

# Depression and parenting in youth with type 1 diabetes: Are general and diabetes-specific parenting behaviors associated with depressive symptoms over a 2-year period?

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**Abstract** To examine cross-sectional and longitudinal associations of general parenting style and diabetes-specific parenting behaviors with depression in youth with type 1 diabetes. Participants ( $n = 390$ ) completed self-report measures of depression at baseline and 2-year follow-up, general parenting style at baseline, and diabetes-specific parenting (conflict, task involvement, and collaborative involvement) at baseline and every 6 months. Logistic regression examined associations of parenting with depression at baseline and 2-year follow-up. A less authoritative parenting style, lower parent collaborative involvement, and greater diabetes-related conflict were associated with baseline depression in the model simultaneously including all parenting variables and covariates. Lower parent collaborative involvement and higher diabetes-related conflict were associated with depression at 2-year follow-up, adjusting for baseline depression and covariates. Parent task involvement was not associated with depression at either time. Findings suggest a protective role of parenting in reducing the risk of depression in youth with type 1 diabetes.

**Keywords** Adolescence · Youth with type 1 diabetes · Depression · Parenting behavior · Parenting style

Adolescence is characterized by psychological vulnerability, which is heightened among adolescents living with chronic disease (Nardi et al., 2008). Among youth with type 1 diabetes, depression is the most common psychological condition (Grey et al., 2002; Hood et al., 2006), and is associated with poor diabetes management adherence (Herzer & Hood, 2010; McGrady et al., 2009; Rewers et al., 2002). The demands of type 1 diabetes management may give rise to adjustment problems that influence depression (Herzer & Hood, 2010; Hood et al., 2006), and adolescence is a particularly crucial period due to developmentally-related declines in diabetes management (Streisand & Monaghan, 2014). Depressive symptoms often interfere with diabetes management and are associated with poorer glycemic control (B. Anderson et al., 1997; Johnson et al., 2013; Kongkaew et al., 2014; Lustman et al., 2000; Mortensen et al., 1998). However, parents may be helpful in decreasing risk of depressive symptoms as they are vital to the promotion of positive disease adaptation, management, and coping during adolescence (Hauser et al., 1993; Helgeson et al., 2009; Seiffge-Krenke, 1998). This study focuses on parenting and youth depression in the context of type 1 diabetes, as parenting behavior may be a targetable factor to mitigate risk of depressive symptoms among youth with type 1 diabetes.

Research among adolescents in the general population indicates that parenting styles characterized by controlling and intrusive behavior or lack of affection are associated with depression (Biggam & Power, 1998; McFarlane et al., 1995; Patton et al., 2001). From an ecological perspective, children's behavior and well-being are strongly influenced

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by their interpersonal relationships, including those with parents (Bronfenbrenner, 1977). A secure and trusting relationship with parents promotes optimal psychosocial development; an insecure attachment is associated with internalizing problems (Brumariu & Kerns, 2010). An authoritative parenting style, which comprises high responsiveness (i.e., warmth) and demandingness (i.e., expectations), contributes to youths' overall well-being and autonomy while encouraging secure parent–child attachments (Karavasilis et al., 2003). Parental responsiveness creates an atmosphere of warmth and support, affection and acceptance, security, involvement in the child's academic and social development, and acknowledgement of the child's achievements. Parental demandingness establishes clear and reasonable boundaries and expectations to actively monitor children's activity and maintain structure in the child's life. The influence of the parent–child relationship extends to other domains. Poor relationships between adolescents and parents may inhibit social and personality development, (Bowlby, 2008) impair self-confidence, and result in difficulties establishing relationships with peers (Kraaij et al., 2003), placing adolescents at greater risk for depression.

The importance of parenting style (Goethals et al., 2017; Monaghan et al., 2012; Radcliff et al., 2018; Shorer et al., 2011) and diabetes-specific parenting behaviors (Ellis et al., 2007; King et al., 2014) for promoting optimal diabetes management is well-documented. Parent–child conflict generally increases in adolescence (Holmbeck, 1996), and discordance may arise regarding decision-making autonomy, disease management tasks, and adherence to diabetes regimen (Helgeson et al., 2014). However, parents who monitor diabetes management by responding to adolescents' need for independence with warmth and guidance are able to help their children maintain better diabetes outcomes (Allen et al., 1983; Anderson et al., 1997; Ingersoll et al., 1986; Wiebe et al., 2005). Similarly, better management of diabetes occurs when adolescents view parents as supportive collaborators and not intrusive or controlling (B. J. Anderson et al., 1999; Wiebe et al., 2005).

However, less is known about the association of depression with general or diabetes-specific parenting behaviors in youth with type 1 diabetes. In two small cross-sectional studies ( $n = 84$  and  $78$ , respectively), more critical parenting behaviors (i.e. criticism, nagging, and negativity) (Armstrong et al., 2011) and greater maternal psychological control (Butler et al., 2007) were associated with greater depressive symptoms in youth with type 1 diabetes. In a longitudinal study ( $n = 132$ ), shared responsibility for diabetes management was associated with fewer depressive symptoms in cross-sectional analysis, but was unassociated with change in depressive

symptoms over time (Vicki S. Helgeson et al., 2008). Among high school seniors with ( $n = 117$ ) and without ( $n = 122$ ) type one diabetes, parental support was associated with reduced depressive symptoms, while parental control was associated with increased depressive symptoms (V. S. Helgeson et al., 2014). Additionally, in a study of 61 parent–child dyads, parental depressive symptoms were indirectly associated with youth depressive symptoms through lower parental involvement (Eckstain et al., 2010). While this small body of research suggests the relevance of parent behaviors on youth depressive symptoms, an important limitation is that most examined only a single parenting construct, and none assessed both general and diabetes-specific parenting. As such, they cannot inform the contribution of different aspects of parenting behavior as they relate to youth depressive symptoms in this vulnerable population. Additionally, since parenting style is believed to impact specific parenting practices (Darling & Steinberg, 1993), it would be informative to determine whether parenting style is independently associated with depression after accounting for diabetes specific parenting practices, and whether parenting style indirectly effects depression through diabetes specific parenting practices.

The purpose of this study was to examine cross-sectionally and longitudinally the relationships of general parenting style and diabetes-specific parenting behaviors - including diabetes-related conflict, parent collaborative involvement, parent diabetes management task involvement, and parent–child diabetes management task responsibility-sharing - with depression in youth with type 1 diabetes. We hypothesized that youth whose parents demonstrate a more authoritative parenting style (that is, more responsive, more demanding, and less controlling) will report lower levels of depressive symptoms. Given the centrality of diabetes management to the lives of youth with type 1 diabetes, we also hypothesized that youth who report greater parent collaborative involvement, task involvement, and responsibility-sharing, and lower diabetes-related conflict will report lower levels of depressive symptoms. Additionally, we hypothesized that general parenting style will be indirectly associated with depression through these diabetes-specific parenting behaviors.

## Methods

### Sample and procedure

Participants were enrolled in a multicenter randomized controlled trial testing the efficacy of a clinic-integrated, family-based behavioral intervention on glycemic control and adherence. The intervention focused on enhancing parent–child teamwork and problem-solving skills for

diabetes management. It was designed to assist families in adhering to the tasks of day-to-day diabetes management during the pre-adolescent and early adolescent developmental period, which is marked by transitions in parent-child roles and during which adherence and glycemic control generally decline. Primary outcomes were glycemic control and adherence; the intervention had a positive effect on glycemic control at 2-year follow-up (Nansel et al., 2012).

The study was conducted from January 2006 to March 2009 at four pediatric endocrinology clinics in the United States (Massachusetts, Florida, Illinois, and Texas). Research assistants recruited participants during routine clinic visits. Study enrollment criteria included ages 9–14.9 diagnosed with type 1 diabetes mellitus for at least 3 months with a minimum insulin dose of at least 0.5 U/kg/day for those diagnosed > 1 year and 0.3 U/kg/day for those diagnosed < 1 year, mean HbA1c > 6% and < 12%, and no other chronic, cognitive disability, or psychiatric illness. Parent eligibility included geographically stable home with telephone access, able to speak and understand English, history of at least two clinic visits within the previous 12 months, and no major psychiatric diagnosis. Baseline assessments were conducted by two-person interviewing teams not affiliated with the clinics, in the families' homes or other locations convenient to participants. Subsequent self-report measures were completed during routine clinic visits. Subject retention through study completion was 92% and there were no differences between families retained and those who withdrew by age, gender, ethnicity, baseline HbA1c, or duration of diabetes. Further details on the study design, recruitment, the behavioral intervention and primary outcomes have been published previously (Nansel et al., 2012). The study protocol was approved by the Institutional Review Boards of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development and each of the participating clinical sites.

## Measures

**Depression** The Children's Depression Inventory (CDI) was completed by youth at baseline and 2-year follow-up. The 27-item measure has been validated in children aged 7–17 years (Kovacs, 2003). Responses for the 27 depressive symptoms are rated from no symptom (0) to distinct symptom (2), with response options specific to each symptom. CDI scores range from 0 to 54; higher scores indicate greater depressive symptoms. Cronbach alpha at baseline was .89 (Kovacs, 1992).

**Parenting style** Based on the conceptualization of authoritative parenting as consisting of warmth/responsiveness, demandingness (i.e., behavioral control), and

accepting of psychological autonomy (i.e., low psychological control) (Darling & Steinberg, 1993), the 16-item Authoritative Parenting Index (Jackson et al., 1998) and the 8-item Psychological Control Scale (Barber, 1996) were completed by youth at baseline to measure authoritative parenting style (including subscales of parental responsiveness, demandingness, and psychological control). Response options for both measures range from (1) strongly disagree to (4) strongly agree. The Authoritative Parenting Index consists of two subscales—responsiveness and demandingness. Greater authoritative parenting is indicated by higher responsiveness and demanding, and lower psychological control. Both measures have previously demonstrated good psychometric properties. Cronbach alpha in the current sample was .82 for responsiveness, .72 for demandingness, and .82 for psychological control.

**Parent collaborative involvement** Youth completed the 16-item Collaborative Parent Involvement Scale at baseline and every 6 months. This measure assesses aspects of parent involvement that reflect a consultative or collaborative role, such as consulting, supporting, planning, problem-solving, and trouble-shooting—dimensions of parent involvement that may remain high even as youth assume greater responsibility for conducting specific tasks like insulin injections and blood glucose monitoring. Items include assisting with planning diabetes care within the youth's schedule, helping the youth learn how to manage difficulties with diabetes, knowing when to give the youth more autonomy, and knowing when the youth requires extra assistance. Response options range from (1) almost never to (5) always. The measure has previously shown good internal consistency, expected age-related changes, and differential relationships with adherence (Nansel et al., 2009). Cronbach alpha in the current sample was .93.

**Diabetes-related conflict** Youth completed the revised Diabetes Family Conflict Scale at baseline and every 6 months. The measure queries family conflict around 19 aspects of diabetes management (Hood et al., 2007). Response options are on a 3-point scale, of (1) never argue through (3) always argue. Higher scores indicate greater conflict. Cronbach alpha in the current sample was .92.

**Diabetes management responsibility** Youth completed the Diabetes Family Responsibility Questionnaire at baseline and every 6 months, to assess the degree of parent involvement in 17 diabetes management tasks, such as taking insulin, adjusting insulin, deciding what to eat, and remembering to do blood sugar checks (B. J. Anderson et al., 1990). For each item, participants indicate whether responsibility for the task (1) belongs to the child, (2) is shared equally between child and parent, or (3) belongs to the parent. Traditionally, the sum of the items is used as a measure of overall parent involvement in diabetes man-

agement tasks (in this study, termed parent task involvement). We also calculated a shared responsibility score, as the total number of responses indicating that responsibility is shared equally between child and parent (termed shared responsibility for tasks). Cronbach alpha in the current sample was .69.

**Hemoglobin A1c (HbA1c)** Blood samples were obtained at each visit by finger stick and frozen for shipment to a central laboratory (Joslin Diabetes Center Laboratory, Boston, MA). HbA1c was assayed by HPLC (Tosoh 2.2 device, Tosoh Corporation, South San Francisco, CA, USA); reference range is 4.0–6.0%.

**Data analysis**

Descriptive statistics were used to examine variable distributions. Analysis of variance (ANOVA), t-tests, and linear regression were performed to estimate bivariate associations of baseline depression with gender, race/ethnicity, family structure, diabetes regimen, age, socioeconomic status, diabetes duration, and HbA1c. Based on previous literature defining authoritative parenting as a constellation of high responsiveness, high demandingness, and low psychological control (Darling & Steinberg, 1993), factor analysis of the three parenting subscales was conducted. The subscales loaded a single factor, and the resulting factor score was used in subsequent analyses to represent authoritative parenting style. For each child, the longitudinal profile of each parenting behavior measure (parent collaborative involvement, diabetes-related conflict, parent task involvement, and shared responsibility for tasks) was summarized into intercept and rate of change and was obtained from fitting a linear mixed-effect model. Baseline values of each measure were used for analysis of associations with baseline depression; for variables assessed longitudinally, individual intercepts and rates of change were used for analysis of associations with depression at follow-up.

Linear regression was used to quantify associations of parenting variables with depression at baseline and follow-up. Adjusted models controlled for all significant parenting variables and for demographic variables (diabetes regimen, race/ethnicity, and family income) associated with baseline depression at  $p < 0.10$ . Analyses examining depression at follow-up also controlled for baseline depression. Linear regression was used to test for an association of intervention status with depression at follow-up. Intervention status was not associated with depression, and therefore not included in the models testing associations of parenting variables with depression. However, potential moderation of associations by intervention status was tested using linear regression with interaction terms of intervention status (intervention vs. control) by each parenting variable

(intercept and rate of change). Separate models were conducted to test interactions with each parenting variable. Additionally, potential moderation of associations by age were tested using the same approach. Because the theoretical conceptualization of parenting style hypothesizes that parenting style influences outcomes through specific parenting behaviors (Darling & Steinberg, 1993), path analysis using structural equation modeling (SEM) was performed to assess the indirect effect of parenting style on depression as mediated by the diabetes-specific parenting behaviors (intercepts and rates of change). All analyses were performed using SPSS (Version 22) and SAS (Version 9.4).

**Results**

**Sample characteristics**

Participants’ demographic information is summarized in Table 1. Of 390 participating families, 385 youth completed the depression measure at baseline, and comprise the sample for this analysis. Mean baseline depression score was 5.94 (SD = 6.6).

**Table 1** Participant characteristics at baseline

	N	%
Gender		
Female	197	51.17
Male	188	48.83
Race/ethnicity		
White	274	74.86
Racial/ethnic minority	92	25.14
Marital status		
Married/living together	309	82.84
Separated/divorced	42	11.26
Widowed	4	1.07
Never married	18	4.83
Regimen		
Pump	131	34.11
Injection	253	65.89
Family income		
< 50 K	122	31.69
50– < 100 K	138	35.84
100– > 150 K	125	32.47
	Mean	SD
Age	12.43	1.73
Diabetes duration (months)	58.27	39.39
HbA1c	8.37	1.15

### Intervention effect on depression

Intervention status was not associated with depression at 2-year follow-up. At follow-up, mean depression score was 5.83 (SD = 5.94) for intervention participants and 5.59 (SD = 6.67) for control participants ( $p = .73$ ).

### Relations of parenting style and diabetes-related parenting behaviors with depression at baseline

Parenting style was moderately correlated with collaborative parent involvement ( $r = .55, p < .001$ ); other correlations among parenting variables were modest (Table 2). In unadjusted baseline models (Table 3), a more authoritative general parenting style ( $p = .0001$ ), greater parent collaborative involvement in diabetes management ( $p = .0001$ ), lower diabetes-related conflict ( $p = .0001$ ), and greater shared responsibility for tasks ( $p = .0004$ ) were each associated with lower risk for depression. Parent task involvement was not associated with depression. In the adjusted model including all parenting variables simultaneously and controlling for regimen, race, and income, general parenting style ( $p = .0001$ ), parent collaborative involvement ( $p = .0001$ ), and diabetes-related conflict ( $p = .006$ ) were significantly associated with depression.

### Relations of baseline parenting style and longitudinal diabetes-related parenting behaviors with depression at 24 months

In unadjusted models, baseline general parenting style ( $p = .0001$ ), the intercept ( $p = .0001$ ) and rate of change ( $p = .001$ ) for parent collaborative involvement, and the intercept ( $p = .0001$ ) and rate of change ( $p = .0001$ ) for diabetes-related conflict, and the intercept ( $p = .02$ ) for shared responsibility for tasks were each associated with depression at 2-year follow-up. Parent task involvement was not associated with depression at follow-up (Table 4). In the adjusted model including all significant parenting variables simultaneously and controlling for baseline depression status, regimen, income, and race, the rate of change of parent collaborative involvement ( $p = .0001$ ) and the intercept and rate of change of diabetes-related conflict ( $p = .004$  and  $p = .002$ , respectively) were associated with depression.

Results from the path analysis testing the indirect effect of baseline general parenting style as mediated by diabetes-related parenting behaviors on depression at follow-up showed significant mediating effects through the intercepts of parent collaborative involvement ( $p < .0001$ ) and diabetes-related conflict ( $p = .0003$ ) (Table 5).

**Table 2** Intercorrelations of parenting variables at baseline

	General parenting style	Parent collaborative involvement	Diabetes-related conflict	Parent task involvement
Parent collaborative involvement	0.55***			
Diabetes-related conflict	− 0.26***	− 0.16**		
Parent task involvement	0.04	0.20***	0.12*	
Shared responsibility for tasks	0.16**	0.27***	− 0.13**	0.17**

\* $p < 0.5$

\*\* $p < .01$

\*\*\* $p < .001$

**Table 3** Associations of parenting behaviors with child depression at baseline using linear regression models

Parenting	Depression at baseline					
	Unadjusted*			Adjusted*		
	B	SE	<i>p</i>	B	SE	<i>p</i>
General parenting style	− 3.46	0.29	0.0001	− 2.21	0.36	0.0001
Parent collaborative involvement	− 3.81	0.36	0.0001	− 2.07	0.43	0.0001
Diabetes-related conflict	0.22	0.04	0.0001	0.11	0.04	0.006
Parent task involvement	0.02	0.07	0.83			
Shared responsibility for tasks	− 0.45	0.13	0.0004	− 0.10	0.11	0.38

\*Unadjusted analyses reflect separate models of each parenting variable with depression. The adjusted model includes all significant parenting variables, with regimen, race, and income as covariates

**Moderation of associations by intervention status and age**

There were no significant interactions of intervention status with any parenting variable on depression status at follow-up, indicating that associations of parenting with depression did not differ by intervention status. Further, there were no significant interactions of age with any parenting variable on depression status, indicating that the associations of parenting with depression did not differ by age.

**Discussion**

In this sample of youth with type 1 diabetes participating in a behavioral intervention efficacy trial, parent collaborative involvement in diabetes management and diabetes-related conflict were each independently associated with depression at baseline and 2-year follow-up. Additionally, general parenting style was independently associated with baseline depression, and with depression at 2-year follow-up in analyses unadjusted for diabetes-specific parenting. Shared responsibility for tasks was associated with depression at baseline and follow-up only in unadjusted analyses, and parent involvement in diabetes management tasks was not associated with depression at either time point. Findings highlight the relevance of parenting behaviors as a potential protective factor for depressive symptoms among youth with type 1 diabetes.

The association of parenting style with depression observed in this study is consistent with previous research among children and adolescents in the general population demonstrating the association of authoritative parenting with lower risk of depression and more optimal psychosocial functioning across a variety of dimensions (Karavasilis et al., 2003; Kaufmann et al., 2000; Maccoby & Martin, 1983). In youth with type 1 diabetes, authoritative parenting may also facilitate parents’ ability to remain involved in their children’s diabetes management in a responsive and collaborative way. Notably, the association of parenting style with depression at baseline was significant in models also containing these diabetes-specific parenting practices, suggesting a protective role of parenting style beyond its potential influence on diabetes-specific parenting practices. At 2-year follow-up, the association of baseline general parenting style with depression was not significant after adjusting for diabetes-specific parenting. However, path analyses suggested an indirect effect of parenting style on depression mediated by parent collaborative involvement and diabetes-related conflict. These findings are consistent with theoretical understanding and empirical findings that specific parenting practices are influenced by general parenting style (Darling & Steinberg, 1993; Spera, 2005).

Consistent with a small body of previous research, diabetes-specific parenting behaviors, specifically collaborative parent involvement and diabetes-related conflict, were associated with depression at baseline and 2-year follow-up (Grey et al., 2011; V. S. Helgeson et al., 2014).

**Table 4** Associations of parenting behaviors with child depression at follow up using linear regression models

Parenting	Depression at follow-up					
	Unadjusted*			Adjusted*		
	B	SE	<i>p</i>	B	SE	<i>p</i>
General parenting style	− 1.39	0.34	0.0001	0.58	0.39	0.13
Parent collaborative involvement						
Intercept	− 3.67	0.61	0.0001	− 1.24	0.73	0.09
Rate of change	− 2307.98	418.42	0.001	− 1981.88	406.73	0.0001
Diabetes-related conflict						
Intercept	0.70	0.10	0.0001	0.30	0.10	0.004
Rate of change	551.24	136.84	0.0001	395.4	124.77	0.002
Parent task involvement						
Intercept	− 0.04	0.10	0.67			
Rate of change	27.21	142.85	0.85			
Shared responsibility for tasks						
Intercept	− 0.48	0.20	0.02	− 0.05	0.18	0.76
Rate of change	− 159.81	134.54	0.24			

\*Unadjusted analyses reflect separate models of each parenting variable with depression. The adjusted model includes all significant parenting variables with regimen, race, income, and baseline depression as covariate

**Table 5** Indirect association of parenting style on depression through diabetes-specific parenting behaviors using structural equation modeling

Indirect effect of general parenting style on depression through	Effect	SE	t	p
Parent collaborative involvement				
Intercept	− 0.96	0.23	− 4.16	< .0001
Rate of change	0.11	0.08	1.31	0.19
Diabetes-related conflict				
Intercept	− 0.53	0.15	− 3.64	0.0003
Rate of change	0.03	0.05	0.65	0.51
Parent task involvement				
Intercept	0.006	0.04	0.14	0.89
Rate of change	0.002	0.02	0.09	0.93
Shared responsibility for tasks				
Intercept	− 0.03	0.05	− 0.53	0.59
Rate of change	0.005	0.01	0.37	0.71

Inconsistent with previous literature, there was no association of parent involvement in diabetes tasks with depression (Grey et al., 1998; Skinner et al., 2000; Wysocki & Greco, 2006). Conflict between youth with chronic illness and their parents is associated with poorer disease management, lower decision-making autonomy, and lower sharing of disease management tasks (B. J. Anderson et al., 1990; Whittemore et al., 2012). The complexity of diabetes management can bring about an emotionally-charged family environment with resulting negative impact on the youth's psychological functioning (Grey et al., 2002; Hood et al., 2006). Depressive symptoms may thus be more likely to manifest in an environment with poorer diabetes-related parenting behaviors and may disrupt disease management which ultimately impacts health outcomes. The independent associations of parent collaborative involvement and diabetes-related conflict with depression at 2-year follow-up, even after controlling for baseline depression, suggests a pervasive influence of diabetes-specific parenting with depression.

This study is the first to examine longitudinally the association of both general and diabetes-specific parenting behaviors with depression in youth with type 1 diabetes. Strengths of the study include a large sample size with youth from diverse geographic locations, socio-demographic status, and racial status. However, findings should be interpreted considering study limitations. All parenting variables were assessed by child report because measurement of these constructs by parent report is subject to social desirability bias. As parenting style is thought to be relatively consistent over time (Kerr et al., 2003), it was only measured at baseline. Therefore, we cannot determine the potential impact of any change in parenting style on depression at follow-up. These analyses are limited to an examination of selected parenting variables collected in the context of a behavioral intervention trial designed to pro-

mote improved adherence to diabetes management practices. Data collection for the study ended in 2009, and approximately 1/3 of the sample used an insulin pump regimen; findings could vary in more contemporary samples with greater use of advanced technology. The sample had a limited number of youth exceeding the threshold for depression. A multitude of factors, including genetic susceptibility, peer relationships, life events, and individual coping skills may impact the course of depressive symptoms over time. Future research to comprehensively examine environmental, social, and biological factors that may be associated with depression among youth with type 1 diabetes would be informative.

Adolescence is an important developmental period with an increased susceptibility to poorer mental health. While previous research has documented the adverse effect of depression on adherence and glycemic control in youth with type 1 diabetes, few studies have examined potentially modifiable predictors of depression in this population. Findings from the current study suggest that general and diabetes-specific parenting behaviors may serve a protective role in reducing the risk of depression in youth with type 1 diabetes, and thus provide support for efforts to promote positive parenting practices to promote mental health among youth with type 1 diabetes.

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#### Compliance with ethical standards

**Conflict of interest** Katherine W. Dempster, Aiyi Liu, and Tonja R. Nansel declare that they have no conflict of interest.

**Human and animal rights and Informed consent** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

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