Diabetes Care
American Diabetes Association

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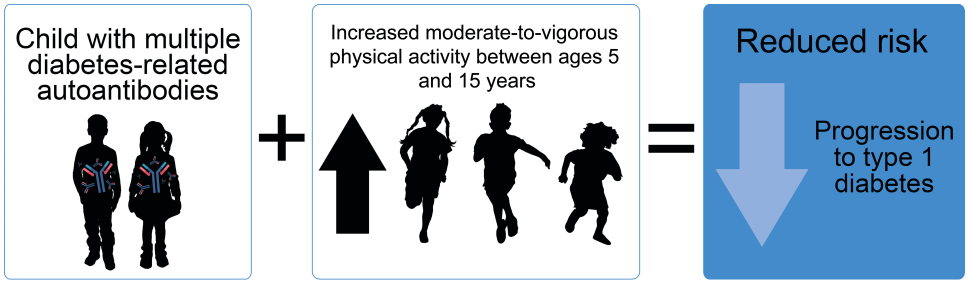
Diabetes Care 2023;46(7):1–8 | https://doi.org/10.2337/dc23-0036



ARTICLE HIGHLIGHTS

- An active lifestyle is known to benefit glycemic control and pancreatic islet cell functions.
- The association between time spent in moderate to vigorous physical activity and the development of type 1 diabetes was examined using longitudinal accelerometry data collected in the Environmental Determinants of Diabetes in the Young (TEDDY) study.
- Among children aged 5–15 years who had developed multiple autoantibodies, every 10-min increase in daily moderate to vigorous physical activity was associated with an 8% lower risk of progressing to type 1 diabetes.
- Study findings suggest physical activity could play an important role in slowing the progress of type 1 diabetes.

Physical Activity and the Development of Islet Autoimmunity and Type 1 Diabetes in 5–15-Year-Old Children Followed in the TEDDY Study

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ORIGINAL ARTICLE

OBJECTIVE

This study investigated physical activity and its association with the development of islet autoimmunity and type 1 diabetes in genetically at-risk children aged 5–15 years.

RESEARCH DESIGN AND METHODS

As part of the longitudinal Environmental Determinants of Diabetes in the Young (TEDDY) study, annual assessment of activity using accelerometry was conducted from age 5 years. Time-to-event analyses using Cox proportional hazard models were used to assess the association between time spent in moderate to vigorous physical activity per day and the appearance of one or several autoantibodies and progression to type 1 diabetes in three risk groups: *1*) 3,869 islet autoantibody (IA)-negative children, of whom 157 became single IA positive; *2*) 302 single IA–positive children, of whom 73 became multiple-IA positive; and *3*) 294 multiple IA–positive children, of whom 148 developed type 1 diabetes.

RESULTS

No significant association was found in risk group 1 or risk group 2. A significant association was seen in risk group 3 (hazard ratio 0.920 [95% CI 0.856, 0.988] per 10-min increase; $P = 0.021$), particularly when glutamate decarboxylase autoantibody was the first autoantibody (hazard ratio 0.883 [95% CI 0.783, 0.996] per 10-min increase; $P = 0.043$).

CONCLUSIONS

More daily minutes spent in moderate to vigorous physical activity was associated with a reduced risk of progression to type 1 diabetes in children aged 5–15 years who had developed multiple IAs.

A physically active lifestyle benefits glycemic control, and regular participation in exercise is an important aspect of disease management for people with either type 1 or type 2 diabetes and for those with glucose intolerance who are not yet diagnosed with type 2 diabetes (1). Type 1 diabetes differs from type 2 diabetes in that it has an autoimmune etiology and pathogenesis resulting in the destruction of insulin-producing islet β-cells in the pancreas. Besides the evidence that physical activity is associated with insulin sensitivity in children (2,3) and adults (4), exercise studies in autoimmune

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Received 6 January 2023 and accepted 13 April 2023

Clinical trial reg. no. NCT00279318, clinicaltrials.gov

This article contains supplementary material online at https://doi.org/10.2337/figshare.22647574.

*A complete list of members of the TEDDY Study Group can be found in supplementary material online.

conditions such as Graves' thyroid disease, psoriasis, and multiple sclerosis have demonstrated that physical activity has a direct positive effect on the autoimmune process beyond its impact on insulin sensitivity (5).

The Environmental Determinants of Diabetes in the Young (TEDDY) study seeks to identify environmental triggers of islet autoantibodies (IAs) that mark type 1 diabetes development and its clinical onset in genetically at-risk children followed from birth to 15 years of age (6). TEDDY researchers previously reported that the appearance of insulin autoantibodies (IAAs) alone was greatest within the first year of life and declined over the following 5 years (7), whereas the incidence of glutamate decarboxylase autoantibodies (GADAs) as the first appearing autoantibodies increased until the second year of life and remained relatively constant through 6 years of life (6). This is consistent with the established recognition that IAAs appear first in very young children, whereas GADAs usually appear later (8). TEDDY investigators have also reported that environmental predictors of autoantibody seroconversion and progression to clinical diabetes differ by the type of first-appearing autoantibody (9). We previously reported that higher physical activity levels among children with multiple positive IAs was associated with better blood glucose and C-peptide outcomes on an oral glucose tolerance test (10). The objective of this study is to examine the role of physical activity in the development of IAs and progression to clinical type 1 diabetes in children who participated in the TEDDY study.

RESEARCH DESIGN AND METHODS

The TEDDY study identified infants with type 1 diabetes high-risk HLA genotypes at birth through cord blood screening. Parents of eligible infants were invited to join the study when the baby was aged 3.0–4.5 months. The study was conducted at six clinical research centers: three in the U.S. (Colorado, a center serving Georgia and Florida, and Washington) and three in Europe (Finland, Germany, and Sweden). Written informed consent was obtained for all study participants from a parent or a primary caretaker for both genetic screening and participation in the prospective follow-up. Detailed study design and methods have been published previously (11).

A total of 8,676 genetically at-risk children aged ≤4.5 months were enrolled between 2004 and 2010. Blood samples were collected for measurements of IAs, including IAA, GADA, and insulinoma-associated protein 2 (IA-2A), by radiobinding assays conducted in two laboratories (11). IA assessments occurred every 3 months until 4 years of age and continued at this interval for all children who were IA positive; a 6-month assessment protocol was initiated for children who were IA negative. Parents were informed of all IA results. Weight and height (length before aged 2 years and standing height afterward) were measured at each clinical visit from which BMI z scores were calculated according to the Centers for Disease Control and Prevention growth chart. All children were followed until aged 15 years or onset of type 1 diabetes. Type 1 diabetes was diagnosed using the American Diabetes Association criteria (12). The study was approved by local institutional review or ethics boards and is monitored by an external evaluation committee formed by the National Institutes of Health.

Physical Activity Assessment

Beginning at 5-years-old, children in the TEDDY study were asked to wear an ActiGraph accelerometer (model GT3×+; Fort Walton Beach, FL) annually on an elastic belt around the waist during waking hours for at least 7 consecutive days, exclusive of water activities. The protocol was changed in August 2018, and only children with positive IAs continued with the annual assessment after 10-years-old. The accelerometers were initialized to collect data at 80 Hz and were downloaded as 1-s epoch data. Data were reintegrated to 60-s epoch data and analyzed for activity intensity levels. Periods of ≥60 min of consecutive zero counts were defined as nonwear. Age-specific cut points were used to determine the minutes a child spent in light-, moderate-, or vigorous-intensity physical activity per day; minutes with <100 counts were categorized as sedentary (13). Days on which a child had ≥8 h of wear time were considered valid. At every annual assessment, data with at least three valid days were included, and the average amount of time a child spent in moderate to vigorous (mod+vig) physical activity across all valid days was the focus of the study.

Study Populations

Of the 8,676 participants enrolled at the beginning of the TEDDY study, 120 were excluded because they had ineligible HLA genotypes. Another 54 were excluded because of indeterminate autoantibodies, and 3,849 more were excluded because of lack of activity data at any age. Of the remaining 4,653 participants, three risk groups were constructed for analysis. Risk group 1 consisted of 3,869 children who were IA negative at the first activity assessment, of whom 157 (4.1%) subsequently developed a single persistent IA (GADA, IAA, or IA-2A) at a median follow-up of 3.4 (quartile 1 [Q1]–Q3 1.8–5.1) years since their first activity assessment; 109 (69.4%) of these single IA–positive children had GADAs, 40 children (25.5%) had IAAs, and 8 children (5.1%) had IA-2A at initial seroconversion. Risk group 2 consisted of 302 children with a single persistent, confirmed IAs to IAA or GADA and mod+vig physical activity assessments at the time of initial seroconversion or thereafter; 73 (24.2%) progressed to multiple IAs (i.e., developed a second persistent, confirmed autoantibody) with a median follow-up of 2.1 (Q1–Q3 0.8–3.4) years from the detection of the first autoantibody. Risk group 3 included 294 children with multiple positive autoantibodies and mod+vig physical activity assessments at the time of or after their development of multiple IAs; 148 of these children (50.3%) progressed to type 1 diabetes at a median follow-up of 5.0 (Q1–Q3 3.4–6.6) years since the detection of multiple IAs (Supplementary Fig. 1).

Statistical Analyses

Time-to-event analyses using Cox proportional hazards (PH) models were performed to examine associations between mod+vig physical activity and three phases of development of type 1 diabetes: *1*) development of a single IA; *2*) progression from single to multiple IAs (i.e., development of a second IA after the onset of the first IA); and *3*) progression from multiple IAs to type 1 diabetes. Analyses of a single IA and progression to multiple IAs were also restricted and repeated using a homogenous group of children who developed GADA as their first IA because GADA is typically the dominant first IA after 4 years of age (6). Analyses of progression from multiple IAs to type 1 diabetes were repeated and restricted to subgroups of children stratified by their first IA (IAA, GADA, or IA-2A/≥2 IA).

As of 28 February 2021, a total of 19,159 measurements of mod+vig physical

activity were available for the 4,653 children in the TEDDY study from all age points between 5 and 15 years of age. Because the time spent in mod+vig physical activity (minutes per day) tends to decline with increasing age (Supplementary Fig. 2) (14,15), mod+vig physical activity data were adjusted for the child's age at every assessment and then the age-adjusted minutes per day were included as a time-dependent covariate in the PH model to examine its association with each end point. The first step of the age adjustment was to determine the mean number of minutes per day of mod+vig physical activity at every age using data available from all enrolled children in the TEDDY study. The age-adjusted minutes per day were calculated as the residual value for each observed number of minutes per day subtracting the mean minutes per day at the child's age when the activity data were collected. Interaction terms of the age-adjusted mod+vig physical activity with time were used to test the proportional hazards assumption, and no violation was detected.

Analysis End Points

Risk Group 1

Development of single-IA positivity was defined as confirmed positive autoantibodies to GADA, IAA, or IA-2A in at least two consecutive samples by both TEDDY laboratories. The time to the development of single IAs was the age at the initial of two or more consecutive positive tests. The censoring time for single IAs was the age at the last collection of negative samples for IAs. There were 16 children who developed multiple autoantibodies at the time of initial seroconversion and were thus censored at the age of initial seroconversion. In other words, they were considered IA negative up to the time of IA detection. Cause-specific PH models for competing risk were subsequently conducted to study the risk of developing GADA as the first IA, by further censoring IAA-first and IA-2A–first IA at the time of initial seroconversion (16). Risk group 1 was used to examine the association between the amount of time spent in mod+vig physical activity and development of single persistent IA, as well as the association and development of GADA as the first IA.

Risk Group 2

Progression from single IA to multiple IAs was defined as the development of a second IA in single IA–positive children. The time-to-event variable was the duration calculated from the onset date of the first IA to the onset date of a second IA or to the date at the last blood sample collected to test for autoantibodies for those who did not develop a second IA (censoring).

Risk Group 3

Progression from multiple IAs to type 1 diabetes was defined as the development of type 1 diabetes in children with multiple IAs. The time-to-event variable was the duration from the date at onset of multiple IAs to the diagnosis date of type 1 diabetes or the last TEDDY visit for those who did not develop type 1 diabetes (censoring).

Covariates

Known IA risk factors, including HLA-DR-DQ genotype (DR 3/4 vs. non-DR 3/4), family history of type 1 diabetes (yes vs. no), sex, country of residence, and BMI *z* score (as a time-dependent covariate) were adjusted in the analyses of developing single IAs as well as progression from a single to multiple IAs. In addition, age at initial IA onset and type of the first IA (GADA or IAA) were also included as covariates in the PH model for progression from a single to multiple IAs. In the analysis of progression from multiple IAs to type 1 diabetes, age at onset of multiple IAs, type of the first IA (GADA, IAA, or IA-2A/≥2 IA), sex, and BMI *z* score (as a time-dependent covariate) were adjusted in the PH model; HLA genotype, family history of type 1 diabetes, and country were dropped as covariates because they are not significantly associated with this end point (17). We adjusted for accelerometer wear time by including it as a time-dependent covariate in all models.

All analyses were performed using Statistical Analysis Software (version 9.4; SAS Institute, Cary NC). A two-tailed $P < 0.05$ was deemed statistically significant. No adjustment in type 1 error was made for multiple comparisons except in the context of the multivariable Cox regression analysis. The magnitude of the association was described by hazard ratios (HRs) for every 10 more minutes spent in mod+vig physical activity per day with 95% CIs.

Data and Resource Availability

The data sets generated and analyzed during this study will be made available in the National Institute of Diabetes and Digestive and Kidney Diseases Central Repository at https://repository.niddk.nih.gov/studies/teddy.

RESULTS

Characteristics of the three study risk groups stratified by their end point status are provided in Table 1.

Risk Group 1

The multivariable Cox proportional hazards analysis revealed that the time spent in mod+vig physical activity was not associated with the risk of developing a single IA (HR 1.038 [95% CI 0.978, 1.102] per 10-min increase; $P = 0.224$), adjusting for sex, HLA genotype, BMI *z* score, family history of type 1 diabetes, country of residence, and accelerometer wear time (Table 2). Similar results were observed in the analysis on the risk of developing GADA as the first IA (HR 1.034 [95% CI 0.964, 1.108] per 10-min increase in mod+vig physical activity; $P = 0.350$) (Table 2).

Risk Group 2

In the Risk group 2 analysis, the HR of mod+vig physical activity amount was 0.926 (95% CI 0.848, 1.011, per 10-min increase; $P = 0.086$), adjusting for sex, HLA genotype, BMI *z* score, family history of type 1 diabetes, country of residence, age at onset of the single IA, type of the first IA (GADA or IAA), and accelerometer wear time (Table 3). The HR was 0.913 (95% CI 0.827, 1.007, per 10-min increase; $P = 0.069$) in the subgroup analysis with participants who had GADA as their first IA. They represented the majority of children who seroconverted at this age ($n = 204$ of 302). No other variable was associated with progression from single to multiple IAs, although having GADA as the first IA was associated with an increased likelihood of progression to multiple IAs (Table 3).

Risk Group 3

The amount of time spent in mod+vig physical activity was significantly associated with reduced risk of progression from multiple IAs to type 1 diabetes (HR 0.920 [95% CI 0.856, 0.988] per 10-min increase; $P = 0.021$), adjusting for sex,

Table 1—Characteristics of study risk groups

	Risk group 1: IA negative IA negative at the first activity measurement (n = 3,869)		Risk group 2: single-IA positive Activity data available at or after onset of a single IA (n = 302)		Risk group 3: multiple-IA positive Activity data available at or after onset of multiple IAs (n = 294)	
	Single IA		Multiple IAs		Type 1 diabetes	
Progressed to	No*	Yes	No	Yes	No	Yes
N	3,712	157	229	73	146	148
Country						
U.S.	1,438 (38.7)	55 (35.0)	75 (32.8)	26 (35.6)	46 (31.5)	59 (39.9)
Finland	763 (20.6)	30 (19.1)	46 (20.1)	12 (16.4)	27 (18.5)	38 (25.7)
Germany	185 (5.0)	7 (4.5)	10 (4.4)	4 (5.5)	7 (4.8)	8 (5.4)
Sweden	1,326 (35.7)	65 (41.4)	98 (42.8)	31 (42.5)	66 (45.2)	43 (29.1)
Family history of type 1 diabetes: yes	409 (11.0)	22 (14.0)	32 (14.0)	14 (19.2)	24 (16.4)	32 (21.6)
Female sex	1,835 (49.4)	76 (48.4)	114 (49.8)	38 (52.1)	57 (39.0)	63 (42.6)
HLA genotype DR3/4: yes	1,396 (37.6)	73 (46.5)	95 (41.5)	39 (53.4)	71 (48.6)	87 (58.8)
Type of first IA						
GADA		109 (69.4)	143 (62.4)	61 (83.6)	69 (47.3)	51 (34.5)
IAA		40 (25.5)	86 (37.6)	12 (16.4)	44 (30.1)	53 (35.8)
IA-2A		8 (5.1)			5 (3.4)	6 (4.1)
≥2 IA					28 (19.2)	38 (35.7)
Age at first activity assessment (years)						
Mean (SD)	6 (1.3)	6 (0.9)	6 (1.4)	6 (1.1)	6 (1.6)	6 (1.3)
Median	6	5	6	5	6	5
Q1–Q3	5.0–7.0	5.0–6.0	5.0–6.0	5.0–6.0	5.0–7.0	5.0–6.0

Data are presented as number (percentage) unless otherwise indicated. *Sixteen children developed multiple autoantibodies at the time of initial seroconversion and, were therefore censored at the age of initial seroconversion. In other words, they were considered IA negative up to the time of IA detection in the time-to-event analyses.

BMI *z* score, age at onset of multiple IAs, type of the first IA (GADA, IAA, or IA-2A/≥2 IA), and accelerometer wear time (Table 4). This effect was observed among U.S. participants (HR 0.896 per 10-min increment) and their European counterparts (HR 0.938 per 10-min increment). A similar association was found between the mod+vig physical activity minutes and the risk of progression to type 1 diabetes in those who had GADA as the first IA (HR 0.883 [95% CI 0.783, 0.996] per 10-min increment; *P* =

Table 2—Multivariable Cox proportional hazards regression analyses data on moderate-to-vigorous physical activity and other characteristics with the risk of developing single IAs and GADA-first IA (risk group 1)

Parameter	Single IA (n/N = 157/3,869)	GADA-first IA (n/N = 109/3,869)
Mod+vig physical activity (per 10 min/day)	1.038 (0.978, 1.102); 0.224	1.034 (0.964, 1.108); 0.350
Accelerometer wear time (per 10 min/day)	0.998 (0.984, 1.011); 0.714	1.006 (0.990, 1.022); 0.459
Sex		
Female	0.914 (0.604, 1.382); 0.670	0.839 (0.519, 1.356); 0.473
Male	Reference	Reference
Family history of type 1 diabetes		
Yes	1.535 (0.848, 2.778); 0.157	1.781 (0.925, 3.430); 0.084
No	Reference	Reference
HLA DR34 genotype		
Yes	1.659 (1.123, 2.451); 0.011	1.748 (1.112, 2.748); 0.016
No	Reference	Reference
Country		
Finland	1.050 (0.608, 1.812); 0.861	1.070 (0.552, 2.074); 0.840
Germany	0.523 (0.123, 2.217); 0.379	0.750 (0.172, 3.261); 0.701
Sweden	1.015 (0.638, 1.614); 0.950	1.232 (0.718, 2.114); 0.449
U.S.	Reference	Reference
BMI *z* score	1.258 (1.029, 1.539); 0.025	1.341 (1.060, 1.697); 0.014

Data are reported as hazard ratio (95% CI); *P* value, unless otherwise indicated. n/N = number of events per number of at-risk participants.

Table 3—Multivariable Cox proportional hazards regression analyses data on moderate-to-vigorous physical activity and other characteristics with the risk of progression from single to multiple autoantibodies (risk group 2)

Parameter	Overall (*n*/*N* = 73/302)	Subgroup with GADA-first IA (*n*/*N* = 61/204)
Mod+vig physical activity (per 10 min/day)	0.926 (0.848, 1.011); 0.086	0.913 (0.827, 1.007); 0.069
Accelerometer wear time (per 10 min/day)	0.995 (0.978, 1.013); 0.602	0.989 (0.971, 1.008); 0.270
Age at seroconversion (per month)	0.998 (0.987, 1.008); 0.654	0.998 (0.987, 1.009); 0.741
Sex		
Female	0.891 (0.491, 1.616); 0.705	1.092 (0.569, 2.094); 0.792
Male	Reference	Reference
Family history of type 1 diabetes		
Yes	1.280 (0.610, 2.683); 0.514	1.504 (0.705, 3.208); 0.291
No	Reference	Reference
HLA DR34 genotype		
Yes	1.448 (0.831, 2.525); 0.192	1.242 (0.681, 2.265); 0.480
No	Reference	Reference
Country		
Finland	1.194 (0.512, 2.787); 0.681	1.479 (0.549, 3.982); 0.439
Germany	0.787 (0.174, 3.563); 0.756	1.055 (0.223, 5.000); 0.946
Sweden	1.494 (0.782, 2.858); 0.225	2.243 (1.060, 4.745); 0.035
U.S.	Reference	Reference
BMI *z* score	0.907 (0.670, 1.227); 0.526	0.885 (0.633, 1.237); 0.475
Type of first IA		
GADA	2.358 (1.092, 5.091); 0.029	
IAA	Reference	

Data are reported as hazard ratio (95% CI); *P* value, unless otherwise indicated. *n*/*N* = number of events per number of at-risk participants.

0.043). A lack of association between mod+vig physical activity and the risk of progression to type 1 diabetes was seen in children who had IAA as the first IA (HR 0.917 [95% CI 0.813, 1.035] per 10-min increment; *P* = 0.161) and also in the children who had IA-2A or two or more IAs as the first IA (HR 0.972 [95% CI 0.841, 1.123] per 10-min increment; *P* = 0.696). The only other variable associated with the risk of progression to type 1 diabetes was having IA-2A or having two or more islet antibodies as the first IA (HR 1.846; [95% CI 1.054, 3.232]; *P* = 0.032, compared with IAA). Removal of the BMI *z* score from the model did not change the significant association between mod+vig physical activity and progression from multiple IAs to type 1 diabetes.

Additional analyses using total time spent on any level of physical activity (sum of light-, moderate-, and vigorous-physical activity) or sedentary time did not reveal significant association between either factor and the study end points and are not presented here.

CONCLUSIONS

In this study, we found that every 10-min increase in daily mod+vig physical activity was associated with an 8% reduced risk of progression to type 1 diabetes in children with multiple IAs. When limiting to those children who had only GADA at the initial seroconversion, a 10-min increase in mod+vig physical activity was associated with a 12% reduction in the risk of progression to type 1 diabetes. The smaller number of children who developed IAA or IA-2A (Table 1) as their first autoantibody after the inception of activity data collection contributed to the lack of significance seen in such individuals.

This study design focused on physical activity among children aged 5–15 years among whom GADA is typically the first IA to appear (14). A focus on this age group is particularly important because the peak incidence of type 1 diabetes is between 12 and 14 years of age (18). Repeated annual estimates provided the opportunity to assess how the amount of time spent in various levels of physical activity plays a role in the years leading up to the clinical onset of the disease.

We considered the three phases of type 1 diabetes development in the analysis: *1*) development of a single IA, *2*) progression from a single to multiple IAs, or *3*) progression from multiple IAs to type 1 diabetes. The number of repeated measurements averaged to three or four in the risk groups (the maximum was nine). When analyzing each phase, the Cox modeling with time-dependent covariates used all observed data in the corresponding phase and examined the instantaneous association with the risk by comparing the minutes per day at the event time points. This avoids the potential bias introduced by the change in physical activity levels observed as children grow older (19).

Besides activity level, childhood growth and body size are also hypothesized environmental triggers of type 1 diabetes (20), but the evidence in literature is inconclusive (21–25). A prior TEDDY analysis found a lower rate of linear growth during infancy and higher rate of linear growth in early childhood (up to 4 years of age) were associated with increased risk of progression from IA to type 1 diabetes (26). A similar finding was observed in a combined analysis of several cohort studies from Europe and the U.S. (27). The Trial to Reduce IDDM in the Genetically at Risk (TRIGR) study (25), whose participant characteristics closely resemble those of TEDDY except that they

Table 4—Multivariable Cox proportional hazards regression analyses data on moderate-to-vigorous physical activity and other characteristics with the risk of progression from multiple autoantibodies to type 1 diabetes (risk group 3)

		Subgroup stratified by type of the first IA		
Parameter	Overall (*n*/*N* = 148/294)	GADA (*n*/*N* = 51/120)	IAA (*n*/*N* = 53/97)	IA-2A/≥2 IA (*n*/*N* = 44/77)
Mod+vig physical activity (per 10 min/day)	0.920 (0.856, 0.988); 0.021	0.883 (0.783, 0.996); 0.043	0.917 (0.813, 1.035); 0.161	0.972 (0.841, 1.123); 0.696
Accelerometer wear time (per 10 min/day)	1.012 (0.997, 1.028); 0.121	0.994 (0.970, 1.019); 0.639	1.011 (0.982, 1.041); 0.446	1.031 (0.998, 1.066); 0.069
Age becoming multiple IAs positive (per month)	0.999 (0.989, 1.008); 0.779	0.991 (0.977, 1.007); 0.266	0.999 (0.977, 1.022); 0.922	1.011 (0.994, 1.028); 0.197
Sex				
Female	0.964 (0.612, 1.519); 0.875	1.223 (0.578, 2.588); 0.599	0.778 (0.331, 1.828); 0.565	0.947 (0.396, 2.267); 0.902
Male	Reference	Reference	Reference	Reference
BMI z-score	1.187 (0.964, 1.461); 0.106	1.332 (0.959, 1.851); 0.087	1.259 (0.877, 1.806); 0.211	0.786 (0.499, 1.238); 0.299
Type of first IA				
GADA	1.322 (0.764, 2.287); 0.318			
IA-2A/ ≥2 IA	1.846 (1.054, 3.232); 0.032			
IAA	Reference			

Data are reported as hazard ratio (95% CI); *P* value, unless otherwise indicated. *n*/*N* = number of events per number of at-risk participants.

were born to mothers with type 1 diabetes, observed a strong association between being overweight at 2 to 10 years of age and increased risk of progression from IA to type 1 diabetes (28). In this analysis, BMI *z* score was associated with development of IA but not progression. However, if mod+vig physical activity was removed from the model examining progression to clinical diabetes in children with multiple autoantibodies, the BMI *z* score became a significant predictor ($P = 0.0374$). In contrast, the significant association of mod+vig physical activity with type 1 diabetes progression remained significant with ($P = 0.021$) or without ($P = 0.017$) the BMI *z* score in the model. This would suggest that part of the association between BMI and type 1 diabetes–related outcomes may be explained by BMI's association with mod+vig physical activity. In this study, mod+vig physical activity was negatively correlated with BMI (Spearman correlation coefficient $r = -0.260$; $P < 0.0001$). The correlation between mod+vig physical activity and BMI is echoed in prior work that examined the association between activity and risk of hypertension (29), suggesting that both factors need to be considered when evaluating their effects on health outcomes.

Besides the potential impact on BMI, exercise helps decrease insulin resistance by increasing glucose transporters in the cell membranes and glucose uptake in skeletal muscles (30), which is another possible mechanism contributing to the observed protective effect.

Additionally, exercise lowers the risk of respiratory diseases (31,32), reduces visceral fat mass (a source of fat-derived cytokines) (33), and could potentially switch the cytokine environment to an anti-inflammatory profile that may modulate the immune response that leads to β-cell destruction in type 1 diabetes (5). Such a modulatory effect could also be attributed to exercise's impact on innate immunity by reducing the expression of Toll-like receptors on monocyte/macrophage immune cells (34). The likelihood of β-cell death, which could result from chronically elevated levels of plasma glucose or serum lipids, may also be lowered due to physical activity's benefits on normalizing glucose and lipid levels (35,36).

This study has several limitations. First, although our analyses took advantage of longitudinal, prospective observations collected by accelerometry, our sample size (i.e., the number of events) in the statistical analyses was markedly reduced by 35%, 25%, and 41% due to cases that did not have an activity measurement at the time of single-IA seroconversion, multiple-IA seroconversion, and type 1 diabetes diagnosis, respectively. To assess potential attrition bias, we compared participants and events with and without activity measurement at each outcome event with respect to their characteristics by using $\chi^2$and Wilcoxon rank-sum tests (as appropriate). No difference was detected (Supplementary Table 1). However, despite the reduced power associated with this loss, significant findings emerged.

We acknowledge that the genetic background of TEDDY participants differs from that of the general population. Data from the Type 1 Diabetes TrialNet Pathway to Prevention Study suggest the effect of overweight and obesity was almost four times stronger in Hispanic than in non-Hispanic children (37). The TEDDY study population is overwhelmingly White, so it is unclear whether the results from TEDDY can be generalized to children with other genetic backgrounds.

Furthermore, all parents of children in the TEDDY study are notified of their children's IA status, which might possibly influence children's physical activity behavior. The average minutes of mod+vig physical activity per day among children in the TEDDY study who were aged 9–11 years ranged from 67 to 44 in the U.S., 84 to 62 in Finland, 79 to 55 in Germany, and 81 to 57 in Sweden, which hovered around the average 60 min/day of mod+vig physical activity estimated with the same GT3×+

ActiGraph accelerometer in children of the same ages from the International Study of Childhood Obesity, Lifestyle and the Environment study (ISCOLE) (38). Additionally, the observation that U.S. children in the TEDDY study had fewer minutes of mod+vig physical activity per day than European children in the TEDDY study(39) is consistent with the findings from the ISCOLE study. These comparisons suggest the mod+vig physical activity of children in the TEDDY study reported here do not differ markedly from larger samples of similar aged children with no known risk of type 1 diabetes.

The role of dietary exposures, such as total energy intake in the development of type 1 diabetes, was not specifically investigated beyond the inclusion of BMI. Although the focus of this article is on the association of physical activity with the development of IA and disease progression, future reports will examine whether dietary exposures such as carbohydrate and sugar intake affect disease progression in children in the TEDDY study.

The ActiGraph GT3×+ monitor is not waterproof and must be taken off during activities such as swimming. This might have resulted in an underestimated amount of time spent in mod+vig physical activity in some children. Furthermore, this model does not differentiate between indoor and outdoor activities, leaving us unable to control for any effect of sunlight exposure (40).

Finally, this study focused on children aged 5–15 years for whom GADA is the most common type 1 diabetes–related autoantibody. Consequently, we are unable to draw conclusions regarding the possible impact of mod+vig physical activity on children who develop a different antibody as their first IA.

To date, we are not aware of any study that has examined the association between physical activity—objectively measured by accelerometry—and the progression to clinical type 1 diabetes in children positive for IAs. The findings are intriguing and suggest that activity could play a significant role in slowing progression to type 1 diabetes in high-risk children aged 5–15 years. Additional investigation and clinical trials to validate whether activity can reduce the risk of progression in high-risk children are warranted.

Funding. The TEDDY Study is funded by National Institutes of Health grants U01 DK63829, U01 DK63861, U01 DK63821, U01 DK63865, U01 DK63863, U01 DK63836, U01 DK63790, UC4 DK63829, UC4 DK63861, UC4 DK63821, UC4 DK63865, UC4 DK63863, UC4 DK63836, UC4 DK95300, UC4 DK100238, UC4 DK106955, UC4 DK112243, UC4 DK117483, U01 DK124166, U01 DK128847, and contract HHSN267200700014C from the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute of Allergy and Infectious Diseases, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, the National Institute of Environmental Health Sciences, Centers for Disease Control and Prevention, and JDRF. This work is supported in part by the National Center for Advancing Translational Sciences of the National Institutes of Health to the University of Florida (UL1 TR000064) and the University of Colorado (UL1 TR002535). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. X.L., S.B.J., and J.Y. researched data, contributed to discussion, and wrote, reviewed, and edited the manuscript. K.F.L., K.C., R.P., M.D.B., Å.L., W.A.H., M.J.R., R.A.M., J.T., A.-G.Z., B.A., and J.P.K. reviewed and edited the manuscript. X.L. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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