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The association of physical activity to oral glucose tolerance test outcomes in multiple autoantibody positive children: The TEDDY Study

Suzanne Bennett Johnson[1] | Roy Tamura[2] | Kerry L. McIver[3] | Russell R. Pate[3] | Kimberly A. Driscoll[4] | Jessica Melin[5] | Helena Elding Larsson[5,6] | Michael J. Haller[7] | Jimin Yang[2] | the TEDDY Study Group

[1]Department of Behavioral Sciences and Social Medicine, Florida State University College of Medicine, Tallahassee, Florida, USA

[2]Health Informatics Institute, University of South Florida, Tampa, Florida, USA

[3]Department of Exercise Science, Arnold School of Public Health, University of South Carolina, Columbia, South Carolina, USA

[4]Department of Clinical and Health Psychology, School of Public Health and Health Professions, University of Florida, Gainesville, Florida, USA

[5]Department of Clinical Sciences, Lund University, Malmö, Sweden

[6]Department of Paediatrics, Skane University Hospital, Malmö, Sweden

[7]Department of Pediatrics, College of Medicine, University of Florida, Gainesville, Florida, USA

Correspondence
Suzanne Bennett Johnson, Department of Behavioral Sciences and Social Medicine, Florida State University College of Medicine, Tallahassee, FL, USA.
Email: suzanne.johnson@med.fsu.edu

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Abstract

Objective: To examine the association of physical activity (PA), measured by accelerometry, to hemoglobin AIC (HbA1c) and oral glucose tolerance test (OGTT) outcomes in children who were multiple persistent confirmed autoantibody positive for type 1 diabetes (T1D).

Methods: The Environmental Determinants of Diabetes in the Young (TEDDY) multinational study followed children from birth. Children ≥3 years of age who were multiple persistent confirmed autoantibody positive were monitored by OGTTs every 6 months. TEDDY children's PA was measured by accelerometry beginning at 5 years of age. We examined the relationship between moderate plus vigorous (mod + vig) PA, HbA1c, and OGTT in 209 multiple autoantibody children who had both OGTT and PA measurements.

Results: Mod + vig PA was associated with both glucose and C-peptide measures (fasting, 120-min, and AUC); higher mod + vig PA was associated with a better OGTT response primarily in children with longer duration of multiple autoantibody positivity. Mod + vig PA also interacted with child age; lower mod + vig PA was associated with a greater increase in C-peptide response across age. Mod + vig PA was not related to fasting insulin, HOMA-IR or HbA1c.

Conclusions: The OGTT is the gold standard for diabetes diagnosis and is used to monitor those at high risk for T1D. We found higher levels of mod + vig PA were associated with better OGTT outcomes in children ≥5 years of age who have been multiple autoantibody positive for longer periods of time. Physical activity should be the focus of future efforts to better understand the determinants of disease progression in high-risk children.

KEYWORDS
multiple autoantibody positive, OGTT, physical activity

Additional member of the TEDDY Study Group and their affiliations are available online in the electronic supplemental materials.

1 | INTRODUCTION

Physical activity (PA) is associated with insulin sensitivity in both children[1–4] and adults.[5] PA is recommended for people with both type 1 and type 2 diabetes and for those with glucose intolerance but not yet diagnosed with type 2 diabetes.[6,7] The overload hypothesis suggests that both overweight and sedentary behavior may play a role in the development of type 1 diabetes (T1D).[8] However, the possible role of PA in the development of T1D has yet to be determined.

The Environmental Determinants of Diabetes in the Young (TEDDY) study seeks to identify environmental triggers of T1D in genetically at-risk children followed from birth to 15 years of age. The study protocol includes annual PA assessment via accelerometry from 5 to 10 years, with continued annual PA assessments for children positive for T1D-related autoantibodies thereafter. Children ≥3 years of age who are multiple autoantibody positive are given an oral glucose tolerance test (OGTT) every 6 months.

OGTTs are commonly used to measure possible disease progression in individuals at high risk for T1D.[9–11] However, the possible role of PA to OGTT response in high-risk individuals has not been extensively studied. The average number of minutes engaged in moderate to vigorous (mod + vig) PA using accelerometers was estimated in first degree relatives of individuals with T1D who were given an OGTT.[12] Mod + vig PA was inversely related to both insulin and C-peptide response to the glucose challenge; those with higher mod + vig PA had lower insulin and C-peptide levels at 120 min and as measured by area under the curve (AUC).

The purpose of this study was to examine the association of PA, objectively measured by accelerometry, to OGTT response in children who are multiple autoantibody positive for T1D.

1.1 | The TEDDY Study

Children with T1D-related human leucocyte antigen (HLA) genotypes were identified at birth at three sites in the United States (Colorado, Georgia/Florida, and Washington) and three sites in Europe (Finland, Germany, and Sweden). HLA eligible children were invited to participate in TEDDY, a natural history study seeking to identify environmental triggers of T1D in genetically at-risk children followed for 15 years. Written informed consents were obtained from parents of all participants and the study was approved by each site's institutional review or ethics board. Participating children are regularly tested for diabetes-related autoantibodies, children's height and weight are measured, and other biologic specimens (e.g., nasal swabs, urine, and fecal matter) are collected. Questionnaires and interviews with parents assess other environmental exposures (e.g., diet and stress). The TEDDY design and protocol has been extensively described elsewhere.[13–15]

1.2 | Study sample

TEDDY children are regularly tested for autoantibodies against insulin (IAA), GAD (GADA) and insulinoma-associated protein 2 (IA-2A). The assay methods have been published elsewhere.[16] Beginning at 3 years of age, children with two or more autoantibodies are placed on an every 6-months OGTT protocol. Beginning at 5 years of age, children's PA is assessed annually using accelerometry until 10 years of age and annually thereafter in all autoantibody positive children. Children are considered persistent confirmed multiple autoantibody positive if they are positive for at least two of three autoantibodies (IAA, GADA, and IA-2A) on two consecutive occasions, 3–6 months apart at both certified autoantibody testing laboratories. As of February 28, 2021, there were 340 children with persistent confirmed multiple autoantibodies with at least one OGTT assessment who had reached the 5-year study window. Of these, 209 also had a PA measurement and are the focus of the current study.

1.3 | PA assessment

Annually, starting from the 5-year study clinic visit, children were asked to wear an ActiGraph accelerometer (model GT3X+, Fort Walton Beach, FL) around their waist, during all waking hours, exclusive of water activities, for at least 7 days. Days on which a child had 8+ hours of wear time were considered valid and children had to have at least three valid days to be included in the analysis. Data were averaged across days and age-specific cut-points[17,18] were used to determine the average amount of time a child spent in light, moderate, and vigorous PA. The current analysis focused on moderate to vigorous (mod + vig) PA. A subsequent analysis using total PA did not improve the analytic models and is not presented here.

1.4 | OGTT and measurement of hemoglobin A1c

The TEDDY protocol includes an OGTT every 6 months for multiple autoantibody children ≥3 years of age. Children are asked to come in fasting and to consume an oral glucose dose of 1.75 g/kg body weight (to a maximum of 75 g) in a solution of flavored water within 5 min. Before 2016, the TEDDY protocol used a two-time point OGTT (0 and 120 min). A protocol change occurred in March 2016, when the six-time point (−10, 0, 30, 60, 90, and 120) OGTT was recommended. However, families were permitted to complete a two-time point protocol instead of the six-time point protocol and many did. The two-time point protocol consists of a venous glucose sample at time 0 and 120 min; a capillary glucose is permitted at 120 min. Available samples permitted analysis of fasting glucose, fasting insulin, fasting C-peptide and 120-min glucose and glucose AUC. Insulin resistance was measured by homeostasis model assessment (HOMA-IR) using fasting glucose and fasting insulin.[19] Sufficient venous samples were available to measure 120-min C-peptide in 164 children and C-peptide AUC in 162 children. There were insufficient venous samples to measure 120-min insulin or insulin AUC. Samples were sent to a central TEDDY OGTT laboratory for processing.

A whole blood sample for HbA1c assay is collected at each clinic visit for all children who have tested positive for at least one

autoantibody at the 9-month visit or later and sent to the TEDDY HbA1c measurement laboratory. This analysis used the HbA1c measurement collected at the same time as the OGTT.

1.5 | Data analysis

Each PA assessment was assigned to the OGTT visit closest in time (mean of 10 days, median 1 day a part). Since OGTT measures were collected at a greater frequency than PA, we imputed PA for certain visits that had an OGTT but were missing a PA record. However, imputation was limited to those children who had at least two PA measurement time points and the imputation was only done between those two time points. The imputation was done linearly for each category of activity (light, moderate, and vigorous) as a function of time between the two PA measurements. No imputation was conducted for children with only a single PA measurement time point nor before the first PA measurement time point or after the last PA measurement time point. Imputation was possible for 110 children. The mean number of PA/OGTT observations per child was 2.4 with a range from 1 to 9.

Linear mixed effect models for longitudinal data were used to test for the association of mod + vig PA as a time-dependent variable with the longitudinal study outcomes: Fasting Glucose, 120-min Glucose, Glucose AUC, HbA1c, Fasting Insulin, HOMA-IR, Fasting C-peptide, 120-min C-peptide, and C-peptide AUC. Fixed covariates included: country, sex, and HLA (DR3/4: yes vs. no). Time-dependent covariates included: BMIz score, child age, duration since the child became persistent confirmed multiple autoantibody positive, and average accelerometer wear time. Child age and duration since the child became persistent confirmed multiple autoantibody positive were considered to vary randomly across subjects. Possible interactions between mod + vig PA and the study covariates were explored.

2 | RESULTS

The characteristics of the sample of persistent confirmed multiple autoantibody positive children who have reached the 5-year study window and who have at least one OGTT as well as the subsample of these children with both an OGTT and a PA assessment are shown in Table 1. The groups are similar, suggesting the OGTT/PA subsample is representative of the larger sample of multiple autoantibody children at least 5 years of age in TEDDY.

The descriptive statistics for the PA measures and study outcome measures for our targeted group of 209 children at the time of their first PA assessment associated with an OGTT are provided in Table 2. Children spent most of their time in sedentary (Mean = 54.3% of wear time) or light activity (Mean = 35.7% of wear time) and little in vigorous activity (Mean = 1% of wear time). On average, they spent 101 min per day in mod + vig PA (Mean = 10.0% of wear time). However, there was considerable variability across children. The sample means for glucose and insulin/C-peptide OGTT outcomes and HbA1c were within the normal reference ranges.[20–22] However, there was considerable variability across the sample in both glucose and insulin-related study outcomes.

TABLE 1 Characteristics of multiple autoantibody study sample[a]

	≥1 OGTT (*N* = 340)	≥1 OGTT plus ≥1 PA measurement (*N* = 209)
Country		
United States	116 (34%)	69 (33%)
Finland	89 (26%)	52 (25%)
Germany	16 (5%)	12 (6%)
Sweden	119 (35%)	76 (36%)
Sex		
Female	141 (42%)	78 (37%)
Male	199 (58%)	131 (63%)
HLA		
DR3/4	177 (52%)	106 (51%)
DR4/4	82 (24%)	49 (23%)
DR4/8	45 (13%)	33 (16%)
DR3/3	28 (8%)	14 (7%)
Other	8 (2%)	7 (3%)
BMIz score at first OGTT/OGTT + PA assessment		
Mean (SD)	0.2 (1.1)	0.1 (1.1)
Median	0.3	0.2
Range	−3.4 to 2.5	−3.3 to 2.4
Age at first OGTT/OGTT + PA assessment (years)		
Mean (SD)	6.9 (2.3)	7.5 (2.3)
Median	5.8	7.1
Range	4.7–14.5	4.9–14.1
Age became persistent confirmed multiple autoantibody positive (years)		
Mean (SD)	5.3 (3.2)	4.9 (2.9)
Median	4.5	4.0
Range	0.5–14.0	0.5–13.0
Duration of multiple autoantibody positivity at first OGGT/OGTT + PA assessment (years)		
Mean (SD)	1.6 (1.5)	2.6 (2.0)
Median	1.0	2.2
Range	0–6.7	0–9.3

Abbreviations: HLA, human leucocyte antigen; OGGT, oral glucose tolerance test; PA, physical activity.

[a]Study sample was restricted to multiple autoantibody children at or after the 5-year assessment because physical activity assessment was started at the 5-year assessment window.

Correlations between the study outcome measures showed that fasting Glucose correlated as well with the fasting insulin measures (Fasting Insulin, Fasting C-peptide, and HOMA-IR) as it did with Glucose AUC (Table 3). HOMA-IR and Fasting insulin were extremely highly correlated in this sample ($r = 0.99$). As expected, 120-min Glucose was highly correlated with Glucose AUC ($r = 0.82$) and 120-min C-Peptide was highly correlated with C-peptide AUC ($r = 0.90$).

TABLE 2 Physical activity and study outcome measures at first physical activity assessment associated with an OGTT

	N	Mean (SD)	Range
Physical activity (average minutes per day)			
Wear time	209	1032 (162)	643–1328
Sedentary	209	568 (151)	213–913
Light	209	363 (55)	209–533
Moderate	209	89 (43)	12–231
Vigorous	209	12 (9)	0–45
Moderate + vigorous	209	101 (49)	12–261
Study outcomes			
Fasting glucose (mg/dl)	209	88 (10)	60–128
120-min glucose (mg/dl)	200	112 (32)	47–252
Glucose AUC (mg/dl)	200	105 (23)	61–227
Hemoglobin A1	197	5.27 (0.29)	4.7–6.4
Fasting insulin (mcU/ml)	196	4.46 (2.71)	0.5–14.3
HOMA-IR	196	1.00 (0.65)	0.08–3.50
Fasting C-peptide (ng/ml)	197	0.99 (0.52)	0.06–3.93
120-min C-peptide (ng/ml)	117	4.16 (1.98)	0.98–12.34
C-peptide AUC (ng/ml)	114	3.12 (1.78)	0.94–10.32

Abbreviations: AUC, area under the curve; OGGT, oral glucose tolerance test.

TABLE 3 Correlations between study outcome measures at first physical activity assessment associated with an OGTT

Study outcome	Fasting glucose	120 min glucose	Glucose AUC	HbA1c	Fasting insulin	HOMA-IR	Fasting C-peptide	120-min C-peptide
120-min glucose	0.16							
Glucose AUC	0.39**	0.82**						
HbA1c	0.29**	0.44**	0.42**					
Fasting insulin	0.45**	−0.04	0.22*	0.01				
HOMA-IR	0.55**	−0.01	0.26**	0.05	0.99**			
Fasting C-peptide	0.41**	−0.01	0.20*	0.05	0.76**	0.76**		
120-min C-peptide	0.25*	0.35**	0.46**	0.00	0.67**	0.65**	0.62**	
C-peptide AUC	0.26*	0.24*	0.55**	−0.04	0.67**	0.66**	0.66**	0.90**

Abbreviations: AUC, area under the curve; OGTT, oral glucose tolerance test.
*$p < 0.01$. **$p < 0.001$.

Glucose AUC and C-peptide AUC were moderately related ($r = 0.55$). In contrast, HbA1c only correlated with the other glucose measures.

Table 4 provides the results of the mixed models testing the association of mod + vig PA to the glucose-related outcomes. Significant covariates included Country (Fasting Glucose only), BMIz score (Fasting Glucose only), and Child Age (Fasting Glucose and Glucose AUC). Duration of Multiple Autoantibody Positivity was significant in all models but interacted with mod + vig PA in its association with Fasting Glucose, 120 min Glucose and Glucose AUC; higher mod + vig PA was associated with lower glucose levels in children who had been multiple antibody positive for longer periods of time. Figure 1A illustrates the predicted Glucose AUC for children at age 8 who vary in both mod + vig PA and duration of multiple autoantibody positivity. For children who had been multiple autoantibody positive for only 1 year, there was little difference in Glucose AUC between those with low (30 min) versus high (120 min) mod + vig PA. In contrast, for children who had been multiple autoantibody positive for 5 years, Glucose AUC was significantly lower for those with high (120 min) compared to those with low (30 min) mod + vig PA. Also noteworthy is the higher Glucose AUC in children with 5 years multiple autoantibody duration compared to children with 1 year multiple autoantibody duration for those with low (30 min) mod + vig PA. This difference was far less for children with high (120 min) mod + vig PA.

Mod + vig PA was not related to HbA1c in the study sample. In fact, the only variable associated with HbA1c was Duration of

TABLE 4 Linear mixed model results for moderate + vigorous physical activity associations with glucose-related study outcomes

	Fasting glucose ($n = 209$)		120 min glucose ($n = 206$)		Glucose AUC ($n = 206$)		HbA1c ($n = 202$)	
	B (SE)	*p* value	*B* (SE)	*p* value	*B* (SE)	*p* value	*B* (SE)	*p* value
Intercept	76.1 (4.4)	<0.001	86.7 (17.4)	<0.001	54.4 (12.2)	<0.001	5.1 (0.1)	<0.001
Country (Ref = USA)		0.002		0.324		0.421		0.135
Finland	3.6 (1.5)		−3.8 (5.8)		−2.5 (4.0)		0.076 (0.051)	
Germany	−6.0 (2.6)		−18.3 (9.9)		−11.6 (7.0)		0.121 (0.099)	
Sweden	2.0 (1.4)		−4.1 (5.2)		−2.6 (3.7)		0.102 (0.046)	
Sex (Ref = Female)	1.2 (1.2)	0.338	−2.4 (4.7)	0.613	−0.3 (3.4)	0.918	−0.039 (0.041)	0.351
HLA (Ref = NOT DR3/4)	1.6 (1.1)	0.172	4.7 (4.3)	0.287	3.2 (3.4)	0.302	0.045 (0.039)	0.244
BMIz score	1.7 (0.4)	<0.001	1.5 (1.5)	0.330	0.7 (1.1)	0.500	0.005 (0.010)	0.631
Child age	1.0 (0.4)	0.016	1.2 (1.6)	0.448	4.9 (1.2)	<0.001	0.008 (0.012)	0.501
Duration of multiple autoantibody positivity (MA+)	0.9 (0.4)	0.011	5.9 (1.5)	<0.001	4.2 (1.1)	<0.001	0.051 (0.012)	<0.001
Accelerometer wear time	−0.00 (0.00)	0.639	0.01 (0.01)	0.421	0.01 (0.01)	0.399	−0.00 (0.00)	0.958
Moderate + vigorous physical activity (mod + vig PA)	−0.00 (0.03)	0.930	0.12 (0.10)	0.258	0.15 (0.07)	0.031	−0.00 (0.00)	0.640
Mod + vig PA × age	0.004 (0.004)	0.311	−0.10 (0.016)	0.535	−0.018 (0.012)	0.127	0.00 (0.00)	0.963
Mod + vig PA × duration of MA+	−0.009 (0.004)	0.035	−0.035 (0.016)	0.026	−0.023 (0.011)	0.041	0.00 (0.00)	0.972

Note: *n* = number of subjects in analysis, *B* represents the estimate from the model and SE represents its estimated standard error.
Abbreviations: AUC, area under the curve; HLA, human leucocyte antigen; PA, physical activity.

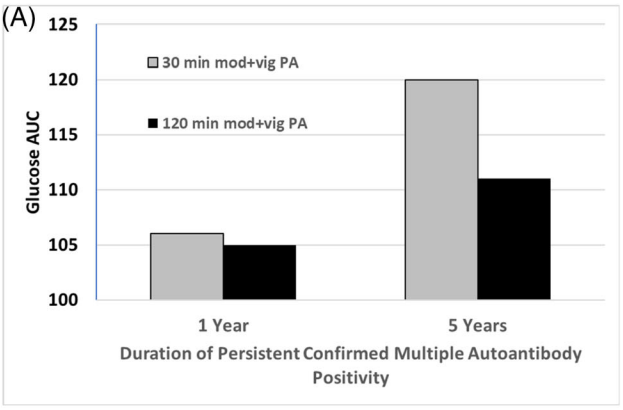

Figure estimates are based on the regression equation for Glucose AUC provided in Table 4. The remaining covariates are held constant for illustration purposes as follows: Country = US; Sex = female; HLA = NOT DR3/4; BMIz = 0; Age = 8; Accelerometer wear time = 900 minutes

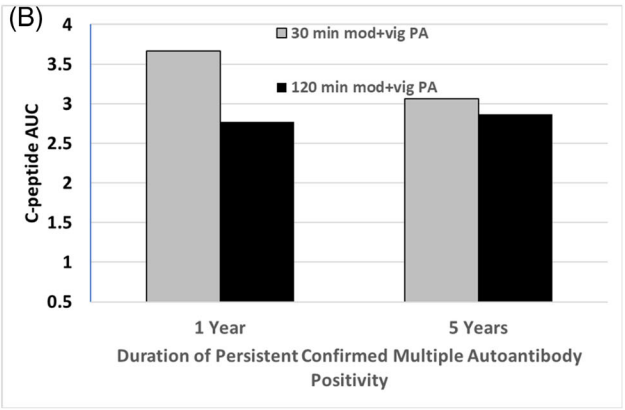

Figure estimates are based on the regression equation for C-peptide AUC provided in Table 5. The remaining covariates are held constant for illustration purposes as follows: Country = US; Sex = female; HLA = NOT DR3/4; BMIz = 0; Age = 8; Accelerometer wear time = 900 minutes

FIGURE 1 (A) The association of low (30 min) and high (120 min) moderate + vigorous physical activity (mod + vig PA) to glucose AUC for children with short (1 year) versus long (5 years) duration of multiple autoantibody positivity. (B) The association of low (30 min) and high (120 min) moderate + vigorous physical activity (mod + vig PA) to C-peptide AUC for children with short (1 year) versus long (5 years) duration of multiple autoantibody positivity. AUC, area under the curve; PA, physical activity

Multiple Autoantibody Positivity; the longer the duration, the higher the HbA1c.

Table 5 provides the results of the mixed models testing the association of mod + vig PA to the insulin-related outcomes. BMIz score was a significant covariate in all models; higher BMIz scores were associated with higher Fasting Insulin, HOMA-IR, Fasting C-peptide, 120-min C-peptide and C-peptide AUC. Longer duration of Multiple Autoantibody Positivity was associated with lower 120-min C-peptide and lower C-peptide AUC. However, Duration of Multiple Autoantibody Positivity interacted with mod + vig PA; the difference in C-

TABLE 5 Linear mixed model results for moderate + vigorous physical activity associations with insulin-related study outcomes

	Fasting insulin mcU/ml × 100 ($n = 201$)		HOMA-IR ($n = 201$)		Fasting C-peptide ng/ml × 100 ($n = 202$)		120-min C-peptide ng/ml × 100 ($n = 164$)		C-peptide AUC × 100 ($n = 162$)	
	B (SE)	*p* value	*B* (SE)	*p* value	*B* (SE)	*p* value	*B* (SE)	*p* value	*B* (SE)	*p* value
Intercept	−36.1 (119.6)	0.774	−0.28 (0.31)	0.359	4.3 (19.0)	0.819	192.7 (80.4)	0.017	−69.9 (62.6)	0.254
Country (Ref = USA)		0.148		0.071		0.652		0.052		0.147
Finland	50.7 (34.4)		0.15 (0.09)		−5.6 (5.7)		−42.0 (26.0)		−34.6 (20.7)	
Germany	−78.6 (59.6)		−0.22 (0.15)		−5.6 (9.8)		−81.6 (48.8)		−37.7 (38.7)	
Sweden	20.0 (32.8)		0.06 (0.08)		−6.3 (5.4)		−63.3 (24.3)		−42.9 (19.5)	
Sex (Ref = Female)	−17.1 (29.4)	0.561	−0.03 (0.07)	0.726	−5.5 (4.8)	0.255	−17.0 (21.5)	0.430	−5.7 (17.2)	0.741
HLA (Ref = NOT DR3/4)	−3.7 (26.7)	0.891	0.01 (0.07)	0.902	−2.3 (4.4)	0.596	3.6 (20.0)	0.858	−2.0 (16.0)	0.899
BMIz score	73.7 (10.2)	<0.001	0.19 (0.03)	<0.001	10.9 (1.6)	<0.001	19.7 (6.6)	0.003	17.2 (5.1)	<0.001
Child age	71.3 (11.8)	<0.001	0.18 (0.03)	<0.001	15.8 (1.9)	<0.001	43.3 (8.0)	<0.001	62.1 (6.3)	<0.001
Duration of multiple autoantibody positivity (MA+)	−13.4 (10.7)	0.212	−0.02 (0.03)	0.399	−4.5 (1.7)	0.009	−24.3 (7.1)	<0.001	−21.3 (5.6)	<0.001
Accelerometer wear time	0.03 (0.07)	0.653	0.00 (0.00)	0.786	0.00 (0.01)	0.840	0.02 (0.05)	0.725	−0.01 (0.04)	0.779
Moderate + vigorous physical activity (mod + vig PA)	0.50 (0.75)	0.507	0.00 (0.00)	0.367	0.31 (0.12)	0.009	0.50 (0.51)	0.319	1.2 (0.4)	0.003
Mod + vig PA × age	−0.16 (0.12)	0.177	−0.00 (0.00)	0.182	−0.06 (0.02)	<0.001	−0.21 (0.08)	0.006	−0.3 (0.06)	<0.001
Mod + vig PA × duration of MA+	0.02 (0.12)	0.849	−0.00 (0.00)	0.969	0.03 (0.02)	0.162	0.18 (0.08)	0.020	0.2 (0.06)	0.002

Note: n = number of subjects in analysis, *B* represents the estimate from the model and SE represents its estimated standard error.
Abbreviations: AUC, area under the curve; HLA, human leucocyte antigen; PA, physical activity.

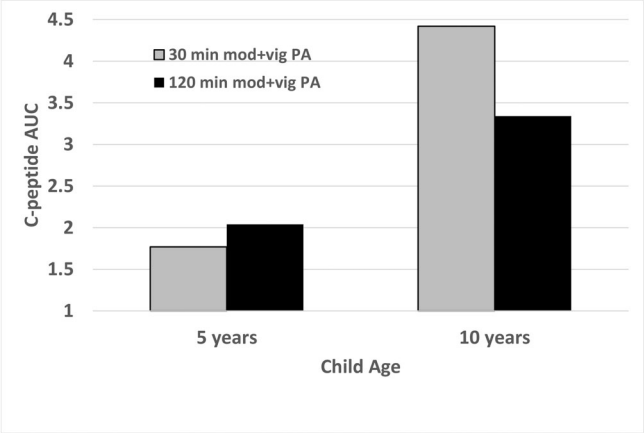

Figure estimates are based on the regression equation for C-peptide AUC provided in Table 5. The remaining covariates are held constant for illustration purposes as follows: Country = US; Sex = female; HLA = NOT DR3/4; BMIz = 0; Duration of Multiple Autoantibodies = 3; Accelerometer wear time = 900 minutes

FIGURE 2 The association of low (30 min) and high (120 min) moderate + vigorous physical activity (mod + vig PA) to C-peptide AUC for children at 5 and 10 years of age. AUC, area under the curve; PA, physical activity

peptide response between children with short versus long multiple autoantibody duration was seen primarily in children with low mod + vig PA. This effect is illustrated in Figure 1B. For children with 1 year multiple autoantibody duration, high (120 min) mod + vig PA was associated with lower C-peptide AUC compared to low (30 min) mod + vig PA. This was no longer the case for children who had been multiple autoantibody positive for 5 years. Noteworthy is the lower C-peptide AUC in the those with low (30 min) mod + vig PA at 5 years multiple autoantibody duration compared to 1 year. For this low mod + vig PA group, there were marked differences in both Glucose and C-peptide AUC at 5 years multiple autoantibody duration compared to 1 year; Glucose AUC is higher while C-peptide AUC is lower. These marked differences were not seen in those with high (120 min) mod + vig PA at 1 versus 5 multiple autoantibody duration (see Figure 1A,B).

Child age was also a significant covariate in all models with insulin-related outcomes. However, child age also interacted with mod + vig PA in its association with the three C-peptide measures; the association of higher mod + vig PA with lower C-peptide levels was seen primarily in older children. Figure 2 illustrates this interaction for children at 5 and 10 years of age who vary in time spent in low (30 min) versus high (120 min) mod + vig PA. At child-age 5 years, there were no differences in C-peptide AUC in those with low (30 min) versus high (120 min) mod + vig PA. As expected, C-peptide AUC increased for all children as they become older. However, this effect was most marked in children who had low (30 min) mod + vig PA.

Mod + vig PA was not related to Fasting Insulin or HOMA-IR although both were associated with child age and BMIz score; older age and higher BMIz scores were associated with higher Fasting Insulin and HOMA-IR.

In subsequent sensitivity tests, we considered the following alternative analyses: (1) only the observed PA visits were included and no imputation was done, (2) the duration of autoantibody positivity was changed from the start of the second antibody to the start of the first antibody, and (3) Sex and HLA were removed from the model. For all three sensitivity analyses, the results did not change appreciably except that when only observed PA data were included, standard errors were increased and significance levels decreased, supporting the use of imputed PA data. Although country was not a significant factor in any of the analyses except for Fasting Glucose—where Finland and Sweden had higher Fasting Glucose than the United States, we reran the models for Europe and the United States separately. The findings were similar although the significance levels were reduced due to the decrease in power associated with reduced sample sizes; we found no evidence of differential effects for Europe versus the United States.

3 | DISCUSSION

In this sample of multiple autoantibody positive children, mod + vig PA was associated with lower fasting glucose, lower 120-min glucose and lower glucose AUC in those who had been multiple autoantibody positive for longer periods of time. Our findings suggest that the association of mod + vig PA to glucose outcomes (fasting glucose, 120-min glucose, and glucose AUC) may be stronger in multiple autoantibody children than antibody negative first-degree relatives or those who are not at risk for T1D. The fact that the association was strongest in those who had been multiple autoantibody positive for longer periods of time suggests that PA might contribute to slowing the disease progression in at least some very high-risk children. However, we cannot conclude such a causal role for PA based on the correlational analyses presented herein. Our findings are novel and appear different from other studies of healthy school-aged children that found no association between PA measured by accelerometry and fasting glucose.[2,23,24,26,27,29–31] The only study using accelerometry with children at risk for T1D, defined by their relationship to a first degree relative with the disease, also did not find an association between PA and fasting glucose.[12] That study also did not find any association between PA and 120-min glucose or glucose AUC.

While prior studies of healthy school-age children have not found an association between PA and fasting glucose, associations between PA and fasting insulin, or between PA and HOMA-IR, are common[3,23–32]; higher PA is associated with lower fasting insulin or HOMA-IR. In our study, mod + vig PA was not related to fasting insulin or HOMA-IR but was related to fasting C-peptide, 120-min C-peptide, and C-peptide AUC; particularly in older children, higher mod + vig PA was associated with lower C-peptide levels. Ungethum et al.[12] study of 9–14 year old children who were offspring or siblings of patients with T1D also did not find an association between PA and fasting insulin or HOMA-IR. However, consistent with our results, they found 120-min C-peptide as well as C-peptide AUC were related

to PA. C-peptide is considered to be a better measure of beta cell function than insulin[20]; our findings support the greater sensitivity of C-peptide over insulin as a measurement strategy. In fact, when HOMA-IR was recalculated using C-peptide instead of insulin,[33] significant mod + vig PA findings emerged, similar to those found for fasting C-peptide (data not shown).

Children are known to decrease PA as they grow older.[17,27,34] Aging is also associated with an increase in insulin resistance.[35] In our high-risk sample, higher mod + vig PA was associated with lower fasting C-peptide and a better response to the OGTT in older children. These findings suggest that children who maintain higher mod + vig PA as they grow older, may be able to reduce age-related increases in insulin resistance, reducing stress on the pancreatic beta cells. Because our sample was limited to multiple autoantibody children we do not know if this association occurs in most children or is limited to those at very high-risk for T1D.

Mod + vig PA was also found to interact with duration of autoantibody positivity in its association with 120-min C-peptide and C-peptide AUC. In our sample, longer duration of multiple autoantibody positivity was strongly associated with a decline in C-peptide response to the OGTT in those with low mod + vig PA. In the healthy child, the increased insulin resistance associated with normal aging is managed by an increase in insulin production. However, in individuals with autoimmune destruction of beta cells in the pancreas, at some point the pancreas is unable to meet these demands and blood glucose rises in response. Our findings suggest—but certainly do not prove—that PA may slow or delay this process. The consistent association of mod + vig PA with both Glucose AUC and C-peptide AUC in individuals with long multiple autoantibody duration is intriguing and warrants further study.

The OGTT is considered the gold standard for diagnosis of diabetes and is commonly used to monitor those at risk for the disease. Both glucose and C-peptide measures have proved useful in predicting T1D onset in autoantibody positive individuals,[9–11] highlighting the importance of associations between mod + vig PA and fasting glucose, 120-min glucose, glucose AUC, and fasting C-peptide, 120-min C-peptide, and C-peptide AUC as reported herein. We also confirmed the association of both child age and BMIz score to C-peptide results, supporting prior work suggesting that any effort to identify C-peptide cut-points to classify individuals as having loss of beta-cell function must take these factors into account.[35]

In these children at high risk for T1D, mod + vig PA was not related to HbA1c. In fact, the only variable associated with HbA1c was duration of multiple autoantibody positivity; longer duration was associated with higher HbA1c. Compared to glucose and C-peptide measures in response to the OGTT, HbA1c may be a less sensitive predictor of T1D in high-risk subjects.[10]

Study strengths include the use of an objective measure of PA—accelerometry—in a very high-risk sample of multiple autoantibody children monitored by OGTT across time. To our knowledge no other published study has evaluated the potential role of PA in such high-risk children. We acknowledge that accelerometry is not a perfect measure of PA since certain activities are precluded (e.g., water sports). Further, the 3–7 days accelerometry annual data collection used in this study represents a limited sampling of the child's overall PA. Other study limitations include the sample's restriction to children 5 years of age or older and the fact that blood sampling limitations did not permit 120-min C-peptide or C-peptide AUC to be measured in all study children. However, significant findings emerged in the analyses of these measures despite limited sampling of PA and the reduced sample size.

Although multiple autoantibody children are at very high risk for T1D, the time between becoming multiple autoantibody positive and diagnosis with T1D is highly variable. Identifying factors that contribute to delay or rapid progression to disease diagnosis is critical. The results reported here suggest PA may be one factor worthy of consideration in future efforts to better understand the determinants of disease progression in high-risk children. Our next step in the TEDDY study is to examine the extent to which PA is associated with progression to clinical disease in this high risk population.

AUTHOR CONTRIBUTIONS

Suzanne Bennett Johnson conceptualized the study, contributed to data analysis and interpretation, collected relevant literature, and wrote the manuscript. Roy Tamura conducted the data analysis and helped write the manuscript. Kerry L. McIver and Russell R. Pate provided expertise on accelerometry data collection, analysis and interpretation, and reviewed the manuscript. Kimberly A. Driscoll and Jessica Melin provided input on OGTT data collection and interpretation and edited the final manuscript. Helena Elding Larsson, Michael J. Haller, and Jimin Yang helped conceptualize the study, contributed to data interpretation, and edited the final manuscript.

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CONFLICT OF INTEREST

The authors declare that there are no relationships or activities that might bias, or be perceived to bias, their work.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The datasets generated and analyzed during the current study will be made available in the NIDDK Central Repository at https://repository.niddk.nih.gov/studies/teddy.

PATIENT CONSENT/ETHICS STATEMENT

Written informed consents were obtained from parents of all participants and the study was approved by each site's institutional review or ethics board. Child assent was obtained when the children reached 7–12 years of age, with the age of assent varying by each site's institutional review or ethics board requirements.

ORCID

Suzanne Bennett Johnson https://orcid.org/0000-0001-5721-7524
Kimberly A. Driscoll https://orcid.org/0000-0002-3006-4633
Jessica Melin https://orcid.org/0000-0002-8858-2126
Michael J. Haller https://orcid.org/0000-0002-2803-1824

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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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