Revista de Psicología Clínica con Niños y Adolescentes

The relationship between depressive symptom severity and attentional bias in children with type 1 diabetes

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Abstract

According to cognitive models, attentional bias to mood-congruent emotional information could give rise to the development of depression. However, the role of different components of attentional bias in this vulnerability is not clear. In this context, the aim of this study was to investigate the relationship between depressive symptom severity and different components of attentional bias to sad stimuli in children with T1D. Twenty-seven children with T1D (59% girls) aged 8 - 12 (M = 10.6, SD = 1.3) and 27 age-matched healthy controls (78% girls) participated in this study. Participants completed the Reynolds' Children's Depression Scale and a modified version of the dot-probe task. Contrary to previous studies emphasizing the role of disengagement biases in depression, we observed an association between depressive symptoms and attentional engagement bias for mood-congruent materials in children with T1D. We discussed that early allocation of attentional resources to mood-congruent emotional information in children with T1D could be a risk factor for depressive symptoms in these children.

Keywords: attentional bias; attentional engagement; dot-probe task; depressive symptoms; type 1 diabetes.

Resumen

La Relación entre la Gravedad de los Síntomas Depresivos y el Sesgo Atencional en Niños con Diabetes Tipo 1. Los niños que viven con diabetes tipo 1 (DT1) tienen un mayor riesgo de depresión. Según los modelos cognitivos, el sesgo de atención hacia la información emocional congruente con el estado de ánimo podría dar lugar al desarrollo de depresión. Sin embargo, el papel de los diferentes componentes del sesgo atencional en esta vulnerabilidad no está claro. En este contexto, el objetivo de este estudio fue investigar la relación entre la gravedad de los síntomas depresivos y los diferentes componentes del sesgo atencional hacia estímulos tristes en niños con DT1. Veintisiete niños con DT1 (59% niñas) de edades entre 8 y 12 años (M = 10.6, SD = 1.3) y 27 controles sanos de edad similar (78% niñas) participaron en este estudio. Los participantes completaron la escala de depresión infantil de Reynolds y una versión modificada de la prueba de punto-probe. Al contrario de estudios previos que enfatizan el papel de los sesgos de desvinculación en la depresión, observamos una asociación entre los síntomas depresivos y el sesgo de compromiso atencional para materiales congruentes con el estado de ánimo en niños con DT1. Discutimos que la asignación temprana de recursos atencionales hacia información emocional congruente con el estado de ánimo en niños con DT1 podría ser un factor de riesgo para síntomas depresivos en estos niños.

Palabras clave: sesgo de atención; participación atencional; tarea de puntos-probe; síntomas depresivos; diabetes tipo 1 (DT1).

Type 1 Diabetes (T1D) is a metabolic disorder that occurs when the pancreas gland does not produce enough- or any- insulin (Atkinson et al., 2014). T1D is one of the most common chronic diseases in childhood (Gale, 2005). Previous research has shown that people with T1D are at increased risk for psychological and cognitive dysfunctions (van Duinkerken et al., 2020). One of the most commonly reported psychological problems in T1D is depression (Ducat et al., 2014). In Iran, in particular, 14.4% of children with diabetes were reported to experience depression (Sayarifard et al., 2020). Depression in T1D not only damages patients'

quality of life but because of its association with poor disease management has further adverse consequences (e.g., Grey et al., 2002; Jurgen et al., 2020; Khater & Omar, 2017). For example, Jurgen et al. (2020) found that in children and adolescents with T1D, more depressive symptoms predicted worse glycemic control. The authors observed that the association between depression and glycemic control was mediated by poor adherence to management behaviors. More hospitalization for disease complications was also reported in children with T1D who had higher depressive symptom severity (Khater & Omar, 2017). Given the association between depressive symptoms and T1D complications, it is crucial to investigate the correlates of depression in T1D. One of the promising approaches to this issue is focusing on the cognitive explanation of depression. According to cognitive models, biases at different levels of information processing serve as a vulnerability factor for depression (Beck, 2008; Beck & Clark, 1988). More specifically, an excessive tendency to attend to negative information would increase the susceptibility to developing depression (Gotlib & Joormann, 2010; Suslow et al., 2020). This tendency, referred to as attentional bias, has been argued to play a pivotal role in both the onset and recurrence of depression (Gotlib & Joormann, 2010).

Previous research revealed that attentional bias consists of engagement (AKA vigilance), disengagement, and avoidance components (See Cisler & Koster, 2010, for more details). Although it is argued that these three components should not be considered mutually exclusive (Weierich et al., 2008), studies with adults showed that depression is more associated with disengagement bias rather than other components (Cisler & Koster, 2010; Mathews & MacLeod, 2005; Suslow et al., 2020). It remains to be seen, however, if similar patterns of attentional bias exist in pediatric depression. Platt et al. (2017) conducted a comprehensive review of 21 studies and determined that pediatric depression is linked to attentional bias for sad stimuli in general. Nonetheless, the specific role of different components of attentional biases in pediatric depression remains ambiguous (Elvin et al., 2020). For example, some studies have reported preferential attention (i.e., engagement and/or disengagement bias) for sad stimuli in currently depressed (Hankin et al., 2010) and at risk children (Joormann et al., 2007; Kujawa et al., 2011), whereas others have revealed the opposite pattern, that is attentional avoidance of sad facial stimuli in children currently diagnosed with depression (Harrison & Gibb, 2015) and children at familial risk of depression (Gibb et al., 2009; Gibb et al., 2016). In a recent study focusing on the developmental trajectory of attentional bias in at risk children, Gibb and colleagues (2023) showed that before the age of eight and a half, attentional bias manifested as avoidance of sad stimuli, but then gradually transitioned to attentional preference for such stimuli by age 14.5. This study employed eye-tracking technology to draw conclusions by analyzing gaze duration data that was primarily indicative of disengagement bias, while not reporting indices of engagement bias. In this context, it is imperative to explore whether attentional preference for sad stimuli in at risk children is confined to disengagement bias or if it encompasses attentional engagement bias as well.

To address this inquiry, the utilization of an assessment tool capable of effectively distinguishing engagement and disengagement biases is warranted. Importantly, discrete assessment of engagement and disengagement biases requires that (a) participants' initial attention be fixated on a predetermined locus, (b) emotional and neutral stimuli appear either distal or proximal to this initial locus of attention, and (c) indices of attentional engagement and disengagement biases be calculated based on the difference in the deployment of attention between the two loci proximal or distal to the initial attentional focus (see Grafton & Macleod, 2014, for a detailed discussion).

Therefore, in this study, we utilized Attentional Response to the Distal vs. Proximal Emotional information (ARDPEI) task which is believed to be a sensitive measure of engagement and disengagement biases of attention by addressing the above-mentioned requirements (Grafton & Macleod, 2014). Therefore, the aim of the current study was to compare the performance of children with T1D – who are at risk of developing depression- and healthy controls on the ARDPEI task. Specifically, we investigated what component(s) of attentional

bias was/were engaged during attention allocation in the presence of sad stimuli. We also aimed to examine the association between components of attentional bias and depressive symptom severity in children with T1D.

Method

Participants

Twenty-seven children (16 girls) with T1D aged 8 to 12 years (M = 10.6, SD = 1.3) and 27 age-matched controls (21 girls) (M = 10.0, SD = 1.2) participated in this study. Diabetic children were recruited from the Iranian Diabetes Society in 2019. Inclusion criteria for children with T1D were as follows: (i) age between 8 and 12 years, (ii) being a member of the Iranian Diabetes Society, (iii) parents' consent for their children's participation in the study, (iv) children's willingness to take part in the study. Children in the control group were recruited from a cultural center offering educational and recreational activities for kids during summer vacation of 2019 in the Velanjak neighborhood in Tehran. Inclusion criteria for children in the control group were: (i) age between 8 and 12 years, (ii) not having a history of chronic disorders or neurological problems, verified by their parents' report, (iii) parents' consent for their children's participation in the study, (iv) Children's willingness to take part in the study. A summary of the socio-economic status of the children based on their parents' education and profession is provided in Table 1. All participants had normal or corrected-to-normal visual acuity. This study was reviewed and approved by the Bio-medical Ethical Committee of Shahid Beheshti University (IR.SBU.ICBS.98/1001).

Table 1. Parents' educational and professional status in both groups of children with diabetes and controls.

	Education			Profession		
-	Primary	Diploma	University	Labor	Employee	Self-
	school		education	worker		employed
T1D (%)	11	51.7	37.3	3.7	48.1	48.1
Control (%)	26	33.3	40.7	26	40.7	33.3

Note: Abbreviations: T1D= Type 1 Diabetes.

Instruments

Reynolds' Children's Depression Scale (RCDS). The RCDS (Reynolds, 1989) is a self-report measure of depressive symptom severity for clinical and non-clinical children aged 8 to 12. The scale includes 30 items which are scored on a Likert-type scale ranging from 1 (almost never) to 4 (all the time). Example items of the RCDS are "*I feel happy*", "*I worry about school*" or "*I feel lonely*". The last item comprises 5 facial expressions, ranging from sad to happy. Children indicate how they feel by choosing one of them. The total score varies from 30 to 121. A higher score represents higher depressive symptomatology. The Persian version of the RCDS (Ebrahimi-Moghaddam & Jolanian, 2016) was used in this research, which was reported to have acceptable internal reliability (*Cronbach* α = .83). The internal consistency of the RCDS for this study was acceptable, too (*Cronbach* α = .88).

ARDPEI task. Attentional bias was assessed using the ARDPEI task. The task was written in Microsoft Visual Studio Express. Each trial of the ARDPEI task began with the presentation of two white rectangles ($5.5 \text{ cm} \times 7 \text{ cm}$), each displayed on either side of the screen at a distance of 5 cm from the center, subtending a visual angle of 7.86°.

A 2 cm × 2 cm red square outline (2.86° of visual angle) was also displayed inside one of the white rectangles with equal probability across trials. Participants were required to initially fixate their attention on the red square outline. After a 1000 ms interval, an anchor probe in the shape of a horizontal or vertical red line (0.5cm) appeared inside the red square outline for 150 ms. In half the trials, the line appeared horizontally and in the other half, it appeared vertically. Participants were required to notice the orientation of the red line. Upon the disappearance of the anchor probe, a face pair (i.e., an emotional and a neutral face) was displayed for 500 ms in the loci previously occupied by the white rectangles. The emotional image appeared either proximally to the initial attentional focus (that is in the locus previously occupied by the white rectangle with the anchor probe in it) or distally from the initial attentional focus (within the other white rectangle) with equal probability across trials. Following the presentation of the face pair, the red line - now functioning as the target probe- appeared for a second time within the locus previously occupied either by the emotional or neutral faces (hereafter called emotional and neutral target probes, respectively). The line appeared either vertically or horizontally with equal probability across trials and was equally distributed between the two screen loci. Participants were required to decide whether the orientation of the target and anchor probes was matched. The orientation was similar in half of the trials. The target probe would remain on the screen until response. If there was no response within 6000 ms, the next trial would begin after an interval that varied between 750 and 1250 ms across trials. Reaction times and response accuracy were recorded. Figure 1 shows the illustration of the ARDPEI task.

The Emotional faces used in this task were selected from the Karolinska Directed Emotional Faces (KDEF) database (Lundqvist et al., 1998). This particular database has been employed in studies involving Iranian participants (e.g., Kord et al., 2016; Ramesh et al., 2018).

Forty-eight images with sad facial expressions were selected for experimental trials. 48 happy and 48 angry face images were also used in control trials. Faster reaction times for emotional target probes than for neutral target probes indicated attentional bias to emotional stimuli. The task included 15 practice trials and 144 main trials organized into two blocks.

Procedure

Parents of the children who participated in the study provided their written informed consent before testing. The children's consent was obtained verbally. The children were tested individually. They were seated on an adjustable chair in front of the laptop monitor at an approximate distance of 40 cm from the screen. Participants first completed the ARDPEI task. The task was presented on a GIGABYTE laptop with a 12-inch screen size. Responses were captured using the Z and M buttons of the laptop keyboard. These keys were labeled with colorful stickers for easy identification. To give the children an idea about the task, the examiner used paper drawings. Then, the children were shown practice trials on the laptop. They were asked to press the M button on the laptop keyboard if both probes matched, and the Z button if they were mismatched. For ease of answering, participants were instructed to keep their right index finger on the M button and their left index finger on the Z button and press the relevant keys as accurately and quickly as possible. By the end of the practice trials, all participants reported they had fully understood what they were supposed to do. Then, the children were told to press the space button on the keyboard to start the main task which took almost 15 minutes. After the participants completed the ARDPEI task, the RCDS was administered. For younger children who had difficulty reading the test, the items were read to them by the same female examiner. At the end of the testing session, the children were offered small gifts (such as balloons, bobby pins, marbles) for their participation. The parents of children with T1D received educational brochures.

Statistical analysis

The Mann-Whitney U test was used to compare the severity of depressive symptoms between participants with T1D and their healthy counterparts.

Analysis of the data from the ARDPEI task was performed on participants' response latencies in correctly performed trials. Incorrect trials were excluded from analysis. This led to the exclusion of 14.9% and 14.8% of trials in the groups of children with T1D and controls, respectively. The frequency of true and false responses differed across neither group (X2 = .08, p = .77) nor emotion (X2 = 3.15, p = .20). To control for outliers, reaction times falling outside three standard deviations (3SD) from each participant's mean reaction time were removed. This led to the exclusion of 3.00% of the entire trials. To provide an attentional bias index, the difference in response latencies for emotional and neutral target probes were computed as follows (scores above zero represented attentional bias for emotional stimuli):

To discretely assess engagement and disengagement biases, the attentional bias index was computed in two different types of trials: a) trials where the emotional face image appeared distal to the initial attentional focus, i.e., the loci of the anchor probe, which yielded an attentional engagement bias index, and b) trials where the emotional face image appeared proximal to the initial attentional focus,

Figure 1. Example of the flow of events on an engagement trial.



which yielded an attentional disengagement bias index (Grafton & MacLeod, 2016). Then, the attentional bias scores were applied to a $2\times2\times3$ mixed-design ANOVA with the diabetics vs. controls as a between-group factor and attentional bias type (engagement bias) vs. disengagement bias) and emotion type (sad vs. anger vs. happy) as within-group factors.

Due to the skewed distribution of data, the Spearman correlation test was used to examine the correlation between depression and attentional bias. Statistical analysis of all data was performed using R software (version 3.6.0).

Results

Results from the Mann-Whitney U test on the RCDS scores revealed no statistically significant difference between the T1D group (M = 41.1, SD = 10.8) and the controls (M = 45.1, SD = 11.8) (U = 277.5, p = .13).

Regarding attentional bias engagement and disengagement indices, our results showed an attentional engagement bias with all different emotional expressions in both children with T1D and healthy controls. Contrary to this, no attentional disengagement bias was observed across either groups or emotions (Table 2).

Table 2. Means of attentional bias indices under each unique experimental condition.

	Attentional bias					
	Engagement			Disengagement		
	Sad	Angry	Нарру	Sad	Angry	Нарру
T1D	100.22	183.1760	139.81	-107.7635	-122.75	-108.88
Control	126.68	161.5738	113.32	-140.1494	-161.10	-117.81

Note: Abbreviations: T1D= Type 1 Diabetes.

Having established the normality and homogeneity of variances of attentional bias scores (Tables 3 & 4), the scores were applied to a 2×2×3 mixed-design ANOVA with the diabetics vs. controls as a between-group factor and attentional bias type (engagement bias vs. disengagement bias) and emotion type (sad vs. anger vs. happy) as within-group Factors. The analysis revealed a significant effect of attentional bias type, F(1, 52) = 16.71, p < .001, $\eta 2 = .09$, which reflected an attentional bias characterized by engagement with rather than difficulty disengaging from emotional facial expressions. The analysis also showed the main effect of emotional type F(2, 104) = 3.22, p = .044, $\eta 2$ = .02. Using the Tukey post hoc test, we found a significant difference between attentional bias scores for angry vs. happy facial expressions, t = 2.37, p = .04. The results of the comparison between attentional bias scores for sad vs. happy expressions t = -.85, p = .67, and sad vs. angry expressions t = 1.52, p = .28; were not significant. Moreover, the analysis did not yield any significant effect of group, F(52, 1) = .26, p = .61, indicating that both children with T1D and controls reflected attentional engagement bias with emotional expressions compared to neutral ones. None of the interactional effects were found to be significant.

Table 3. Levene's test of homogeneity of variance.

	df	F	p-value
Levene's test	1	1.322	0.2511

Note: Abbreviations: df = degrees of freedom, F = F statistic of Levene's test

Table 4. Mauchly's test of sphericity.

effect	Mauchly's W	p-value
emotion	0.913663	0.10001
group * emotion	0.913663	0.10001
attentional bias * emotion	0.952618	0.290024
attentional bias * emotion * group	0.952618	0.290024

The Spearman correlation test was used to examine the correlation between depression and attentional engagement bias. As revealed in Table 5, attentional engagement bias was found to be associated with sad stimuli but only in children with T1D. In other words, diabetic children with higher depression scores displayed more robust attentional engagement with sad facial expressions, $r_s = 1983.4$, p = .04.

Table 5. Correlation between depression and attention bias indices.

	Engagement			Disengagement		
	Spearman	S	p	Spearman	S	р
T1D	0.39	1983.4	0.04	-0.15	3773	0.45
Control	-0.01	3340.1	0.92	0.17	2711.1	0.39

Note: Abbreviations: T1D= Type 1 Diabetes, s = S statistic (standard error), p = p-value.

Discussion

In this study, we sought to investigate the engagement and disengagement components of attentional bias in a group of children who were assumed to be at a higher risk of developing depressive symptoms due to the diagnosis of T1D. Consequently, we compared the performance of children with T1D with their healthy counterparts. Additionally, we examined the association between the severity of depressive symptoms and the aforementioned components of attentional bias.

In line with the emotionality hypothesis (e.g., Bujanow et al., 2020; Calvo & Lang, 2004), the first part of our results revealed that both children with T1D and healthy controls showed attentional bias to faces with an emotional expression. Additionally, in both groups, attentional bias to emotional stimuli only involved the engagement component which is in line with a series of eye-tracking studies reporting an early shift of attention to emotional stimuli when presented concurrently with neutral stimuli (Calvo & Lang, 2004; Calvo et al., 2008; but see Acunzo & Henderson, 2011, for contradicting results). Calvo and Lang (2004), in their study, reported an early hold of attention which lasted for 500 ms following the stimulus onset. This finding may sound contrary to the results from our study which did not reveal a disengagement bias during the 500-ms presentation duration. This inconsistency can be explained by different task demands. In our task, attention could have been held by the emotional stimuli, but participants managed to successfully disengage attention from them because it was demanded to correctly identify the orientation of the target probe. This goal-directed behavior involves effortful or strategic control ability - known as effortful control - which could aid children in the modulation of their behavioral, attentional, and emotional reactivity (Rothbart & Ahadi, 1994). Specifically, attention control, as a component of effortful control, has been shown to affect the allocation of attention to emotionally salient stimuli in children (Henderson & Wilson, 2017; Liu & Bell, 2020).

Another important finding from our study is concerned with how the valence of emotional information modulates attentional bias: We observed that in both groups (i) there was a significantly robust attentional engagement with angry faces compared to happy ones; (ii) sad faces caused a weaker attentional engagement relative to angry faces and a stronger attentional engagement relative to happy faces; however, in neither case, was the difference statistically significant. Although both anger and sadness have negative valence – so, they caused a rather stronger engagement bias compared to happy faces - "but" should be omitted here the motivational intensity of anger is higher than sadness (Harmon-Jones et al., 2013), therefore, this could explain the slightly lower engagement score for sad faces relative to angry faces.

The first two findings revealed important aspects of selective attention in children in general; however, our last finding was directly related to the link between the components of attentional bias and depressive symptoms in at-risk children (i.e., children with T1D): we observed a relationship between the severity of depressive symptoms and an engagement bias of attention towards sad facial expressions in children with T1D. While previous studies have mostly associated depression in adults with disengagement bias (e.g., Bradley et al., 1997), we found that in children and adolescents with T1D, who are at risk of depression, early attentional capture to emotionally mood-congruent information is associated with depressive symptom severity. We believe that our finding carries significant developmental implications. Although studies on the components of attentional bias in pediatric depression are scarce, the few available studies suggest that the pattern of attentional bias in pediatric depression may vary across development. For example, Gibb et al. (2023) observed a changing trend from attentional avoidance to longer gaze duration on sad stimuli during the transition from childhood to adolescence in at-risk children. It is reasonable to consider that the reported preferential attention in Gibb et al's study also involved an engagement bias (e.g., a higher fixation frequency for sad stimuli), which may have been more pronounced between ages eight to 12, as revealed in our study. This notion, however, is speculative and warrants further research investigating both engagement and disengagement attention biases during development.

One potential explanation for the absence of a robust disengagement bias in children at risk of depression, in contrast to findings in the literature of depressed adults, could be linked to depressogenic cognitions that may not be fully stable in children (see Jacobs et al., 2008, for an in-depth review). Specifically, LaGerange et al. (2008) depicted that Beck's negative cognitive triad (Beck, 1995), which is central to the etiology and maintenance of depression, does not stabilize until early adolescence. It is plausible that during childhood and early adolescence, when depressogenic cognitions are not yet fully stable, adverse life experiences directly contribute to the onset of depressive mood and an engagement with mood-congruent stimuli. However, as depressive cognitive styles become increasingly stable later in life, the attentional mechanism shifts from vigilance towards mood-congruent stimuli to an inability to disengage from such stimuli. An alternative explanation pertains to the differences between children and adults in terms of attentional mechanisms that guide visual processing behavior. It has been demonstrated that during childhood, viewing behavior predominantly depends on bottom-up attentional mechanisms. However, as individuals age, bottom-up influences diminish and top-down mechanisms become predominant (Açık et al., 2010; Elvin 2020). As a result, it is expected that maladaptive attention allocation engages bottom-up processes in children and top-down processes in adults. That said, pediatric depression should be associated with an engagement bias, which is purportedly mediated by bottom-up automatic mechanisms (Cisler & Koster, 2010), as these mechanisms dominate visual attention during childhood. Conversely, a disengagement attentional bias, which is mediated by top-down attentional control (Cisler & Koster, 2010), is anticipated to be evident in adults, whose visual attention is primarily guided by top-down processes. Given the limited research on the developmental trajectory of cognitive biases, it is imperative for future studies to empirically investigate these explanations.

Although the association we observed between attentional bias and depressive symptom severity cannot be interpreted as causation, significant symptom reductions reported in studies that used the Attentional Bias Modification (e.g., Beevers et al., 2015, Li et al., 2023) provide support for the causal role of attentional bias in depression. With this in mind, it seems plausible to consider attentional bias in children with T1D as a risk factor for the development of depressive symptoms over time. Future longitudinal research can shed light on this in particular and, more generally, on whether attentional bias to unpleasant emotional stimuli in children suffering from chronic diseases or adverse life events could predict a diagnosis of depressive symptoms in later years.

Despite the significant contribution of the current study to attentional bias research in both pathological and non-pathological cases, some limitations must be noted. First, in the ARDPEI task, we could have presented emotional and neutral faces in separate trials to realize whether there was a difference in performance when a neutral or an emotional stimulus was presented. However, this strategy could lengthen the task and increase the risk of fatigue in young children. Second, the ARDPEI task exerts a memory load which could affect performance. That is, successful performance in this task requires remembering the spatial orientation of the anchor probe throughout the trial to correctly decide which key to press upon its second appearance at the end of the trial. Although combining eye-tracking technology with the ARDPEI task can eliminate the need for presenting the anchor probe (Grafton & MacLeod, 2014), one should not fail to notice concerns regarding the validity of eye movements to assess covert attention (the allocation of mental resources without gaze reorientation). Since gaze and attention can be dissociated during covert attention, it is likely that eye movements do not fully reflect the allocation of attentional resources. Behavioral tasks, however, can fill this gap because the effects of both overt and covert attention are reflected in data from such tasks.

In the ARDPEI task used in the current study, we aimed to investigate attention allocation to photographic faces during a 500-ms presentation period. Sears et al. (2019), however, reported higher reliability for attentional bias indices for naturalistic images compared to face images. Given this, it is proposed for future research to replace faces in the ARDPEI task with naturalistic scenes to see if any differences in attentional bias patterns might emerge as a result of this modulation. Moreover, given the evidence that attentional bias for mood-congruent stimuli in depression is observed at long exposure durations (Gotlib et al., 2004; Joormann et al., 2007; Oehlberg et al., 2012), it remains to be seen in future research how lengthening stimulus presentation beyond 500 ms could lead to a difference in performance between children with T1D and controls.

In summary, this study provides support for the association between depressive symptom severity and attentional biases for mood-congruent information in children with T1D. Although no difference in performance was found between the diabetics and the controls on the attentional bias task, the significantly positive correlation observed between the self-report depressive symptoms and attentional bias for sad information in children with T1D points to the role of cognitive biases in depression.

Conflict of interest

The authors declare no conflict of interest.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Acknowledgments

The authors would like to thank the Iranian Diabetes Society for facilitating access to children with type 1 diabetes who participated in our study.

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