



# Excess BMI in Childhood: A Modifiable Risk Factor for Type 1 Diabetes Development

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## OBJECTIVE

We aimed to determine the effect of elevated BMI over time on the progression to type 1 diabetes in youth.

## RESEARCH DESIGN AND METHODS

We studied 1,117 children in the TrialNet Pathway to Prevention cohort (autoantibody-positive relatives of patients with type 1 diabetes). Longitudinally accumulated BMI above the 85th age- and sex-adjusted percentile generated a cumulative excess BMI (ceBMI) index. Recursive partitioning and multivariate analyses yielded sex- and age- specific ceBMI thresholds for greatest type 1 diabetes risk.

## RESULTS

Higher ceBMI conferred significantly greater risk of progressing to type 1 diabetes. The increased diabetes risk occurred at lower ceBMI values in children <12 years of age compared with older subjects and in females versus males.

## CONCLUSIONS

Elevated BMI is associated with increased risk of diabetes progression in pediatric autoantibody-positive relatives, but the effect varies by sex and age.

Studies report conflicting data regarding the roles of weight and obesity on type 1 diabetes risk (1–5). Most studies limit analyses to BMI at a single time point prior to diabetes diagnosis. Further, the influence of sex and age remain unexplored. We evaluated the longitudinal influence of cumulative excess BMI (ceBMI), a calculated aggregate measure of BMI elevation over time, on progression to type 1 diabetes in children of the TrialNet Pathway to Prevention (PTP) cohort.

## RESEARCH DESIGN AND METHODS

The TrialNet PTP study screened 3,285 individuals from March 2004 to June 2014 and monitored them for progression to diabetes through November 2015 (6). This analysis included participants aged 2–18 years at their first BMI evaluation with  $\geq 2$  BMI measurements before 20 years of age ( $n = 1,117$ ). Baseline was defined as the first visit with a BMI evaluation.

Standard protocol oral glucose tolerance test and HbA<sub>1c</sub> were obtained at each visit (7). Diabetes was diagnosed according to American Diabetes Association criteria (8). HbA<sub>1c</sub>  $\geq 6.5\%$  was part of confirmatory testing (9).

BMI was calculated as weight (kg)/height (m<sup>2</sup>). ceBMI was adopted to measure persistent BMI elevation  $\geq 85$ th percentile for age- and sex- adjusted BMI. Weighted sums of the differences between actual BMI and corresponding 85th percentile at each BMI assessment were calculated (10,11) and then further annualized to

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accommodate irregular timing of BMI assessment in relation to time to diabetes or censoring (for calculation of ceBMI, see Supplementary Data). For individuals who progressed to diabetes, the last BMI used was  $\geq 6$  months prior to diagnosis date.

### Statistical Considerations

Pearson's  $\chi^2$  tests, Fisher exact tests, Wilcoxon rank-sum tests, Kruskal-Wallis tests, and nonparametric Spearman rank correlation tests were used as appropriate. Analyses of BMI were based on relevant Centers for Disease Control and Prevention cutoffs ([www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm](http://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm)). ceBMI was analyzed both as a continuous measure and a dichotomized measure. ceBMI  $\geq 0$  indicated that an individual's average BMI was  $\geq 85$ th age- and sex-adjusted percentile during the observation period.

The primary outcome was time to type 1 diabetes (i.e., time from first BMI evaluation to date of diagnosis). Those not diagnosed with type 1 diabetes were censored at their last follow-up or enrollment in a prevention trial. Kaplan-Meier methods assessed distribution differences in the time to type 1 diabetes among groups, and Cox proportional hazards models evaluated the influence of continuous and categorical variables. Assumptions for proportionality of hazards were tested. All time-to-event analyses were adjusted for age, sex, and antibody number confirmed at screening (single vs. multiple). Additional adjustment for the presence of the highest risk HLA genotype (i.e., DR3-DQ2/DR4-DQ8) did not alter significance of the results. Recursive partitioning analysis was used to identify critical cut points for ceBMI and age at first BMI evaluation for influence on diabetes development and risk stratification of time-to-event (12) (rpart package in R).

Inferential tests were two-sided. Any  $P$  values  $< 0.05$  (0.1 for interaction terms) were considered significant. All analyses were conducted in R (version 3.1.2; Windows; Microsoft).

## RESULTS

We analyzed a total of 1,117 pediatric subjects of the PTP cohort between the ages of 2 and 18 years (median: 10.1 years; interquartile range [IQR]: 6.7–13.3 years), of whom 20% ( $n =$

220) developed diabetes. Median first BMI percentile was 63.8% (IQR: 36.6–84.8%), with 14% overweight (BMI  $\geq 85$ th to  $< 95$ th percentile) and 11% obese ( $\geq 95$ th percentile). ceBMI ranged from  $-10$  to  $15.1$  kg/m<sup>2</sup> (median:  $-1.86$  kg/m<sup>2</sup>; IQR:  $-3.6$  to  $-0.03$  m<sup>2</sup>/kg). Nearly 25% of subjects had ceBMI values  $\geq 0$  kg/m<sup>2</sup> representing sustained excess BMI above the Centers for Disease Control and Prevention thresholds of overweight/obesity (Supplementary Table 1).

Higher ceBMI was associated with significantly greater risk of progression to type 1 diabetes, which persisted after adjusting for age at first BMI evaluation, antibody number, and sex. For each 1-kg/m<sup>2</sup> increase in ceBMI, there was a 6.3% increased relative risk of type 1 diabetes progression (hazard ratio [HR]: 1.063 [95% CI 1.03–1.10];  $P = 0.0006$ ). Individuals who, on average, were persistently overweight or obese (ceBMI  $\geq 0$ ) had a 63% greater type 1 diabetes risk, adjusted for age, sex, and antibody number (HR: 1.63 [95% CI: 1.22–2.18];  $P = 0.0009$ ).

Age at baseline was a significant independent risk factor for type 1 diabetes progression (HR: 0.94;  $P = 0.0006$ ), adjusted for ceBMI, sex, and antibody status. A significant interaction between age and sex, together with ceBMI in relation to time to diabetes ( $P = 0.072$ ) triggered investigation of age- and sex-specific strata. By recursive partitioning algorithms, we first identified 12 years as the age cut point that best discriminated risk for type 1 diabetes progression for the combined cohort and for males or females independently. Recursive partitioning analysis as well as multivariable model-based diagnostics identified cut points for ceBMI that best differentiated risk for disease progression (ceBMI diabetes risk threshold). The ceBMI diabetes risk threshold was lower in children  $< 12$  years, regardless of sex ( $-1.4$  kg/m<sup>2</sup>) than older children ( $4.6$  kg/m<sup>2</sup>). That is, the increase in type 1 diabetes risk occurs at lower levels of sustained excess BMI in younger children.

Males overall had a higher ceBMI diabetes risk threshold influencing progression to type 1 diabetes than females, suggesting an increased sensitivity to BMI in female subjects. Males  $\geq 12$  years of age were least affected by ceBMI and had a risk threshold ( $5$  kg/m<sup>2</sup>) much higher than the threshold defining

overweight/obese. In contrast, females  $< 12$  years old appeared to be most influenced by body weight, as the ceBMI risk threshold was  $-1.35$  kg/m<sup>2</sup>, suggesting that BMI percentiles below the overweight/obese threshold still increase type 1 diabetes risk in this subgroup (Fig. 1).

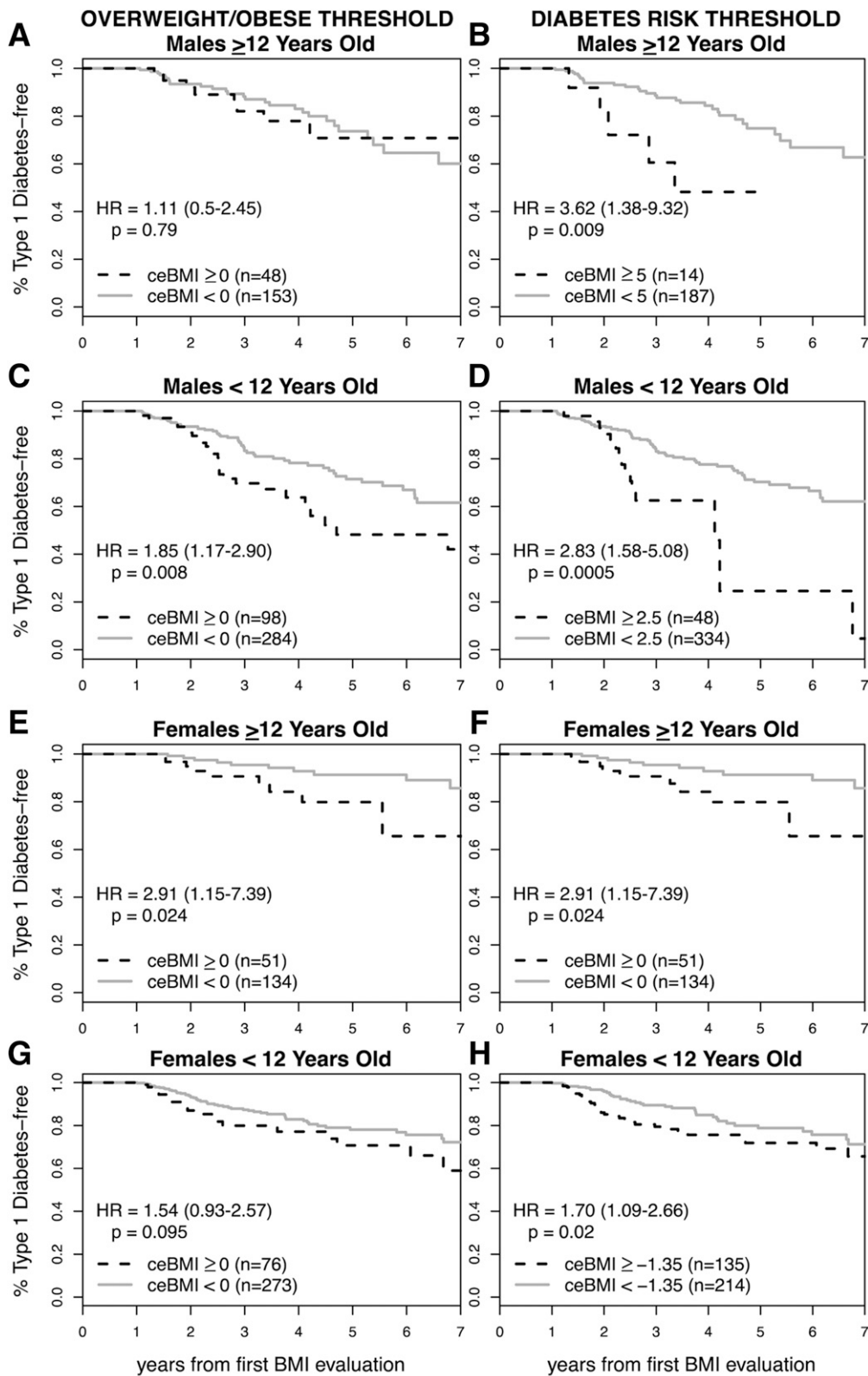
## CONCLUSIONS

Our study is the first to apply ceBMI methodology to type 1 diabetes, and results support that sustained elevation of BMI is associated with type 1 diabetes progression, with effects varying by sex and age. Older age diluted the effect of elevated BMI on type 1 diabetes progression as seen by a lower ceBMI diabetes risk threshold in individuals  $< 12$  years old compared with those  $\geq 12$  years old. This age-dependent effect of sustained excess BMI on type 1 diabetes progression is present in both sexes, but females were more sensitive to the effect of elevated BMI.

These findings lend insight into prior studies that reported inconsistent results of the effects of BMI on type 1 diabetes risk (2–5). Beyond incorporation of longitudinal data, ceBMI measurement offers the additional advantage of an unrestricted upper limit compared with BMI percentile and may offer greater resolution than BMI Z-score.

Limitations include the lack of Tanner staging and sex hormone measurements that could elucidate mechanisms of the identified age- and sex-specific ceBMI diabetes risk thresholds. Our study was not designed to specifically address the effects of acute changes in BMI on disease onset, and the small number of diabetes events in some age and sex strata further hindered this ability. Finally, we investigated an at-risk cohort of autoantibody-positive relatives of patients with type 1 diabetes and, although heterogeneous, may not be broadly generalizable to the general population.

Our results indicate that sustained elevation of BMI is associated with increased progression to type 1 diabetes in an at-risk pediatric population and that the BMI 85th percentile may not appropriately differentiate this risk for all pediatric subjects. Our data suggest that lifestyle modifications may delay disease onset in an at-risk population and suggest



**Figure 1**—Effect of ceBMI on type 1 diabetes risk comparing traditional overweight/obese ceBMI definitions to age- and sex-specific ceBMI diabetes risk thresholds. Proportion type 1 diabetes free among pediatric subjects of the PTP cohort for age ( $\geq 12$  vs.  $< 12$  years old) and sex strata (males vs. females). A, C, E, and G: Assessment of overweight/obese threshold based on 85th percentile for age- and sex-adjusted BMI. Dotted lines indicate ceBMI  $\geq 0$  (overweight/obese); solid gray indicates ceBMI  $< 0$  (nonoverweight/obese). B, D, F, and H: Assessment of ceBMI diabetes risk thresholds identified by recursive partitioning. Dotted lines indicate greater than or equal to age- and sex-specific ceBMI diabetes risk threshold; solid gray indicates less than age- and sex-specific ceBMI diabetes risk threshold. All models adjusted for antibody number (single vs. multiple).

age- and sex-specific ceBMI thresholds to implement such changes.

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**Author Contributions.** C.T.F. designed the analysis and study design, researched data, and wrote the manuscript. S.M.G. analyzed the data and contributed statistical support and writing of the manuscript. C.E.-M., Y.-F.L., I.M.L., R.B., D.J.B., H.R., A.M., and S.E.G. reviewed and edited the manuscript and contributed to discus-

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