Association of physical activity metrics with indicators of cardiovascular function and control in children with and without type 1 diabetes

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Contribution Statement

Z.M conceived the study, collected all data, performed data and statistical analysis, and drafted manuscript; M.M conceived the study, aided with physical activity data analysis and drafting of the manuscript; K.M conceived the study, aided physical activity data analysis and drafting of the manuscript; M.L assisted with design of study, assisted with autonomic equipment training and provided equipment, processed autonomic data and aided analysis; E.E assisted with design of study, assisted with vascular equipment training and provided equipment, aided vascular data processing and interpretation, and drafting of the manuscript. All authors have read and approved the final version of the manuscript and agree with the order of presentation of the authors.

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Declaration of Interest

The authors declare that they have no competing interests

Abstract

Objective: Little is known about the role of physical activity accumulation in cardiovascular disease risk for children with type 1 diabetes. Improved insight to identify factors of influence in key health outcomes could be provided by considering the entire physical activity profile.

Methods: Pulse wave velocity (PWV), augmentation index and heart rate variability (HRV) were assessed cross-sectionally in children with (n=29, 12.1 ± 2.1 years) and without (n=19, 12.1 ± 2.1 years) type 1 diabetes. Time spent sedentary and in each physical activity intensity, intensity gradient and average acceleration were derived from seven consecutive days of monitoring with wrist-worn accelerometry. Comparison between groups and influence of physical activity accumulation on cardiovascular metrics were explored with linear mixed models.

Results: Diabetic children demonstrated a higher PWV and a greater volume of light physical activity ($p<0.01$), a more negative intensity gradient ($p<0.01$), a lower average acceleration and less time in bouted moderate-to-vigorous physical activity (MVPA) ($p<0.05$). Overall, intensity gradient was strongly correlated with average acceleration, MVPA and bouted MVPA ($r^2=0.89$, $r^2=0.80$, $r^2=0.79$, respectively; all $p<0.05$), while average acceleration was correlated with MVPA and bouted MVPA ($r^2=0.85$, $r^2=0.83$, respectively; $p<0.05$). Accounting for disease status, intensity gradient and average acceleration were significant predictors of HRV indices ($p<0.05$) and PWV ($p<0.01$, $p<0.05$, respectively).

Conclusion: Overall, MVPA was *most* associated with central arterial stiffness, highlighting the importance of meeting activity guidelines. Diabetic children demonstrated poorer cardiovascular health than their counterparts, likely attributable to a lower intensity and physical activity volume, identifying physical activity intensity as a key target for future interventions.

Keywords: average acceleration, arterial stiffness, heart rate variability, intensity gradient, pulse wave velocity

1. Introduction

Type 1 diabetes, characterised by chronic and lifelong insulin deficiency, is estimated to affect 400,000 people in the UK, 7.25% of whom are children [1]. The most prevalent cause of mortality in type 1 diabetes is cardiovascular disease (CVD), and individuals with type 1 diabetes have a four-fold higher risk of developing cardiovascular complications relative to their non-diabetic peers [2]. Pre-clinical indications of this increased cardiac risk may be evident as early as two years post-diagnosis, suggesting that those who develop type 1 diabetes early in life have a significantly increased premature risk of developing CVD, compared with their non-diabetic peers and those with a later onset [3,4].

The aetiology of the increased CVD risk in those with type 1 diabetes is suggested, at least in part, to be related to chronic hyperglycaemia and its deleterious effects on the vascular and nervous systems caused by increases in oxidative stress and inflammation [5,6]. Vascular dysfunction, which is typically characterised by poor vascular elasticity and reactivity [7], is a common complication in type 1 diabetes [8,9]. This reduced arterial compliance also potentially exacerbates the direct role of chronic hyperglycaemia in the autonomic dysfunction often reported in the paediatric diabetic population [10,11]. The consequently impaired control of cardiac rhythm and heart rate responsiveness, mediated by the autonomic nervous system and measurable through the indices of heart rate variability (HRV), is associated with an increased risk of short- and long-term complications, and specifically with an elevated risk of CVD [11,12].

Physical activity, along with the application of exogenous insulin and the strict control of diet, is essential for the management of type 1 diabetes and is associated with a reduced risk of both acute and long-term complications, and improved quality of life [6].

Moreover, research suggests that meeting the UK physical activity recommendations of, on average, 60 minutes of moderate-to-vigorous physical activity (MVPA) per day across the week [13], is strongly correlated with additional health-associated benefits for those with type 1 diabetes [14,15]. In children with type 1 diabetes, physical activity improves glucose control [14,16,17], helps prevent insulin resistance [18-20], reduces traditional CVD risk factors [19,21,22] and maintains a healthy vascular reactivity [23] and healthy autonomic function [24-26]. However, recent research found that only 39% of children with type 1 diabetes met the current UK physical activity guidelines [13], with these children engaging in significantly less MVPA than their non-diabetic peers [27].

While MVPA is associated with important health benefits, longer durations of light-intensity physical activity (LPA) in healthy children have also been associated with multiple benefits [28], including a lower stiffness in the small arteries [29,30]. This suggests that all physical activity, irrespective of intensity, can elicit health-associated benefits and highlights the need to consider the whole physical activity profile. However, research has predominantly focused on exploring the health influences of the volume of time spent in different intensities, rather than exploring the overall effect of accumulated physical activity, irrespective of intensity. Furthermore, this focus on the volume of physical activity has been almost exclusively based on various cut-points that were derived from different protocols, segmenting the available data [31] and largely precluding inter-study comparisons. In contrast, utilising all available movement data to determine the distribution of physical activity intensity and volume accrued, in the form of the activity profile, enables the identification of those patterns and variances in physical activity that are most strongly associated with health outcomes [32]. Vitally, such metrics enable inter-study comparisons [32] and could thereby facilitate the accumulation of sufficient evidence to support individually-targeted interventions for

reducing long-term health complications. Such approaches would be particularly valuable in a diabetic population, as even relatively small changes can elicit improvements in disease management, cardiovascular health and quality of life [33].

The primary aim of the current study was therefore to determine the influence of type 1 diabetes on the accumulation of physical activity in diabetic youths and to determine whether it is the volume or the intensity of physical activity, or a combination of these, that has the greater influence on their cardiovascular health.

2. Methods

The present cross-sectional study was conducted in paediatric diabetes clinics and schools in South Wales, across a 2-year period. Interested participants were referred by their paediatric diabetic team to the first author for further information. Following written informed assent and consent from participants and parents/guardians, respectively, measurements and assessments were taken over a 2-hour testing period, with physical activity subsequently assessed over seven consecutive days. The study was approved by a National Health Service (NHS) Research Ethics Committee (16/NE/0082 195492) and conducted in accordance with the Declaration of Helsinki.

2.1 Participants

29 children with type 1 diabetes (12.1 ± 2.1 years; 14 girls) and 19 without type 1 diabetes (11.8 ± 2.2 years; 6 girls) participated in this study. Potential participants with any known cardiovascular disease, kidney disease, metabolic disease or hypertension were excluded. Diabetes-specific exclusion criteria were: a diabetes duration of less than 1 year; currently being in poor glycaemic control and at an increased risk of diabetic ketoacidosis (HbA1c ≥80.0 mmol·mol^{-1}); or identified by the paediatric diabetes team as otherwise unsuitable for participation in the study.

2.2 Anthropometric, Maturity and Metabolic Measures

Standing and sitting stature were measured to the nearest 0.1 cm using a Holtain stadiometer (Holtain, Crymych Dyfed, UK), with body mass measured to the nearest 0.1 kg using electronic scales (Seca 803, Seca, Chino, CA, USA). Body mass index (BMI) and BMI z-score (BMIz) were subsequently calculated. Data on each participant's blood glucose control, lipid profile and HbA1c were obtained from medical records. Maturity was estimated using sex-specific maturity offset equations in order to approximate the time in years pre- or post-peak height velocity (PHV). Maturity status was defined as prepubertal if >1 year pre-PHV, pubertal if 1 year pre- or post-PHV, and post-pubertal if >1 year post-PHV [34].

2.3 Habitual Physical Activity Measurements

Participants wore a GENEActiv triaxial accelerometer (GENEActiv, Activinsights Ltd, Cambridgeshire, UK) sampling at 20 Hz on their right wrist for seven consecutive days from midnight following the study visit. The GENEActiv has been validated for use in children [35] and has been shown to be reliable in comparison to other validated accelerometers [36]. During the habitual physical activity assessment period,

participants were given diaries to monitor sleep quality and duration, and to record times and reasons for accelerometer removal.

2.4 Vascular Assessment

Non-invasive assessment of vascular function was carried out employing a cuff-based osillometric technique (Vicorder, Skidmore Medical, Bristol, UK; D.E.Hokanson Inc, Bellevue, WA, USA), with the participant in a supine position, torso elevated to approximately 30^{o}, in a quiet environment and having rested for five-minutes prior to assessment to ensure stable haemodynamics (heart rate and blood pressure). Pulse wave analysis (PWA) was completed with a cuff on the upper left arm, at the brachial artery. A stable blood pressure (BP) was initially obtained to inform the inbuilt automated protocol, then the pulse-pressure waveform was recorded deriving central augmentation pressure (AP) and index (AIx) by integral transfer function. Specifically, AP was calculated as the difference in pressure between peaks one and two on the systolic waveform and AIx was equal to AP expressed as a percentage of pulse pressure [37]. Aortic stiffness was estimated from the carotid to femoral pulse wave velocity (PWV), completed by placing a partial cuff over the carotid pulse and a cuff at the upper thigh, then measuring the distance between the sternal notch and the middle of the femoral cuff. Carotid and femoral waveforms were then recorded, deriving PWV in m/s. Three recordings for each process, PWA and PWV, were taken to obtain at least two congruent measures within 0.5 m/s, 5 mmHg and 5 % of each other, respectively.

2.5 Assessment of HRV

A short-term ECG recording, from which RR-intervals can be derived, was obtained with the use of a 3-lead Reynolds CF Holter monitor (Spacelabs Medical Ltd, Hertford,

UK), producing 12-bit resolution ECG data at a sampling frequency of 1,024 Hz. Three electrodes were positioned on the anterior of the torso, at the manubrium of the sternum and the V5 and V5R positions. Accurate placement of each electrode was ensured by visually observing each channel prior to recording. A representative resting measure of autonomic function was obtained by recording for 5-minutes during paced breathing at 6-breaths per minute in a supine position, after a 15-minute rest period.

2.6 HRV Data Processing

ECG data from the Reynolds CF Holter recorder were exported and processed using the Reynolds Pathfinder ECG analysis system (Spacelabs Medical Ltd, Hertford, UK). The pathfinder system classified QRS cycles as either normal (resulting from sinus node depolarisations) or aberrant, and normal cardiac (RR) interval data were then extracted using the Reynolds Research Tools software (Spacelabs Medical Ltd, Hertford, UK). The resulting RR data were visually assessed to identify and delete any obvious artefacts (those of non-physiological origin). The processed RR data were then analysed using Kubios HRV V3.0 (Biomedical Signal Analysis Group, Department of Applied Physics, University of Kuopio, Finland) to derive time-domain, frequency-domain and geometric indices of HRV. The RR data was initially detrended using the 'Smoothn priors' option, with Lamdba set to 500. Time domain analysis of the RR data yielded RMSSD (the square root of the mean of the sum of the squares of differences between adjacent RR intervals), a short-term measure indicative of parasympathetic activation [38]. Frequency domain indices were spectrally estimated by Welch's method of power spectral density estimation and autoregressive modelling and then divided into low frequency (LF; 0.04 – 0.15 Hz) and high frequency (HF:

237 0.15-0.40 Hz) bands. These indices were then expressed in both absolute and relative
238 terms following normalisation to total spectral power (TSP; 0.04-0.40 Hz). HF was
239 included as an indication of parasympathetic activity, while LF can be both an
240 indication of parasympathetic/sympathetic balance and sympathetic activation [38]. The
241 geometric indices derived were SD1 and SD2 (the standard deviations of short-term
242 and long-term variations in RR, respectively), which were determined from the axes of
243 the Poincaré plot [38].
244
245 2.7 Habitual Physical Activity Data and Analysis
246 Raw accelerometer data were extracted using the GENEActiv PC software v2.2
247 (Activinsights Ltd, Cambridgeshire, UK). Signal processing was subsequently
248 completed with R software (https://cran.r-project.org) using the GGIR package
249 (https://cran.rproject.org/web/packages/GGIR/vignettes/GGIR.html) to convert the
250 triaxial acceleration values to an omnidirectional acceleration in the form of the signal
251 vector magnitude (SVM). Raw acceleration values were processed by the 'Euclidian
252 norm minus one' (ENMO) method [39], then reduced to 5 second epochs and expressed
253 in milligravity-based acceleration units (mg) [40]. Minimum wear-time was classified as
254 ≥16 hours during waking hours, defined as 0600 to 2300, over three weekdays and
255 one weekend day [41]. Hildebrand et al.'s raw acceleration thresholds [42] were utilised to
256 determine the time spent in different intensity domains (<50 mg for sedentary time
257 (ST), 50-99 mg for light physical activity (LPA), ≥100 mg for MVPA; [40]). Tolerance
258 thresholds for LPA and MVPA bouts were set as ≥10 minutes of continuous 5s
259 epochs, where 80% of epochs were ≥ 50 or ≥ 100 mg, respectively [43]. Bouted time
260 was presented as an average of the included participants and valid days, therefore
261 depending on engagement in bouts by participants the average can be below the set
262 bout time (ie. 10 minutes). Sleep was classified based on the van Hees et al. [44]

nocturnal sleep algorithm as no arm angle change > 5^{o} for ≥ 5 minutes. Total movement was quantified as the average acceleration over a 24-hour period [31].

The intensity gradient, a metric of physical activity intensity distribution [32], was calculated for each participant. Specifically, the curvilinear relationship between intensity and time spent in in each successive 25 mg time bin between 0 and 4,000 mg was transformed to a linear relationship using the natural log of each variable. The R^2 value obtained indicated the goodness of fit of the linear model, whilst the gradient and constant of the linear regression represented the activity distribution. A higher constant and a more negative gradient represent a steeper decline and therefore less time accumulated at mid-to-high intensities. Conversely, a lower constant and a less negative gradient represents a shallower drop and is therefore indicative of more time spread across the intensities [32].

2.8 Statistical analysis

The SPSS software package (IBM SPSS Statistics for Macintosh, Version 22.0) was used to perform statistical analyses, with significance set as $p<0.05$ and all data expressed as mean ± SD. Initially, independent t-tests were used to compare included and excluded participants and to assess participant characteristics according to group (children with and without diabetes). Linear mixed models with a random intercept were then conducted to compare physical activity metrics between children with and without type 1 diabetes. Separate models were constructed with model 1 only including the physical activity metrics, and model 2 adjusted for age, sex, maturation and BMI. The final model was further adjusted for the alternative metric (intensity gradient or average acceleration) to test the independence between volume and intensity metrics. Pearson's correlations were used to determine the magnitude of

association between the intensity gradient, average acceleration, MVPA and bouted MVPA, and to ascertain whether the intensity gradient showed greater independence to average acceleration than MVPA or bouted MVPA. Finally, both samples were pooled and linear mixed modelling with random intercept was utilised to explore the associations between the volume/intensity of physical activity and measures of cardiovascular function and control. Model 1 adjusted for clustering of disease status, whereas model 2 was adjusted for disease status, age, sex and maturity, and model 3 was further adjusted for the alternative physical activity metric (intensity gradient or average acceleration) to assess for an independent effect.

3. Results

Following the exclusion of eight participants (n=6 type 1 diabetes, due to failed calibration and failing to meet the wear-time criteria; n=2 controls, due to failing to meet wear-time criteria), the final sample consisted of 40 participants (23 type 1 diabetes, 17 non-diabetic). There were no significant differences between those included or excluded with regards to age, anthropometric measures or maturity (data not shown). Participant descriptive characteristics and physical activity outcomes are presented in Table 1. Participants with type 1 diabetes were observed to have HbA1c levels greater than the NICE recommended level of 48 mmol·mol^{-1} (above which the risk of developing long-term complications is significantly increased) [45].

Insert Table 1 here

Multiple mixed model analyses highlighted significant differences in the intensity gradient ($p<0.01$), average acceleration ($p<0.05$) and time spent in LPA ($p<0.05$) for diabetic and non-diabetic children, when accounting for age, sex, maturity status and

BMI (Table 2). There were no significant differences in MVPA ($p>0.05$), bouted MVPA ($p=0.058$), bouted LPA ($p>0.05$) or ST ($p>0.05$) between the two groups. Amongst the boys, those without diabetes showed the highest average acceleration and highest intensity gradient but the lowest LPA; amongst the girls, those with diabetes demonstrated the lowest LPA, lowest intensity gradient and lowest average acceleration.

Intensity gradient was strongly associated with both MVPA and bouted MVPA ($r=0.80$, $p<0.01$; $r=0.79$, $p<0.01$, respectively), but less strongly correlated with sedentary time ($r=-0.36$, $p<0.05$). Average acceleration was similarly strongly correlated with both intensity gradient and cut-point metrics. Specifically, average acceleration was correlated with the intensity gradient ($r=0.89$, $p<0.01$), MVPA ($r=0.85$, $p<0.01$) and bouted MVPA ($r=0.83$, $p<0.01$), while only moderately correlated to sedentary time ($r=-0.36$, $p<0.05$). Intensity gradient and average acceleration showed no significant correlation with LPA or bouted LPA.

Insert Table 2 Here

Cardiovascular outcomes for both groups are presented in Table 3. Modest negative correlations were observed between PWV and intensity gradient ($r^2=-0.38$, $p<0.05$), average acceleration ($r^2=-0.40$, $p<0.05$), MVPA ($r^2=-0.43$, $p<0.05$) and bouted MVPA ($r^2=-0.45$, $p<0.05$). Average acceleration was also modestly correlated to resting absolute LF ($r^2=0.44$, $p<0.05$) and TSP ($r^2=0.43$, $p<0.05$). Neither intensity gradient nor average acceleration were significantly correlated to AIx, augmentation pressure or any of the HRV indices measured under conditions of stress ($p>0.05$).

Insert Table 3 Here

The association between physical activity metrics and measures of cardiovascular function are presented in Table 4. Both intensity gradient and average acceleration were significant predictors of PWV, RMSSD, LF, total spectral power and SD1 when unadjusted, but not when adjusted for covariates.

Insert Table 4 Here

4. Discussion

This is the first study to explore physical activity in children with type 1 diabetes using more novel, intensity-based, rather than conventional volume-based, measures to consider how physical activity is accumulated. Moreover, this study sought to investigate whether these metrics differ according to disease status and health outcomes. The key findings from the study were: (i) children with type 1 diabetes engaged in significantly less higher intensity physical activity than their non-diabetic peers; (ii) intensity gradient was not independent of average acceleration or MVPA; (iii) type 1 diabetic children had a poorer (higher) PWV and short-term HRV tended to be decreased compared to their non-diabetic peers; and (iv) intensity of physical activity was most strongly associated with a more favourable PWV and HRV indices.

Physical activity is known to be associated with numerous short- and long-term health benefits in children [46], as well as in the management of type 1 diabetes [17]. In accordance with previous research [47,48], the current study found that children with type 1 diabetes typically undertake less MVPA than their non-diabetic peers. Indeed, previous research has postulated that those with type 1 diabetes might engage in a

lower volume of MVPA because of a lack of understanding about how to compensate for different types and intensities of exercise, and due to a fear of subsequent hypoglycaemia [49]. However, whilst conventional, volume-based measures of physical activity have been extensively researched in the paediatric diabetic population, little is known regarding the physical activity profile as a whole. The current study therefore extends these earlier studies, demonstrating that diabetic children have a steeper, less favourable, intensity profile and lower average acceleration than their non-diabetic peers. These findings indicate that diabetic participants engaged in significantly more LPA than MVPA and moved less at higher intensities compared to their non-diabetic peers. Whilst these findings highlight LPA as a potential target for interventions, with suggestions that targeting LPA may represent a more feasible and sustainable target than MVPA for those with low physical activity levels at baseline [50,51], it is worth noting that the greatest health benefits are elicited through MVPA, with significantly longer periods of LPA required to obtain similar benefits [52]. Therefore, future studies in children with chronic diseases should utilise the activity profile to gain a greater insight into the accumulation of physical activity, to facilitate an accurate comparison of physical activity patterns between populations, and to identify key targets for intervention.

Previous studies in healthy children found that the intensity gradient was associated with conventional volume-based metrics, independent of average acceleration [31,32]. The strongest association in these studies was demonstrated between the intensity gradient and MVPA, suggesting that the intensity gradient best represents more vigorous intensity physical activity [31,32]. In contrast, time spent in MVPA in the current sample was similarly correlated with both the intensity gradient and average acceleration (r^2=0.80 and 0.85 respectively, both $p<0.01$). Consequently, the intensity

393 gradient was not independently associated with conventional cut-points, a finding in
394 contrast with previous literature. This lack of independence from MVPA might
395 therefore limit the ability to explore the relative importance of physical activity volume
396 and intensity in cardiovascular health [53]. Such discrepancies might be partially due to
397 the high volume of physical activity in which both populations engaged, which could
398 mask the importance of intensity. Alternatively, accelerometer wear-location is thought
399 to influence the magnitude of average acceleration, possibly resulting in increased
400 variance in intensity gradient [32].
401
402 Research has suggested that physical activity slows the progression of premature
403 arterial stiffening in children with type 1 diabetes, thereby reducing the risk of long-
404 term complications later in life [54,55]. Congruent with previous research [56], significant
405 differences were observed in PWV, with diabetic children presenting a 10% higher
406 PWV than their non-diabetic peers. This difference may indicate premature central
407 stiffening, a likely indicator of increased long-term CVD risk. Furthermore, negative
408 associations were observed, irrespective of disease status, between PWV and
409 intensity gradient, average acceleration, MVPA and bouted MVPA, but not LPA. Thus,
410 a more positive or shallow gradient, indicative of engagement in more vigorous
411 intensities, and a higher average acceleration, suggesting higher volumes of physical
412 activity were associated with a lower PWV. Such findings suggest that higher volumes
413 and a greater engagement in more vigorous intensities of physical activity positively
414 influenced central stiffness. Additionally, the steeper gradient, lower average
415 acceleration and the lower volume of MVPA, observed in this diabetic sample,
416 suggests that the volume and intensity undertaken might not be sufficient to
417 ameliorate the negative changes in central stiffening. Therefore, these findings further
418 support a need to encourage and aid children with type 1 diabetes to engage in more

vigorous intensity physical activity, in order to slow the progression of disease-related central arterial stiffening.

Previous research has demonstrated that children with type 1 diabetes who participate in lower volumes of physical activity have significantly lower HRV at rest, than more physically active participants with and without diabetes [24]. The clinical sample in the current study participated in significantly lower volumes of physical activity and showed non-significant, but characteristically lower values for absolute HF, total power, RMSSD and SD1, in comparison to their healthy controls. Lower magnitudes of total power, RMSSD, HF and SD1 in the short-term can indicate reduced overall cardiac autonomic activity, particularly of the parasympathetic (vagally-mediated) neural control of heart rate [38]. This suggests a possible shift towards systemic autonomic dysfunction that may increase the risk of developing autonomic neuropathy, a common complication in type 1 diabetes [57]. However, a positive association between physical activity intensity/volume and cardiac autonomic function, across both populations in this study, suggests that both intensity and volume could positively influence age- and disease-related decline in autonomic function [26,58]. Specifically, attaining a greater volume of physical activity, represented by a greater average acceleration, and accruing more vigorous intensities of physical activity were both associated with greater overall autonomic activity and vagal tone, therefore suggesting a potentially reduced risk of developing autonomic neuropathy. Furthermore, increased autonomic activity and vagal tone has been found to be a predictor of central arterial stiffness, a pre-clinical indicator of CVD in type 1 diabetes [59], as observed in the current study. Thus, taken together, physical activity of sufficient volume and intensity may ameliorate age- and disease-related declines in autonomic function and central arterial stiffening in children with type 1 diabetes.

There are numerous strengths associated with the current research, not least the use of recently devised physical activity metrics to explore how disease status influences physical activity accumulation. Nonetheless, this study is not without limitations, such as the sample size and sex distribution within the samples, which could limit the generalisability of the results. Furthermore, the potential presence of a Hawthorne effect should be considered when interpreting the current results [60]. However, the metrics utilised facilitate inter-study comparisons, potentially enabling the use of this data in larger cohort analyses.

In conclusion, this study demonstrated that the accumulated daily volume of vigorous intensity physical activity has the greatest influence on arterial stiffening and cardiac autonomic function, both of which are indicators of CVD risk for children with type 1 diabetes. Therefore, future physical activity interventions should focus on increasing the intensity of physical activity undertaken by this population. Children with type 1 diabetes demonstrated significantly increased in central arterial stiffness and impaired cardiac in autonomic function, compared to those without diabetes. Finally, quantifying intensity gradient and average acceleration enabled the identification of overall physical activity accumulation, which is important in preventing long-term risk of CVD in this population.

Data Availability

The datasets generated during and/or analysed during the current study are available from the corresponding author or guarantor on reasonable request.

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635 Table 1 – Participant characteristics

	Children with type 1 diabetes (n=23)	Non-diabetic children (n=17)
Age (yrs)	12.1 (2.1)	11.8 (2.2)
BMI (kg·m^{-2})	20.7 (3.7)	19.3 (4.1)
BMIz	0.87 (1.03)	0.43 (1.21)
Maturity offset (yrs)	-1.55 (1.65)	-1.30 (2.04)
Sedentary time (mins·day^{-1})	492.0 (119.4)	527.8 (101.3)
LPA (mins·day^{-1})	471.0 (61.6)**	410.9 (71.5)
Bouted LPA (mins·day^{-1})	166.4 (66.0)	148.0 (63.6)
MVPA (mins·day^{-1})	82.9 (37.2)	114.0 (72.1)
Bouted MVPA (mins·day^{-1})	4.5 (4.7)*	12.9 (15.3)
Average acceleration (mg)	37.2 (9.7)*	46.2 (18.1)
Intensity gradient	-2.11 (0.18)**	-1.90 (0.23)
Intensity constant	13.02 (0.66)**	12.36 (0.76)
Intensity R^2	0.84 (0.05)	0.86 (0.05)
Sleep efficiency (%)	82.9 (11.0)	83.1 (11.5)
HbA1c (mmol·mol^{-1})	68.24 (12.14)	-
HbA1c (%)	8.4 (1.1)	-
Total- C (mmol·l^{-1})	4.22 (0.39)	-
LDL-c (mmol·l^{-1})	2.30 (0.33)	-
Disease duration (yrs)	5.0 (3.2)	-

636 Values are presented as mean (SD).

637 Body mass index (BMI), Sedentary time (ST), Light physical activity (LPA), Moderate-
638 to-vigorous physical activity (MVPA)

639 Glycated haemoglobin (HbA1c), Total cholesterol (Total-C), Low density lipoprotein
640 (LDL-c)

641 *denotes significant difference between groups at p<0.05, with **significant at p<0.01

642

643 Table 2 - Linear mixed model of between-group differences in activity metrics and
644 disease status

	Model 1		Model 2		Model 3		
	β	95% CI	β	95% CI	β	95% CI	Independent (model 3)
Intensity gradient	-0.22**	-0.35, -0.08	-0.19**	-0.33, -0.05	-0.13*	-0.25, -0.02	Y
Intensity constant	0.66**	0.19, 1.13	0.60*	0.10, 1.11	0.45	-0.01, 0.91	X
Average acceleration (mg)	-9.58*	-19.07, -0.10	-4.67	-11.84, 2.49	2.08	-3.77, 7.94	X
Sedentary time (mins·day^{-1})	-35.8	-111.1, 39.5	-36.4	-110.8, 38.0	-63.2	-141.7, 15.3	Y
LPA (mins·day^{-1})	60.1**	15.1, 105.1	63.5**	8.5, 108.4	74.7**	26.3, 123.1	Y
Bouted LPA (mins·day^{-1})	18.5	-25.5, 62.4	10.4	-33.1, 54.0	19.9	-27.2, 67.0	Y
MVPA (mins·day^{-1})	-31.2	-69.4, 7.1	-12.6	-44.3, 19.1	0.6	-32.3, 33.6	X
Bouted MVPA (mins·day^{-1})	-8.3*	-15.8, -0.8	-6.3	13.3, 0.7	-0.9	-7.0, 5.3	Y

645 Model 1 unadjusted model grouped with disease status, model 2 adjusted for potential
646 covariates: age, sex, maturity status, BMIz, model 3 adjusted for covariates and
647 alternative physical activity metric to determine if independent (average acceleration
648 for intensity gradient, intensity gradient for all other metrics), with an independent and
649 non-independent relationships denoted by Y and X, respectively.
650 Light physical activity (LPA), moderate to vigorous physical activity (MVPA)
651 *denotes significant difference between groups at $p<0.05$, with **significant at $p<0.01$

652 Table 3 – Measures of cardiovascular function for diabetic and non-diabetic
653 participants

	Children with type 1 diabetes (n=29)	Non-diabetic children (n=19)
Resting blood pressure (mmHg)	114/60	116/62
MAP (mmHg)	83.5 (6.6)	84.9 (5.4)
Augmentation pressure (mmHg)	7 (4)	8 (4)
Augmentation index (%)	13.52 (6.47)	15.25 (7.02)
Pulse wave velocity (m/s)	5.04 (0.66)**	4.58 (0.70)
Heart rate variability:		
TSP (ms^2)	3291 (3982)	5060 (7308)
LF (ms^2)	1309 (1217)	2204 (2720)
HF (ms^2)	1917 (2806)	2715 (5283)
LF (n.u)	50.9 (16.9)	53.1 (14.0)
HF (n.u)	49.0 (16.9)	46.7 (14.0)
RMSSD (ms)	53.5 (32.1)	65.2. (52.3)
SD1 (ms)	37.9 (22.7)	46.1 (37.1)
SD2 (ms)	67.3 (26.6)	78.4 (45.6)

654 Values are presented as mean (SD).
655 Mean arterial pressure (MAP), total spectral power (TSP), Low frequency (LF), High
656 frequency (HF), Root mean square of the successive differences of RR (RMSSD),
657 standard deviations of the Poincare plot 1 and 2 (SD1and SD2).
658 **significant difference between groups $p<0.01$
659
660

661 Table 4 - Associations between physical activity metrics and measures of
662 cardiovascular function and control for the overall study population

	Model 1		Model 2		Model 3		Independent
	β	95% CI	β	95% CI	β	95% CI	(model 3)
PWV							
Intensity gradient	-1.62**	-2.82, -0.42	-1.27	-2.77, 0.23	-1.27	-3.56, 1.02	Y
Average acceleration	-0.02*	-0.04, -0.004	-0.01	-0.03, 0.01	-0.00	-0.03, 0.03	X
Augmentation pressure							
Intensity gradient	-2.23	-9.25, 4.78	3.14	-6.32, 12.61	-7.03	-20.54, 6.48	X
Average acceleration	0.01	-0.08, 0.10	0.10	-0.01, 0.22	0.17	-0.00, 0.34	Y
Augmentation index							
Intensity gradient	-1.26	-13.30, 10.78	8.14	-8.09, 24.37	-5.79	-29.55, 17.97	X
Average acceleration	0.03	-0.13, 0.19	0.18	-0.02, 0.37	0.23	-0.07, 0.53	Y
MAP							
Intensity gradient	10.53	-0.45, 21.51	5.96	-8.14, 20.05	11.31	-10.05 ,32.66	Y
Average acceleration	0.10	-0.04, 0.25	0.02	-0.16, 0.20	-0.10	-0.36, 0.18	X
RMSSD							
Intensity gradient	78.0*	1.8, 154.3	44.4	-74.6, 163.3	16.1	-148.3, 180.4	Y
Average acceleration	1.1*	0.1, 2.2	0.7	-0.9, 2.3	0.6	-1.7, 2.8	Y
LF							
Intensity gradient	4,403*	759, 8,046	1,822	-3,777, 7421	-1,634	-9,171, 5,903	X
Average acceleration	73**	25, 120	53	-22, 127	68	-35, 172	Y
HF							
Intensity gradient	6,333	-1,245, 13,910	3,776	-8,127, 15,680	2,681	-13,713, 19,075	Y
Average acceleration	82	-22, 186	43	-119, 205	20	-204, 245	Y
TSP							
Intensity gradient	11,025*	742, 21,309	5,440	-10,550, 21,448	978	-21,091, 23,047	Y
Average acceleration	158*	19, 298	98	-120, 316	88	-214, 391	Y
SD1							
Intensity gradient	55.3*	1.3, 109.3	31.5	-52.7, 115.7	11.4	-105.0, 127.8	X
Average acceleration	0.8*	0.055, 1.5	0.5	-0.6, 1.7	0.4	-1.2, 2.0	Y
SD2							
Intensity gradient	73.9*	9.7, 138.0	29.1	-71.1, 129.3	1.6	-136.7, 139.8	X
Average acceleration	1.1*	0.2, 1.0	0.6	-0.8, 1.9	0.5	-1.4, 2.4	X

663 Model 1 unadjusted model; model 2 adjusted for potential covariates: age, sex, and
664 maturity status; model 3 adjusted for covariates and alternative physical activity metric
665 to determine if independent.
666 95% confidence interval (CI), Pulse wave velocity (PWV), Mean arterial pressure
667 (MAP), Root mean square of successive differences of RR (RMSSD), Low frequency

668 (LF), High frequency (HF), Total spectral power (TSP), standard deviations of the

669 Poincare plot 1 and 2 (SD1 and SD2)

670 Significant prediction between independent and dependent variable *p<0.05, **p<0.01

671