


ORIGINAL ARTICLE

Effect of severe obesity in childhood and adolescence on risk of type 2 diabetes in youth and early adulthood in an American Indian population

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Funding information

National Institute of Diabetes and Digestive and Kidney Diseases, Grant/Award number: Intramural Research Program

Objectives: The risk of early-onset type 2 diabetes associated with the severity of obesity in youth is not well understood. This study aims to determine metabolic alterations and type 2 diabetes risk among American Indian children who are obese or severely obese.

Methods: Incidence rates of diabetes before 20 years (youth-onset) and 45 years were computed in 2728 children who were from 5 to <10 years and 4317 adolescents who were from 10 to <18 years without diabetes examined between 1965 and 2007. Obesity was defined as age-sex-adjusted body mass index (BMI) \geq 95th percentile, and its severity was quantified as the percentage of the 95th percentile (%BMI_{p95}).

Results: In the younger cohort, 0.9% of those non-obese and 2.9% of those with 100% to <120%BMI_{p95} had impaired glucose tolerance (IGT) compared to 8.6% of those with \geq 140%BMI_{p95}. In the older cohort, 2.9% of those non-obese and 9.8% of those with 100% to <120%BMI_{p95} had IGT compared to 13.3% of those with \geq 160%BMI_{p95}. The incidence of youth-onset diabetes was 3.8 and 4.9/1000 person-years in the child and adolescent cohorts, respectively, and before the age of 45 was 12.3 and 16.8/1000 person-years, respectively. Incidence rates of youth-onset diabetes in those with the most severe obesity (\geq 140%BMI_{p95}) were 2.3 to 5.1 times as high as in those with the least severe obesity (100 to <120%BMI_{p95}), and for onset of diabetes before the age of 45 were 1.6 to 2.2 times as high.

Conclusions: Severe obesity in an American Indian population is a major driver of type 2 diabetes developing in adolescents and young adults.

KEYWORDS

children, diabetes, obesity, severe, youth

1 | INTRODUCTION

Although the overall prevalence of overweight and obesity among children and adolescents in several countries has stabilized in recent years,^{1,2} the prevalence of severe obesity continues to rise, particularly in the United States.³ We previously compared obesity trends across birth cohorts in an American Indian population and found that children in later birth cohorts had a right shift in their body mass

index (BMI) distribution, toward higher values, compared to children who were born earlier.⁴ In the same population, we also found greater risks for diabetes with a metabolic phenotype of obesity and impaired glucose tolerance (IGT).⁵ Less is known about the impact of different degrees of obesity in these children and adolescents, and the associated long-term metabolic risk.

Adiposity is most commonly assessed by BMI. In the American Indian population described in this study, BMI was strongly correlated

with adiposity measures from dual energy X-ray absorptiometry in children and adolescents⁶ and, in adults, BMI performs at least as well as other adiposity measures such as waist circumference and percent body fat in predicting risk of diabetes development.⁷ In the United States, pediatric healthcare providers use the Centers for Disease Control and Prevention (CDC) growth charts for children and adolescents 2 to 20 years of age,⁸ where overweight is defined by the 85th to <95th BMI percentile and obesity by ≥ 95 th percentile. One limitation of these growth charts is their inability to track children and adolescents with very high BMI.⁹ To account for this limitation, Flegal et al suggested that high BMI values should instead be presented as percent of the 95th percentile ($\%BMI_{p95}$).⁹ While cross-sectional analyses have examined cardiometabolic risk factors in children with severe obesity,¹⁰ prior studies have rarely examined the longitudinal risk of type 2 diabetes mellitus development in children and adolescents with severe obesity. Between 1991 and 2003 in this American Indian population, the prevalence of diabetes was 3.3% in children aged 5 to 14 and 6.4% in youth aged 15 to 24, a 2- to 11-fold increase from just 0.3% and 3.3% in 1965 to 1977, respectively.¹¹ This increase in prevalence was largely attributed to a rising diabetes incidence over the same time period, given that all-cause mortality remained stable in those aged <25 years. As obesity is an important predictor of diabetes, the aim of this study was to determine metabolic abnormalities and early-onset type 2 diabetes risk among American Indian children and adolescents who are obese or severely obese.

2 | METHODS

A longitudinal study of diabetes among American Indians in the southwestern US began in 1965. Subjects aged ≥ 5 years were examined approximately every 2 years until 2007. The examination included a medical history, physical examination, biochemical measurements, and review of medical records. Blood was drawn for measurement of total cholesterol and plasma glucose.¹² Venous plasma glucose concentration was measured using hexokinase or glucose oxidase methods. Fasting plasma glucose was not routinely measured prior to 1975; therefore the diagnosis of impaired fasting glucose was not determined in this analysis. A modified oral glucose tolerance test was performed following a 75-g oral glucose load in all participants whether fasting or not.⁵ Diabetes was defined by WHO criteria¹³ as plasma glucose concentration ≥ 11.1 mmol/L (200 mg/dL) 2 hours after the glucose load or if diabetes was documented between research examinations in the course of routine medical care. IGT was defined as 2-hour post-load glucose of 7.8 to 11.0 mmol/L (140-199 mg/dL).¹³ Diabetes was considered youth onset if it developed before age of 20 years.

This study includes children and adolescents aged 5 to <18 years and who did not have diabetes at baseline, divided into 2 age cohorts: 5 to <10 years and 10 to <18 years. The cohorts were not independent; participants were included in both age cohorts if they had at least 1 examination each between ages 5 to <10 and 10 to <18. The examination closest to the midpoint of the respective age cohort was chosen as the baseline examination. For analysis of youth-onset diabetes, participants were followed from baseline until

they developed diabetes, their last examination, or age 20, whichever came first. Accordingly, those followed to the age of 20 years were required to have a non-diabetic examination after the age of 20 or a diabetes diagnosis after age 20 to confirm they did not have diabetes at age 20 years. Similar analyses were performed for onset of diabetes before the age of 45, where participants were followed from baseline until they developed diabetes, their last examination, or age of 45, whichever came first, and those followed to the age of 45 were required to have a non-diabetic examination or a diabetes diagnosis after age of 45. Age of 45 was selected as diabetes incidence declines in older age,¹⁴ and there was little follow-up past age of 45 in our population who initiated follow-up in youth. Written informed consent was obtained from adults and from the parents of minors, and assent was obtained from minors. The Institutional Review Board of the National Institute of Diabetes and Digestive and Kidney Diseases approved the study.

At each examination, height and weight were measured with the subject wearing light clothing and no shoes. Blood pressure (BP) was measured to the nearest 2 mm Hg with the subject resting in the supine position. Mean arterial pressure (MAP) was calculated as: $(2 \times \text{diastolic BP} + \text{systolic BP})/3$. Age- and sex-specific BMI percentiles were determined using the CDC BMI growth charts and computer program.¹⁵ Obesity was further classified using $\%BMI_{p95}$ for age and sex: 100 to <120% BMI_{p95} , 120% to <140% BMI_{p95} , or $\geq 140\%BMI_{p95}$ (younger cohort) or 140 to <160% and $\geq 160\%BMI_{p95}$ (older cohort).

2.1 | Statistical analysis

Spearman's rank correlation was used to determine the association between BMI percentile and baseline age, 2-hour glucose, total cholesterol, and MAP. BMI percentile was defined using centiles up to the 95th percentile and $\%BMI_{p95}$ thereafter. Differences in sex and prevalence of IGT at baseline by BMI percentile were assessed using the Cochran-Armitage test for trend. Sex and age cohort-specific diabetes incidence rates were computed as incident cases/1000 person-years of follow-up. Five-year cumulative incidence of diabetes was calculated from incidence rates of youth-onset diabetes, and 10-year cumulative incidence of diabetes was calculated from incidence rates of diabetes diagnosed before age of 45 as: $1 - e^{-(\text{Incidence Rate} \times \text{Time})}$. Incidence rate ratios (RRs) were computed using the 65th to <85th BMI percentile category as reference because this was the modal category of the frequency distribution of children aged 5 to <10 years. To further illustrate differences in diabetes incidence by severity of obesity, RRs were also computed using 100 to <120% BMI_{p95} as the reference. Ninety-five percentage confidence intervals for RR were calculated as

$$CI = \exp \left[\ln(RR) \pm 1.96 \left(\frac{1}{A1} + \frac{1}{A0} \right)^{\frac{1}{2}} \right],$$

where A1 is the number of incident diabetes cases in the group of interest, and A0 is the number of incident diabetes cases in the reference group.¹⁶

Parental diabetes was defined as either or both parents having a diabetes diagnosis by age of 45 years, based on examinations in this study. If neither parent had a diabetes diagnosis by age of 45 years,

they were classified as either no parental diabetes, defined as neither parents having a diabetes diagnosis at age of 45, confirmed by at least one non-diabetic examination after age of 45, or as unknown if both parents did not participate in our study or if one or both parents did not have diabetes at their last examination but were not seen after age of 45. Exposure to diabetes in utero was classified for children and adolescents whose mothers participated in the study. Individuals were considered exposed to intrauterine diabetes if the mother was diagnosed with diabetes before the child's birth and unexposed if the mother was never diagnosed with diabetes, or if she was diagnosed after the child's birth and if she was found to not have diabetes at a research examination following the child's birth. Otherwise, this variable was considered missing.

2.2 | Sensitivity analysis

All analyses were repeated using BMI z-scores (BMI_z), where age- and sex-specific z-scores were determined using the CDC BMI growth charts and computer program. We used the modified BMI_z as described previously,⁴ where BMI is expressed as a z-score relative to the median BMI.⁸ We did not use the alternate z-score method that uses a strong normalizing transformation that severely compresses the distribution of z-scores such that very few have values >3 , and is thus unsuitable for quantifying extreme BMI values.⁴

3 | RESULTS

The age 5 to <10 -year cohort included 2728 children, and the age 10 to <18 -year cohort included 4317 adolescents; 1805 youth were included in both cohorts. Seven children from the younger and 118 adolescents from the older cohort had diabetes at baseline and were excluded from this study (Figure S1, Supporting information). The mean age of the study population was 8.0 (standard deviation, SD 1.1) years in the younger cohort and 14.1 (SD 1.5) years in the older cohort. The frequency distribution of children and adolescents in each BMI percentile category by age cohort is presented in Figure 1. Eighteen percentage of the younger age cohort were obese ($100\% < 120\%BMI_{p95}$) and 12% were severely obese ($\geq 120\%BMI_{p95}$), while 21% of the older cohort were obese and 17% were severely obese (Table 1). BMI percentiles correlated positively with 2-hour glucose, total cholesterol, and MAP. The prevalence of IGT was also greater at higher BMI percentiles. In the younger cohort, 0.9% of those not obese and 2.9% of those with $100\% < 120\%BMI_{p95}$ had IGT compared to 8.6% of those with $\geq 140\%BMI_{p95}$. In the older cohort, 2.9% of those not obese and 9.8% of those with $100\% < 120\%BMI_{p95}$ had IGT compared to 13.3% of those with $\geq 160\%BMI_{p95}$.

3.1 | Diabetes incidence

Over a median follow-up of 10.8 years (interquartile range [IQR]: 6.9–12.2), 98 children in the 5 to <10 -year-old cohort developed youth-onset diabetes (3.8/1000 person-years), while over a median follow-up of 5.5 years (IQR: 4.1–6.5), 111 children and adolescents in the

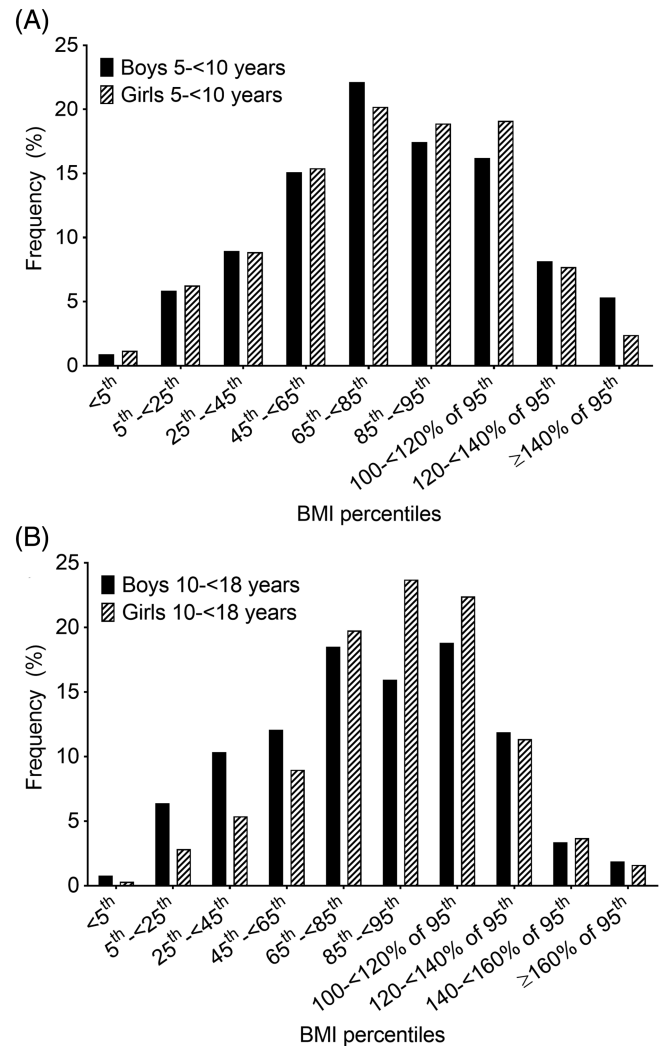


FIGURE 1 Relative frequency distribution of body mass index percentile categories by sex and age group: (A) aged 5 to < 10 years and (B) 10 to < 18 years

10 to <18 -year-old cohort developed youth-onset diabetes (4.9/1000 person-years). For onset of diabetes before age of 45 years, the median follow-up was 13.7 (IQR: 6.9–24.8) years in the 5 to <10 -year-old cohort and 12.1 (IQR: 5.8–21.5) years in the 10 to <18 -year-old cohort, with 543 incident cases (12.3/1000 person-years) and 1014 incident cases (16.8/1000 person-years) of diabetes, respectively. In both age cohorts and sexes, diabetes incidence rates and cumulative incidence of diabetes increased with increasing BMI percentile categories (Figures S2,S3). Compared to participants without obesity in the 65th to <85 th percentile, the RR for developing youth-onset diabetes in those with $100\% < 120\%BMI_{p95}$ was 5.7 (95% CI: 1.9, 17.2) in boys and 2.3 (95% CI: 0.9, 5.8) in girls in the younger cohort, and 3.3 (95% CI: 0.9, 12.1) in boys and 7.4 (95% CI: 2.2, 24.5) in girls in the older cohort (Figure S4). These RRs increased with greater severity of obesity, where children and adolescents with $BMI \geq 140\%BMI_{p95}$ had diabetes incidence rates that were 10- to 18-fold greater than those in the 65th to <85 th percentile. For onset of diabetes before the age of 45, compared to participants in the 65th to <85 th percentile, the RR for diabetes in those with $100\% < 120\%BMI_{p95}$ was 1.8 (95% CI: 1.2, 2.7) in boys and 1.6 (95% CI: 1.2, 2.3) in

TABLE 1 Baseline characteristics of the study population by BMI percentile category

	Non-obese	Obese				Correlation coefficient (P-value) ^b
	<95th percentile	100- < 120% BMI _{p95}	120- < 140% BMI _{p95}	140- < 160% BMI _{p95} ^a	≥160% BMI _{p95}	
Age 5 to < 10 years						
N	1925	482	216	105	-	
Age	8.0 ± 1.2	8.2 ± 1.1	8.2 ± 1.0	8.2 ± 1.0	-	.10 (<.001)
Female (%)	50.6	54.6	49.1	31.4	-	.25
2-hour PG (mmol/L)	5.1 ± 1.0	5.5 ± 1.1	5.9 ± 1.2	6.1 ± 1.1	-	.28 (<.001)
IGT (%)	0.9	2.9	7.9	8.6	-	<.001
Cholesterol (mmol/L)	3.7 (3.4-4.1)	3.9 (3.5-4.4)	4.0 (3.5-4.4)	3.9 (3.4-4.4)	-	.12 (<.001)
MAP (mm Hg)	68.6 ± 10	72 ± 10	75 ± 10	77 ± 11	-	.29 (<.001)
Age 10 to < 18 years						
N	2692	897	500	153	75	
Age	14.1 ± 1.5	14.1 ± 1.5	14.0 ± 1.3	14.1 ± 1.3	14.1 ± 1.4	.01 (.52)
Female (%)	53.5	59.0	53.6	56.9	50.7	<.001
2-hour PG (mmol/L)	5.3 ± 1.2	5.9 ± 1.3	6.4 ± 1.4	6.3 ± 1.4	6.5 ± 1.3	.32 (<.001)
IGT (%)	2.9	9.8	15.0	15.0	13.3	<.001
Cholesterol (mmol/L)	3.6 (3.3-4.1)	3.9 (3.4-4.3)	3.9 (3.5-4.4)	4.0 (3.4-4.4)	3.9 (3.2-4.3)	.19 (<.001)
MAP (mm Hg)	77.9 ± 9	81 ± 10	82 ± 10	82 ± 10	85 ± 10	.22 (<.001)

Abbreviations: BMI, body mass index; IGT, impaired glucose tolerance; MAP, mean arterial pressure; 2-hour PG, 2-hour plasma glucose. Data are mean ± standard deviation, median (interquartile range) or *n* (%). 1 mmol/L = 18.02 mg/dL for 2-hour glucose and 38.67 mg/dL for total cholesterol.

^a ≥140%BMI_{p95} in those aged 5 to <10 years.

^b Spearman correlation coefficient and *P*-value for relationship between BMI percentiles and baseline characteristic; Cochran-Armitage test for trend for relationship between BMI percentiles and sex and IGT.

girls in the younger cohort, and 1.5 (95% CI: 1.1, 2.1) in boys and 2.1 (95% CI: 1.7, 2.7) in girls in the older cohort. This ratio increased to 2.9- to 3.7-fold in those with BMI ≥140%BMI_{p95} (younger cohort) or ≥160%BMI_{p95} (older cohort), compared to the 65th to <85th percentile.

3.2 | Diabetes incidence within obese categories

When compared to those with 100% to <120%BMI_{p95}, risk of youth-onset diabetes in children and adolescents with ≥140%BMI_{p95} was at least twice as high: RR was 2.3 (95% CI: 1.0, 5.1) in boys and 5.1 (95% CI: 2.0, 12.5) in girls in the younger cohort, and 3.1 (95% CI: 1.2, 7.8) in boys and 2.4 (95% CI: 1.2, 4.8) in girls in the older cohort. Similar results were found when comparing risk of diabetes onset before the age of 45 in the most and least severe obesity categories, though with lower RRs: RR 1.6 (95% CI: 1.0, 2.7) in boys and 2.1 (95% CI: 1.1, 3.9) in girls in the younger cohort, and 2.2 (95% CI: 1.3, 3.9) in boys and 1.7 (95% CI: 1.0, 3.0) in girls in the older cohort.

The corresponding analysis using BMI_Z found similar patterns of diabetes incidence to those computed with BMI percentiles, where incidence of diabetes was greater with increasing severity of obesity (data not shown).

3.3 | Diabetes incidence by parental diabetes

Parental diabetes was determined in 1630 children in the younger cohort of which 1536 had at least one parent who developed diabetes by age of 45. In the older cohort, parental diabetes was determined in 2458 children and adolescents of which 2229 had at least 1 parent who developed diabetes by age of 45. The prevalence of

severe obesity (≥120%BMI_{pct95}) was greater in those who had at least 1 parent with diabetes compared to those with no known parental diabetes (15% vs 5% in the younger cohort, 21% vs 9% in the older cohort) (Figure S5). No incident cases of youth-onset diabetes were found in the 94 children from the younger cohort who had no parental diabetes, and only 3 cases were found in the 229 adolescents in the older cohort (Figure 2). Comparatively, incidence of youth-onset diabetes in children and adolescents who had at least 1 parent with diabetes ranged from 0.9 to 21.5/1000 person-years depending on age and BMI percentile group. Twenty-five children in the younger age group and 75 children and adolescents in the older age group who had no parental diabetes developed diabetes by age of 45 years. Within the same BMI percentile category, incidence rates for diabetes onset before age of 45 were 1.1 to 2.1 times as high in children who had at least 1 parent with diabetes compared to those with no known parental diabetes, except in the <65th BMI percentile category in the 5 to <10 year age group and the 85th to <95th BMI percentile category in the 10 to <18 year age group. Diabetes incidence rates increased with increasing severity of obesity regardless of parental diabetes.

3.4 | Intrauterine exposure to diabetes

Information on maternal diabetes before and during pregnancy was available for 2453 children in the younger and for 3627 children in the older cohort. Of these, the mothers of 147 children in the younger and 140 children in the older age cohort were diagnosed with diabetes before the child's birth. Children whose mothers had diabetes during pregnancy were more likely to be severely obese (≥120%

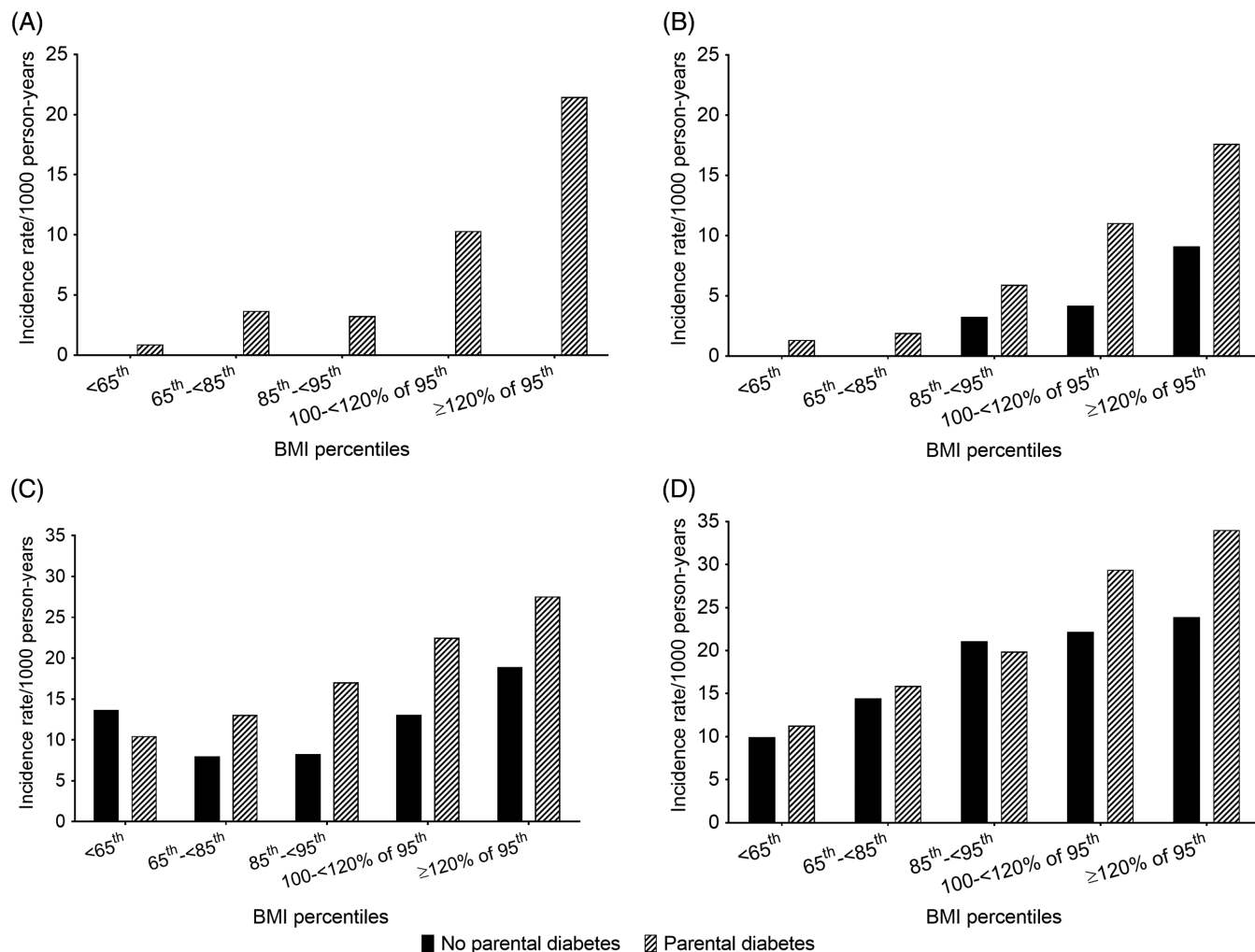


FIGURE 2 Diabetes incidence rates for age of onset <20 years (A: age 5 to <10 and B: age 10 to <18) or <45 years (C: age 5 to <10 and D: age 10 to <18) by parental diabetes and body mass index percentile categories. Absence of a bar indicates that the incidence rate is 0 (rather than missing data)

BMI_{pct95}) than those whose mothers did not have diabetes during pregnancy (31% vs 10% in the younger cohort, 45% vs 16% in the older cohort) (Figure S6). Within the same BMI percentile category, incidence rates for youth-onset diabetes in children who were exposed to diabetes in utero were 2.7 to 11.2 times as high as in those who were not exposed to diabetes in utero, while incidence rates for diabetes onset before the age of 45 were 1.7 to 4.6 times as high (Figure 3). Diabetes incidence rates increased with increasing severity of obesity in children and adolescents who were not exposed to diabetes in utero. This pattern was also generally observed among those who were exposed to diabetes in utero, except for diabetes onset before age of 45 in children and adolescents in the older cohort (Figure S3D).

4 | DISCUSSION

The risk of early-onset diabetes in children and adolescents was greatly magnified with increasing severity of obesity. Children with the most severe obesity in this population had 2- to 5-fold increased risk of developing diabetes by age 20 compared to their peers with

the least severe obesity, and an almost 2-fold increased risk of developing diabetes before age of 45 years. In prior studies in this population, obesity during childhood was an important predictor of type 2 diabetes^{17,18} and, along with glucose intolerance and hypertension, was associated with increased rate of premature deaths from endogenous causes.¹⁹ In this study, we further studied metabolic risk differentiation between obesity severities by dividing the obese category into 3 or 4 different levels of severity based on BMI percentiles. Clear positive gradients were observed for cardiometabolic risk factors, such as BP and 2-hour glucose.

In this population of American Indian children, parental diabetes and exposure to maternal diabetes in pregnancy are profound risk factors for obesity and type 2 diabetes in the child.^{17,20-22} The 10-year cumulative incidence of diabetes was zero in American Indian youths with no parental diabetes compared to 8.2% to 16.0% in their peers who have 2 parents with diabetes, depending on age group.¹⁷ In this study, no child in the 5 to <10 year age cohort and only 3 in the 10 to <18 year age cohort with no parental diabetes developed diabetes before age 20, suggesting a much stronger influence of parental diabetes on youth-onset diabetes than on diabetes that develops later in life.

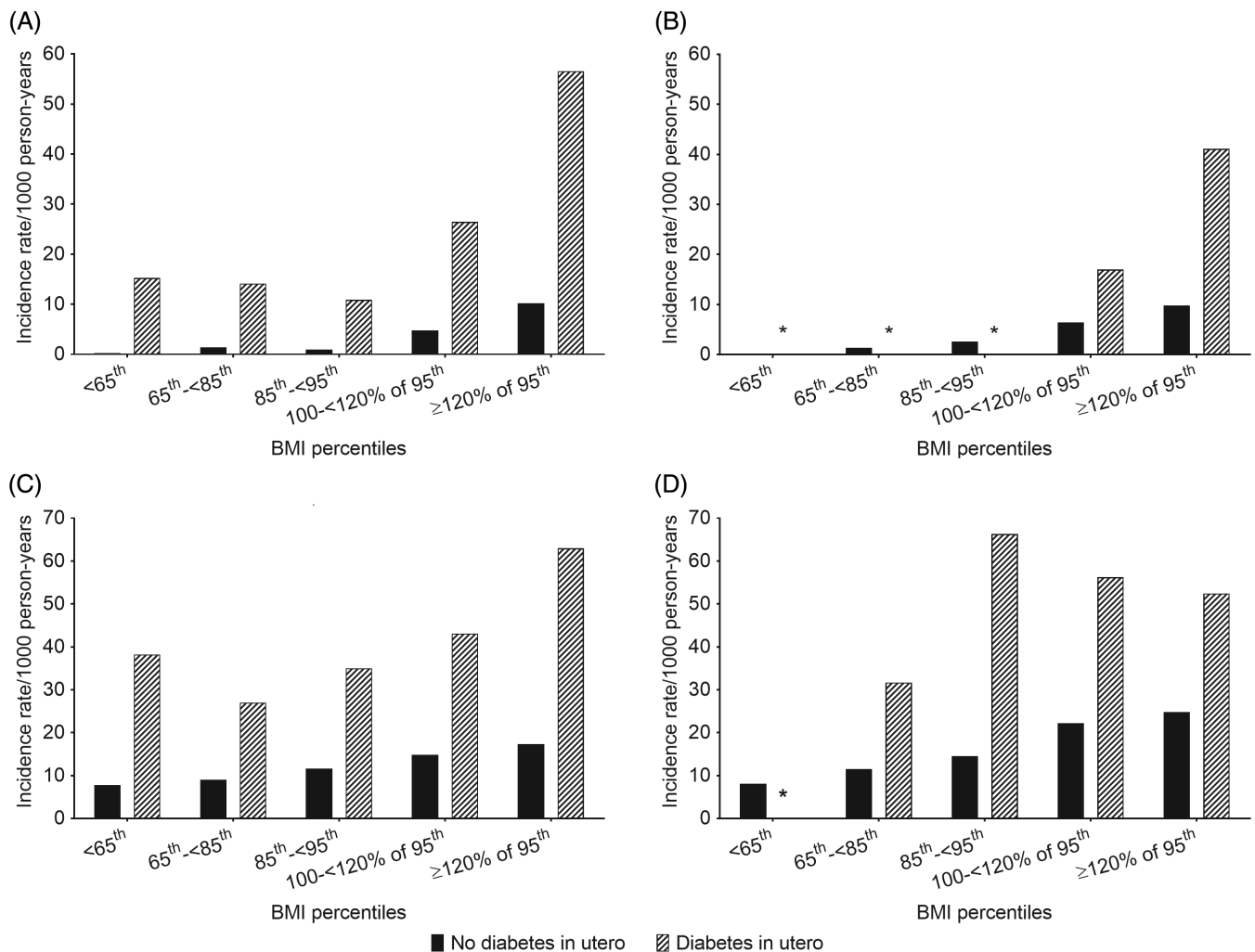


FIGURE 3 Diabetes incidence rates for age of onset <20 years (A: age 5 to <10 and B: age 10 to <18) or <45 years (C: age 5 to <10 and D: age 10 to <18) by exposure to maternal diabetes in utero and BMI percentile categories. Asterisk (*) indicates there were too few individuals with too little follow-up to reliably calculate diabetes incidence rates

Among children and young adults aged 3 to 19 years who participated in the National Health and Nutrition Examination Survey between 1999 to 2012, greater severity of obesity was associated with higher prevalence of dyslipidemia, hypertension, and hyperglycemia.¹⁰ This study extends these findings in American Indians by demonstrating that more severe obesity in youth was associated not only with greater metabolic abnormalities but also with greater 5 and 10-year cumulative diabetes incidence, and with risk of type 2 diabetes developing before age 20 years and in adulthood before age of 45 years. The incidence of type 2 diabetes in US youth aged 10 to 19 years rose dramatically between 2002 and 2012, particularly in American Indians and Non-Hispanic Blacks.²³ With earlier onset of diabetes, individuals are also at greater risk of developing complications related to diabetes earlier in life. Among teenagers and young adults who were diagnosed with type 2 diabetes before age of 20, 72% had at least one complication by the age of 21 years and after a mean diabetes duration of 7.9 years.²⁴ In this study, the incidence of diabetes before age 20 was much more magnified with greater severity of obesity than incidence of diabetes before age of 45. Thus, childhood obesity may be a particularly important determinant of youth-onset diabetes than diabetes that develops later in life when

those most susceptible to effects of obesity on diabetes have already developed it. The rising incidence of diabetes in youth and young adults that is related to the epidemic of childhood obesity is likely largely driven by the increase in diabetes developed by age of 20.

Abnormal glucose tolerance, insulin resistance, dyslipidemia, and high BP are common in children who are obese, and they are more common or more severe with greater severity of obesity.²⁵ The proportion of children with IGT also increases directly with more severe obesity as evident in this study. Obesity in children is commonly associated with IGT and increased insulin resistance. Transient insulin resistance can occur during puberty even under normal physiological conditions.²⁶ In adolescents who are obese, this may accentuate the metabolic dysfunction already present due to obesity and could result in a myriad of clinical manifestations such as hypertension, hepatic steatosis, polycystic ovarian syndrome, early atherosclerosis, as well as a predisposition for diabetes.^{27,28} Thus, it is important to explore how these changes manifest with greater severity of obesity, and whether these risks undergo a gradual or an acute increase at a specific threshold.

The strengths of this study include a large sample size that enabled classification of participants into multiple obesity categories, and a long follow-up period. Additionally, all anthropometric

measurements and laboratory testing were done using uniform and standardized methods during the entire study period in the same research clinic and laboratory. Our study population resides in the southwestern US, is of American Indian heritage, and is known to have a higher prevalence of obesity and diabetes than the general US population. The relationships we observed likely reflect the impact of severe obesity generally, although the magnitude of risks may differ among populations, and are therefore highly relevant to the many world-wide populations in which obesity is an important risk factor for diabetes. Further exploration of these associations in other populations with different diabetes incidence rates would be worthwhile. We could not distinguish type 1, type 2, or other types of diabetes in each individual. However, very few individuals in this American Indian population present with islet cell or glutamic acid decarboxylase antibodies at the time of diabetes diagnosis, and virtually none display insulin dependence, suggesting that almost all diabetes in this population is type 2.^{29,30}

The prevalence of more severe obesity in children and adolescents continues to increase worldwide. This study suggests that severe obesity in youth is driving the epidemic of youth-onset diabetes and this will undoubtedly lead to development of late-stage complications of diabetes in mid-life as well as premature mortality. Children and adolescents who are severely obese rarely transition to a lower weight category,⁴ therefore isolating the effect of childhood obesity independent of BMI trajectory was not feasible in this cohort. Nevertheless, early identification of those with severe obesity and prompt institution of effective interventions or therapeutic measures may help mitigate future health risks.

ACKNOWLEDGEMENTS

This research was supported by the Intramural Research Program of the National Institute of Diabetes and Digestive and Kidney Diseases. Dr Sinha, the corresponding author, had full access to all the data in the study and had final responsibility for the decision to submit for publication. The paper was previously presented in abstract form as an oral presentation at the American Diabetes Association, June 2016. The authors thank the participants and their parents for participation in the study.

Conflict of interest

The authors have no financial relationships relevant to this article or potential conflicts of interest to disclose.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Tanamas SK, Reddy SP, Chambers MA, et al. Effect of severe obesity in childhood and adolescence on risk of type 2 diabetes in youth and early adulthood in an American Indian population. *Pediatr Diabetes*. 2017;1-8. <https://doi.org/10.1111/pedi.12627>