Predictors of Increased Carotid Intima-Media Thickness in Youth With Type 1 Diabetes: The SEARCH CVD Study

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OBJECTIVE

Youth with type 1 diabetes have worse cardiovascular (CV) risk factors and higher carotid intima-media thickness (IMT) than their peers without diabetes. Whether the burden of CV risk factors over time is associated with carotid IMT at follow-up in youth with type 1 diabetes is not known.

RESEARCH DESIGN AND METHODS

Two hundred ninety-eight youth with type 1 diabetes (mean age 13.3 ± 2.9 years, 87.6% non-Hispanic white, 53.7% male) had two study visits 5 years apart. CV risk factors, including BMI, lipids, blood pressure, hemoglobin A_{1c}, and smoking status, were assessed at both visits, and carotid IMT was measured at follow-up using B-mode ultrasonography. Linear regression models with an area under the curve measurement that incorporated the baseline and follow-up CV risk factors were used to evaluate the relationship with carotid IMT at follow-up.

RESULTS

All CV risk factors worsened significantly over time (except LDL cholesterol) ($P < 0.05$). From baseline to follow-up, the number of abnormal CV risk factors also increased ($P < 0.05$). Predictors of carotid IMT were older age, male sex, and higher BMI *z* score area under the curve (all $P < 0.05$).

CONCLUSIONS

The CV risk factor burden increases over time in youth with type 1 diabetes. BMI *z* score was the only modifiable CV risk factor that predicted carotid IMT. This study highlights the critical need to better understand the risk factors that influence carotid IMT early in the course of type 1 diabetes.

Adults with childhood-onset type 1 diabetes are at increased risk for premature cardiovascular disease (CVD) morbidity and mortality compared with the general population (1). The antecedents of CVD begin in childhood (2), and early or preclinical atherosclerosis can be detected as intima-media thickening in the artery wall (3). Carotid intima-media thickness (IMT) is an established marker of atherosclerosis because of its associations with CVD risk factors (4,5) and CVD outcomes, such as myocardial infarction and stroke in adults (6,7).

Prior work, including data from our study, has shown that youth with type 1 diabetes have higher carotid IMT than control subjects (8–13). In cross-sectional studies, risk factors associated with higher carotid IMT include younger age at

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diabetes onset, male sex, adiposity, higher blood pressure (BP) and hemoglobin A_{1c} (HbA_{1c}), and lower vitamin C levels (8,9,11). Only one study has evaluated CVD risk factors longitudinally and the association with carotid IMT progression in youth with type 1 diabetes (14). In a German cohort of 70 youth with type 1 diabetes, Dalla Pozza et al. (14) demonstrated that CVD risk factors, including BMI *z* score (BMIz), systolic BP, and HbA_{1c}, worsened over time. They also found that baseline HbA_{1c} and baseline and follow-up systolic BP were significant predictors of change in carotid IMT over 4 years. No studies have evaluated CVD risk factors over time in a U.S. cohort, and no study has attempted to quantify the burden of CVD risk factors over time on carotid IMT.

Thus, the aims of the current study were *1*) to evaluate CVD risk factors over time in youth with type 1 diabetes by using measurements that incorporate risk factor data from a baseline and follow-up visit, and *2*) to determine the association between the burden of CVD risk factors over time and follow-up carotid IMT.

We hypothesized that a worse CVD risk factor burden over time will be associated with a higher carotid IMT at follow-up.

RESEARCH DESIGN AND METHODS

Study Participants

Participants in this study were enrolled in SEARCH CVD, an ancillary study to the SEARCH for Diabetes in Youth that was conducted in two of the five SEARCH centers (Colorado and Ohio). Extensive details of the main SEARCH study have been published and are summarized by Hamman et al. (15). Participants were eligible for SEARCH CVD if they had physician-diagnosed type 1 diabetes. The baseline SEARCH visit of 406 participants with type 1 diabetes was conducted in 2004–2005 and included questionnaires, demographics, anthropometrics, and laboratory data. A follow-up SEARCH CVD visit was conducted between 2009 and 2011, where questionnaires, demographics, anthropometrics, and laboratory data were repeated and carotid IMT measurements were obtained. The goal of the follow-up study was to recruit >200 adolescents with type 1 diabetes from the original cohort. This report includes 298 youth who completed both baseline and follow-up SEARCH CVD visits (16,17). The study was reviewed and approved by each local institutional review board, and all participants provided written informed consent or assent.

Anthropometric and Metabolic Measurements

The baseline and follow-up research visits followed the same standard protocol (16,17). Each visit was conducted after at least an 8-h fast. Medications, including short-acting insulin, were withheld until blood draw was completed. Race and ethnicity were self-reported, and participants were categorized as non-Hispanic White (NHW) or other racial/ethnic group (Hispanic, African American, and Asian/Pacific Islander). Participants completed standardized questionnaires for medical history, medications, and smoking status (never, former [no cigarettes in the past 30 days], or current) (18). Height and weight were measured twice during each visit and averaged. BMI was calculated as an average of two measures of weight (kg) divided by height in meters squared, and age and sex-specific BMIz were derived (19). Resting systolic and diastolic BPs were measured three times with an aneroid sphygmomanometer and averaged. Mean arterial pressure (MAP) was calculated as ([2 × diastolic BP] + systolic BP) / 3.

Measurements of HbA_{1c}, total cholesterol, triglycerides, and HDL cholesterol (HDL-C) were performed as previously described (17). LDL cholesterol (LDL-C) was calculated by the Friedewald equation or measured by beta quantification if triglycerides were ≥400 mg/dL.

Definitions of CVD Risk Factors

The thresholds for defining CVD risk factors in this study were generated from published criteria for ideal targets in youth with diabetes (20–22). CVD risk factors were defined as present if

1) BMI ≥85th percentile for sex and age;
2) systolic or diastolic BP ≥90th percentile for sex, age, and height;
3) LDL-C ≥130 mg/dL;
4) HDL-C ≤30 mg/dL;
5) triglycerides ≥130 mg/dL if age ≥10 years or ≥100 mg/dL if age <9 years;
6) HbA_{1c} ≥7.5%; or
7) patient-reported status as a current smoker.

Carotid Outcome Measurements

Carotid IMT measurements were obtained using standardized B-mode ultrasound images from the right- and left-side neck at the common, bifurcation (bulb), and internal carotid arteries in the longitudinal and transverse views. All ultrasound images were obtained with a variable frequency linear array probe (5–12 MHz). Pulsed Doppler echocardiographic measurements were obtained at the internal carotid artery to confirm correct placement. Images were obtained at the predetermined angles of 90°, 120°, and 150° on the right side and 210°, 240°, and 270° on the left side for each participant. Multiple loops were stored, burned to disk, and transmitted to the vascular reading center in Ohio for reading of far wall mean IMT by a manual trace method (AMICAS VERICIS software, Merge Healthcare, Chicago, IL). A mean IMT value calculated by averaging the IMT measurements from the six predetermined angles for each carotid segment is reported. Analyses of carotid studies on >800 participants had coefficients of variability for all carotid measures ranging from 1.8 to 5.5%, indicating good reproducibility within published guidelines (10).

Statistics

Data are presented as mean and SD or number and percentage. Differences between baseline and follow-up anthropometrics and CVD risk factors were tested with paired *t* tests for continuous variables or McNemar test for categorical variables. CVD risk factor thresholds are as described in "Definitions of CVD Risk Factors."

To determine significant CVD risk factors associated with carotid IMT, a stepwise approach was taken using general linear models. All models adjusted for age at baseline (in years), race (NHW vs. other), sex (male vs. female), duration of diabetes at follow-up (in years), and clinic site (OH vs. CO). An area under the curve (AUC) measurement (a continuous variable) for each CVD risk factor (except smoking) was derived using baseline and follow-up data and length of time between visits. Separate models were explored for common, bulb, and internal carotid IMT. Models 1–5 explored

individual effects of AUC measurements of standard lipids, BP, insulin sensitivity, HbA_{1c}, and BMI over time on carotid IMT. Model 6 assessed the association between current smoking status (yes/no) at either the baseline or the follow-up visit and carotid IMT.

Model 1 assessed the effects of the LDL-C, HDL-C, and triglycerides AUC. Model 2 assessed MAP AUC. MAP was used instead of systolic or diastolic BP to account for baseline distending pressure of the artery wall (23). Model 3 included insulin sensitivity AUC because lower insulin sensitivity (or insulin resistance) is believed to partially explain some of the increased CVD risk in youth with type 1 diabetes (24). Insulin sensitivity was estimated using the following equation: log IS = 4.64725 − 0.02032 × waist in cm − 0.00235 × TG in mg/dL − 0.09779 × HbA_{1c} %. This equation was developed and validated using direct measurements of glucose disposal rate from euglycemic-hyperinsulinemic clamps (25). Model 4 evaluated HbA_{1c} AUC, model 5 assessed BMIz AUC, and model 6 evaluated smoking. Model 7 included all significant variables from models 1–6 and can be viewed as the overall model. For all models, variables with $P < 0.05$ were considered significant.

RESULTS

Characteristics of SEARCH participants at baseline and follow-up are presented in Table 1. At the initial visit, youth with type 1 diabetes were a mean age of 13.3 ± 2.9 years (range 7.6–21.3 years) and had an average disease duration of 3.6 ± 3.3 years. NHW accounted for 87.6% of the cohort, and 53.7% of the cohort was male. At baseline, 3.4% of the cohort reported to be currently smoking. Four participants reported taking an ACE inhibitor/angiotensin receptor blocker, and one reported use of a lipid-lowering medication.

Follow-up data were obtained at a mean age of 19.2 ± 2.7 years, when the average duration of type 1 diabetes was 10.1 ± 3.9 years. At follow-up, frequency of current smoking had increased to 23.8%. CVD risk factors, including BMIz, systolic and diastolic BP, HbA_{1c}, lipid levels, and insulin sensitivity, were all significantly worse at follow-up except for LDL-C, which was not significantly different. At follow-up, 12 (3.0%) participants reported taking an ACE inhibitor/angiotensin receptor blocker, and 25 (6.0%) reported taking a lipid-lowering drug.

Table 1—Characteristics of SEARCH CVD study participants at the baseline and follow-up visits

	Baseline (n = 298)	Follow-up (n = 298)	P value
Age (years)	13.3 ± 2.9	19.2 ± 2.7	<0.001
Duration of diabetes (years)	3.6 ± 3.3	10.1 ± 3.9	<0.001
Race (NHW)	261 (87.6)		—
Male sex	160 (53.7)		—
Smoking status			<0.001
Never	233 (88.6)	160 (53.7)	
Former	21 (8.0)	67 (22.5)	
Current	9 (3.4)	71 (23.8)	
Height (cm)	157.3 ± 14.2	171.4 ± 9.4	<0.001
Weight (kg)	53.4 ± 17.0	73.8 ± 15.2	<0.001
BMI (kg/m^2)	21.1 ± 4.3	25.1 ± 4.8	<0.001
BMIz	0.5 ± 1.0	0.6 ± 0.9	0.003
Systolic BP (mmHg)	103 ± 9	112 ± 10	0.003
Diastolic BP (mmHg)	67 ± 9	70 ± 9	<0.001
Total cholesterol (mg/dL)	166 ± 27	171 ± 35	0.008
LDL-C (mg/dL)	97 ± 23	98 ± 29	0.469
HDL-C (mg/dL)	55 ± 13	53 ± 14	0.010
Triglycerides (mg/dL)	70 ± 38	96 ± 60	<0.001
HbA_{1c} (%)	8.2 ± 1.4	8.9 ± 1.8	<0.001
HbA_{1c} (mmol/mol)	66 ± 15.3	74 ± 19.7	<0.001
Insulin sensitivity score	9.10 ± 2.6	6.37 ± 2.0	<0.001

Data are mean ± SD or n (%). P values were determined by paired t tests for continuous variables and McNemar test for categorical variables.

CVD Risk Factors

Table 2 shows the frequency of CVD risk factors at baseline and follow-up. At baseline, high HbA_{1c} was the most common CVD risk factor, present in 72.6% of the cohort. High BMI was observed in 26.7%. High LDL-C level was the most common lipid abnormality, present in 10.3%. Forty percent of participants had two or more CV risk factors (Fig. 1).

At follow-up, the frequency of participants in each risk category increased significantly, except for HDL-C where the frequency decreased significantly from baseline to follow-up (all $P <$ 0.05). At follow-up, high BMI was present in more than one-third of the cohort, and high triglyceride levels were the most frequently observed lipid abnormality (32.3%). Figure 1 shows that more than one-half (53%) of participants had two or more CVD risk factors at follow-up.

Predictors of Follow-up Carotid IMT

At follow-up, the mean IMT for youth with type 1 diabetes in the common carotid was 0.60 ± 0.10 mm, the bulb IMT was 0.62 ± 0.10 mm, and the internal IMT was 0.55 ± 0.12 mm. General linear models were constructed to explore risk factors associated with follow-up common, bulb, and internal carotid IMT (Table 3*A–C*). Older age at the baseline visit and male sex were significantly associated with all carotid IMT outcomes. HDL-C AUC (model 1), MAP (model 2), insulin sensitivity AUC (model 3), and BMIz AUC (model 5) were significantly associated with follow-up common carotid IMT after adjusting for age, race, sex, duration of diabetes, and clinic site. However, in the final model (model 7) for common carotid IMT that included each significant CV risk factor, only BMIz was significant. Similarly, HDL-C AUC, insulin sensitivity AUC, and BMIz AUC were associated with follow-up internal carotid IMT, but in the final model, only BMIz AUC was significant. HbA_{1c} AUC and smoking were not associated with any carotid IMT outcomes in either the individual models or the final model. Of all the CVD risk factors explored, higher BMIz AUC was the only one significantly associated with follow-up common and internal carotid IMT in multivariable analyses. A borderline association was

Table 2—CVD risk factors at baseline and follow-up (n = 298)

	Baseline	Follow-up	P value
Elevated BMI	79 (26.7)	102 (34.5)	<0.001
Elevated systolic or diastolic BP	29 (9.9)	58 (19.5)	<0.001
Elevated LDL-C	30 (10.3)	39 (13.5)	<0.001
Low HDL-C	9 (3.0)	4 (1.3)	<0.001
Elevated triglycerides	23 (7.9)	93 (32.3)	<0.001
Elevated HbA_{1c}	212 (72.6)	234 (78.8)	<0.001
Current smoker	9 (3.4)	71 (23.8)	<0.001

Data are n (%). Elevated defined as BMI ≥85th percentile for sex and age; systolic or diastolic BP ≥90th percentile for sex, age, and height; LDL-C ≥130 mg/dL; and triglycerides ≥130 mg/dL if age ≥10 years or ≥100 mg/dL if age <9 years. Low HDL-C defined as ≤30 mg/dL. All P values were determined by McNemar test.

also observed for BMIz AUC and the carotid bulb IMT ($P = 0.075$).

CONCLUSIONS

This study demonstrates for the first time to our knowledge that the degree and burden of CVD risk factors increases over time in youth with type 1 diabetes. This study also shows that higher BMIz over time was the only modifiable risk factor associated with follow-up carotid IMT.

Previous cross-sectional studies have demonstrated that adolescents with type 1 diabetes have worse CVD risk profiles and higher carotid IMT than control subjects (8–13). Risk factors shown to associate with higher IMT are age of diabetes onset; higher adiposity, lipid levels, BP, and HbA_{1c}; and lower vitamin C levels (8,9,11). Specifically, Dalla Pozza et al. (14) found that younger age at diabetes onset, systolic BP (mean 111.3 ± 11.3 mmHg) and total cholesterol levels (mean for females 185 ± 32.0 mg/dL, mean for males 168 ± 28.4 mg/dL) were significantly associated with a higher common carotid IMT in adolescents at age 14 years. In addition, Heilman et al. (9) found HbA_{1c} (mean 9.8 ± 1.5%) was borderline associated with a higher carotid IMT ($r = 0.39$, $P = 0.05$).

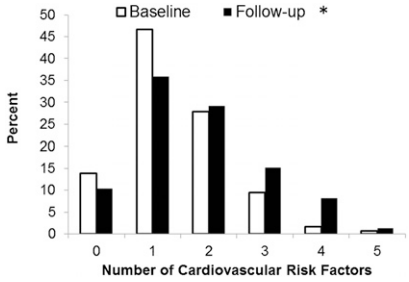

Figure 1—Number of cardiovascular risk factors at baseline and follow-up. Shown are the percentage of participants with zero to five cardiovascular risk factors at baseline and follow-up data. Cardiovascular risk factors were BMI ≥85th percentile for sex and age; systolic or diastolic BP ≥90th percentile for sex, age, and height; LDL-C ≥130 mg/dL; and triglycerides ≥130 mg/dL if age ≥10 years or ≥100 mg/dL if age <9 years. Low HDL-C was defined as ≤30 mg/dL. *Mean number of risk factors was higher from baseline to follow-up ($P < 0.05$).

Before the current study, no published reports had assessed the impact of changes in CVD risk factors and carotid IMT in U.S. adolescents with type 1 diabetes. A study conducted in 70 German children with type 1 diabetes (mean baseline age 12.6 ± 2.5 years) examined longitudinally the effect of CVD risk factors on carotid IMT, reporting that over 4 years, BMIz, systolic BP, and HbA_{1c} worsened, whereas LDL-C and HDL-C did not (14). Additionally, the authors noted that higher baseline HbA_{1c} and higher baseline and follow-up systolic BP were signficantly associated with change in carotid IMT over time in linear regression models. Limitations of that study included loss of >50% of the original cohort, use of individual baseline and follow-up CVD risk factor data instead of an AUC measurement that accounts for burden of risk factors over time, and no report of diastolic BP, triglycerides, or insulin sensitivity measurements (14).

In the current study, we show that older age (at baseline) and male sex were significantly associated with follow-up IMT. By using AUC measurements, we also show that a higher BMIz exposure over ~5 years was significantly associated with IMT at follow-up. From baseline to follow-up, the mean BMI increased from within normal limits (21.1 ± 4.3 kg/m^2) to overweight (25.1 ± 4.8 kg/m^2), defined as a BMI ≥25 kg/m^2 in adults (26,27). This large change in BMI may explain why BMIz was the only modifiable risk factor to be associated with follow-up IMT in the final models. Whether the observed increase in BMIz over time is part of the natural evolution of diabetes, aging in an obesogenic society, or a consequence of intensive insulin therapy is not known. However, this finding points to obesity as a common CVD risk factor in both type 1 and type 2 diabetes, despite the clear differences in the pathophysiology of the two types of diabetes. Weight loss in obese adolescents has been shown to be beneficial at improving carotid IMT (28,29). Whether weight loss improves carotid IMT and reduces CVD risk in youth with type 1 diabetes remains to be determined.

After adjusting for baseline covariates, we found no association between lipids, BP, and HbA_{1c} over time and follow-up IMT. The reasons for the lack of independent association are not known, but we postulate that although total cholesterol, HDL-C, triglycerides, and systolic and diastolic BP worsened over time, the mean values at baseline and follow-up remained below thresholds defined as CVD risk factors (20–22). This could explain the discrepant results between our study and the study by Dalla Pozza et al. (14), in which an association between mean systolic BP and change in IMT over time was observed. The systolic BP at follow-up in the Dalla Pozza et al. cohort was in the prehypertension range (mean systolic BP 122 ± 11.5 mmHg), whereas that in the current study at follow-up BP was in the normal range (mean systolic BP 112 ± 10 mmHg). Alternatively, lipid levels and BP may only be important CVD risk factors when duration of diabetes has been >5 years. Similar findings have been observed in the Diabetes Control and Complications Trial (DCCT) and its follow-up cohort the Epidemiology of Diabetes Interventions and Complications (EDIC) study, where traditional CVD factors did not associate with future IMT until nearly one decade later (30). This may also explain why HbA_{1c} AUC, although clearly abnormal at both baseline and follow-up, was not associated with follow-up carotid IMT in the current study.

Table 3—Predictors associated with follow-up common, bulb, and internal carotid IMT

A: Predictors associated with follow-up common carotid IMT

	Model 1			Model 2			Model 3			Model 4			Model 5			Model 6			Model 7		
	β	SE	*P* value	β	SE	*P* value	β	SE	*P* value	β	SE	*P* value	β	SE	*P* value	β	SE	*P* value	β	SE	*P* value
Age at baseline (years)	0.005	0.002	**0.011**	0.007	0.002	**0.001**	0.005	0.002	**0.034**	0.006	0.002	**0.003**	0.007	0.002	**<0.001**	0.005553	0.002227	**0.0133**	0.008	0.002	**<0.001**
NHW	−0.015	0.017	0.365	−0.015	0.016	0.344	−0.011	0.017	0.508	−0.019	0.017	0.252	−0.010	0.016	0.521	−0.01695	0.0177	0.3392			
Male sex	0.040	0.011	**0.001**	0.046	0.011	**<0.001**	0.048	0.012	**<0.001**	0.043	0.011	**<0.001**	0.046	0.011	**<0.001**	0.038555	0.011522	**0.0009**	0.043	0.012	**<0.001**
Duration of diabetes (years)	0.005	0.002	**0.012**	0.004	0.002	**0.030**	0.003	0.002	0.054	0.003	0.002	0.083	0.001	0.001	0.474	0.00187	0.001556	0.2307			
Clinic site (OH)	0.016	0.012	0.173	0.015	0.011	0.191	0.017	0.012	0.137	0.013	0.011	0.245	0.007	0.011	0.523	0.014295	0.011687	0.2224			
LDL-C AUC (per 100 mg/dL × year increase)	0.000	0.003	0.935																		
HDL-C AUC (per 100 mg/dL × year increase)	−0.016	0.006	**0.011**																−0.007	0.008	0.345
Triglycerides AUC (per 100 mg/dL × year increase)	−0.004	0.002	0.062																		
MAP BP AUC (per 100 mmHg × year increase)				−0.017	0.007	**0.016**													−0.007	0.008	0.379
Insulin sensitivity AUC (per 10 units × year increase)							−0.009	0.004	**0.028**										0.003	0.005	0.528
HbA_{1c} AUC (per 10% × year increase)										−0.009	0.005	0.062									
BMIz AUC (per 1 *z* score × year increase)													0.003	0.001	**0.011**				0.003	0.001	**0.006**
Current smoker at either visit																0.000461	0.012746	0.9711			
Model R^2		0.142			0.126			0.121			0.119			0.131			0.094			0.132	

B: Predictors associated with follow-up internal carotid IMT

	Model 1			Model 2			Model 3			Model 4			Model 5			Model 6			Model 7		
	β	SE	*P* value	β	SE	*P* value	β	SE	*P* value	β	SE	*P* value	β	SE	*P* value	β	SE	*P* value	β	SE	*P* value
Age at baseline (years)	0.007	0.003	**0.004**	0.008	0.002	**0.001**	0.005	0.003	0.046	0.008	0.002	**0.001**	0.008	0.002	**<0.001**	0.006497	0.002749	0.0188	0.008	0.002	**<0.001**
NHW	0.005	0.020	0.802	0.006	0.020	0.746	0.011	0.020	0.590	0.006	0.020	0.779	0.010	0.019	0.614	0.006108	0.02175	0.7791			
Male sex	0.053	0.014	**<0.001**	0.057	0.013	**<0.001**	0.063	0.014	**<0.001**	0.055	0.013	**<0.001**	0.060	0.013	**<0.001**	0.054763	0.014237	**0.0002**	0.058	0.014	**<0.001**
Duration of diabetes (years)	0.003	0.002	0.202	0.002	0.002	0.260	0.004	0.002	0.060	0.002	0.002	0.315	0.001	0.002	0.550	0.002136	0.001927	0.2686			
Clinic site (OH)	0.026	0.014	0.065	0.030	0.013	0.025	0.029	0.014	0.036	0.028	0.014	0.037	0.022	0.014	0.107	0.029792	0.014469	0.0405	0.023	0.014	0.113
LDL-C AUC (per 100 mg/dL × year increase)	0.006	0.004	0.129																		
HDL-C AUC (per 100 mg/dL × year increase)	−0.016	0.008	**0.032**																−0.006	0.008	0.427
Triglycerides AUC (per 100 mg/dL × year increase)	−0.001	0.003	0.765																		
MAP BP AUC (per 100 mmHg × year increase)				−0.006	0.008	0.456															
Insulin sensitivity AUC (per 10 units × year increase)							−0.012	0.005	**0.012**										−0.002	0.006	0.680
HbA_{1c} AUC (per 10% × year increase)										−0.003	0.006	0.575									

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Table 3—Continued

	B: Predictors associated with follow-up internal carotid IMT																				
	Model 1			Model 2			Model 3			Model 4			Model 5			Model 6			Model 7		
	β	SE	*P* value	β	SE	*P* value	β	SE	*P* value	β	SE	*P* value	β	SE	*P* value	β	SE	*P* value	β	SE	*P* value
BMIz AUC (per 1 z-score × year increase)													0.003	0.001	**0.009**				0.003	0.001	**0.031**
Current smoker at either visit																0.001315	0.015758	0.9336			
Model R^2		0.141			0.129			0.146			0.126			0.149			0.111			0.149	

	C: Predictors associated with follow-up bulb carotid IMT																				
	Model 1			Model 2			Model 3			Model 4			Model 5			Model 6			Model 7		
	β	SE	*P* value	β	SE	*P* value	β	SE	*P* value	β	SE	*P* value	β	SE	*P* value	β	SE	*P* value	β	SE	*P* value
Age at baseline (years)	0.005	0.002	**0.027**	0.005	0.002	**0.017**	0.004	0.003	0.080	0.005	0.002	**0.022**	0.006	0.002	**0.013**	0.003702	0.002481	0.1369	0.005	0.002	**0.013**
NHW	−0.018	0.019	0.347	−0.014	0.018	0.428	−0.017	0.019	0.362	−0.017	0.019	0.374	−0.015	0.018	0.419	−0.01089	0.019656	0.5881			
Male sex	0.030	0.010	**0.008**	0.029	0.012	**0.020**	0.036	0.013	**0.006**	0.032	0.012	**0.011**	0.034	0.012	**0.006**	−0.02382	0.012827	0.0645	−0.031	0.012	**0.011**
Duration of diabetes (years)	0.000	0.002	8.993	−0.001	0.002	0.707	0.001	0.002	0.551	0.000	0.002	0.993	−0.001	0.002	0.754	0.000	0.001734	0.9708			
Clinic site (OH)	−0.016	0.013	0.218	−0.018	0.013	0.153	−0.013	0.013	0.328	−0.015	0.013	02229	−0.022	0.013	0.080	−0.0134	0.013034	0.3049			
LDL-C AUC (per 100 mg/dL × year)	0.007	0.004	0.052																		
HDL-C AUC (per 100 mg/dL × year increase)	−0.006	0.007	0.434																		
Triglycerides AUC (per 100 mg/dL × year increase)	−0.002	0.003	0.458																		
MAP BP AUC (per 100 mmHg × year increase)				0.004	0.008	0.592															
Insulin sensitivity AUC (per 10 units × year increase)							−0.005	0.005	0.300												
HbA_{1c} AUC (per 10% × year increase)										0.000	0.006	0.972									
BMIz AUC (per 1 *z* score × year increase)													0.002	0.001	**0.033**				0.002	0.001	**0.075**
Current smoker at either visit																0.005913	0.014173	0.6769			
Model R^2		0.067			0.018			0.057			0.050			0.064			0.028			0.050	

Bolded *P* values are significant. Only parameters considered in each model are listed.

Current smoking status (at either baseline or follow-up) was also not associated with carotid IMT. Potential explanations for this lack of association may be due to underreporting of self-reported smoking behaviors (31). Additionally, the duration of smoking may have been short, or the quantity of cigarettes smoked may have been too small to have detectable effects on the vasculature. Finally, there may be a threshold effect of smoking (in terms of both dose and duration) at which accelerated vascular changes occur. Given that prior work in middle-aged adults has clearly documented adverse effects of smoking on the vasculature (32), additional studies with quantification of cotinine are needed before conclusions can be drawn about the effects of smoking on carotid IMT in youth with type 1 diabetes.

Similar to studies in adults (30), we identified few risk factors that associate with follow-up carotid IMT. Other work, including previously published data from our group, suggested that worsening insulin resistance (or decreased insulin sensitivity) may be an important CVD risk factor in youth with type 1 diabetes (33). However, after adjusting for BMIz in the current study, we did not find a statistically significant association between insulin sensitivity AUC and follow-up IMT, despite the worsening of insulin sensitivity over time. This finding suggests that the duration or degree of exposure may be important.

Data from the DCCT/EDIC cohorts have suggested nontraditional risk factors, including acute phase reactants, thrombolytic factors, cytokines/adipokines (34), oxidized LDL, and advanced glycation end products (30) may be important biomarkers of increased CVD risk in adults with type 1 diabetes. However, many of these nontraditional risk factors, including acute phase reactants, thrombolytic factors, and cytokines/adipokines, were not found to associate with IMT until 8–12 years after the DCCT ended, at the time when traditional CVD risk factors were also found to predict IMT. Collectively, these findings suggest that many traditional and nontraditional risk factors are not identified as relevant until later in the atherosclerotic process and highlight the critical need to better identify risk factors that may influence carotid IMT early in the course of type 1 diabetes because these may be important modifiable CVD risk factors of focus in the adolescent population.

Strengths of the current study include a large cohort of youth with type 1 diabetes, follow-up CVD risk factor data after 5 years (the longest follow-up to date in youth), and the ability to evaluate the association between CVD risk factors over time and follow-up IMT in a young adolescent cohort (mean age 18 years at follow-up). Limitations of the study include carotid IMT measurements obtained only at one time point, lack of physical activity data, and the inability to assess nontraditional biomarkers. Additionally, we quantified adiposity only in terms of BMI, which does not capture information on lean body mass or types of fat. Finally, generalizability of the results to other type 1 diabetes cohorts with a worse CVD risk profile may be limited. However, the risk factor profile we report is consistent with that of the larger SEARCH cohort (35), large type 1 diabetes cohorts in the U.S. and U.K. (36,37), and the DCCT study cohort at baseline (38).

In conclusion, we demonstrate that the CVD risk factor burden increases over time in youth with type 1 diabetes. Although BMIz was the only identified risk factor to predict follow-up IMT at this age, it is possible that increases in dyslipidemia, BP, smoking, and HbA_{1c} are related to carotid IMT but only after longer duration of exposure.

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