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COMPLICATIONS

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Higher frequency of cardiovascular autonomic neuropathy in youth with type 2 compared to type 1 diabetes: Role of cardiometabolic risk factors

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Abstract

Objective: Cardiovascular autonomic neuropathy (CAN) is an overlooked but common and serious diabetes complication. We examined CAN in youth with diabetes and associations with cardiovascular risk factors.

Research Design and Methods: This was a prospective cohort of youth aged <20 years with type 2 or type 1 diabetes ($n = 66/1153$, median age 15.4/16.5 years, duration 1.7/8.0 years), assessed between 2009 and 2020. CAN was defined as ≥2 abnormal heart rate variability measures across time, geometric, and frequency domains. Obesity was defined as BMI ≥ 95th percentile and severe obesity as ≥120% of 95th percentile. Multivariable generalized estimating equations (GEE) were used to examine putative risk factors for CAN, including diabetes type, obesity, and HbA_{1c}.

Results: At most recent assessment, youth with type 2 versus type 1 diabetes had median: HbA_1c 7.1% (54 mmol/mol) versus 8.7% (72 mmol/mol) and BMI SDS (2.0 vs. 0.7); frequency of CAN (47% vs. 27%), peripheral nerve abnormality (47% vs. 25%), hypertension (29% vs. 12%), albuminuria (21% vs. 3%), and severe obesity (35% vs. 2%). In multivariable GEE, CAN was associated with type 2 diabetes: Odds Ratio 2.53, 95% CI 1.46, 4.38, $p = 0.001$, higher BMI SDS: 1.49, 95% CI 1.29, 1.73, $p < 0.0001$, and obesity: 2.09, 95% CI 1.57, 2.78, $p < 0.0001$.

Conclusions: Youth with type 2 diabetes have a higher frequency of CAN, peripheral nerve abnormality, hypertension, albuminuria and severe obesity despite shorter diabetes duration and younger age. Our findings highlight the importance of targeting modifiable risk factors to prevent cardiovascular disease in youth with diabetes.

KEYWORDS
cardiovascular autonomic neuropathy, cardiovascular disease, heart rate variability, obesity, youth

1 | INTRODUCTION

The prevalence of youth onset type 2 diabetes has increased in recent decades,[1] with higher rates and earlier onset of complications[2,3] particularly albuminuria and hypertension, compared with type 1 diabetes.[2–4] Youth-onset type 2 diabetes is also associated with greater mortality compared to type 1 diabetes.[5,6]

Cardiovascular autonomic neuropathy (CAN) is an overlooked but relatively common and serious complication in people with diabetes,[7] including youth.[8] CAN is a pathology of the autonomic nerve fibers that innervate the heart and blood vessels, resulting in abnormalities of heart rate control and vascular tone, which can manifest as resting tachycardia, orthostatic hypotension and hypertension,[7] however, may also be asymptomatic and detected using heart rate variability (HRV). CAN is an independent risk factor for all-cause and cardiovascular mortality[7,9] in diabetes.

Obesity in childhood is associated with cardiometabolic morbidity and early mortality, which emerge in young adulthood.[10] CAN is present in adolescents with overweight or obesity without diabetes,[11,12] and indices of CAN have been associated with higher BMI in young adults with youth-onset type 1[13] and type 2 diabetes.[14] Only three studies have compared CAN between youth-onset type 1 versus type 2 diabetes using HRV, with inconsistent findings between the frequency of CAN.[4,15,16] In our previous cross-sectional study, we found a higher frequency of CAN, vascular complications and obesity in youth with type 2 diabetes compared to type 1 diabetes.[16] However, due to the sample ($n = 166$), multivariable analysis was limited and we were unable to explore associations with CAN. The other two studies reported conflicting CAN frequency rates.[4,15] Understanding the frequency of CAN and determining the risk profile of youth with type 2 versus type 1 diabetes is important to identify and treat those at increased risk of cardiovascular disease.

Our primary aim was to compare the frequency of CAN in young people with type 1 versus type 2 diabetes and examine the predictive role of cardiovascular risk factors such as obesity on CAN.

We hypothesized that adolescents with type 2 versus type 1 diabetes would have higher frequency of CAN and vascular complications.

2 | METHODS

This was a prospective cohort study of young people with type 1 diabetes or type 2 diabetes from a clinical registry of the Diabetes Complications Assessment Service at the Children's Hospital at Westmead in Sydney, Australia. Inclusion criteria were: age <20 years and HRV measurement from at least one visit to the Diabetes Complications Assessment Service between May 2009 and March 2020. Type 1 diabetes was diagnosed clinically and confirmed by positive diabetes-associated autoantibodies, while type 2 diabetes was diagnosed clinically with negative autoantibodies and without monogenic or secondary diabetes.[17] The study was approved by the Human Research Ethics Committee at the Children's Hospital at Westmead (2020/ETH00326).

2.1 | Complications assessment

Complications assessment was conducted every 1–2 years according to ISPAD guidelines for vascular complications.[18] All visits were conducted in the morning after breakfast. Participants did not smoke or consume alcohol prior to assessment. Participants were not asked about caffeine intake prior to assessment due to published findings that caffeine intake does not influence heart rate or HRV in this population.[19] Height was measured by Harpenden stadiometer and weight using electronic scales. Height, weight and BMI percentile and standardized deviation scores (SDS) were calculated according to the 2000 Centres for Disease Control and Prevention reference standards, as previously described[13]: normal weight was defined as BMI ≥ 3rd to <85th percentile, overweight as BMI ≥ 85th to <95th percentile, obesity as BMI ≥ 95th to <120% of 95th percentile for BMI, and severe obesity as ≥120% of the 95th percentile for BMI. Blood pressure (BP) was measured after 5 min rest in a seated position, with SDS for systolic BP (SBP) and diastolic BP (DBP) calculated according to standards for age and sex.[20] Hypertension was defined as SBP or DBP ≥ 95th percentile or 130/80 in children <13 years old (whichever was lower), or ≥130/80 in children ≥13 years old.[21]

Participants underwent 10 min of continuous electrocardiogram in a supine position and in a quiet room using LabChart-Pro (AD Instruments, Sydney, Australia) to assess HRV. HRV refers to variations between consecutive heartbeats and cardiac cycles under control of the autonomic nervous system. Reduced HRV is the earliest indicator of CAN, which can be detected asymptomatically.[22] A single blinded operator reviewed all traces. Seven HRV parameters were evaluated across three domains: (i) time-domain measuring the overall HRV and including the standard deviation and root-mean squared difference of successive normal-to-normal intervals, and heart rate; (ii) geometric-domain measuring the Triangular index, another measure of overall HRV, whereby the total number of all RR intervals divided by the height of the histogram of all RR intervals measured on a discrete scale with bins of 7.8125 ms (1/128 s), and (iii) frequency-domain measuring low frequency (LF), defined as >0.04 and <0.15 Hz, high frequency (HF), defined as >0.15 and <0.4 Hz, and LF:HF, which represents the balance between the sympathetic and parasympathetic branches.[23] CAN was defined as ≥2 HRV abnormalities[7] (out of 7) based on ≤5th or ≥ 95th percentiles of age- and sex-matched local control subjects using the same equipment.[13]

Peripheral nerve function was assessed using thermal threshold testing for hot and cold sensations at the dorsum of the left foot and vibration stimuli at the left malleolus (Neurosensory TSA-II and Vibratory Sensory Analyzer; Medoc Ltd, Ramat Yishai, Israel) with ≥1 of these three tests outside the 95th percentile for age and gender considered abnormal and retinopathy defined as the presence of at least 1 microaneurysm or hemorrhage based on 7-field fundal photography.[13,16] Biochemical measures: HbA1c, lipids, liver function tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST], gamma-glutamyl transferase [GGT]), c-reactive protein (CRP), albumin, random c-peptide, and sex hormone binding globulin (SHBG) were analyzed in the Children's Hospital at Westmead clinical laboratories as previously described.[13,16] HbA1c was

TABLE 1 Participant characteristics compared between diabetes type at most recent visit

	Type 1 diabetes $n = 1153$	Type 2 diabetes $n = 66$	p value
Demographics			
Male	576 (50)	25 (38)	0.056
Age (years)	16.5 [14.6, 17.7]	15.4 [13.4, 16.9]	0.001
Diabetes duration (years)	8.0 [5.3, 11.0]	1.7 [0.3, 3.5]	<0.0001
HbA_{1c} (%)	8.7 [7.9, 9.8]	7.1 [5.7, 9.8]	<0.0001
mmol/mol	72 [63, 84]	54 [39, 84]	<0.0001
Height SDS	0.18 [−0.51, 0.85]	0.44 [−0.32, 1.31]	0.101
Weight SDS	0.72 [0.13, 1.28]	2.01 [1.53, 2.53]	<0.0001
BMI SDS	0.71 [0.07, 1.29]	2.01 [1.62, 2.33]	<0.0001
Overweight	272 (23.6)	13 (20)	
Obesity	105 (9.1)	25 (39)	<0.0001
Severe obesity	26 (2.3)	23 (35)	
SBP SDS	0.01 [−0.64, 0.63]	0.51 [−0.06, 1.26]	<0.0001
DBP SDS	−0.13 [−0.60, 0.49]	0.09 [−0.30, 0.95]	0.005
SES disadvantaged	265 (23)	30 (46)	<0.0001
Complications			
CAN[a]	309 (27)	31 (47)	<0.001
Retinopathy	173 (15.4)	1 (2)	0.003
Peripheral nerve abnormality	281 (25.2)	30 (47)	<0.001
Hypertension	141 (12.2)	19 (29)	<0.001
Albuminuria	33 (3)	10 (21)	<0.0001
Early elevation of AER	282 (26)	30 (49)	<0.0001

Note: Data presented as median [IQR] or *n* (%).
Abbreviations: AER, albumin excretion rate; CAN, cardiovascular autonomic neuropathy; DBP, diastolic blood pressure; SBP, systolic blood pressure; SDS, standardized deviation score; SES, socioeconomic status.
[a]Defined as 2 or more abnormal HRV measures.

measured using high-performance liquid chromatography (Adams Arkray Inc., Kyoto, Japan) and CRP by high-sensitivity turbidimetry (Roche, Diagnostics, Basel, Switzerland on a Cobas Integra 400+). Early elevation of albumin excretion rate (AER) was defined as AER ≥ 7.5 mcg/min in at least 2 of 3 samples from timed overnight urine collections or mean albumin: creatinine ratio (ACR) ≥ 1.0 mg/mmol (male) and ≥1.4 mg/mmol (female). Albuminuria was defined as AER ≥ 20 mcg/min in at least 2 of 3 samples from timed overnight urine collections or mean ACR ≥ 3.5 mg/mmol (male) and ≥4.0 mg/mmol (female).

Socioeconomic status was determined using a postcode-based system derived from the Australian Bureau of Statistics Socioeconomic Indexes for Areas (SEIFA) Database.[24] Participants were classified as either socioeconomically disadvantaged (1st–3rd deciles) or socioeconomically advantaged (4th–10th deciles).[24]

2.2 | Statistical analysis

Cross-sectional analysis: Descriptive statistics at the most recent visit are reported as mean and SD or median and IQR. Independent sample *t*-tests or Mann–Whitney *U* Tests were performed to assess differences between groups. Chi-Square or Fisher's Exact tests were used to compare categorical data. Post hoc Bonferroni adjustments were made to compare the frequency of CAN within BMI categories. Unadjusted and adjusted linear regression models were used to compare means of HRV measures as continuous variables at the most recent visit between diabetes type, adjusting for age, sex, and BMI SDS. All HRV values were log transformed for regression analyses.

Longitudinal analysis: Multivariable logistic generalized estimating equations (GEE) were used to explore associations between CAN and obesity using all available time points in all participants, and separately by type 1 or type 2 diabetes. Models were adjusted for potential confounders such as age, HbA_{1c} and sex. In another model, we explored the association between CAN and BMI as a continuous variable using BMI SDS. Separate models using all participants were constructed to examine associations between CAN outcomes, diabetes type, risk factors, and other microvascular complications, adjusting for potential confounders including age, sex, BMI SDS, obesity, and HbA_{1c}. Explanatory variables were expressed as odds ratios (OR) and 95% confidence intervals (CI). Statistical analyses were performed using IBM SPSS Statistics, version 27.1 (Chicago, IL). A significance level of $p < 0.05$ was used for all analyses.

3 | RESULTS

3.1 | Participant characteristics

Characteristics of participants at the most recent visit are described in Table 1. Overall, 66 youth with type 2 diabetes (38% male) and 1153 with type 1 diabetes (50% male) met the inclusion criteria. The number of visits per participant varied depending on age of diagnosis until transition to adult care. Youth with type 2 diabetes attended a median of 1 (range 1–4) assessment, median 1.3 years between visits (range 0.9–3.7), with 41% attending 2 or more assessments and 17% attending 3 or more. Youth with type 1 diabetes attended a median of 2 (range 1–9) assessments, median 1.8 years between visits (range 0.1–5.7), with 57% attending 2 or more assessments and 30% attending 3 or more.

At the most recent assessment, youth with type 2 versus type 1 diabetes were younger, had shorter diabetes duration, higher BMI SDS, higher SBP, and DBP SDS, higher rates of socioeconomic disadvantage and lower HbA_{1c} (Table 1).

In linear regression models of continuous HRV variables at the most recent visit, HRV measures were significantly lower across all domains in youth with type 2 compared to type 1 diabetes after adjusting for age and sex (Table S1). Youth with type 2 versus type 1 diabetes also had a higher resting heart rate. After adjusting for age, sex, and BMI SDS, heart rate and triangular index were not significantly different between diabetes types.

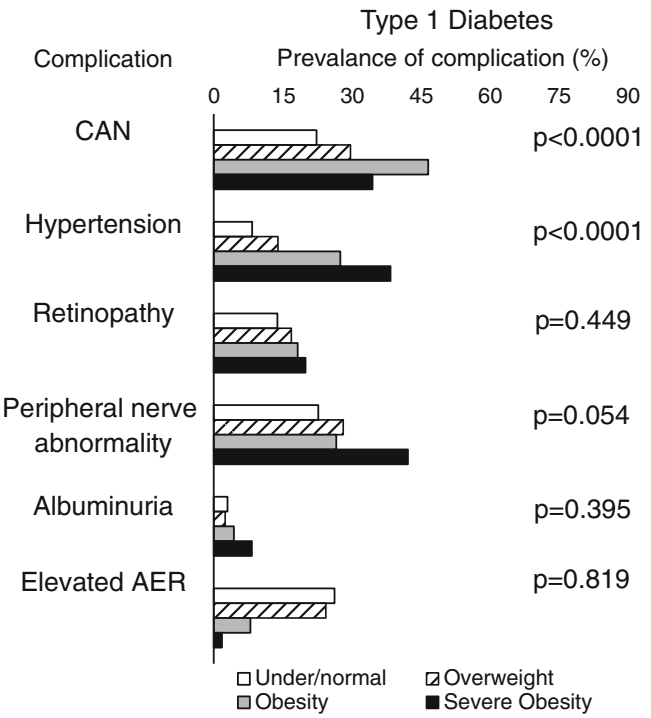

FIGURE 1 Frequency of diabetes complications by BMI category for youth with type 1 diabetes at most recent visit. *p* values calculated with Chi square. T1D: under/normal $n = 750$, overweight $n = 272$, obesity $n = 105$, severe obesity $n = 26$. AER, albumin excretion rate; CAN, cardiovascular autonomic neuropathy

3.2 | Diabetes complications

Youth with type 2 versus type 1 diabetes had higher frequency of peripheral nerve abnormality, hypertension, albuminuria, and early elevation of AER and lower frequency of retinopathy (Table 1).

CAN (≥2 HRV abnormalities) was present in 47% of youth with type 2 versus 27% with type 1 diabetes, with an overall frequency of 28% (Table 1). Participant characteristics stratified by CAN status and diabetes type are shown in Table S2. Youth with type 2 diabetes and CAN were older, had higher SBP SDS, DBP SDS, total cholesterol and triglycerides, and higher frequency of albuminuria compared to type 2 diabetes without CAN. Youth with type 1 diabetes and CAN were also older, had higher HbA_{1c}, BMI SDS, SBP SDS, DBP SDS total cholesterol and triglycerides, and higher frequency of retinopathy, and albuminuria compared to those with type 1 diabetes without CAN.

Among all participants, the frequency of CAN was highest in those with obesity (46.2%) and severe obesity (44.9%), compared to those with overweight (29.8%), underweight, or normal weight (22.6%). In type 1 diabetes, the frequency of CAN was highest in youth with obesity (46.7%) versus other weight categories, whereas there was no difference in the frequency of CAN between BMI categories in youth with type 2 diabetes. The frequency of CAN and hypertension were highest in youth with type 1 diabetes and obesity or severe obesity (Figure 1), whereas there was no difference in the prevalence of diabetes complications by BMI category for youth with type 2 diabetes.

Youth with type 2 versus type 1 diabetes had higher liver enzymes (ALT, AST, and GGT), C-reactive protein (CRP), triglycerides, with no difference in total cholesterol, and lower HDL cholesterol, and SHBG (Table S3).

In multivariable logistic GEE models, CAN was associated with severe obesity after adjusting for HbA_{1c}, sex, and age, with the highest OR for youth with type 2 diabetes compared to type 1 diabetes and all participants (Table 2). When the association between CAN and BMI as a continuous variable was explored, CAN was associated with higher BMI SDS in all participants (OR 1.49, 95% CI 1.29, 1.73, $p < 0.0001$), and separately in those with type 1 diabetes (OR 1.37, 95% CI 1.19, 1.59, $p < 0.0001$) or type 2 diabetes (OR 2.93, 95% CI 1.13, 7.56, $p = 0.027$), with HbA_{1c}, age, and sex included in each model. In separate models, CAN was associated with type 2 diabetes, retinopathy, albuminuria, hypertension, and elevated AER after adjusting for age, sex, HbA_{1c}, and BMI SDS (Table 3).

4 | DISCUSSION

In this cohort of 1219 youth with diabetes, CAN was considerably more frequent in those with type 2 versus type 1 diabetes (47% vs. 27%), despite lower HbA_{1c} and shorter diabetes duration in those

TABLE 2 Multivariable models exploring the association between cardiovascular autonomic neuropathy and clinical risk factors in youth with diabetes using all available time points

	Type 1 and type 2 diabetes $n = 1219$		Type 1 diabetes $n = 1153$		Type 2 diabetes $n = 66$	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Severe obesity[a]	3.65 (2.04, 6.55)	<0.001	2.12 (1.01, 4.45)	0.046	5.45 (1.70, 17.39)	0.004
Obesity[a]	2.09 (1.57, 2.78)	<0.0001	2.00 (1.48, 2.69)	<0.0001	2.15 (0.64, 7.27)	0.217
Age	1.27 (1.21, 1.32)	<0.0001	1.26 (1.21, 1.32)	<0.0001	1.61 (1.24, 2.08)	<0.001
HbA_{1c}	1.26 (1.19, 1.34)	<0.0001	1.32 (1.24, 1.40)	<0.0001	0.97 (0.80, 1.18)	0.762
Sex[b]	1.75 (1.39, 2.20)	<0.0001	1.76 (1.39, 2.24)	<0.0001	1.48 (0.49, 4.51)	0.487

Note: Analysis performed using multivariable GEE, with three distinct models. Cardiovascular autonomic neuropathy is defined as 2 or more abnormal HRV measures.

[a]Compared to under/normal/overweight BMI reference group.

[b]Compared to male reference group.

TABLE 3 Factors associated with cardiovascular autonomic neuropathy in youth using all available time points

	Univariate		Adjusted for HbA_{1c} and BMI SDS		Multivariable model	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Type 2 diabetes versus type 1 diabetes	2.65 (1.68, 4.20)	<0.0001	2.24 (1.28, 3.91)	0.005	2.53 (1.46, 4.38)	0.001
Hypertension	2.33 (1.81, 3.00)	<0.0001	2.11 (1.61, 2.77)	<0.0001	1.94 (1.47, 2.55)	<0.0001
Albuminuria	1.96 (1.28, 3.01)	0.002	1.66 (1.04, 2.66)	0.034	1.66 (1.05, 2.61)	0.031
Retinopathy	1.82 (1.47, 2.25)	<0.0001	1.65 (1.32, 2.07)	<0.0001	1.29 (1.02, 1.63)	0.031
Early elevation of AER	1.50 (1.23, 1.84)	<0.0001	1.36 (1.11, 1.68)	0.004	1.37 (1.11, 1.69)	0.003

Note: Multivariable model: adjusted for HbA_{1c} and BMI SDS + age, and female sex. Cardiovascular autonomic neuropathy is defined as 2 or more abnormal HRV measures.

Abbreviations: AER, albumin excretion rate; SDS, standardized deviation score.

with type 2 diabetes. CAN was associated with BMI and obesity across diabetes types, and with HbA_{1c}. In one of the largest comparative studies in youth with diabetes to date, we also found a higher frequency of other complications in youth with type 2 versus type 1 diabetes, despite fewer per participant complication assessments, including peripheral nerve abnormality, early elevation of AER, albuminuria, and hypertension. Our study highlights the early development of chronic complications in youth with type 2 versus type 1 diabetes[2–4] and the need to target modifiable risk factors including overweight/obesity.

This longitudinal study supports our smaller previous cross-sectional study that reported a higher frequency of CAN and other complications in youth with type 2 diabetes.[16] In the SEARCH for Diabetes in Youth Study, the frequency of CAN (when defined as ≥3 abnormal HRV indices) was higher in young people with type 2 compared to type 1 diabetes (17% vs. 12%).[15] It is unclear why the frequency is much higher in our study (47% vs. 27% when defined as ≥2 abnormal HRV indices). When ≥3 abnormal HRV indices were used to define CAN in the present study, the frequency of CAN in youth with type 2 compared to type 1 remained high (41% vs. 22%). We speculate this may be due to differences in population demographics, CAN diagnostic criteria and more sensitive HRV measurement. In our study, youth with type 1 or type 2 diabetes and CAN had higher SBP, DBP, total cholesterol and triglycerides, and higher frequency of albuminuria compared to those without CAN, which is similar to participants from SEARCH.[15] However, we also demonstrate associations between CAN, type 2 diabetes and microvascular complications. Taken together, both studies highlight the importance of targeting modifiable risk factors such as blood pressure and dyslipidaemia in cardiovascular disease prevention.

The frequency of CAN in young people with diabetes varies considerably in published studies and is therefore difficult to generalize. In our systematic review of young people with type 1 diabetes, the frequency of CAN in 19 studies ranged from 16% to 75% (21% using HRV); the lack of standard definition, number of tests to define abnormal HRV and differences in testing methods may have contributed to heterogeneity in the reported frequency.[25] Among young people with type 2 diabetes, the reported frequency of CAN ranges from 8.1% to 54%.[4,14–16] Currently, there is no widely accepted criterion nor standard testing modality for the diagnosis of CAN,[7] which may explain the high variance in reported frequency in studies of young people with diabetes and CAN.

The gold standard for the diagnosis of CAN is via cardiovascular reflex tests,[7] however HRV can be used to detect CAN even when asymptomatic.[22] Therefore, early assessment of CAN via measurement of HRV could be used as a screening tool for youth with diabetes or pre-diabetes, in particular individuals with additional risk factors, to identify those with increased cardiovascular risk. However, we recognize that such screening may be difficult in clinical settings.

As we found associations between CAN, its risk factors and vascular complications, treatment of modifiable risk factors should be implemented to reduce cardiovascular risk and slow CAN progression. Management of CAN in youth with type 1 or type 2 diabetes requires a multifactorial approach for those who present with multiple diabetes-associated comorbidities such as hypertension, albuminuria and peripheral nerve abnormalities and obesity, as seen in our cohort. Furthermore, management should also include blood glucose control for those with type 1 diabetes and targeting severe obesity for those with type 2 diabetes. Weight loss in adults with type 2 diabetes improves HRV,[26] however randomized trials are needed to evaluate the efficiency of weight loss on CAN in young people with diabetes.

Our study is the first to demonstrate an association between obesity or severe obesity in the development of CAN among youth with both type 1 and type 2 diabetes. In a longitudinal study of adolescents and young adults with type 1 diabetes, lower HRV was associated with overweight/obesity, higher BMI SDS and central adiposity,[13] and in young adults with type 2 diabetes from the TODAY study, lower HRV was associated with higher BMI.[14] Higher BMI is associated with CAN development in children with overweight or obesity without diabetes.[11,12] In our study, there was no difference in the prevalence of CAN and other diabetes complications by BMI categories in youth with type 2 diabetes and is likely due to most youth with type 2 diabetes falling in to either the obesity or severe obesity BMI categories. However, our data from GEE suggest higher BMI plays an important predictive role in the development of CAN in young people with diabetes, whereby young people with type 2 diabetes and severe obesity are at greatest risk.

Inflammation may play a role in mediating the association observed between increased BMI and CAN.[9,26] In our recent cross-sectional study of youth with type 1 diabetes and type 2 diabetes, inflammatory markers, including hsCRP, were highest in those with obesity compared to underweight, normal, and overweight BMI.[16] Children with severe obesity without diabetes also have elevated CRP.[27] In the present study, CRP was significantly higher in those with type 2 diabetes compared to type 1 diabetes. These CRP levels are of concern as they exceeded 3 mg/L, which is considered high risk for cardiovascular complications in adults.[28] In GEE, CAN was associated with CRP in youth with type 1 diabetes ($p < 0.001$), but not in type 2 diabetes ($p = 0.452$). This finding is likely due to the higher CRP levels in youth with type 2 diabetes compared with youth with type 1 diabetes, in parallel with the high frequency of obesity and severe obesity among youth with type 2 diabetes in our cohort.

A strength of our study was the comparison of CAN frequency between diabetes types in a large youth population, and the demonstration of important modifiable risk factors for developing CAN. Other risk factors such as smoking status and waist circumference were not measured, and we did not analyze participant ethnicity. We were unable to match participants for age and sex, but potential variables were adjusted for in multivariable analysis. Although our cohort consists of a large number of youth with type 1 diabetes, we acknowledge the smaller number of youth with type 2 diabetes and therefore our findings should be interpreted with caution. In our study of >10 years, a single technician reviewed all HRV traces from a single site. We also used seven HRV domains to diagnose individuals with CAN, which differs from other studies using five[4,15] or six[14] and may have affected the frequency of CAN in our population. Additional measures of oxidative stress, in particular TNFα, IL-6, and hsCRP, would provide greater insight to the pathophysiology of CAN and its interaction with diabetes.

5 | CONCLUSIONS

Compared to type 1, youth with type 2 diabetes have higher frequency of CAN, despite shorter diabetes duration and younger age, and present with more vascular complications. Our findings highlight the importance of implementing strategies that target modifiable risk factors for CAN across both diabetes types such as obesity, albuminuria, hypertension, and peripheral nerve abnormality, as well as HbA_{1c} in youth with type 1 diabetes to reduce cardiovascular risk and CAN progression. Further research is needed to determine the impact of early screening of CAN on treatment outcomes and to better understand the role of inflammation in the development of CAN in youth with diabetes. Standardization for the diagnosis of CAN is needed to allow for appropriate comparisons.

AUTHOR CONTRIBUTIONS

Alison Pryke, Janine Cusumano, Yoon Hi Cho, Maria E. Craig, and Kim C. Donaghue were involved in recruitment/data collection. Benjamin J. Varley analysed the data. Benjamin J. Varley, Megan L. Gow, Kim C. Donaghue, and Maria E. Craig were involved the interpretation of the data. Benjamin J. Varley drafted the initial manuscript and revisions and final approval of manuscript were performed by Benjamin J. Varley, Megan L. Gow, Yoon Hi Cho, Paul Benitez-Aguirre, Janine Cusumano, Alison Pryke, Albert Chan, Vallimayil Velayutham, Kim C. Donaghue, and Maria E. Craig. All authors had full access to the data in this study and accept responsibility for the decision to submit for publication. Benjamin J. Varley and Maria E. Craig verified the data, and Maria E. Craig is guarantor of this work.

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CONFLICT OF INTEREST

All authors declare no conflict of interest.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

Data from this study will not be made available because accessing patient level data requires an application and permissions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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