ORIGINAL PAPER

Progression to hypertension in youth and young adults with type 1 or type 2 diabetes: The SEARCH for Diabetes in Youth Study

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Abstract

Central obesity may contribute to the development of hypertension in youths with diabetes. The SEARCH for Diabetes in Youth Study followed 1518 youths with type 1 diabetes (T1D) and 177 with type 2 diabetes (T2D) diagnosed when <20 years of age for incident hypertension. Incident hypertension was defined as blood pressure ≥95th percentile (or ≥130/80 mm Hg) or reporting antihypertensive therapy among those without hypertension at baseline. Poisson regression models were stratified by diabetes type and included demographic and clinical factors, clinical site, and waist-to-height ratio (WHtR). Youths with T2D were more likely to develop hypertension than those with T1D (35.6% vs 14.8%, $P < .0001$). For each 0.01 unit of annual increase in WHtR, adjusted relative risk for hypertension was 1.53 (95% CI 1.36-1.73) and 1.20 (95% CI 1.00-1.43) for youths with T1D and T2D, respectively. Effective strategies targeted toward reducing central obesity may reduce hypertension among youths with diabetes.

1 | INTRODUCTION

Between 2002 and 2012, the incidence of US youth-onset (<20 years of age) type 1 increased by 1.4% annually (from 19.5 cases/100 000 youths per year to 21.7 cases/100 000 youths per year); the incidence of youth-onset type 2 diabetes increased by 4.8% during the same time (from 9.0 cases/100 000 youths per year in 2002-2003 to 12.5 cases/100 000 youths per year in 2011-2012).[1] A similar trend has been observed worldwide.[2-4] The increase in type 1 and type 2 diabetes incidence affects in both sexes, and almost all racial/ethnic groups.[5] Adolescents and young adults with youth-onset diabetes may experience complications such as kidney disease, retinopathy, and peripheral neuropathy after <10 years diabetes duration suggesting that early- versus late-onset diabetes is particularly aggressive.[6] Cardiovascular disease and mortality are higher in patients with young-onset type 2 than in type 1 diabetes, which is primarily driven by accompanying factors such as obesity and high blood pressure.[7-9] Comorbidities such as hypertension in youths and young adults with diabetes increase the risk for cardiovascular disease and diabetes-related complications in adulthood.[6] The clustering of unfavorable cardiometabolic risk factors at a very early age contributes to a poor long-term prognosis particularly in youth-onset type 2 diabetes. However, our knowledge on the complications and progression of type 1 and type 2 diabetes in youths is still limited.

The SEARCH for Diabetes in Youth study (SEARCH) previously reported that the prevalence of high blood pressure is higher in youths and young adults with type 1 or type 2 diabetes compared to those without diabetes.[10,11] This may be explained in part by a higher body mass index (BMI) of youths and young adults with type 1 or type 2 diabetes compared to those without diabetes.[12] Compared to BMI, central obesity has been previously examined as a better predictor for hypertension in ethnically diverse populations of adults,[13,14] but this relationship is controversial in youth.[15] In youths with diabetes, central obesity is associated with greater arterial stiffness, independent of diabetes type.[11] Adjusting for central obesity but not BMI attenuated the difference in risk for arterial stiffness and hypertension for youths and young adults with type 1 versus type 2

diabetes to non-significance—indicating that central obesity may be a better indicator for diabetes-related complications.[6] Considering the implications for future risk of cardiovascular disease, a better understanding of how changes in central obesity and other risk factors are associated with risk for hypertension among youths and young adults with diabetes is necessary to reduce the future burden of the sequelae of diabetes diagnosed in childhood.

To expand on previous analyses on the prevalence of hypertension using cross-sectional data in youths with type 1 or type 2 diabetes,[10] the objectives of the present study were to quantify the risk associated with increasing central obesity on the incidence of hypertension among youths and young adults with type 1 or type 2 diabetes.

2 | PATIENTS AND METHODS

2.1 | Study design and subjects

SEARCH is a prospective, multicenter study which identifies and follows youths diagnosed with diabetes prior to age 20 years from diverse racial and ethnic backgrounds. The SEARCH study design and methods have been previously described in detail.[6] Youths and young adults included in this analysis were diagnosed with diabetes in calendar years 2002-2006 or 2008, completed a brief survey and participated in a baseline research visit after diagnosis (mean of 9.2 months [SD, 6.4], Figure 1A). Participants were later invited for a SEARCH outcome visit between 2011 and 2015 at which time diabetes-related complications and comorbidities were assessed. The study was approved by institutional review board(s) with jurisdiction. For each visit, participants ≥18 years of age and the parent/guardian of participants <18 years of age provided consent and participants <18 years of age provided assent.

For the current analysis, we included participants diagnosed with type 1 diabetes or type 2 diabetes. There were 4,095 participants with a baseline visit. We excluded participants with other or unknown diabetes type, hypertension or unknown hypertension status at baseline, and those with missing data for variables of interest (Figure 1B). After exclusions, 1,695 participants were included in the analysis.
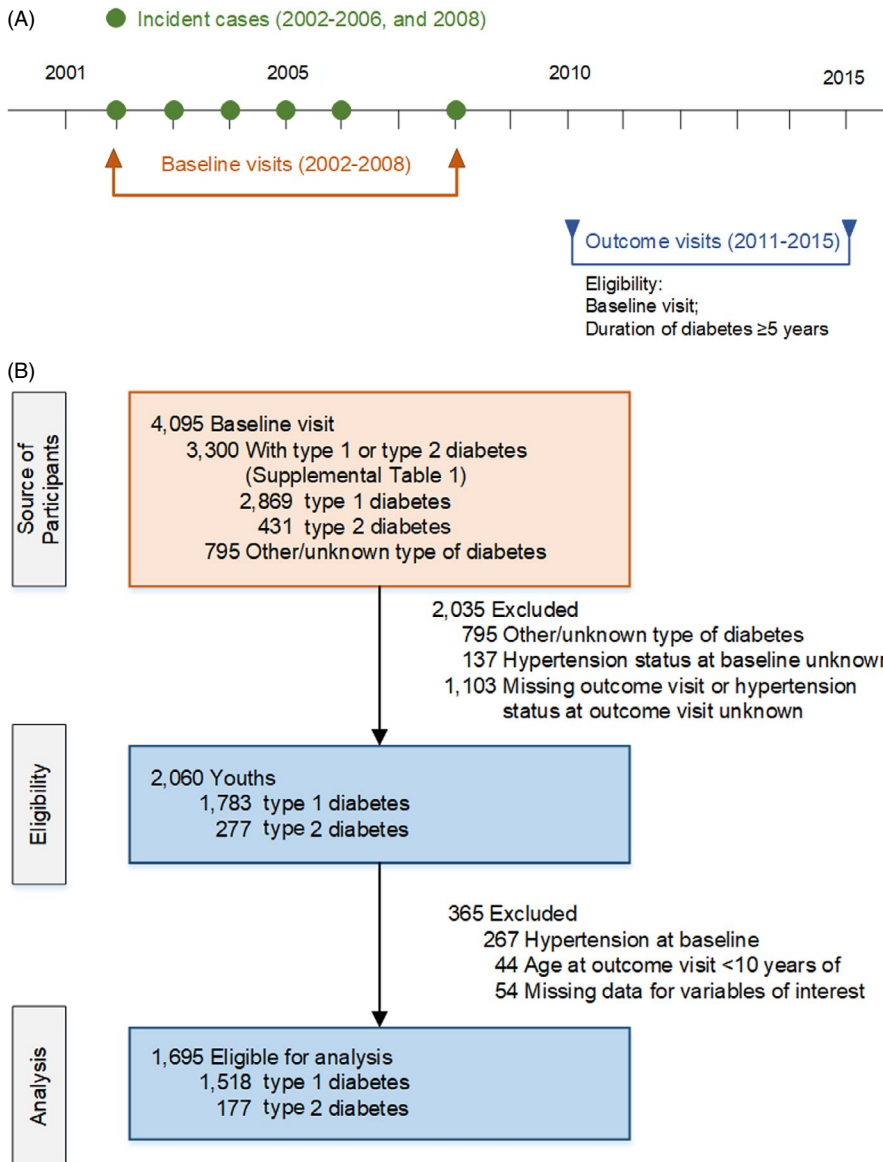
(A)

(B)

2.2 | Study procedures and variable definitions

Trained research staff conducted the in-person baseline and outcome visits. Before each visit, participants were instructed to fast overnight for at least 8 hours and abstain from medications (including short-acting insulin) on the morning of the visit. Participants (or parents, for participants <18 years of age) self-reported their date of birth, sex, race, ethnicity, annual household income, type of health insurance, and highest level of parental education on their initial survey. Date of diabetes diagnosis was obtained from medical records and was used to calculate age at diagnosis and diabetes duration at each visit.[16]

To define diabetes type, baseline blood samples were analyzed for glutamic acid decarboxylase-65, insulinoma-associated-2, and zinc-T8 autoantibodies.[17] Insulin sensitivity was estimated using a validated equation that includes waist circumference, glycated hemoglobin (HbA1c), and triglyceride concentrations measured at the visit.[17] Type 1 diabetes was defined as at least one positive antibody result (regardless of insulin sensitivity), or no positive antibody results and an insulin sensitivity score of at least 8.15.[17] Type 2 diabetes was defined as being negative for the three antibodies tested and insulin resistance (score <8.15).[17]

Participant height and weight were measured in light indoor clothing without shoes and used to calculate BMI, and BMI z-scores adjusted for age and sex.[18] Youths were categorized as under/normal weight (BMI-for-age <85th percentile or a BMI <25), overweight (BMI-for-age ≥85th to <95th percentile or a BMI ≥ 25 to <30 kg/m^2), and obesity class 1 (BMI-for age ≥95th to <97th percentile or a BMI ≥ 30 to <35 kg/m^2), and obesity class 2 or higher (BMI-for age ≥97th percentile or a BMI ≥ 35 kg/m^2). Waist circumference was measured twice using the natural waist defined as midway between the lowest rib margin and the right iliac crest at the mid-axillary line. A third measurement was made if the second measure differed from the first by >1.0 cm. We then calculated the ratio of waist-to-height (WHtR) to quantify central obesity.[19-21] If the rib margin could not be identified, the measurement was made

at the point of natural bend (after asking the participant to lean to the side without swaying backward or forward).[21]

Blood pressure at baseline was measured using a standard mercury sphygmomanometer with one of five cuff sizes chosen based on the circumference of the participant's arm according to guidelines.[22] Follow-up blood pressure was measured using a Welch Allyn Tycos 767-series mobile aneroid manometer (Welch Allyn, Inc). Mean blood pressure was calculated based on the average of three readings, each taken 1 minute apart, after the participant had 5 minutes of seated rest. Using the American 2017 Academy of Pediatrics Clinical Practice Guidelines, prehypertension was defined for youths <13 years as a blood pressure between the 90th percentile to <95th percentile for age, sex, and height or 120/80 mm Hg to <95th percentile (whichever was lower); for youths ≥13 years and adults, it was defined as a blood pressure of 120-129/<80 mm Hg.[22]

Hypertension was defined for youths <13 years as a blood pressure ≥95th percentile for age, sex, and height or ≥130/80 mm Hg (whichever was lower); for youths ≥13 years and adults, it was defined as ≥130/80 mm Hg. Participants with self-reported antihypertensive therapy were defined as having hypertension, regardless of age.[22,23]

2.3 | Statistical analysis

Descriptive data were presented as mean ± standard deviation (SD) for continuous and count (%) for categorical variables. Delta WHtR was defined as annualized change in WHtR measures from the baseline visit to the outcome visit (change in WHtR over time in years between baseline and outcome visit). The association between WHtR at baseline, WHtR change during follow-up, and incident

TABLE 1 Demographic and clinical characteristics at baseline and outcome visits of 1,695 participants with youth-onset type 1 and type 2 diabetes and without baseline hypertension in the SEARCH for Diabetes in Youth Cohort Study

Characteristic[a]	Type 1 (N = 1518)	Type 2 (N = 177)	P value[b]
Demographics			
Male sex, N (%)	753 (49.6)	51 (28.8)	<.001
Age at diagnosis (y)	10.0 (3.8)	13.9 (2.7)	<.001
Non-Hispanic white race, N (%)	1184 (78.0)	51 (28.8)	<.001
Parental education: some college or more, N (%)	1242 (81.8)	90 (50.8)	<.001
Baseline visit measures			
Duration of diabetes (mo) at visit	9.1 (6.3)	10.7 (7.2)	.0033
Weight class, N (%)			<.001
Under/normal weight	1036 (68.4)	14 (8.0)	
Overweight	290 (19.1)	21 (11.9)	
Obesity class 1	78 (5.1)	22 (12.5)	
Obesity class ≥2	111 (7.3)	119 (67.6)	
HbA1c(%), mean (SD)	7.6 (1.4)	7.5 (2.3)	.466
HbA1c in mmol/mol, mean (SD)	59.6 (15.8)	58.1 (25.6)	.466
Prehypertensive, N (%)	122 (8.0)	41 (23.2)	<.001
Waist-height ratio	0.45 (0.05)	0.60 (0.09)	<.001
BMI z-score	0.5 (1.0)	2.0 (0.6)	<.001
Outcome Visit Measures			
Interval (y) from baseline visit to follow-up visit	7.1 (1.9)	6.8 (2.0)	.164
Waist-height ratio	0.47 (0.06)	0.61 (0.10)	<.001
Annual change in waist-height ratio[c]	0.0017 (0.0079)	0.0015 (0.0094)	.846
BMI (kg/m^2)	24.1 (5.0)	34.3 (8.2)	<.001
Annual change in BMI[c]	0.65 (0.51)	0.18 (0.88)	<.001
HbA1c (%)	9.1 (1.8)	9.2 (3.0)	.592
HbA1c,(mmol/mol)	76.0 (20.1)	77.4 (33.1)	.592
Annual change in HbA1c (%)[c]	0.23 (0.32)	0.28 (0.51)	.210
Annual change in HbA1c (mmol/mol)[c]	2.49 (3.53)	3.03 (5.54)	.210

[a]Data are shown as count (%), or mean (SD).

[b]P-value evaluating differences in characteristics across DM types: t tests (continuous) or chi-square tests (categorical).

[c]Annualized change from the baseline visit to follow-up visit.

hypertension was evaluated. Because WHtR is often not measured as part of clinical care, we also evaluated the association between BMI z-score at baseline, delta BMI during follow-up, and incident hypertension in a similar manner.

The relative risk of WHtR, BMI, and incident hypertension was estimated using modified Poisson regression models with robust standard errors for confidence intervals (CI). Analyses included unadjusted and adjusted models including sex, race/ethnicity, age at diagnosis, duration of diabetes at baseline, parental education, and clinical site. Considering differences between youths with type 1 and type 2 diabetes with regard to sample size, demographics, and mechanism of diabetes (insulin deficiency versus insulin resistance), as well as observing statistically significant or trending to significant diabetes by WHtR interactions, the analyses were a priori stratified by diabetes type. The selection of adjustment variables was informed by development of a directed acyclic graph.[24] All analyses were conducted using SAS version 9.4 (SAS Institute).

3 | RESULTS

The analytic sample was comprised of 1695 youths without hypertension at their baseline visit: n = 1,518 with type 1 diabetes and n = 177 with type 2 diabetes and was similar to those excluded from the analyses (see Table S1). Participants with type 1 diabetes excluded due to hypertension at baseline were less likely to be non-Hispanic white, were more likely to be obese, and had a higher baseline BMI z-score and WHtR than those excluded for other reasons such as incomplete information (P < .05 for each). Participants with type 2 diabetes excluded due to prevalent hypertension at baseline had a higher baseline BMI z-score and WHtR than those excluded for other reasons (P < .05 for each).

Participants with type 2 diabetes were more likely to have class II obesity (67.6% vs 7.3%) and to have prehypertension (23.2% vs 8.0%) at their baseline visit compared to participants with type 1 diabetes (Table 1). Participants with type 1 diabetes and type 2 diabetes had a comparable baseline HbA1c and annual change in HbA1c during follow-up. Participants with type 2 diabetes had a higher baseline WHtR than youths with type 1 diabetes.

The average follow-up was 7.1 ± 1.9 years for participants with type 1 and 6.8 ± 2.0 years for participants with type 2 diabetes (P = .164). During follow-up, 225 participants with type 1 and 63 with type 2 diabetes developed hypertension. Participants with type 2 diabetes were more likely to develop hypertension during follow-up than those with type 1 diabetes (35.6% vs 14.8%, P < .0001, Figure 2). Participants with prehypertension at baseline were more likely to develop hypertension when compared to those without prehypertension at baseline (P < .001 and P = .044 for type 1 or type 2 diabetes, respectively).

For each 0.1 unit increase in WHtR at baseline, the unadjusted relative risk (95% CI) of progression to hypertension was 1.31 (1.08, 1.61) and 1.19 (0.97, 1.45) in participants with type 1 or type 2 diabetes, respectively (Figure 3A). After adjusting for sex, race/ethnicity, age at diagnosis, parental education, diabetes duration, and clinical site, the magnitude of association increased marginally to 1.36 (1.13, 1.63) and 1.22 (1.00, 1.49) for participants with type 1 or type 2 diabetes, respectively.

For each 0.01 unit increase in change in WHtR per year of follow-up, the relative risk (95% CI) of progression to hypertension was 1.48 (1.31, 1.67) and 1.14 (0.93, 1.40) in participants with type 1 or type 2 diabetes, respectively (Figure 3B). After adjusting for sex, race/ethnicity, age at diagnosis, parental education, diabetes duration, clinical site, and baseline WHtR, the relative risk was 1.53 (1.36, 1.73) and 1.20 (1.00, 1.43) for participants with type 1 or type 2 diabetes, respectively.
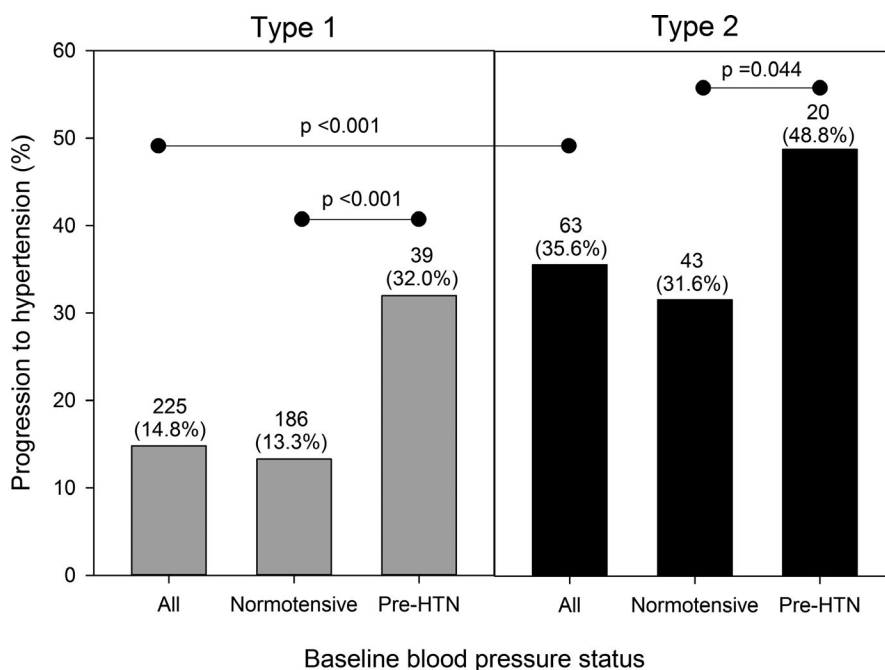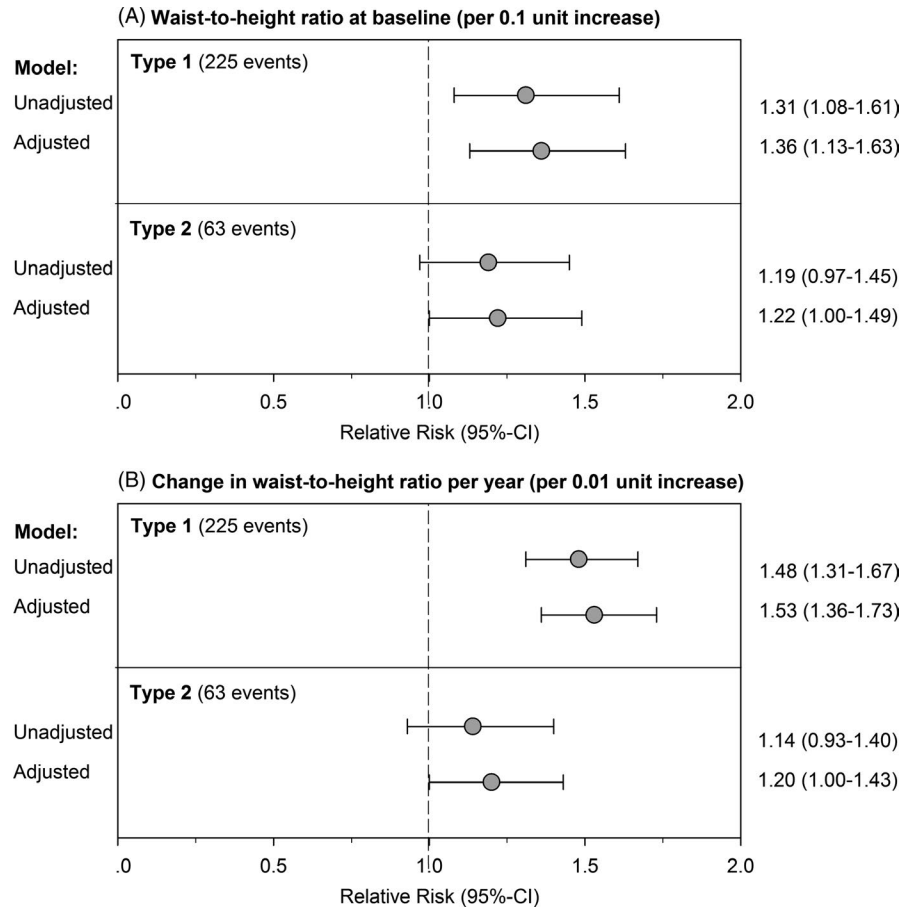

FIGURE 2 Progression to hypertension by baseline blood pressure status of 1695 participants with youth-onset type 1 and type 2 diabetes in the SEARCH for Diabetes in Youth Cohort Study

FIGURE 3 Relative risk of progression to hypertension for each 0.1 unit increase in waist-to-height ratio at baseline (3A) and for 0.01 unit increase in change per year (3B) by diabetes type in 1695 participants in the SEARCH for Diabetes in Youth Cohort Study

(A) Waist-to-height ratio at baseline (per 0.1 unit increase)

Model: **Type 1** (225 events)

Unadjusted 1.31 (1.08-1.61)
Adjusted 1.36 (1.13-1.63)

Type 2 (63 events)

Unadjusted 1.19 (0.97-1.45)
Adjusted 1.22 (1.00-1.49)

Relative Risk (95%-CI)

(B) Change in waist-to-height ratio per year (per 0.01 unit increase)

Model: **Type 1** (225 events)

Unadjusted 1.48 (1.31-1.67)
Adjusted 1.53 (1.36-1.73)

Type 2 (63 events)

Unadjusted 1.14 (0.93-1.40)
Adjusted 1.20 (1.00-1.43)

Relative Risk (95%-CI)

The association between BMI z-score at baseline, BMI change during follow-up, and the risk of progression to hypertension was similar but slightly less pronounced with lower magnitude of association and wider confidence intervals than the association observed with WHtR (Figure S1).

4 | DISCUSSION

In this cohort of youths and young adults with diabetes, we found a mild-to-moderate association between baseline WHtR as well as change in WHtR, and incident hypertension. This relationship was observed in both participants with type 1 and with type 2 diabetes. This relationship was less pronounced in participants with type 2 diabetes, in part due to the much smaller sample size among this group.

Several mechanisms link obesity and high blood pressure, including upregulation of pro-inflammatory adipokines due to adipose tissue dysfunction, increased sympathetic nervous system, abnormal kidney function associated with increased tubular sodium reabsorption, and increasing arterial stiffness.[25-31] It has also been hypothesized that obesity-related changes in the composition and function of gut microbiota might be associated with hypertension.[32] Central obesity, rather than BMI, has been shown to be a better predictor for hypertension and cardiovascular disease mortality in adults.[13,14] Visceral fat accumulation has been proposed as "dysfunctional adipose tissue," resulting in an altered metabolic profile which may not be present in individuals with obesity and subcutaneous but low visceral fat deposition.[25,33] Results from the present study indicate that WHtR as a marker of central obesity may be an important factor for hypertension in youths and young adults with diabetes.

The SEARCH study has previously shown that the number of cardiovascular risk factors did not change significantly in participants with type 1 diabetes, but increased over time in participants with type 2 diabetes, a diabetic phenotype with a higher prevalence of obesity at diagnosis.[34] Early complications of diabetes co-occurred in adolescents and young adults with diabetes, and included arterial stiffness and hypertension.[35] Youths and young adults with type 2 diabetes had a higher age-adjusted prevalence of macrovascular outcomes such as arterial stiffness and hypertension than youths and young adults with type 1 diabetes.[6] Moreover, adjusting for WHtR attenuated the difference in risk for arterial stiffness and hypertension for youths and young adults with type 1 versus type 2 diabetes to non-significance, indicating that central obesity explains, statistically, the higher burden of macrovascular outcomes in youths with type 2 versus those with type 1 diabetes.[6] While type 1 diabetes is

characterized by insulin deficiency mostly due to autoimmune destruction of the pancreatic beta cells and type 2 diabetes by insulin resistance which may lead to beta-cell failure,[36] it can be speculated that central obesity which is associated with insulin resistance, adds to the burden of disease in both type 1 and type 2 diabetes. Central obesity has been linked with metabolic outcomes, particularly through their impact on β-cell function and insulin sensitivity. However, growing evidence suggests that they might also interact with the immune system to amplify the autoimmune response in type 1 diabetes.[37]

The magnitude of the association between BMI and hypertension prevalence in pediatric populations has been estimated with odds ratios ranging from 3.5 to 4.4 for children with obesity compared to normal weight children.[38-42] Three cross-sectional studies suggested that children with severe obesity are 2-6 times more likely to have hypertension than those with moderate obesity.[42,43] However, these studies did not investigate central obesity or the effect among youths with diabetes. In the present study, youths with type 2 diabetes had a higher WHtR and BMI at baseline than youths with type 1 diabetes while the latter showed a more rapid increase in both markers of obesity than the former. Results from our study suggest that the prevention of central obesity may play an important role in the prevention of hypertension in adolescents and young adults with type 1 or type 2 diabetes. This may prevent obesity-related metabolic changes involved in the development of hypertension.[25-31] However, previous analyses also showed that microvascular complications of diabetic kidney disease, retinopathy, and peripheral neuropathy were higher among youths and young adults with type 2 diabetes compared to those with type 1 even after adjustment for central obesity, glycemic control, and other factors over time.[6] This indicates that obesity alone is not responsible for these complications and potential pathways of disease progression need to be explored.

In absence of data to calculate WHtR, BMI, a marker of obesity, may be used as predictor of hypertension in youths and young adults with diabetes. Previous studies in children have shown that BMI correlated reasonably well with body fat[44] and is comparable with WHtR in performance as predictor of metabolic syndrome[45] and hypertension[15] in children. However, in youths with diabetes, central obesity may be a better indicator of risk for diabetes-related complications than BMI.[6,11] In the present analysis, associations between BMI and progression to hypertension were slightly weaker with wider confidence intervals than associations between WHtR and progression to hypertension.

The SEARCH for Diabetes in Youth Study includes a large, racially, and ethnically diverse cohort.[6] The longitudinal measurements of blood pressure, body weight, height, and waist circumference are another strength of the present study. However, the use of blood pressure measured at study visits is a proxy for hypertension because it was not possible to confirm the presence of hypertension at other clinical visits as recommended by current guidelines.[22] Finally, the number of participants in the sample with type 2 diabetes was relatively small, resulting in less precise relative risk estimates.

In conclusion, we found that increasing central obesity was a major risk factor for incident hypertension in youths and young adults with diabetes. The development and implementation of effective strategies to reduce the risk of central obesity and the prevention of weight gain may lead to a reduction in the risk for incident hypertension among youths and young adults with diabetes.

CONFLICT OF INTEREST
None.

AUTHOR CONTRIBUTIONS
C Koebnick and JM Stafford had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. C Koebnick, JM Lawrence, G Imperatore, ET Jensen, JM Stafford, AS Shah, AK Mottl, RA Bell, D Dabelea, AD Liese, SM Marcovina, RB D'Agostino, Jr., and EM Urbina contributed to concept and design; acquisition, analysis, or interpretation of data. C Koebnick, JM Lawrence, ET Jensen, JM Stafford, AK Mottl, and RB D'Agostino, Jr. involved in drafting the manuscript. All authors contributed to critical revision of the manuscript for important intellectual content. C Koebnick, ET Jensen, JM Stafford, and RB D'Agostino, Jr. performed statistical analysis. D Dabelea, RB D'Agostino, Jr., and JM Lawrence obtained funding.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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