Received: 23 January 2023 | Revised: 7 March 2023 | Accepted: 30 March 2023

DOI: 10.1111/sms.14369

ORIGINAL ARTICLE

WILEY

Is fear of hypoglycemia a major barrier to an active lifestyle in children and adolescents with type 1 diabetes? The Diactive-1 Study

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Funding information
Instituto de Salud Carlos III, Grant/Award Number: PI21/01238

Studies on fear of hypoglycemia as a barrier to physical activity among youth with type 1 diabetes (T1D) have been limited and controversial, most of which used self-reported assessment. The aim of the study was to evaluate the relationship between fear of hypoglycemia and physical activity and glycemic metrics in children and adolescents with T1D. Seventy-four participants (6–18 years of age; 44.6% females) with T1D were included in the study. Physical activity was assessed through accelerometry on nine consecutive days, and blood glucose metrics were simultaneously tracked using continuous glucose monitoring (time-in-range and hypoglycemic events). A closed question was used to evaluate the avoidance of physical activity due to fear of hypoglycemia. Fifteen participants (20%) reported avoiding physical activity due to fear of hypoglycemia. The group reporting no fear of hypoglycemia showed lower total physical activity (−35.33 min/day, 95% confidence interval [CI] (−77.57 to −1.47)) and light physical activity (−29.81 min/day, 95% CI −64.01 to −2.75) and higher sedentary time (77.95 min/day, 95% CI 26.46–136.87) per day compared with those with fear of hypoglycemia. No difference was found between those patients with fear of hypoglycemia in terms of meeting the recommendations of glycated hemoglobin, glucose coefficient of variation, and time-in-range when compared to those with no fear of hypoglycemia. In conclusion, children and adolescents with fear of hypoglycemia were more active, less sedentary, and had similar glycemic metrics to those without fear. Our results therefore suggest that fear of hypoglycemia may be less of a barrier to an active lifestyle than previously believed.

KEYWORDS
barriers, hypoglycemia, physical activity, time in range, youth

Section III: Health, Disease & Physical Activity: Mark Hamer (UK).

1 | INTRODUCTION

Children and adolescents with type 1 diabetes (T1D) are encouraged to undertake at least 60 min of moderate-to-vigorous aerobic physical activity (PA) daily, in addition to 3 days a week of vigorous PA and bone and muscular strengthening activities.[1,2] Likewise, time spent in sedentary behaviors should be limited as much as possible.[2] Compliance with these recommendations is especially important, as PA offers numerous health benefits for individuals with T1D, including higher compliance with glycemic targets, better cardiovascular function, and improved lipid profile and psychological well-being.[1,3,4,5] In contrast, higher levels of sedentary behavior seem to be related to poorer glycemic metrics.[5]

Despite these recommendations, PA levels and cardiorespiratory fitness in youth with T1D have been shown to be lower than in peers without T1D,[6,7] underpinning the need to encourage an active lifestyle in this group from a young age. Perceived barriers to active lifestyles reported by youth with T1D include several diabetes-related barriers, such as fear of hypoglycemia (FoH), fear of loss of control of diabetes, risk of hyperglycemia, lack of knowledge in managing diabetes around exercise, the need to plan for exercise, and lack of social or medical support.[8-12] Other common barriers include low fitness levels, tiredness, weather conditions, and lack of time or facilities.[8,9,12,13] Of all these reasons, FoH has been identified as the main barrier to PA across all age groups.[9,10] Fear of hypoglycemia encompasses a variety of anxiety symptoms and concerns related to the occurrence of hypoglycemia,[14] which is particularly worrisome due to its health implications.[15] While it may lead to diligent efforts in some patients, such as regular glucose monitoring and proper carbohydrate consumption, it may cause anxiety disorders in other patients and their families, which are associated with inappropriate reduction in insulin doses and overconsumption of carbohydrates, leading to higher glycemic levels, avoidance of PA, depressive symptoms, and impaired quality of life.[16-18]

Studies assessing the relationship between FoH and PA levels in youth show contrasting results and few of them measure PA levels, mostly through self-report questionnaires.[19-21] For instance, in a cross-sectional study of 201 children and adolescents with T1D, Jabbour et al.[9] found that FoH and loss of control of diabetes were some of the main barriers to PA. The authors also identified parental support as a key factor promoting active lifestyles among youth; however, PA levels were not assessed. Later, the same author reported that FoH was associated with higher vigorous PA levels and that this activity was also associated with the use of continuous glucose monitoring (CGM).[20] Similarly, a study including 1129 youth (10–17 years) with T1D found that FoH was significantly associated with increased vigorous PA levels but not with moderate PA, suggesting that FoH might not be a major barrier to PA.[21]

Given the numerous health benefits of PA in patients with T1D and its key role as part of their treatment,[2] more research is needed on FoH and its potential as a barrier to PA. The use of device-measured PA levels may be more objective than the use of self-report questionnaires to examine this relationship. Such information would be crucial to add more emphasis on the link between PA levels and perceived barriers and to open new horizons for engagement in PA safely among these patients. Accordingly, the objective of the present study was to examine whether children and adolescents with T1D avoid PA due to the risk of hypoglycemia related to this activity and its relationship with device-assessed PA parameters and glycemic metrics.

2 | RESEARCH DESIGN AND METHODS

2.1 | Subjects

This is a cross-sectional study of children and adolescents with T1D living in the Autonomous Community of Navarra, Spain (Diactive-1 Study). Participants were recruited between May 2021 and February 2022 from the Pediatric Diabetes Unit at the University Hospital of Navarra (Spain). Patients were included in accordance with the following criteria: (a) Inclusion criteria: patients with diagnosed T1D from 6 to 18 years old with more than 6 months of disease duration who consented to participate in the study; (b) Exclusion criteria: any comorbidity limiting the capacity to participate in PA or inadequate understanding of the Spanish language. From the 183 patients followed in the Pediatric Endocrinology Unit, 143 were eligible, and 82 patients agreed to participate (participation rate of 57.3%).

All participants signed a written assent form, and their parents signed a written informed consent form before the study. The study was approved by the Drugs Research Ethics Committee of the University Hospital of Navarra (PI_2021/32).

2.2 | Anthropometric and body composition parameters

Standing height was measured in bare feet, with heels together and touching the base of the vertical measuring column, with the back straight and the head positioned in the Frankfurt horizontal plane.[22] Standing height was

determined with a SECA 213 stadiometer (Hamburg, Germany) and recorded to the nearest 0.1 cm.

Body weight was measured in bare feet and light clothing to the nearest 0.1 kg using a SECA electronic scale (Scale 869). Body mass index (BMI) was calculated by dividing the weight in kilograms by the square of height in meters.

Total body fat was measured by dual-energy x-ray absorptiometry (DXA Lunar iDXA, GE Healthcare), with the participant in supine position, with the arms slightly separated from the body and with the feet and legs hip-width apart.

2.3 | Physical activity

The volume and intensity of PA were measured with a GENEActive triaxial accelerometer (ActivInsights) worn on the wrist of the nondominant hand. Accelerometers were programmed to measure at a frequency of 85.7 Hz across 9 consecutive days.[23] The research team deemed that sampling 86 times per second was sufficient to capture the majority of movements performed by patients. Accelerometer data were extracted using GENEActiv PC Software (version 3.3) and processed and analyzed using the R package GGIR.[24] Waking wear time for valid cases represented children and adolescents with at least 7 days and at least 10 h of waking wear time in a 24-h period, including 1 weekend day. Validated cut points were used to determine the following PA variables[25-27]: sedentary activity (for children: 0–56.3 mg; for adolescents: 0–50 mg), light PA (for children: 56.3–191.6 mg; for adolescents: 50–150 mg), moderate PA (for children: 191.6–695.8 mg; for adolescents: 150–500 mg), and vigorous PA (for children: >695.8 mg; for adolescents: >500 mg). Moderate-to-vigorous PA was defined as activities for which at least 80% of 1 min time satisfied the moderate PA threshold criteria (i.e., 191.6 mg for children and 150 mg for adolescents) to remove signals related to random wrist movement.[28]

2.4 | Diabetes assessment

Data on the type of therapy (i.e., multiple daily insulin injections or continuous subcutaneous insulin infusion through a pump system) and duration of the disease were obtained from medical records. During the 9 days of accelerometry, each participant was asked to fill in a diary containing the rations of carbohydrates consumed (1 ration = 10 g carbohydrates) and the daily insulin doses administered. The total carbohydrates (ration/day) and total dose of insulin per kilograms of body weight were then calculated (units/kg/day).

All participants used a CGM FreeStyle 2® Libre device (Abbott Diabetes Care) as part of their everyday diabetes management and were instructed to continue their use during the 9 days of evaluation. The device measures interstitial glucose every 60 s and generates a glucose value every 15 min and the corresponding glucose curves. The data are summarized in the ambulatory glucose profile report as the following percentages of time-in-range (TR): very high (glucose >250 mg/dL), high (181–250 mg/dL), target (70–180 mg/dL), low (54–69 mg/dL), and very low (< 54 mg/dL); the glucose coefficient of variation (CV) is also calculated.[29] We also registered the number of hypoglycemic events per day, mean glucose level during this period, and percentage of time the CGM sensor was active. The most recent glycated hemoglobin (HbA1c) measurement was obtained from the medical records. Those patients who did not have an HbA1c measurement in the last 3 months before the evaluation were asked to repeat the test. HbA1c was measured at the central laboratory of the University Hospital of Navarra (Spain). According to the ADA,[2,30] we considered the following metrics as meeting glycemic targets: HbA1c <7%; CV ≤36%; TR very high <5%; TR high <25%; TR target >70%; TR low <4%; and TR very low <1%.

2.5 | Fear of hypoglycemia

Validated questionnaires measuring FoH, such as the pediatric version of the Hypoglycemia Fear Survey (CFHS), use comprehensive scales that measure a group of worries and behaviors other than those related to exercise.[31] Moreover, the reliability of the CFHS behavior subscale has demonstrated poor internal consistency (Cronbach's α 0.59),[31] and a study using this tool reported that children and caregivers with the highest scores of "Avoid/Prevent low blood glucose" had the lowest HbA1c levels compared with those with lower scores.[32] The widely used "Barriers to Physical Activity in Diabetes (type 1) (BAPAD-1) scale" has not been validated in children and therefore may not be an adequate tool for our purpose.[13] Keeping these gaps in mind, we used the following question to assess FoH as a specific barrier to PA: *"Does fear of hypoglycemia, due to the loss of glycemic control related to physical activity, keep you from practicing this activity?"* Possible answers were "yes," "no," and "sometimes." For the present analysis, "yes" and "sometimes" were grouped as a barrier to PA. To assess FoH as a result of the lack of information regarding the management of PA in diabetes, we also asked the patients the following question: "*Do you consider that*

you need more information on how to manage your diabetes (diet and insulin) in order to perform PA?" Possible answers were "yes" and "no."

2.6 | Statistical analysis

All data analyses were performed using JASP (version 0.16.3, https://jasp-stats.org/). Summary measures (mean, standard deviation [SD], %) or median (interquartile range [IQR]) were used to describe the sample characteristics. Variables were checked for the distributional assumption of normality using normal plots and tested using the one-sample Shapiro–Wilk test. Differences between continuous parametric variables were examined with the *t*-test, continuous nonparametric variables were examined with the Wilcoxon signed rank test, and dichotomous variables were examined with the *chi-squared* test.

We used a bootstrapping method with 1000 iterations and resampling of PA parameters and glycemic metrics with replacement as a nonparametric method of computing the differences between the group means (i.e., those with and without FoH). We also tested whether the confidence intervals (CI) for both groups' means overlapped with the bootstrapping method. The difference between groups was assumed to be valid if the 2.5% and 97.5% quantiles of the resampled group mean did not overlap. The Holm–Bonferroni method was used for post-hoc statistical comparisons.

Finally, multinomial logistic regression analyses were performed to obtain the probability of meeting the recommendations of HbA1c, CV, and time-in-range according to FoH groups (we used no FoH as the reference group). All analyses were adjusted for sex, disease duration, and type of therapy.[31] Analyses involving glycemic metrics were also adjusted for the percentage of time the CGM sensor was active.

3 | RESULTS

Of the 82 subjects who participated in the study, 33 (44.6%) were female, and 74 completed the questionnaires (Table 1).

Fifteen subjects (20%) reported avoiding PA due to FoH. The no FoH group showed lower total PA (−35.33 min/day, 95% CI −77.57 to −1.47) and light PA (−29.81 min/day, 95% CI −64.01 to −2.75) and higher sedentary time per day (77.95 min/day, 95% CI 26.46–136.87) than the FoH group (Table 2). Analysis of glucose metrics showed that FoH was associated with higher HbA1c (−0.58%, 95% CI −1.00 to −0.19), while no differences were found in hypoglycemic events, mean glucose, CV, and time-in-ranges (Table 2).

No association was found between those patients with FoH in terms of meeting the recommendations of HbA1c, CV, and time-in-range compared with those reporting no FoH (Table 3). Finally, no difference was found between FoH and the perception of a lack of information about the management of PA and T1D ($p = 0.281$; data not shown).

4 | DISCUSSION

The present study evaluated FoH as a specific barrier to PA in children and adolescents with T1D and its potential relationship with meeting glycemic targets. We found that children and adolescents who reported avoiding PA to prevent hypoglycemia are indeed more active and spend less time in sedentary behaviors than their peers who

TABLE 1 Baseline participant characteristics of the Diactive-1 Study according to fear of hypoglycemia.

	Total ($N = 74$)	No FoH ($n = 59$)	FoH ($n = 15$)	*p*
Females, *n* (%)	33 (44.60)	24 (40.68)	9 (60.00)	0.179
Age, years	12.77 (2.76)	12.82 (2.98)	12.31 (2.44)	0.536
Duration of diabetes, years	4.89 (3.44)	4.45 (3.56)	5.51 (2.35)	0.279
Height, m	1.57 (16.05)	1.57 (16.96)	1.53 (13.95)	0.431
Body mass, kg	51.79 (16.98)	51.65 (17.43)	49.67 (18.80)	0.798
BMI, kg/m^2	20.39 (4.12)	20.29 (4.09)	20.72 (5.01)	0.725
Percentage of body fat, %	27.82 (7.99)	27.44 (8.21)	30.33 (7.86)	0.211
Insulin pump, *n* (%)	27 (36.49)	19 (32.20)	8 (53.33)	0.129
CGM sensor active, % time	89.76 (14.62)	89.89 (14.80)	87.13 (16.86)	0.538
Carbohydrates, rations/day	16.67 (4.87)	16.52 (4.68)	16.21 (5.40)	0.829
Insulin dose, Units/kg/day	0.75 (0.32)	0.74 (0.28)	0.87 (0.37)	0.163

Note: Data are shown as mean (SD) except for sex and insulin pump: *n* (%).

Abbreviations: BMI, body mass index; CGM, continuous glucose monitoring; FoH, fear of hypoglycemia.

TABLE 2 Differences in physical activity parameters and glucose metrics according to fear of hypoglycemia.

	No FoH ($n=59$)	FoH ($n=15$)	Mean difference ($95\%_{bca}$ CI)	p_{Holm}[a]
PA parameters[a]				
Light-intensity PA, min/day	238.16 (6.79)	269.01 (14.90)	−29.81 (−64.01 to −2.75)	0.028
Moderate-intensity PA, min/day	78.54 (4.39)	94.59 (9.07)	−16.34 (−39.23 to 1.41)	0.088
Vigorous-intensity PA, min/day	10.01 (1.01)	11.83 (2.01)	−2.11 (−6.82 to 1.24)	0.377
MVPA, min/day	36.98 (3.25)	42.66 (5.88)	−5.26 (−22.32 to 4.16)	0.478
Total PA, min/day	275.87 (8.96)	310.65 (17.65)	−35.33 (−77.57 to −1.47)	0.046
Sedentary, min/day	626.35 (15.86)	547.50 (22.26)	77.95 (26.46–136.87)	0.021
Glucose metrics[b]				
Glycated hemoglobin, %	7.14 (0.12)	7.71 (0.20)	−0.58 (−1.00 to −0.19)	0.020
Mean glucose, mg/dL	171.59 (5.03)	169.10 (7.19)	1.49 (−14.52 to 20.51)	0.811
Hypoglycemic episodes, *n*/day	0.88 (0.09)	1.11 (0.14)	−0.21 (−0.54 to 0.12)	0.306
TR very high, %	12.24 (1.83)	15.04 (2.70)	−2.93 (−8.26 to 3.84)	0.444
TR high, %	25.51 (1.46)	26.64 (1.88)	−1.06 (−6.26 to 4.12)	0.647
TR target, %	59.30 (2.45)	56.05 (3.02)	3.20 (−5.40 to 11.01)	0.488
TR low, %	2.72 (0.42)	2.12 (0.62)	0.60 (−0.85 to 2.01)	0.474
TR very low, %	0.31 (0.10)	0.09 (0.15)	0.23 (−0.09 to 0.67)	0.345
Glucose coefficient of variation, %	37.54 (0.98)	39.13 (1.63)	−1.54 (−4.43 to 2.75)	0.466

Abbreviations: Bca, bias-corrected accelerated (mean difference estimate is based on the median of the bootstrap distribution); FoH, fear of hypoglycemia; MVPA, moderate-to-vigorous PA; PA, physical activity; TR, time-in-range.

[a]Analysis adjusted for sex, disease duration, and type of therapy.

[b]Analysis adjusted for sex, disease duration, type of therapy, and percentage of time the continuous glucose monitoring sensor was active.

TABLE 3 Odds of meeting glucose metrics recommendations according to fear of hypoglycemia.

	Odds ratio	95% confidence interval	*p*
Glycated hemoglobin (<7.0%)	0.544	0.136–2.183	0.391
TR very high (<5%)	0.429	0.086–2.142	0.302
TR high (<25%)	0.538	0.106–2.724	0.454
TR target (>70%)	0.335	0.068–1.651	0.179
TR low (<4%)	1.400	0.344–5.700	0.639
TR very low (<1%)	1.744	0.341–8.907	0.504
Glucose coefficient of variation (<36%)	0.612	0.171–2.197	0.452

Note: Reference group (1.00) = no fear of hypoglycemia.

Abbreviation: TR, time-in-range.

Adjusted for sex, disease duration, type of therapy and percentage of time continuous glucose monitoring sensor was active.

reported no FoH, suggesting that FoH does not constitute a major barrier to PA in our cohort. Our results are contrary to what is reported in most studies in both adults and youth,[9,10,18] perhaps because many of them are focused on the barriers to PA or FoH without measuring PA levels. For instance, Jabbour et al.[9] found that FoH and loss of control of diabetes were the main barriers to PA in 201 youths with T1D but did not measure PA levels. Studies including PA levels have shown contrasting results. Livny et al.[19] found that 76% of a pediatric cohort reported FoH as a main barrier to PA and that the average barriers score was negatively associated with PA levels. Likewise, Patton et al.[33] studied the relationship between parents' and preschoolers' FoH, PA, and glycemic variability and found that while parents showed relatively low levels of worry about hypoglycemia and avoidance behaviors, preschoolers' sedentary behavior, and moderate-to-vigorous PA were significantly associated with parental worry scales. Conversely, two recent studies show results similar to ours. A cross-sectional study of 1129 adolescents reported that higher FoH (behavior subscale) was associated with increased days of self-reported vigorous PA but not with moderate PA or sports team participation.[21] Similarly, a study by Jabbour and Bragazzi[20] found a positive relationship between FoH and vigorous PA, although the association seemed to be mediated by the use of CGM as a mitigating factor reducing FoH.

The abovementioned information suggests that FoH is less of a barrier to PA than previously believed, as new technologies can help patients maintain more stable glucose levels, reducing fear and its consequences for avoidance behavior. All participants in the present study used

CGM, which may help them deal with their fear while preserving active living. Studies in this regard have, however, shown inconsistent results, and other factors, such as type of treatment, parental and health professional support and history of hypoglycemia events, seem to play a role in this complex association.[20] Moreover, the educational program our participants received since diagnosis, including continuous telephone medical support and advice of updated recommendations regarding PA, likely had a positive impact on their confidence, allowing engagement in PA.[34] It would also make sense that those patients who are more active are those who actually recognize the threat of hypoglycemia and may fear its appearance more than those who are more sedentary. In addition, not all patients reporting FoH show related overreactions. This may be the case for the patients in our study, while they recognize the threat and their fear, they continue exercising, indicating that they are perhaps more cautious while doing PA.

In terms of glycemic metrics, once all glucose readings were converted into time-in-range metrics and the percentages of compliance with the recommendations were calculated, no association between FoH and any range was observed. In contrast, we found that FoH was associated with increased HbA1c levels. Other studies evaluating the relationship between FoH and HbA1c have reported confounding results.[14,21,31] For instance, Shepard et al.[32] aggregated data from five studies analyzing a total of 259 youth with T1D and 250 parents and found no correlation between HbA1c and child or parent FoH. Conversely, in a cross-sectional study of 196 children and 325 parents, children in the highest FoH group also had higher HbA1c levels than those in the lowest fear quartile.[35] The age of the patient may be determinant in this relationship, as younger patients may be more vulnerable to parents' fear than adolescents who participate more actively in their treatment. Contrary to our findings, Jurgen et al.[36] reported that less FoH was associated with higher HbA1c in 83 youths and that this relationship was mediated through poorer adherence to the treatment. This may be explained by the fact that some level of FoH may actually help to increase adherence to treatments, whereas too much fear may have the opposite impact, resulting in higher glycemic levels.[14] Behaviors associated with FoH that may explain its association with elevated HbA1c include the overtreatment of hypoglycemic events, overeating, intentionally maintaining elevated glucose levels, and/or applying less insulin than needed, among others.[37] Studies in adults with T1D have documented an increased consumption of total calories, carbohydrates, fat and proteins among those with FoH.[18] Although no differences in the mean carbohydrate rations consumed per day or insulin doses were found in our cohort, our results suggest that those reporting FoH and avoiding PA to prevent hypoglycemia may be engaging in other behaviors, such as those mentioned above, leading to an increase in HbA1c levels. However, taking into account that HbA1c may not always be the best biomarker to define the glycemic status, the joint assessment of other parameters such as time-in-range may build on valuable information.[38]

Our study has some limitations and strengths. The main strengths include the use of simultaneous CGM and 24-h accelerometry to assess the temporal associations between PA and glucose metrics across 9 days, allowing the measurement of patients' normal daily activity in a free-living setting. However, our study has several limitations that should be considered. First and most importantly, we did not use a validated questionnaire to assess FoH. Most of the tools that have been used to evaluate this relationship among youth with T1D assess FoH as a whole (i.e., including worry, situation, and behavior subscales, with the latter assessing not only refusing to engage in PA but also other behaviors) or have not been validated in children.[13,14,21,31] However, an adapted version of the"Barriers to Physical Activity in Type 1 Diabetes" (BAPAD1) scale has been successfully used in children and adolescents[19] and may have been a better tool to assess barriers to PA in our cohort. Second, one study[9] reported that lack of parental support is associated with a greater number of barriers to PA, and we did not explore this factor, which could be a mediator in the relationship found between FoH and PA. Third, we did not evaluate other barriers and facilitators to PA that may have influenced our results. Moreover, other behaviors related to FoH that may affect the likelihood of meeting glycemic goals were not examined and might explain, in part, the nature of our findings. Fourth, the CGM period corresponds to 14 days, while the accelerometry assessed PA through only 9 of these 14 days. This discrepancy in times may account for inconsistencies in our results that should be considered. Finally, the use of CGM also presents limitations, including loss of sensitivity during bouts of hypoglycemia and numerical errors.[39]

In conclusion, we observed that youth with FoH were more active and less sedentary and had similar glycemic metrics to those without FoH. Nonetheless, given the great variety of factors that seem to play a role in the relationship between FoH and PA or glycemic metrics, such as educational and social factors, accessibility to CGM, type of treatment, age, sex, previous history of hypoglycemia events, and their severity, among others, it may not be appropriate to generalize our findings to patients in other settings.

5 | PERSPECTIVE

Our results suggest that FoH is less of a barrier to active lifestyle than previously believed. New technologies can

help patients maintain more stable glucose levels, reducing fear and its consequences for avoidance behavior. Therefore, youth with T1D should be encouraged to engage in physical activity with more intensity and minimize sedentary behavior, which can benefit their cardiorespiratory fitness levels and could lead to further improvement in the achievement of glycemic targets.[5]

AUTHOR CONTRIBUTIONS

M.J.C.G., S.B.Z., E.B.S., and M.I. were involved in the conception, design, and conduct of the study and the analysis and interpretation of the results. N.H.U. wrote the first draft of the manuscript, and all authors edited, reviewed, and approved the final version of the manuscript. A.G.H. 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.

FUNDING INFORMATION

This study was funded by grant PI21/01238 from the Instituto de Salud Carlos III (Spain). Dr. García-Hermoso is a Miguel Servet Fellow (Instituto de Salud Carlos III – CP18/0150). The project that gave rise to these results received the support of a fellowship from "la Caixa" Foundation granted to Nidia Huerta Uribe (ID 11780038). Open access funding provided by Universidad Pública de Navarra.

CONFLICT OF INTEREST STATEMENT

The authors have no relevant financial or non-financial interests to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

CONSENT TO PARTICIPATE

Informed consent was obtained from all individual participants included in the study.

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How to cite this article: Huerta-Uribe N, Chueca-Guindulain MJ, Berrade-Zubiri S, Burillo-Sánchez E, Izquierdo M, García-Hermoso A. Is fear of hypoglycemia a major barrier to an active lifestyle in children and adolescents with type 1 diabetes? The Diactive-1 Study. *Scand J Med Sci Sports*. 2023;00:1-8. doi:10.1111/sms.14369