded by the National Institutes of Health to identify environmental causes of type 1 diabetes (11,12). It includes six clinical research centers: three in the U.S. (Colorado, Georgia/Florida, and Washington) and three in Europe (Finland, Germany, and Sweden). In brief, children at genetic risk of type 1 diabetes based on their HLA haplogenotype were enrolled at 3 months of age and followed for serial autoantibody measurements every 3 months until 4 years of age (13,14), then every 6 months until the diagnosis of type 1 diabetes or age 15 years. Autoantibody-positive participants continued to be observed quarterly. Written informed consent was obtained for all study participants from a parent or primary caregiver for genetic screening and separately for 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.

Outcomes

Islet autoantibodies to IAA, GADA, and IA-2 antigen (IA-2A) were measured in two laboratories by radiobinding assays (15,16). In the U.S., all sera were assayed at the Barbara Davis Center for Childhood Diabetes at the University of Colorado Denver; in Europe, all sera were assayed at the University of Bristol in the U.K. Both laboratories have shown high sensitivity, specificity, and concordance in their autoantibody assays. All samples positive for islet autoantibodies and 5% of samples negative for islet autoantibodies were retested in the other reference laboratory and deemed confirmed if concordant. Persistent autoimmunity was defined by detecting a confirmed islet autoantibody (GADA, IA-2A, and IAA) on two or more consecutive visits. Maternal autoantibodies were distinguished as previously described (17). Type 1 diabetes was diagnosed according to World Health Organization and American Diabetes Association criteria (18).

HLA Haplogenotype

As previously published, genotype screening was conducted using a dried blood spot punch or a small-volume whole-blood lysate specimen format (13,14). Infants from the general population and 11% who had a first-degree relative (FDR) with type 1 diabetes were eligible for the study if they had any one of the high-risk HLA-DR-DQ haplogenotypes listed in Supplementary Table 1 (excluding those with DR4 subtype DRB1*0403). Participants were categorized according to the number of inherited HLA-DR3 alleles.

Single Nucleotide Polymorphism Analysis and IGF-I Polygenic Score

Single nucleotide polymorphism (SNP) analysis was conducted at the Center for Public Health Genomics at the University of Virginia using the Illumina Immunochip, a custom array for SNPs from genomic regions associated with autoimmune diseases (19). The polygenic score of IGF-I was calculated according to Sinnott-Armstrong et al. (20).

Anthropometric Measurements

The trained staff at TEDDY sites measured height or length and weight (21). In addition, we used height and weight measurements reported to the TEDDY study staff from other settings, such as well-child and hospital visits. Growth

data were cleaned using the growth-cleanr R package, a validated approach using an exponential moving average algorithm to exclude biologically implausible measurements (22). The growth profiles were inspected visually and transformed to height, weight, and BMI z scores (Supplementary Note 1).

Regulation of growth is proposed to differ among infancy, childhood, and puberty (23). Likewise, BMI trajectory (BMI peak, BMI rebound, and pubertal increase) and the IA incidence curve (infancy peak, leveling off, stable incidence) follow distinct patterns during infancy, childhood, and puberty, respectively. We selected 1.5 years as a cut point between infancy and early childhood to align with BMI modeling in previous studies from the Early Growth Genetics Consortium (4,8,24). Likewise, following the previous reports that BMI rebound takes place at the latest at age 8.5 years, this was the cut point between early childhood and puberty (8).

Statistical Analyses

The child's average infancy, early childhood, and puberty BMI z scores were each modeled concurrently with IA risk using joint models that combine longitudinal and time-to-event data in a single model. The random intercept from the linear mixed-effects longitudinal submodel was used as an estimate of a child's average BMI z score during the interval while at risk for IA. Longitudinal submodels with random intercepts and slopes were used to approximate the child's change in BMI z score during the age interval (i.e., the linear increase in BMI from the start of the respective age period) to assess its association with IA risk. To assist in understanding the BMI associations observed, similar joint models were fitted to determine how height and weight z scores correlated with the risk of IA. Sensitivity analyses were conducted to assess the impact of excluding children whose mother had type 1 diabetes, excluding children born before gestational week 37 or after gestational week 42, or adjusting for birth size. Furthermore, age (in months and years, respectively) and BMI (kg/m^2) at the BMI peak and rebound, the latter estimated by polynomial mixed-effects models (8), were examined in relation to the IA risk in the subsequent age periods using

time-invariant Cox proportional hazards models.

Height, weight, and BMI measurements were only used while the child was at risk for IA. All Cox and joint models were adjusted for sex, FDR with type 1 diabetes (yes/no), the number of carried HLA-DR3 alleles, and country of origin. SEs in joint models were estimated using bootstrapping ($n = 1,000$, $n = 100$ for sensitivity analyses). Missing data were excluded from analyses and not imputed. The children who were lost to follow-up were censored. Unless otherwise stated, hazard ratios (HRs) and 95% CIs are reported per 1-SD difference in the z score.

Time-varying receiver operating characteristic (ROC) curve models were constructed to assess the predictive capability of BMI z score at a specific age to help characterize the clinical impact of BMI on risk of IA. The area under the curve and the optimal cut point determined by the Youden index were calculated for follow-up at regular periods (e.g., every 2 years).

All analyses were done using R version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria). R package lme4 was used in linear mixed-effects modeling, survival in the survival analysis, joiner in joint modeling, and survivalROC for fitting ROC curves.

Data and Resource Availability

Data from TEDDY (<https://doi.org/10.58020/y3jk-x087>) reported here will be made available for request at the National Institute of Diabetes and Digestive and Kidney Diseases Central Repository Resources for Research website (<https://repository.niddk.nih.gov/>).

RESULTS

Participants

In total, 7,724 of the 8,676 TEDDY children were included in the analyses (Supplementary Fig. 1). The demographic data of children at risk for IA, IAA-first, and GADA-first in the three age periods (infancy, age 2 weeks to 18 months; early childhood, age 1.5–8.5 years; puberty, age 8.5–15 years) are summarized in Table 1. A total of 185 (44 GADA-first, 109 IAA-first), 470 (228 GADA-first, 151 IAA-first), and 209 (117 GADA-first, 49 IAA-first) children developed IA during infancy, early childhood, and puberty, respectively. IAA was the predominant first-appearing autoantibody during infancy and GADA during puberty (Fig. 1).

BMI Correlates With IA Risk During Early Childhood and Puberty

A child's BMI z score and the change in BMI z score during the three age periods were examined in relation to the risk of IA (Table 2). During early childhood and puberty, but not infancy, a child's BMI z score correlated with an increased risk of IA. During early childhood, a child's BMI z score correlated with an increase in risk of any IA (HR 1.20 [95% CI 1.04, 1.32]) and specifically with IAA-first (HR 1.27 [95% CI 1.02, 1.54]). During puberty, a child's BMI z score correlated with an increase in the risk of any IA (HR 1.27 [95% CI 1.09, 1.49]) and GADA-first (HR 1.30 [95% CI 1.06, 1.58]). However, no significant interactions between IAA-first and GADA-first phenotypes were observed during each age period. Change in BMI z score was not associated with IA overall; however, a rise in BMI z score from the start of the age period was associated with an increased risk of IAA-first during early childhood (HR 1.59 [95% CI 1.05, 2.46]) (Table 2).

Height and weight z scores were examined in relation to IA risk to help understand BMI correlations (Table 2). During childhood and puberty, associations with IA and first-appearing phenotypes resembled that seen with BMI. However, during infancy, an infant's height and weight z scores correlated with a significantly increased risk of GADA-first, while an increased rise in weight z score marginally correlated with a lower risk of IAA-first.

Effect Modification by IA Risk Factors

Next the BMI z score and its association with IA risk was examined for effect modification by strong risk factors of IA. No interactions with non-HLA SNPs, family history, sex, or country of residence were observed. However, during early childhood, children with HLA-DR4/4 or HLA-DR4/8 haplotypes showed an association with IA risk (HR 1.41 [95% CI 1.17, 1.70]), whereas there was no evidence for correlation among children with either HLA-DR3/4 or HLA-DR3/3 genotypes (HR 1.07 [95% CI 0.93, 1.25]). No such effect modification by HLA (HLA-DR4/4 or HLA-DR4/8 vs. HLA-DR3/3 or HLA-DR3/4) was seen during infancy (HR 1.15 [95% CI 0.87, 1.54] vs. 0.96 [95% CI 0.76, 1.17], respectively) or puberty (HR 1.31 [95% CI 1.02, 1.68] vs. 1.25 [95% CI 1.03, 1.52], respectively). To further characterize

HLA as an effect modifier on the association between BMI and risk of IA, we assessed whether BMI in infancy is associated with the risk of IA during early childhood. BMI z score at the 9-month visit (close to infancy peak) correlated positively with IA risk in early childhood (HR 1.22 [95% CI 1.09, 1.36]). Furthermore, the correlation between BMI at the 9-month visit and early childhood risk of any IA interacted with the number of DR3 alleles carried (0 vs. 1 or 2; interaction $P = 0.002$) (Fig. 2). We next examined the association of the IGF-I polygenic score with risk of early childhood IA and observed a suggestion of a borderline inverse correlation among children with HLA-DR3 (HR 0.29 [95% CI 0.08, 1.01]) that was not observed among children without HLA-DR3 (HR 1.43 [95% CI 0.30, 6.87]).

BMI in Risk Prediction of IA

We assessed the predictive contribution of 9-month BMI z score as an addition to previously identified significant predictors of IA (FDR status and SNPs rs2476601, rs3184504, and rs1004446) while stratifying for HLA haplogenotype (25). The ROC area under the curve for IA follow-up to age 8 years was similar in models without and with BMI z scores for children with at least one DR3 allele (0.60 and 0.61, respectively), but more divergent for children with no DR3 allele (0.64 and 0.68, respectively). The added contribution by BMI was nonlinear, as primarily a high BMI increased the risk of IA. The cumulative incidence curves (Fig. 2) showed an impact on cumulative incidence at a cut point of BMI z score + 0.5 SD, and results were similar for the cut points ranging from 0.42 (the lowest optimal cut point for follow-up to age 6 years in children with DR4/8) to 0.74 (the highest optimal cut point for follow-up to age 2 years in children with DR4/4). High BMI (>0.5 SD) showed an increased risk of IA among children with HLA-DR4/4 and HLA-DR4/8 that was similar to all children with the highest genetic risk (HLA-DR3/4), but no impact of BMI was seen among the latter group or among children with HLA-DR3/3.

BMI at Infancy Peak Correlates With Later IA Risk

We additionally examined associations between BMI peak and BMI rebound with risk of IA. BMI peak positively correlated with risk of early childhood IA (HR 1.14 [95% CI 1.07, 1.23] per kg/m²)

Table 1—Study population characteristics

	Infancy	Early childhood	Puberty
Inclusion criteria	≥1 visits between age 2 weeks and 18 months	≥3 visits between age 2 weeks and 18 months*; ≥1 visit between 18 months and 8.5 years	≥3 visits between 18 months and 13 years†; ≥1 visit between 8.5 and 15 years
Participants, <i>n</i>	7,724‡	6,396‡	4,732‡
IA follow-up age range	2 weeks–1.5 years	1.5–8.5 years	8.5–15 years
Follow-up (years)	1.5 (1.5, 1.5)	8.5 (7.5, 8.5)	15.0 (14.0, 15.0)
IA cases during follow-up, <i>n</i>	185	470	209
First-appearing autoantibody			
GADA	44 (24)	228 (49)	117 (56)
IAA	109 (59)	151 (32)	49 (23)
Multiple or IA-2A	32 (17)	91 (19)	43 (21)
Exposures	BMI, weight, and height z scores	BMI, weight, and height z scores; infancy body size and proportions; BMI infancy peak; BMI z score at 9 months	BMI, weight, and height z scores; BMI peak and rebound
Country			
Finland	1,692 (22)	1,469 (23)	1,080 (23)
Germany	524 (7)	398 (6)	260 (5)
Sweden	2,335 (30)	2,040 (32)	1,545 (33)
U.S.	3,173 (41)	2,489 (39)	1,847 (39)
Sex			
Female	3,783 (49)	3,129 (49)	2,334 (49)
Male	3,941 (51)	3,267 (51)	2,398 (51)
FDR with type 1 diabetes			
No	6,832 (88)	5,645 (88)	4,174 (88)
Yes	892 (12)	751 (12)	558 (12)
HLA-DR3 alleles			
0	3,086 (40)	2,558 (40)	1,896 (40)
1	3,037 (39)	2,509 (39)	1,809 (38)
2	1,601 (21)	1,329 (21)	1,027 (22)
Birth measurements			
Available§	7,510 (97)	6,227 (97)	4,610 (97)
Weight (kg)	3.5 (3.2, 3.9)	3.5 (3.2, 3.9)	3.5 (3.2, 3.9)
Length (cm)	51.0 (49.0, 53.0)	51.0 (49.0, 53.0)	51.0 (49.0, 53.0)
BMI infancy peak			
Available§	—	5,801 (90)	4,179 (88)
BMI (kg/m ²)	—	17.5 (16.6, 18.4)	17.5 (16.6, 18.4)
Timing (months)	—	8.0 (7.3, 8.9)	8.0 (7.3, 8.9)
BMI rebound			
Available§	—	—	4,312 (91)
BMI (kg/m ²)	—	—	15.5 (14.8, 16.4)
Timing (years)	—	—	5.3 (4.3, 6.2)

Data are median (interquartile range) and *n* (%) unless otherwise indicated. *Three or more visits between 2 weeks and 18 months are required for estimating the BMI infancy peak. †Three or more visits between 18 months and 13 years are required for estimating the BMI rebound. ‡Of the 7,724 children in the infancy period, 4,598 had data during both the childhood and puberty periods, 1,798 during the childhood but not puberty period, and 134 during puberty but not the childhood period. §Number of participants with data available.

(Supplementary Fig. 2). A further exploratory analysis of BMI at age 9 months suggested that both the overall infancy body size (the mean of height-weight z scores, i.e., weight explained by height) and body proportions (difference between height and weight z scores, i.e., weight unexplained by height) independently

predicted the risk of early childhood IA (Supplementary Note 2).

Sensitivity Analyses

Maternal type 1 diabetes, preterm birth, birth size, and country of origin may plausibly confound the association between body size and the risk of IA. Therefore, we

further analyzed each of our key analyses, excluding preterm infants and offspring of mothers with type 1 diabetes, and analyzed the models stratified by country and adjusting for birth size (birth height in height models, birth weight in weight models, and birth BMI in BMI models). The results of the analyses

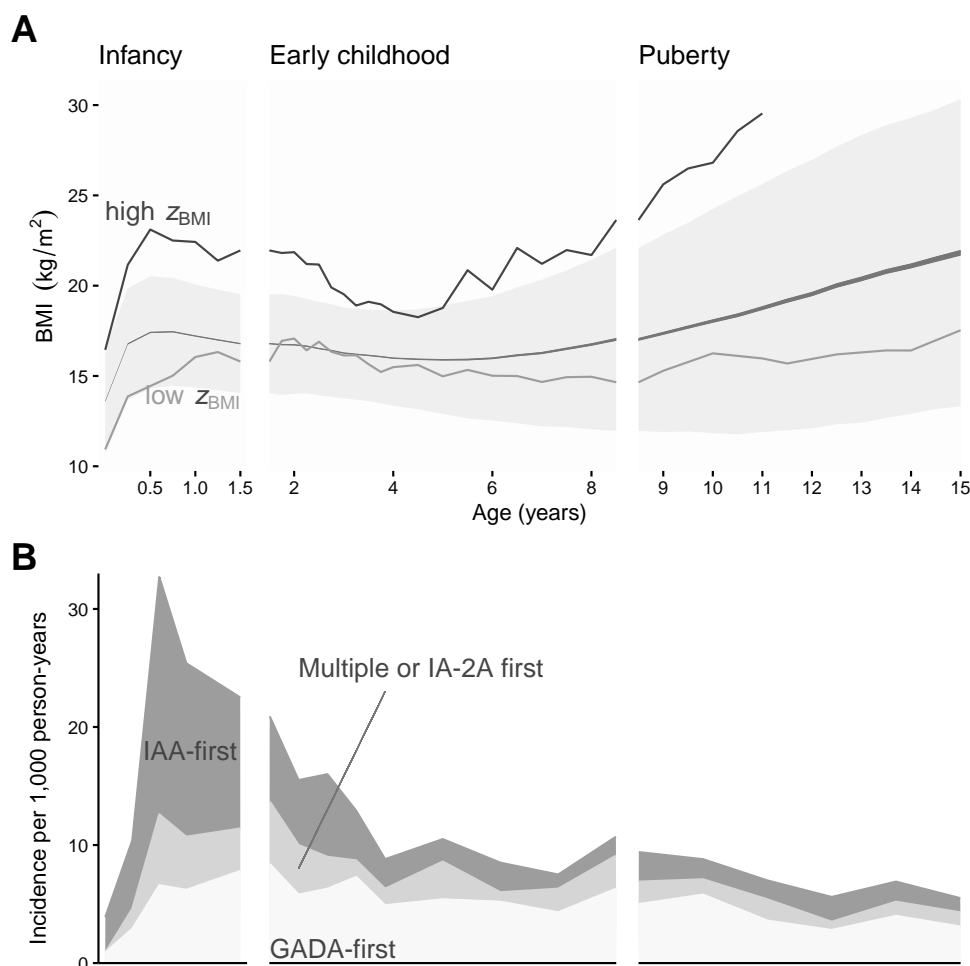


Figure 1—A: The mean curve of BMI, 95% reference range (shaded area), and example curves with high and low child infancy BMI z scores. B: The incidence of IA during childhood in the TEDDY study.

remained similar (Supplementary Figs. 3 and 4).

CONCLUSIONS

BMI and weight have previously been shown to correlate with the risk of IA (2,3,9,10,21,26), and the typical BMI curve bears a striking similarity with infancy IAA-first incidence (3), suggesting that higher infancy BMI could explain the IAA-first peak. Therefore, we analyzed the association between BMI and the risk of IA during three distinct periods: infancy, when BMI and incident IAA-first peak; early childhood, when BMI rebounds and the incidence of IAA-first declines to become as stable as GADA-first; and puberty, when BMI increases again and GADA-first is the more common first-appearing IA. BMI correlated with the risk of IA after, but not during, infancy. The correlation was HLA dependent in early childhood. Our findings are consistent with previous assessments of the

relationship between growth and risk of IA in the TEDDY cohort, when considering the time frames for exposure and outcome follow-up (2,21,27).

Because a child's BMI z score remains relatively stable over time, there is potential for clinicians to use measured BMI to predict future IA risk. We have shown that the 9-month BMI z score is associated with IA risk in early childhood, and it marginally improves IA risk prediction over the previously identified top predictors of IA in TEDDY but only among children with HLA-DR4 and without HLA-DR3. Further examination may establish whether BMI, or BMI-associated SNPs, can improve upon prediction based on type 1 diabetes genetic risk scores.

Previous TEDDY analyses have reported associations between GADA-first and HLA-DR3 and between GADA-first and infancy weight gain (2,17). Therefore, we expected that the role of BMI in IA risk may be explained by infancy IA cases

and HLA-DR3-positive GADA-first cases. Instead, BMI was not associated with IA during infancy, and the association was restricted to children with HLA-DR4/4 or HLA-DR4/8 after infancy, suggesting that BMI interacts with the adaptive immune system. HLA-DR3 is associated with a higher IGF-I concentration (28); therefore, children with an HLA-DR3 haplotype may be protected in early childhood by an inverse correlation between IGF-I and IA risk.

While a child's average BMI did not correlate with IA risk during infancy, a child's height and weight z scores correlated with the risk of GADA-first during infancy. Weight or weight-for-length is generally considered a more accurate description of body size and adiposity than BMI during infancy (5), although BMI at infancy peak is a widely used marker of childhood obesity and correlates with adolescent and adult obesity (6,7). Therefore, infancy size may be a risk factor for GADA-first in infancy.

Table 2—Child's average body size across time and change from start of age period on the risk of developing IA during three distinct age periods

Child-specific body size measure during age period while at risk for IA	First autoantibody	HR (95% CI)		
		Infancy (2 weeks to 1.5 years)	Early childhood (1.5–8.5 years)	Puberty (1.5–15 years)
Average BMI z score during the age period	Any	1.03 (0.88, 1.19)	1.20 (1.04, 1.32)	1.27 (1.09, 1.49)
	IAA	1.06 (0.86, 1.30)	1.27 (1.02, 1.54)	1.21 (0.87, 1.71)
	GADA	1.22 (0.84, 1.72)	1.15 (0.94, 1.38)	1.30 (1.06, 1.58)
Change in BMI z score from start of age period	Any	0.90 (0.64, 1.16)	1.21 (0.97, 1.43)	1.26 (0.99, 1.62)
	IAA	0.88 (0.51, 1.28)	1.59 (1.05, 2.46)	1.57 (0.99, 2.63)
	GADA	1.02 (0.51, 1.75)	1.09 (0.85, 1.32)	1.06 (0.77, 1.50)
Average weight z score during the age period	Any	1.12 (0.93, 1.29)	1.15 (1.02, 1.25)	1.28 (1.09, 1.51)
	IAA	1.07 (0.84, 1.32)	1.21 (0.99, 1.43)	1.20 (0.86, 1.66)
	GADA	1.54 (1.11, 1.93)	1.09 (0.87, 1.32)	1.31 (1.06, 1.61)
Change in weight z score from start of age period	Any	0.76 (0.52, 1.11)	1.87 (1.57, 2.21)	1.02 (0.77, 1.34)
	IAA	0.71 (0.48, 0.98)	2.42 (1.71, 3.13)	1.19 (0.62, 2.32)
	GADA	0.93 (0.44, 1.81)	1.71 (1.34, 2.02)	0.85 (0.64, 1.12)
Average height z score during the age period	Any	1.19 (0.98, 1.39)	1.11 (1.00, 1.23)	1.13 (0.95, 1.32)
	IAA	1.07 (0.85, 1.38)	1.17 (0.99, 1.41)	1.04 (0.76, 1.39)
	GADA	1.79 (1.09, 2.47)	1.03 (0.87, 1.19)	1.16 (0.92, 1.48)
Change in height z score from start of age period	Any	1.29 (0.94, 1.97)	1.54 (1.08, 1.99)	1.19 (0.93, 1.53)
	IAA	1.24 (0.66, 2.06)	1.85 (0.80, 3.02)	1.09 (0.59, 1.93)
	GADA	1.61 (0.73, 2.98)	1.61 (1.16, 2.24)	1.16 (0.86, 1.58)

All joint models were adjusted for FDR with type 1 diabetes (yes/no), the number of carried HLA-DR3 alleles, sex, and country. A child's average height, weight, and BMI z scores and change in height, weight, and BMI z scores were calculated for each age period and represent the average level and change from the beginning of the interval, respectively. Models for IAA-first and GADA-first in puberty excluded Germany because of the low number of IA cases.

However, after infancy, there was no clear difference in the strength of the association between height, weight, or BMI and GADA-first vs. IAA-first.

A constrained weight gain (i.e., negative change in z score) during infancy correlated with an increased risk of IAA-first. However, a relative rise in weight during childhood correlated with an increased risk of IAA-first. These unexpected associations could be explained by infections. TEDDY reported previously that infectious symptoms before enrollment at 3 months of age correlated with the risk of IAA-first early in life, even when birth weight did not (29). Furthermore, gastrointestinal infectious episodes and norovirus during infancy correlated with an increased risk of IAA-first in early childhood (30). Symptomatic infections could plausibly reduce early weight gain during infancy (31) and so mark the impact of early infections on excess risk of IAA-first during infancy; however, this is a speculative theory that will require a more in-depth assessment.

The role of body proportions and obesity as a possible cause of IA and type 1 diabetes has been widely discussed (1), whereas body size (increase in both height

and weight) has received less attention (32). However, not only BMI and weight but also height were associated with the risk of IA both in our study and in prior reports (26,33). Our exploratory analysis of agreement versus discrepancy in height and weight z scores further suggests that body size and body proportions may be independent risk factors of IA.

The associations between IA risk and BMI may be mediated by insulin demand and metabolic stress. Childhood BMI is associated with insulin resistance, which is thought to increase insulin demand and lead to IA and type 1 diabetes (1), although there was no evidence that insulin resistance increases the risk of IA in two small studies (34,35). In experimental models, increased metabolic stress within β -cells may overwhelm the mechanisms that protect against the misfolding of proteins and trigger pathways that lead to apoptosis (36). However, in addition to insulin demand, obesity might also increase the risk of IA by influencing the immune system directly (37); for example, a high BMI at infancy peak is associated with asthma and early wheezing (24). Increased visceral obesity may lead to increased low-grade inflammation and IL-6 signaling (38),

which was a risk factor for type 1 diabetes in a recent Mendelian randomization study (39). Our study lends further support to the interaction between BMI and the immune system in the development of IA since the association was HLA dependent.

Our study has a few limitations. Participants in the TEDDY study are at high genetic risk of type 1 diabetes, and most cases of IA develop early during childhood. As an observational study, we cannot exclude the possibility that the observed associations reflect the influence of less-specific or unknown early-life confounders acting on the risk of IA, even after adjusting for strong IA risk factors, namely HLA genotype, FDR status, country, and sex. However, we saw similar associations when including only children born in gestational weeks 37–42 or whose mothers did not have type 1 diabetes. Furthermore, there were only a limited number of GADA-first cases during infancy ($n = 44$) and IAA-first cases during puberty ($n = 49$), which may limit our statistical power to observe associations between BMI and these phenotypes of IA during these age periods. Future efforts to replicate these findings in other cohorts will strengthen their validity. The strengths of the study

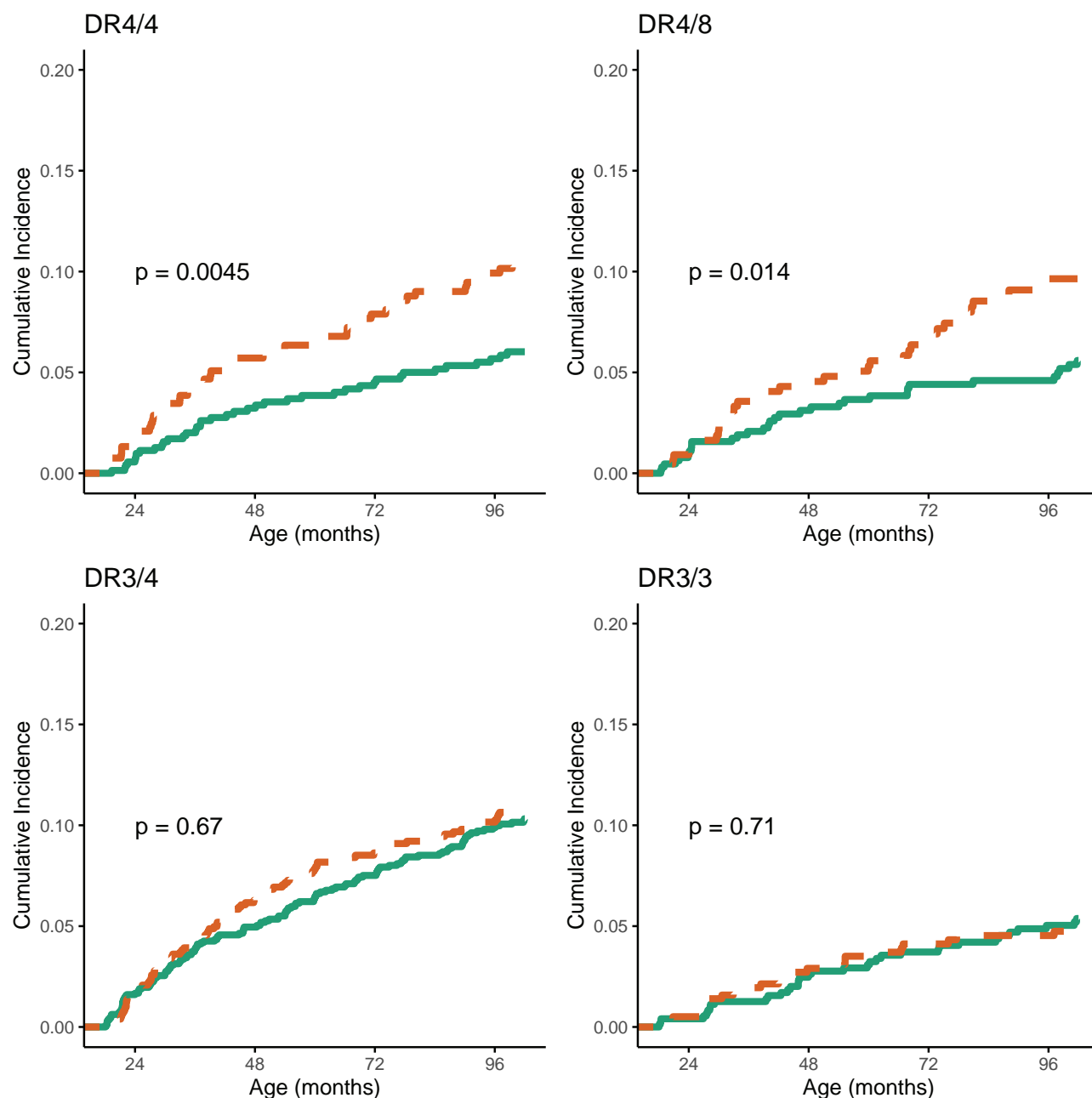


Figure 2—Cumulative incidence of IA during early childhood (1.5–8.5 years) according to BMI z score (SD) at age 9 months (orange dashed line, >0.5; green solid line, ≤0.5), stratified by HLA haplotype.

include its prospective design, systematic measurement protocol, frequent height and weight measurements, and geographic diversity.

In conclusion, BMI is associated with risk of IA after, but not during, infancy. The contribution of BMI to risk of IA during early childhood is dependent on HLA-DR-DQ genotype more so than first-appearing IA phenotype.

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