The Role of Age and Excess Body Mass Index in Progression to Type 1 Diabetes in At-Risk Adults

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Background: Given the global rise in both type 1 diabetes incidence and obesity, the role of body mass index (BMI) on type 1 diabetes pathophysiology has gained great interest. Sustained excess BMI in pediatric participants of the TrialNet Pathway to Prevention (PTP) cohort increased risk for progression to type 1 diabetes, but the effects of age and obesity in adults remain largely unknown.

Objective: To determine the effect of age and sustained obesity on the risk for type 1 diabetes in adult participants in the TrialNet PTP cohort (*i.e.*, nondiabetic autoantibody-positive relatives of patients with type 1 diabetes).

Research Design and Methods: Longitudinally accumulated BMI >25 kg/m^2 was calculated to generate a cumulative excess BMI (ceBMI) for each participant, with ceBMI values ≥ 0 kg/m^2 and ≥ 5 kg/m^2 representing sustained overweight or obese status, respectively. Recursive partitioning analysis yielded sex- and age-specific thresholds for ceBMI that confer the greatest risk for type 1 diabetes progression.

Results: In this cohort of 665 adults (age 20 to 50 years; median follow-up, 3.9 years), 49 participants developed type 1 diabetes. Age was an independent protective factor for type 1 diabetes progression (hazard ratio, 0.95; $P = 0.008$), with a threshold of >35 years that reduced risk for type 1 diabetes. In men age >35 years and women age <35 years, sustained obesity (ceBMI ≥ 5 kg/m^2) increased the risk for type 1 diabetes.

Conclusions: Age is an important factor for type 1 diabetes progression in adults and influences the impact of elevated BMI, indicating an interplay of excess weight, age, and sex in adult type 1 diabetes pathophysiology. (***J Clin Endocrinol Metab*** **102: 4596–4603, 2017)**

Type 1 diabetes is now recognized as a disease that progresses through several discrete stages before the onset of symptomatic hyperglycemia (1). Pancreatic islet autoantibodies are predictive of β-cell failure and ultimate development of clinical type 1 diabetes and therefore are used to define at-risk populations and to investigate factors that influence disease development. The TrialNet Pathway to Prevention (PTP) cohort consists of islet autoantibody–positive individuals considered at risk for development of type 1 diabetes, representing individuals in well-established preclinical stages before onset of clinical disease (stage 3). Early identification of

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Abbreviations: BMI, body mass index; ceBMI, cumulative excess body mass index; HR, hazard ratio; PTP, Pathway to Prevention.

specific subgroups who progress more rapidly to clinical diabetes will allow for interventions before disease onset and prevent advancement through preclinical stages of disease.

Obesity and insulin resistance are well-characterized risk factors for type 2 diabetes. Given the dramatic increase in both obesity and the incidence of type 1 diabetes, several studies have investigated the role of elevated body mass index (BMI) in the development of type 1 diabetes (2–6). This "accelerator hypothesis," first proposed by Wilkin (7), suggests that although different β-cell abnormalities are involved in type 1 and type 2 diabetes, increased insulin resistance can harm the already stressed β-cell and precipitate diabetes onset in both diseases. Previous studies on the role of BMI as a risk factor for the onset of type 1 diabetes, however, have been inconsistent (2, 3, 8), limited by assessing the influence of BMI at a single point in time rather than the longitudinal effects of being overweight or obese. Our group recently demonstrated that a longitudinal, cumulative excess BMI (ceBMI) was associated with an increased risk for type 1 diabetes in pediatric participants of the PTP (9). Of note, we found that the thresholds for ceBMI that led to increased risk for type 1 diabetes in children were distinct from the Centers for Disease Control and Prevention thresholds used to define overweight/obese (10) and were sex and age specific.

Although type 1 diabetes is the most frequent type diagnosed in individuals <20 years of age (11), ~25% of persons with type 1 diabetes are diagnosed in adulthood (12). Type 1 diabetes prevention trials enrolling adults rarely stratify by age or BMI, and the specific role of age and obesity on progression to type 1 diabetes in adults remains unknown. Given the substantial phenotypic heterogeneity in adult type 1 diabetes (11), we assessed chronic effects of sustained elevated BMI (ceBMI) and age-specific effects on progression to diabetes in adult nondiabetic autoantibody-positive at-risk participants enrolled in the PTP cohort.

Participants and Methods

Participants

The TrialNet PTP cohort (ClinicalTrials.gov identifier: NCT00097292) is a prospective study that began in 2004 and has been described previously (13). All study participants gave informed consent, and the ethics committee responsible for each clinical site approved the study. Briefly, nondiabetic first-degree relatives (ages 1 to 45 years) and second- or third-degree relatives (ages 1 to 20 years) of individuals with type 1 diabetes were enrolled and screened for presence of pancreatic islet antibodies (14). Participants were tested first for the presence of glutamic acid decarboxylase 65, insulin, or islet-antigen 2/ICA512 antibodies, and, if positive, they were tested for islet cell antibodies or zinc transporter 8 antibodies (15). Measurement of zinc transporter 8 was initiated in 2004 (16) and was consistently measured in the PTP cohort starting in 2012. Confirmed autoantibody-positive individuals were observed longitudinally with semiannual or annual monitoring. The strategy for monitoring included measurement of height and weight, hemoglobin A1c, diabetes autoantibody status, and performance of a standard protocol oral glucose tolerance test (17).

The TrialNet PTP study screened 134,937 individuals from March 2004 to June 2014 and found 3285 with at least one positive diabetes autoantibody. These participants were monitored for progression to clinical type 1 diabetes, and we analyzed their course through November 2015 (17, 18). Diabetes was diagnosed according to American Diabetes Association criteria (19). A hemoglobin A1c level ≥6.5% (48 mmol/mol) was part of confirmatory testing (13). Baseline assessment for metabolic and anthropometric measurements is defined as the first visit with a BMI evaluation (Supplemental Fig. 1). For this analysis, we focused on participants of this prospective study who were age ≥20 years at their first BMI evaluation (n = 672). After exclusion of those without two or more 2 BMI measurements and ≥6 moths of follow-up, the total sample comprised 665 participants.

ceBMI calculation

BMI was calculated as weight (kg)/height (m^2) with Centers for Disease Control and Prevention definitions of overweight (≥25 kg/m^2) and obesity (≥30 kg/m^2) (18). Cumulative excess BMI, hereby referred to as ceBMI, has been used previously as a measure of persistent elevation of BMI beyond the overweight threshold of 25 kg/m^2 (20, 21). The weighted sums of the differences between the actual BMI and 25 kg/m^2 were calculated by using the method described by Lee *et al.* (20) and Bouchard *et al.* (21) by summing the difference calculated at each BMI assessment while accounting for the irregular timing between evaluations (Equation 1):

$$ceBMIyrsj = \sum_{i=0}^{m} \frac{(BMI_{t_i} - 25) + (BMI_{t_{i+1}} - 25)}{2} x\left(\frac{number\ of\ days\ between\ t_i\ and\ t_{i+1}}{365.25}\right) \quad (1)$$

where $ceBMIyrs_j$ = ceBMI-years for participants j in units kg/m^2 × years, and m = the number of BMI evaluations for participant j. We further annualized ceBMIyrs to accommodate the irregular timing of BMI assessment in relation to time type 1 diabetes outcome or censoring in some participants of our cohort (Equation 2):

$$ceBMIj = \frac{ceBMI_{yrsj}}{\frac{t_m - t_0}{365.25}} \quad (2)$$

where $ceBMI_j$ is a value representing the annual average ceBMI in kg/m^2 for participant j over the number of years participant j had a BMI evaluations, t_m is time in days at the last BMI measurement, and t_0 is the time of first BMI evaluation.

To avoid confounding by the weight loss that frequently precedes diagnosis of type 1 diabetes, for individuals who progressed to diabetes, the last BMI used was ≥6 months prior to the date of diagnosis.

Statistical analysis

Pearson χ^2 tests, Fisher's exact tests, Wilcoxon rank-sum tests, Kruskal-Wallis tests, and nonparametric Spearman rank-correlation tests were used as appropriate to characterize and compare factors of interest. Baseline BMI and the aggregated longitudinal measures of ceBMI were analyzed both as continuous and categorical measures. ceBMI was dichotomized in two ways: ceBMI $\geq$0 kg/m^2 to reflect an individual's average BMI above the threshold for overweight and ceBMI $\geq$5 kg/m^2 to reflect persistent obesity.

The primary outcome was time to type 1 diabetes, defined as the time from first BMI evaluation to date of type 1 diabetes diagnosis. Because participants had variable lengths of follow-up and observing progression to type 1 diabetes in these at-risk participants can be highly time dependent, our primary analyses focused on this time-to-event outcome. As such, standard Kaplan-Meier methods assessed differences in the distributions of time to type 1 diabetes between groups, and Cox proportional hazards models evaluated the influence of ceBMI in univariate models as well as in multivariable models that also adjusted for potential confounders, such as age at first BMI evaluation, sex, and number of positive autoantibodies (single vs multiple). Those not diagnosed with type 1 diabetes were censored at their last follow-up or enrollment in a prevention trial. Assumptions for proportionality of hazards were tested. Recursive partitioning analysis (22) was used to identify cut-points for age at first BMI evaluation and ceBMI that best differentiated the estimated risk for development of stage 3 or clinical diabetes (rpart package in R software; National Institutes of Health, Bethesda, MD). This approach iteratively evaluates all possible cut-points of the factor(s) of interest and identifies variable thresholds that best stratify or group participants based on estimated risk of progression to type 1 diabetes.

Overall, inferential tests were two sided, with P values $<$ 0.05 considered to indicate statistically significant differences, although given the few number of events, borderline results with $P < 0.10$ were also reported. For interaction terms, P values $<$ 0.10 were considered sufficient for further exploration and evaluation of relationships given the sample size and number of events. All analyses were conducted in the statistical program R (version 3.1.2 for Windows).

Results

Demographic characteristics

A total of 665 adult participants age 20 to 51 years at the first BMI evaluation from the TrialNet PTP study were included in this analysis (Table 1). The median age at first BMI evaluation was 37.9 years, and the median BMI was 26.5 kg/m^2 (range, 17.2 to 56.1 kg/m^2). Thirty-three percent of individuals were overweight (BMI $\geq$ 25 kg/m^2 to $<$30 kg/m^2), and 30% were considered obese (BMI $\geq$ 30 kg/m^2). At the time of first BMI evaluation, 372 (55%) of individuals had a single positive autoantibody, and the remaining 293 participants had multiple diabetes autoantibodies. Forty-nine participants (21 men and 28 women) developed type 1 diabetes during the observation time at a mean age of 39.1 years (range, 23.7 to 50.7 years). Although the median time to progression to type 1 diabetes had not yet been reached in the overall cohort, the estimated 5-year rate of progression to type 1 diabetes was 11.5% (95% confidence interval: 15.2% to 7.8%).

The ceBMI had a wide range from -7.8 kg/m^2 to 28.9 kg/m^2 (median, 3.54 kg/m^2). Nearly 65% of participants (424 of 665) had a ceBMI $\geq$ 0 kg/m^2 representing average longitudinal BMI values over the threshold for overweight ($\geq$25 kg/m^2). The baseline BMI was higher in men than women ($P < 0.001$), as was the ceBMI, with 76% of men having a ceBMI $\geq$ 0 kg/m^2, vs 57% of women ($P < 0.001$). No significant differences were noted in age at first BMI evaluation (P = 0.91), number of positive islet autoantibodies (single or multiple) (P = 0.102), progression to type 1 diabetes (P = 0.12), or follow-up time (P = 0.17) between men and women.

Age influences type 1 diabetes progression in adults

In this adult cohort, age was a significant independent protective factor such that for every year of age, the risk was reduced by 5% [hazard ratio (HR), 0.95; P = 0.009], after adjustment for ceBMI, sex, and number of autoantibodies. The protective influence of age was seen in men (HR, 0.94; P = 0.047), but less so in women (HR, 0.96; P = 0.14). Recursive partitioning analysis was used to determine whether there was a specific age cut-point that significantly differentiated risk for type 1 diabetes progression. For the overall cohort, age $\geq$ 35 years significantly reduced the risk for type 1 diabetes [HR, 0.45 (P = 0.007), adjusted for ceBMI, sex, and autoantibody number]. There was no difference in male vs female strata with respect to this age-related effect.

In a subset of adults, ceBMI influences risk for type 1 diabetes

In our adult cohort, ceBMI as a continuous measure was not independently associated with the time to type 1 diabetes progression after adjustment for age, sex, and autoantibody number (P = 0.21). Persistent BMI above the overweight threshold (ceBMI $\geq$ 0 kg/m^2) or obesity threshold (ceBMI $\geq$ 5 kg/m^2) also failed to significantly alter the risk for type 1 diabetes in the overall cohort and within either sex (Table 2).

Although ceBMI was not an independent risk factor for type 1 diabetes progression across all participants within this cohort, it was found to be a significant predictor in a subset of participants. We identified a significant interaction between age, ceBMI, and sex (P = 0.01), leading to stratified analysis of the effect of ceBMI in each of the four subgroups based on sex (men vs women) and age ($\geq$35 vs $<$35 years). In men age $\geq$35 years, ceBMI was a significant risk factor (HR, 1.15;

Table 1. Demographic and Baseline Characteristics of Adult PTP Participants Included in the Study

Characteristic	All Participants (n = 665)	Men (n = 218)	Women (n = 445)	*P* Value
Age at first BMI evaluation, y				0.91
Median	37.9	38.2	37.8	
Range	20.0–51.1	20.0–51.1	20.2–48.4	
Progressed to type 1 diabetes, n (%)				0.06[a]
No	616 (92.6)	197 (90.4)	417 (93.7)	
Yes	49 (7.4)	21 (9.6)	28 (6.3)	
Total follow-up time in study, y				0.07
Median	3.9	3.6	4.0	
Range	0.5–11.6	0.5–10.9	0.5–11.6	
Follow-up time for BMI evaluation (y)				0.17
Median	2.4	2.3	2.5	
Range	0.27–11.1	0.27–10.0	0.28–11.1	
Ethnicity, n (%)				0.80
Non-Hispanic	562 (84.5)	187 (85.8)	374 (84.0)	
Hispanic	71 (10.7)	22 (10.1)	48 (10.8)	
Missing/unknown	32 (4.8)	9 (4.1)	23 (5.2)	
BMI at first BMI evaluation, kg/m^2				
Median	26.5	27.5	25.5	0.0001
Range	17.2–56.1	18.5–45.5	17.2–56.1	
BMI categories at first evaluation, n (%)				
Underweight/normal	253 (38.0)	56 (25.7)	196 (44.0)	0.00002
Overweight	218 (32.7)	89 (40.8)	128 (28.8)	
Obese	194 (29.2)	73 (33.5)	121 (27.2)	
ceBMI, kg/m^2				
Median	1.82	2.96	0.89	0.0002
Range	−7.8 to 28.9	−6.0 to 19.8	−7.8 to 30.8	
ceBMI category, n (%)				
<0	241(36.2)	52 (23.9)	188 (26.5)	<0.0001
≥0	424 (63.7)	166 (76.1)	257 (57.8)	
<5	460 (69.2)	140 (64.2)	318 (71.5)	0.07
≥5	205(30.8)	78 (35.8)	127 (28.5)	
Antibody status, n (%)				
Single confirmed Ab+	372 (55.9)	112 (51.4)	260 (58.4)	0.102
Multiple Ab+	293 (44.1)	106 (48.6)	185 (41.6)	
Antibody type[b], n (%)				
miAA	81 (12.2)	24 (11.0)	57 (12.8)	0.69
GAD	251 (37.7)	75 (34.4)	176 (39.6)	
IA-2	15 (2.3)	6 (2.8)	9 (2.0)	
OGTT result at first BMI evaluation, n (%)				0.42
Normal	471 (70.8)	150 (68.8)	320 (71.9)	
Abnormal	174 (26.2)	63 (28.9)	110 (24.7)	
Missing time point	20 (3.0)	5 (2.3)	15 (3.4)	

Abbreviations: Ab-, antibody negative; Ab+, antibody positive; GAD, glutamic acid decarboxylase; IA-2, islet antigen-2; miAA, micro insulin autoantibody; OGTT, oral glucose tolerance test.

[a]Univariate log-rank *P* value based on Cox regression analysis for sex.

[b]Only calculated in participants who were single confirmed Ab+.

P = 0.013), indicating that in older men there was a 15% increase in type 1 diabetes risk for every 1-kg/m^2 increase in ceBMI. This influence of ceBMI, as a continuous measure, was not seen in male participants age <35 years or females of any age.

Analyzing ceBMI as a categorical measure above a threshold representing persistent obesity (ceBMI ≥5 kg/m^2), we again identified a significant interaction with age and sex (*P* interaction = 0.001). Male individuals age ≥35 years have the lowest risk for type 1 diabetes; however, in stratified analyses we observed that those with persistent obesity (ceBMI ≥ 5 kg/m^2) demonstrated a tendency toward increased risk for type 1 diabetes compared with that of men in the same age group who had ceBMI <5 kg/m^2 (HR, 3.63; *P* = 0.06). In younger men (age < 5 years), persistent obesity did not further significantly increase the risk for type 1 diabetes compared with those >35 years (Table 3, Fig. 1A).

Similar to men, women age <35 years were at increased risk for type 1 diabetes compared with older women. In contrast to men, in whom persistent obesity increased the risk among older (age ≥ 35 years) individuals, persistent obesity in women most affected the

Table 2. ceBMI Is Not an Independent Risk Factor for Type 1 Diabetes in Overall Cohort of Adult Participants

	All Participants (n = 665)		Men (n = 218)		Women (n = 445)	
Variable	HR (95% CI)[a]	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
ceBMI	1.03 (0.98–1.08)	0.21	1.04 (0.96–1.13)	0.3	1.02 (0.96–1.08)	0.50
ceBMI ≥0	1.20 (0.65–2.20)	0.56	0.99 (0.37–2.64)	0.99	1.31 (0.61–2.82)	0.49
ceBMI ≥5	1.53 (0.85–2.75)	0.16	1.38 (0.57–3.32)	0.48	1.53 (0.68–3.44)	0.30

Abbreviation: CI, confidence interval.

[a] Models for all participants were adjusted for age at first BMI evaluation, sex, and single vs multiple antibody status at first BMI evaluation; models for men were adjusted for age at first BMI evaluation; and models for women were adjusted for age at first BMI evaluation and antibody status at first BMI evaluation.

risk for type 1 diabetes progression in the younger strata (age <35 years). Women age <35 years who had sustained obesity were at the highest risk for type 1 diabetes (HR, 4.7; $P = 0.003$) compared with women in the other age and ceBMI groups. In fact, women age <35 years who persistently maintained a BMI below the threshold of obesity appeared to have a risk for type 1 diabetes similar to that in women age ≥35 years. Obesity did not appear to influence type 1 diabetes risk in women age ≥35 years, who maintained lower rates of diabetes progression regardless of ceBMI status (Table 3, Fig. 1B). In looking at differences across the four age- and ceBMI-based groups in women, we found that this composite measure significantly differentiated risk for type 1 diabetes (log-rank $P = 0.01$). In men, the observed differences did not reach statistical significance (log-rank $P = 0.066$), although there was less available power given the fewer number of men in this cohort.

Discussion

The increasing incidence of type 1 diabetes over the past several decades underscores the urgent need to identify risk factors for disease progression (23, 24). Type 1 diabetes is the most common form of pediatric diabetes, and, among children, younger age is a significant risk factor for type 1 diabetes (25–28). Using a method for assessing longitudinal BMI through repeated measures that factors in irregular timing of BMI measurements and incomplete follow-up that often occur in prospective cohorts, we recently reported that sustained excess weight was a risk factor for progression of pediatric type 1 diabetes (9). Type 1 diabetes can also develop in adulthood, but clinical and demographic risk factors in adults have been less well studied. Our results here indicate that, similar to our findings in children, younger age is still an important type 1 diabetes risk factor in the adult PTP population. This observation suggests that those age >20 years remain a heterogeneous population with respect to their risk for type 1 diabetes. In addition, the effect of sustained obesity was significant in a subset of adult participants, with a greater influence in men age ≥35 years and women age <35 years.

The effect of ceBMI on type 1 diabetes progression in this adult cohort is in contrast to our previous findings in the pediatric participants of the PTP, where, in the overall cohort, we observed an increase in the risk for disease with relative mild elevations of ceBMI. In the adult cohort, a more severe ceBMI ≥5 kg/m^2, indicating long-standing obesity, was necessary to significantly increase

Table 3. ceBMI Above Obesity Threshold Influences Progression of Type 1 Diabetes in Specific Subsets of Adults in the PTP Cohort

Sex and Age	ceBMI	Participants (n)	HR[a] (95% CI)	*P* Value
Male				
≥35 y	<5	89	Reference	
	≥5	60	3.63 (0.94–14.1)	0.062
<35 y	<5	51	5.31 (1.4–20.2)	0.014
	≥5	18	3.38 (0.68–17.0)	0.14
Female				
≥35 y	<5	208	Reference	
	≥5	82	0.69 (0.22–2.2)	0.54
<35 y	<5	110	1.38 (0.53–3.59)	0.51
	≥5	45	4.7 (1.67–13.2)	0.003

[a] Models adjusted for antibody status (one positive autoantibody vs two or more positive autoantibodies at the first BMI evaluation) in women. Models did not adjust for any factors (*i.e.*, no adjustment for antibody status) in men because of to the greater limitations of numbers of events in that subgroup.
Abbreviation: CI, confidence interval.

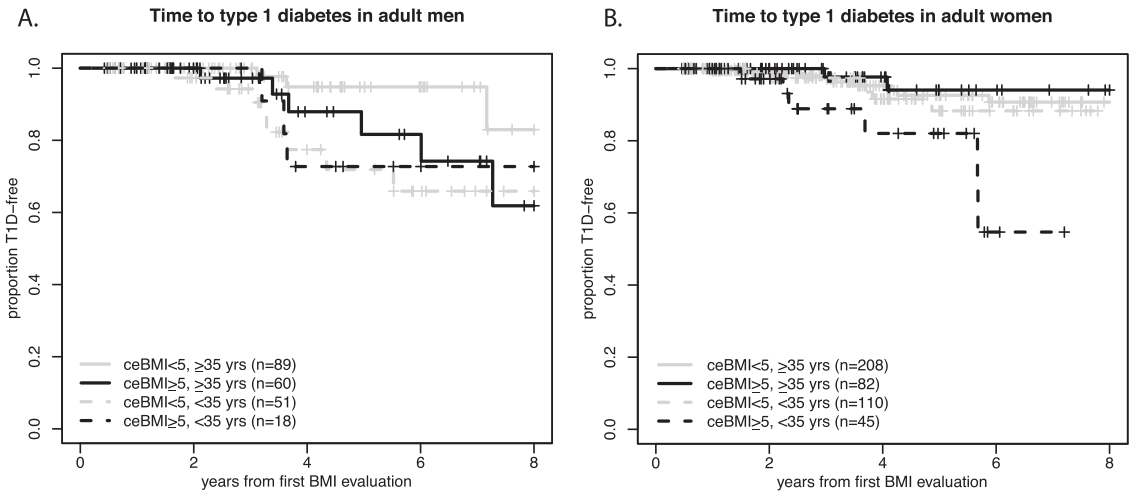

Figure 1. Influence of ceBMI on progression to type 1 diabetes in adults is evident in age and sex subsets. Proportion type 1 diabetes free among (A) male and (B) female adult participants of the PTP cohort comparing age (≥35 years vs <35 years) and ceBMI (≥5 kg/m^2 vs <5 kg/m^2, respectively, corresponding sustained BMI on average above vs below the obesity cut-point) subsets defined by recursive partitioning.

risk for type 1 diabetes, and then only in select age and sex strata. In this adult population, nearly 62% had an initial BMI ≥25 kg/m^2, and 66% had a ceBMI ≥0 kg/m^2, indicating a sustained BMI above the overweight threshold. This is in contrast to the pediatric cohort, where only 25% of individuals had a baseline BMI ≥ 85th percentile and a ceBMI ≥0 kg/m^2. The larger prevalence of overweight/obesity in this adult PTP cohort may have contributed to the higher ceBMI threshold (*i.e.*, above the cutoff for obesity) that was identified by data-driven recursive partitioning to best differentiate those at significantly increased risk for progression to type 1 diabetes.

Younger age is a known risk factor for type 1 diabetes development in pediatrics (29, 30), but the persistent protective influence of age in this adult cohort was unexpected. Enrollment into type 1 diabetes prevention trials is based on regulatory guidelines and, often, 18 years of age to define inclusion criteria. We identified age ≥35 years as that which significantly reduced the risk for type 1 diabetes in our population. We further identified that older men yet younger women were more vulnerable to the effects of ceBMI. Our findings are similar to that of the pediatric PTP participants where a larger degree of excess BMI is required for males age ≥12 years to significantly affect type 1 diabetes risk, yet females age <12 years were vulnerable to sustained BMI values below the threshold for overweight.

A potential explanation for the differential effect of ceBMI on type 1 diabetes risk by sex could be related to the discrepant correlation between BMI and adiposity in males and females (31, 32). Hormonal influences could underlie the sex-specific effect of age and ceBMI on type 1 diabetes progression in this adult cohort as well. Testosterone levels in men peak between ages 35 and 44 years and then decline; this decline is exacerbated in the setting of obesity (33, 34). During puberty, lean body accrual is reflected by a higher BMI in males, and it may be only as testosterone levels decline in adulthood that the elevated BMI contributes as excess adiposity rather than muscle mass. In females, adiposity is more accurately reflected in BMI throughout life, and obesity leads to increases rather than decreases in testosterone levels (35). The age- and obesity-induced imbalance between estrogen and testosterone (35) may thus be playing a role by increasing β-cell demand in the context of adult-onset type 1 diabetes.

The TrialNet PTP study is one of the largest natural history cohorts assessing risk factors for type 1 diabetes development across a broad age range and is well poised to explore the role of these risk factors for progression to type 1 diabetes in an adult at-risk population, especially where there is a distinct paucity of research in this area. This study has uniform regular monitoring of a diabetes autoantibody positive cohort that are not chosen by genetic risk defined by HLA typing. The PTP study screens for all biochemical diabetes autoantibodies, which is in contrast to many epidemiologic studies conducted on adults, allowing for assessment of confounding by this immunologic risk factor. Investigations into factors leading to adult-onset type 1 diabetes have primarily focused on HLA diabetes loci (36) without formal analysis of age within the population. Even fewer studies examine the role of elevated BMI in this age group. The few studies assessing anthropometric risk factors for adult-onset type 1 diabetes include evaluations of perinatal factors (37) and childhood growth trajectories (37), without consideration of measurements proximal to type 1 diabetes onset. Our study is unique in that it considers interval BMI measurements and is the

first to apply this method of ceBMI on adult type 1 diabetes progression. Furthermore, the use of recursive partitioning analysis was an additional strength of this study, allowing us to uncover risk factors and thresholds for adult type 1 diabetes progression that may not have been previously recognized.

Limitations of the dataset include a small number of diabetes events in some age and sex strata, especially males, which may affect the precision of our estimates. Additional limitations of this study include the lack of sex hormone measurements (*i.e.*, testosterone, sex hormone–binding globulin) and insulin resistance that could elucidate potential mechanisms underlying of our findings. Finally, our study investigated an at-risk cohort of autoantibody-positive relatives of patients with type 1 diabetes, and because of the addition of familial risk, it may therefore not be broadly generalizable to the general population.

Conclusions

Our results indicate that older age continues to be an important protective factor in autoantibody-positive adults, with lower risk for progression to clinical stage 3 diabetes in adults greater than age 35 years compared with younger adults. Although clearly the primary pathogenesis in type 1 diabetes is immune-mediated β-cell destruction, insulin resistance secondary to overweight/obesity may increase the rate of β-cell decline in certain individuals. Although adults are not as vulnerable to the effects of sustained elevation of BMI as children in the PTP study, the effects of sustained elevation of BMI above the obese threshold did accelerate the progression to type 1 diabetes in an age- and sex-dependent manner. Additional analyses are underway to characterize the mechanisms underlying the effect of age, sex, and elevated BMI on type 1 diabetes risk, but it should be emphasized to trialists and clinicians that adult individuals remain a heterogeneous population in terms of risk for type 1 diabetes onset.

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