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The Association of Blood Glucose with the Daily Self-Regulation of Everyday Life Stress in Adolescents with Type 1 Diabetes

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THE ASSOCIATION OF BLOOD GLUCOSE WITH THE DAILY SELF-REGULATION OF EVERYDAY LIFE STRESS.

A Thesis Presented

by

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ABSTRACT

Adolescents with type 1 diabetes must learn to balance the complexities of managing a chronic disease with managing non-disease-related experiences in their daily life that also contribute to stress. For example, in addition to diabetes management, these adolescents must also balance ongoing demands from everyday life stressors including school, social interactions, and home and family life. However, it remains unclear if daily diabetes management might contribute to experiences of everyday life stress. The present study assessed the association between daily everyday life stress and blood glucose regulation in adolescents with type 1 diabetes using both linear and nonlinear models. Thirty-nine adolescents diagnosed with type 1 diabetes between the ages of 13-17 completed seven daily diary surveys. Data were analyzed using multilevel modeling, including both linear covariation and autoregressive dynamic systems approaches. Results found that everyday life stress represents a regulatory system (attractor state) at the daily level, but daily blood glucose regulation did not covary with everyday life stress in the linear model nor change the state of the regulatory system in the autoregressive systems model. Future studies should continue to explore the relationship between everyday life stress and blood glucose regulation using a dynamic systems framework with different methodological approaches to better capture within-day nuances in stress and glucose regulation in adolescents with type 1 diabetes.

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The Association of Blood Glucose with the Daily Self-Regulation of Everyday Life Stress in Adolescents with Type 1 Diabetes

Type 1 diabetes (T1D) is an autoimmune disease that is caused by cellular-mediated destruction of β-cells in the pancreas that generate insulin (American Diabetes Association, 2021a). T1D accounts for about 10% of all diabetes cases (American Diabetes Association, 2021a) and is one of the most prevalent chronic illnesses in youth. It is estimated that 210,000 children and adolescents currently have the disease in the United States and there are about 20,000 new cases in youth each year (Centers of Disease Control and Prevention, 2020). Individuals with T1D lack insulin-generating β-cells, requiring them to regulate their blood glucose levels manually by administering exogenous insulin to correct for high levels of blood glucose (hyperglycemia) and consuming glucose either through foods with high levels of carbohydrates or supplements to correct for low levels of blood glucose (hypoglycemia; American Diabetes Association, 2021b). The day-to-day management of the disease involves individuals completing complex tasks multiple times each day. Some of these include frequent blood glucose monitoring, administration of insulin, carbohydrate counting, maintaining and wearing technological equipment (e.g., insulin pump and/or continuous glucose monitor), regulating diet and food intake, and regularly having to make in-the-moment decisions when blood glucose is not at an optimal level (Berg et al., 2020; Chao et al., 2016; Rechenberg et al., 2017). Optimal blood glucose regulation is important because sub-optimal management can have negative outcomes on health such as an increased risk of heart disease, kidney failure, neuropathy, blindness, and nephropathy (Chao et al., 2016; Halford et al., 1990; Seiffge-Krenke & Stemmler, 2003).

Compared to younger children and middle-aged adults, adolescents struggle significantly more with optimally regulating blood glucose levels (Herzer et al., 2011; Rechenberg et al., 2017). Although challenges with glucose regulation may be partially attributed to physiological aspects of puberty that disrupt insulin sensitivity (Seiffge-Krenke & Stemmler, 2003), other psychosocial factors also play a key role. Adolescence is a transitional period involving many changes and new developmental demands outside of the diabetes context (Chao et al., 2016; Herzer et al., 2011). Individuals are developing new and more advanced critical thinking and reasoning skills (Chao et al., 2016), and they are discovering new social and self-identities (Chao et al., 2016; Steinberg & Morris, 2001). For adolescents with T1D, many of the day-to-day hassles typical of adolescence may be perceived as considerable stressors in the context of managing a complex chronic disease. Adolescents with T1D have even reported that these "everyday life stressors" are more burdensome than those associated with living with and managing their diseases (Chao et al., 2016; Hema et al., 2009). For this reason, it is important to consider adolescents' experiences of everyday life stressors and how those stressors may be linked with daily blood glucose regulation in adolescents with T1D.

Adolescents with T1D report experiencing everyday life stressors across three primary domains: peer relationships and social identity; school and family responsibilities; and livelihood and home life (Chao et al., 2016; Hema et al., 2009; Seiffge-Krenke & Stemmler, 2003; Wadsworth & Berger, 2006). Like healthy adolescents, adolescents with T1D experience stress related to peer relationships such as fitting in, making and keeping friends, and navigating issues of popularity, bullying, and peer conflict (Chao et al., 2016; Seiffge-Krenke & Stemmler, 2003). In addition, adolescents with T1D also report experiencing stress associated with schoolwork (such as having a lot of homework or difficult teachers), chores and responsibilities within the home, and extracurricular obligations such as sports practices (Chao et al., 2016; Hema et al., 2009). Finally, adolescents with T1D also report experiencing stress related to family living and home life. Increased family conflict is common during this period of development (Laursen & Collins, 1994; Mastrotheodoros et al., 2020) and often involves issues of increased adolescent desire for autonomy (Chao et al., 2016). Further, hardship within the family, such as poverty or problems with meeting basic needs has been found to be a significant source of stress for adolescents as well (Wadsworth & Berger, 2006). Taken together, adolescents with T1D experience elevations in everyday life stress in addition to the stress associated with managing their disease.

Elevations in everyday life stressors contribute to suboptimal diabetes outcomes in adolescents with T1D through both physiological and behavioral pathways. First, increased everyday life stress has been found to be directly associated with sub-optimal glucose levels (Seiffge-Krenke & Stemmler, 2003) and glucose instability (Gonder-Frederick et al., 2016). Sub-optimal blood glucose levels likely occur because stress releases neuroendocrine hormones such as catecholamines that can directly promote hyperglycemia by increasing glucose production (Aikens et al., 1992; Kramer et al., 2000). Second, everyday life stressors are also indirectly associated with sub-optimal blood glucose levels through decreased engagement in treatment self-management behaviors in adolescents with T1D. For example, everyday life stress is associated with less blood-glucose checking, insulin administration, and less engagement in physical activity (Baucom et al., 2015; Gonder-Frederick et al., 2016). Decreased engagement in diabetes treatment is attributable to multiple mechanisms. Behavioral and emotional changes associated with stress may be significant enough to disrupt executive control of daily disease self-management behaviors (Aikens et al., 1992). In addition, increased social stressors (e.g., fear of negative peer evaluation or rejection) can lead to lower engagement in diabetes management behaviors around peers (Brazeau et al., 2018; Chao et al., 2016; Davidson et al., 2004). Further, activities that create high responsibility stress (e.g., work, school, or family obligations) may also negatively impact diabetes outcomes when adolescents choose to prioritize these tasks over engaging in self-management behaviors (Ingersgaard et al., 2021). Finally, family and home life stressors (e.g., financial hardship or problems in livelihood) can make managing T1D especially challenging. For example, adolescents experiencing food insecurity may not be able to easily address or prevent high or low blood glucose (Gucciardi et al., 2014; Malkin-Washeim, 2018). Although there is strong evidence for increased everyday life stress leading to worse diabetes outcomes, it remains less clear whether experiences of everyday life stress are, in the reverse, exacerbated by factors related to T1D.

Adolescents with T1D who have greater daily exposure to dysregulation of blood glucose levels may also, in turn, experience greater everyday life stress. First, there is evidence suggesting that impaired blood glucose regulation might covary with increased experiences of everyday life stress in adolescents with T1D. For example, episodes of hypo-and hyperglycemia negatively impact work productivity and performance (Kalra et al., 2013; Orozco-Beltrán et al., 2018) as well as relationships and emotional states (Sommerfield et al., 2004) in adults with T1D. These areas of impact overlap with areas where adolescents with T1D report experiencing everyday life stressors including, school performance and peer and family relationships. In addition, in children with T1D, severe hyperglycemia was associated with decreased verbal skills and reaction times, and hypoglycemia may be associated with problems in motor and visual-spatial skills and memory (McCarthy et al., 2003; Ryan, 1988). Impaired cognitive functioning secondary to hyper and hypoglycemia is then likely to affect how adolescents with T1D manage everyday life stressors. Consistent with these findings in non-adolescent T1D samples, it is theorized that sub-optimal daily blood glucose levels may be associated with same-day increased everyday life stress in adolescents with T1D.

Moreover, while it is theorized that blood glucose levels and everyday life stress may covary from day-to-day in adolescents with T1D, it is also possible that the relationship between blood glucose levels and everyday life stress might be better captured when viewing stress as a dynamic regulatory system. Specifically, everyday life stress is argued to be the emergent outcome of a complex regulatory system (Brooks et al., 2021). That is, a person’s perception of increased everyday life stress fluctuates throughout the day and arises from how multiple psychosocial and contextual factors interact together in daily life. For example, psychopathology, coping skills, sleep quality, physical health, poverty, food insecurity, social support, discrimination, school support, and family system factors are all known to be associated with everyday life stress (Almeida et al., 2002; Bremner et al., 2020; Hirotsu et al., 2015; Lee & Goldstein, 2016). Given the variety of factors that interact in the emergence of everyday life stress experiences, it may be helpful to use methodological approaches that assume everyday life stress is a complex self-organizing regulatory system.

Dynamic systems theory provides a framework for examining complex regulatory systems, such as stress, in day-to-day life. First, dynamic systems are complex, self-organizing systems that are composed of many individual parts that come together to form patterns and change into different patterns over time (Thelen & Smith, 2007). Dynamic systems are considered open and allow components to push and pull at each other (Thelen & Smith, 2007). Second, dynamic regulatory systems are systems that have an attractor state where the system is always pulled back to a particular homeostatic state (Thelen & Smith, 2007). Regulatory systems settle at a specific point and via self-organization will return to this state when pulled away from it. Third, the strength of a dynamic system depends on how quickly the system is pulled back to this homeostatic state (J. Butner, 2018). Systems that are more stable return to this state more quickly after a perturbation and perturbations must be more substantial to move the system away from the setpoint even for a brief period. These three concepts are consistent with how perceptions of everyday life stress are theorized to emerge day-to-day (Brooks et al., 2021). Thus, it is also theorized that everyday life stress in adolescents with T1D will function as a regulatory system. Last, factors that control shifts in the homeostatic set-point and stability of the system are called control parameters. It is also theorized that the homeostatic state and strength of an individual's everyday life stress regulatory system, may be shifted dependent on the current state of glucose levels. The dynamic regulatory systems perspective might aid in understanding the relationship between everyday life stress and blood glucose regulation in adolescents with T1D and inform future psychosocial interventions to reduce everyday life stress.

The present study had three aims. The first aim was to assess the linear covariation between daily everyday life stress and blood glucose regulation. It was hypothesized that fluctuations in daily blood glucose levels will covary with the level of everyday life stress on the same day in adolescents with T1D. The second aim was to examine if everyday life stress functions as a dynamic regulatory system in adolescents with T1D. It was hypothesized that there will be a significant negative day-to-day autoregressive association between current everyday life stress and next-day stress, which is the linear representation of a regulatory system with an attractor state. Finally, the third aim explored if the homeostatic set-point and strength of the everyday life stress regulatory system is modified by suboptimal blood glucose levels in the adolescents. It was hypothesized that the current level of blood glucose will moderate the association between current and next-day everyday life stress in that higher blood glucose levels will elevate the homeostatic set point of the stress regulatory system and increase the stability of the system around that elevated level of stress.

Methods

Participants

79 adolescents with T1D consented to participate in the first phase of this study, a survey about diabetes management in teens (Cummings et al., 2022). 44 of those adolescents also participated in a second phase of the study, a 7-day daily diary period, which is the primary dataset for the current study. Of the 44 adolescents who completed both study phases, five were not included in the final dataset due to having completed less than two of the seven daily diaries. Within the final sample of 39 adolescents with

T1D, the average age was 15.43 years (SD = 1.06) and the average length of diagnosis was 7.59 years (SD = 3.43). Twenty-seven of the 39 participants identified as female with the remaining 12 identifying as male. 59% of participants identified as white, non-Hispanic, 10% (n = 4) as white-Hispanic, 5% (n =2) as nonwhite-Hispanic, 5% (n = 2) as Asian, one participant identified as Black, and three participants (8%) selected "other" for their race/ethnicity. The remaining four (10%) participants indicated being of mixed race/ethnicity. Finally, participants were asked to report on their use of an insulin pump and/or a continuous glucose monitor (CGM). Ninety-five percent (n = 37) of participants were currently using an insulin pump at the time of data collection and 97% (n = 38) of participants reported current use of a CGM. Finally, all participants used at least one of these technologies.

Procedures

Participants were recruited before and during the check-in period of a diabetes summer camp in northern Nevada and California in summer 2019. Participants were eligible for the study if they had a diagnosis of T1D, were between the ages of 13 and 17, could participate in surveys in English, and had access to WIFI at home to complete questionnaires. The parents of eligible participants were contacted through email and provided information about the study. Interested families were given the option to have parents sign the consent forms before arrival at camp. Additional eligible participants that did not respond to the initial email were recruited during the camp check-in period during which adolescents and their parents were provided information about the study and consent from parents was acquired. Teens provided assent at camp prior to participation.

While at the camp, participants completed a survey that included questions asking about demographic information as well as additional psychosocial diabetes management questionnaires that were not analyzed in the present study. Participation in the daily diary portion of this study occurred one to three months following summer camp when the adolescents returned to school. Participants completed nightly daily diary surveys across seven days. The surveys were sent to participants through email and were to be completed in the evening before bed on an electronic device. If participants had not completed a survey at the agreed-upon time, an additional reminder email was sent later in the evening. Participants' names were entered into a raffle for a $25 gift card for every survey completed in the study, including the baseline measure.

Measures

Everyday Life Stress. The Daily Stress Severity (DSS; (Baucom et al., 2015) scale was developed to assess the occurrence and severity of five general life stressors and five diabetes-specific life stressors. Only the general stressors subscale was used in this study. The list of stressors was originally adapted from the Daily Inventory of Stressful Events (Almeida et al., 2002) and asked participants if they had experienced an argument or disagreement, a problem with school or schoolwork, a problem with work or chores, needing to deal with another person's problems, and a problem with where they live or something they own in the last 24 hours. If participants indicated that they experienced one of these stressors they were asked to rate how stressful the issue was for them on a five-point scale (0 = not at all stressful, 4 = as stressful as it can get). A daily score of everyday life stress was determined by calculating the sum of the stress severity ratings across all five items. Participant scores ranged from 0 to 18 and cross all seven daily diaries the average everyday life stress score was 2.80 (SD = 3.51). Three stress datapoint that were beyond three standard deviations of the mean were retained in the sample due to the values being critical for visualizing the participants' regulatory system including in response to larger perturbations of the system.

Mean Blood Glucose Levels. Within each daily diary, participants were asked to self-report their blood glucose levels from the last 24 hours. The use of self-reported blood glucose levels was supported in prior daily diary studies (Berg et al., 2014; Lansing et al., 2016). In addition, no significant differences have been found between self-report and meter download data (Herzer & Hood, 2010; McGrady et al., 2009) as well as in recent studies that analyzed the present dataset (Benjamin, 2021; Cummings et al., 2022).

Participants who manually checked their blood glucose levels were asked to provide at least six values and a timestamp for each value. To control for a non-equivalent number of data points between CGM and non-CGM users, participants who used a CGM were asked to report their blood glucose levels from six specific time points (i.e., 6:00am, 9:00am, 12:00pm, 3:00pm, 6:00pm, 9:00pm). CGM users were also asked to upload the data from their sensors to an electronic program that provides research access to glucose levels every 15 minutes throughout the day. These across-day glucose values were summarized into a mean daily blood glucose value that was used in place of self-reported values when they were available. Daily mean blood glucose (MBG) was calculated by averaging each participant's six data points for each day. Participants' MBG levels ranged from 74.67 to 364.83 and cross all seven daily diaries the average MBG was 174.93 (SD = 52.76). Four MBG datapoints that we beyond three standard deviations of the mean were retained in the sample due to the values being critical for visualizing the participants' stress regulatory system in terms of MBG and related health risk.

Analysis

To test the hypotheses, three models were analyzed using multilevel modeling in Mplus to account for the nesting of diary data within persons. First, all variables were examined for normality and no issues of non-normality were found. Next, the daily mean glucose level was grand mean-centered. Finally, full information maximum likelihood estimation was used to allow the estimation of models with missing data and all models included random slopes. 30 participants completed all seven diaries, six participants completed at least four diaries, and the remaining five participants completed at least two diaries.

Aim 1 used multilevel modeling to assess the linear relationship between the daily state of everyday life stress (Y_{ij}) and blood glucose levels $\left(X_{ij}\right)$. When using multilevel modeling, analyses are conducted at two levels; a within-subjects level and a between-subjects level. The intraclass correlation for everyday life stress in the current sample was .28 indicating that substantive variance in this measure is at the day-to-day level within-subjects (72%) rather than between-subjects level (28%). For the aim 1 analyses, the daily mean blood glucose level variable was modified into two variables that deconflated the within and between-subject variance in daily mean blood glucose levels, such that at the within-subjects level a person's deviation from their usual or average blood glucose was entered, while at the between-subjects level that person's average blood glucose across the seven diary days was entered. The within-subjects level equation is as follows:

Level 1:

$$Y_{ij} = \beta_{0j} + \beta_{1j}X_{ij} + \beta_{2j}T_{ij} + \varepsilon_{ij}$$

In this equation β_{1j} represents the strength of the association between day-to-day fluctuations in mean blood glucose level and everyday life stress for each person (see Figure 1 for an example participant), while β_{2j} represents the association between diary day (T_{ij}) and everyday life stress to account for linear changes in everyday life stress attributable to repeated daily diary completion. ε_{ij} represents the residual variance for each person and day-specific prediction in the model.

Since daily diary data are nested within individuals, an additional equation is needed to account for the residual variance at the between-subjects level. For example, the between-subjects equation for the association of day-to-day fluctuations in blood glucose levels and everyday life stress β_{1j} is depicted as:

$$\beta_{1j} = \gamma_{1o} + u_{1j}$$

The above equation calculates β_{1j} by accounting for a fixed slope (γ_{1o}) for the population and any deviation for specific subjects from this slope u_{1j}. The between-subjects equations are as follows:

Level 2:

$$\beta_{oj} = \gamma_{00} + \gamma_{01}Z_j + \gamma_{02}C_j + u_{0j}$$

$$\beta_{1j} = \gamma_{10} + u_{1j}$$

$$\beta_{2j} = \gamma_{20} + u_{2j}$$

In these equations, Z_j represents mean blood glucose across the 7-day diary at the between-subjects level and C_j is used to represent the addition of the covariates in the model, including age, gender, race/ethnicity, and length of diagnosis.

To test hypotheses 2 and 3, autoregressive models were analyzed using multilevel modeling in Mplus that reflects a linear approximation of the core features of a dynamic regulatory system: the existence of an attractor state, the homeostatic set-point of that state and the strength of the state of the system. These models do not assume that X and Y covary and thus X explains Y, but that the emergent state of the system is best explained by the prior state of the system. In Aim 2, we examined the existence of the everyday life stress regulatory system, its set-point and strength only, and then in Aim 3, we examined the role of mean daily blood glucose for that system and included the same covariates added in the aim 1 models.

Aim 2 used the following equation, which represents the within-subjects level of analysis used to determine how everyday life stress (*X*) changes over time:

$$(X_{t+1} - X_t)_{ij} = \beta_{0j} + \beta_{1j}X_{ij} + \beta_{2j}T_{ij} + \epsilon_{ij}$$

The above equation describes the change in everyday life stress from day to day, $(X_{t+1} - X_t)_{ij}$, for a specific subject j at a specific time point i. The slope of the relationship between current and next day stress, β_{1j} , determined the presence of an attractor state, i.e., a significant and negative association between current and next day everyday life stress. The intraclass correlation for everyday life stress change in the current sample was .12 indicating that the majority of variance in this measure is at the day-to-day within-subjects (88%) rather than between-subjects level (12%). Like the Aim 1 models, β_{2j} represented the association between everyday life stress and day of diary (T_{ij}) and ϵ_{ij} accounted for the error in each person-day prediction.

Since Aim 2 did not include between-subjects covariates the between-subjects equations were used only to describe a fixed slope for each within-subjects parameter and describe the error for that fixed slope in each person's prediction:

$$\beta_{oj} = \gamma_{00} + u_{0j}$$

$$\beta_{1j} = \gamma_{10} + u_{1j}$$

$$\beta_{2j} = \gamma_{20} + u_{2j}$$

To test Aim 3, a moderating term (W) was added to the within-subject equation to explain how mean glucose levels may act as a control parameter on the everyday life stress system (see Figure 2 for an example participant). The linear approximation of a control parameter is testing how mean blood glucose level moderates the attractor state, i.e., the relationship between current and future state of everyday life stress. The equations tested were as follows:

Level 1:

$$(X_{t+1} - X_t)_{ij} = \beta_{0j} + \beta_{1j}X_{ij} + \beta_{2j}W_{ij} + \beta_{3j}(X_{ij} * W_{ij}) + \beta_{4j}T_{ij} + \epsilon_{ij}$$

Level 2:

$$\beta_{oj} = \gamma_{00} + \gamma_{01}C_j + u_{0j}$$

$$\beta_{1j} = \gamma_{10} + u_{1j}$$

$$\beta_{2j} = \gamma_{20} + u_{2j}$$

$$\beta_{3j} = \gamma_{30} + u_{3j}$$

$$\beta_{4j} = \gamma_{40} + u_{4j}$$

The final mixed model is depicted as:

$$(X_{t+1} - X_t)_{ij} = \left(\gamma_{00} + \gamma_{01}C_j + u_{0j}\right) + \left(\gamma_{10} + u_{1j}\right)X_{ij} + \left(\gamma_{20} + u_{2j}\right)W_{ij} + \left(\gamma_{30} + u_{3j}\right)(X_{ij} * W_{ij}) + (\gamma_{40} + u_{4j})T_{ij} + \epsilon_{ij}$$

For aim 2 and aim 3 the parameters for the mixed model were used to determine the setpoints and strength of the stress regulatory system. Setpoints were identified by setting $(X_{t+1} - X_t)_{ij}$ equal to 0 and solving the equation in full, including for aim 3 at +1 standard deviation and -1 standard deviation of the moderator (*W*). The strength of the stress regulatory system was set by the slope of the attractor state and for aim 3, $\beta_{1j} + (\beta_{3j} * W)$, was probed at +1 standard deviation and -1 standard deviation of the moderator (*W*) to visualize the change in the strength of the attractor system.

Results

First, a multilevel analysis was conducted to test if day-to-day fluctuations and average levels of daily mean blood glucose were associated with daily everyday life stress (Table 1). Neither fluctuations in day-to-day mean blood glucose level ($\gamma_{10} = 0.003, SE = 0.01, p = 0.58$) nor average mean blood glucose across the diary period ($\gamma_{01} = 0.003, SE = 0.01, p = 0.71$) was associated with everyday life stress. Day of daily diary was significantly associated with everyday life stress ($\gamma_{20} = -0.41, SE = 0.09, p < 0.001$) with decreasing stress reported across the assessment period. None of the covariates were significantly associated with everyday life stress, including length of diagnosis, gender, age, and race (see Table 1). In addition, significant residual variance at the within-subjects level ($\epsilon_{ij} = 7.48, p < 0.001$) and the between-subjects level ($u_j = 2.54, p = 0.003$) remained unexplained by the current model.

Next, an autoregressive multilevel model for day-to-day changes in everyday life stress was analyzed to determine if everyday life stress functioned as a regulatory system (Table 2). There was a significant negative day-to-day autoregressive association between current everyday life stress and next-day everyday life stress ($\gamma_{10} = -0.85, SE = 0.08, p < 0.001$) with a negative autoregressive association suggesting an attractor state that is consistent with a regulatory system (See Table 2). The autoregressive equation was probed to describe two features of the regulatory system, the homeostatic set-point of the system and the stability of the system. The setpoint, where current everyday life stress level would be associated with no change in next day everyday life stress, i.e., Xt+1 = 0, was equal to 3.49. The stability of the system is represented in the slope of the association between current and next day everyday life stress, -.85, such that for every one-unit increase in today's stress, tomorrow's stress will reduce by .85 and for every one unit decrease in today's stress, tomorrow's stress will increase by .85. Day of daily diary was not significant predictor of the day-to-day change in everyday life stress ($\gamma_{20} = -0.29, SE = 0.11, 95\%$ CI $[-0.48, 0.002]$), suggesting the set-point of the regulatory system decreased across the diary period. Additionally, the residual variance at the within-subjects level $\left(\varepsilon_{ij} = 6.44, p < 0.001\right)$ and between-subjects level $\left(u_j = 2.09, p = 0.02\right)$ were significant, suggesting variance in change in everyday life stress was not fully explained by previous day everyday life stress.

Last, a multi-level autoregressive moderation analysis was conducted to assess how the homeostatic set-point and strength of the everyday stress regulatory system were modified by levels of daily mean blood glucose (Table 3). The autoregressive association between current everyday life stress and next-day everyday life stress remained significant when mean blood glucose was added into the model ($\gamma_{10} = -0.75, SE = 0.22, p = 0.001$). There was no significant main effect of daily mean blood glucose levels on next day everyday life stress, suggesting the set point of the everyday life stress regulatory system was not significantly shifted by daily mean blood glucose levels ($\gamma_{20} = 0.002\ , SE = 0.01, p = 0.78$). In addition, daily mean blood glucose did not significantly moderate the strength (or stability) of the everyday life stress regulatory system ($\gamma_{30} = -0.001, SE = 0.001, p = 0.65$). In this model, the set point of the everyday life stress system was also not significantly associated with day of daily diary ($\gamma_{40} = -0.28, SE = 0.12, 95\%\ CI\ [-0.48, 0.02]$). None of the covariates had a significant association with change in everyday life stress (see Table 3). Finally, significant residual variance at the within-subjects level ($\varepsilon_{ij} = 6.54, p = 0.000$) and between-subjects level ($\mu_j = 1.73, p = 0.039$) remained unexplained.

Discussion

The present study explored the linear and non-linear relationships between daily everyday life stress and blood glucose levels in adolescents with T1D. Inconsistent with hypothesis 1, it was found that day-to-day fluctuations in blood glucose and average levels of blood glucose across the diary were not associated with everyday life stress. Consistent with hypothesis 2, everyday life stress functioned as a regulatory system in that a significant negative day-to-day autoregressive association was observed between current everyday life stress and next-day stress. However, inconsistent with hypothesis 3, although the everyday life stress regulatory system remained intact when mean blood glucose was added into the model, daily mean blood glucose did not have a significant effect on the set point or strength of the everyday life stress system. Together these findings suggest that while the systems perspective may best describe the day-to-day state of everyday life stress in adolescents with T1D, there is a limited impact of mean blood glucose on everyday life stress when these variables are examined on day-to-day cycles.

Overall, our finding that everyday life stress is best represented as a regulatory system is consistent with previous research on daily stress regulation in adults and in understanding diabetes stress in adolescents with T1D. First, in a general adult population, it was observed that the physiological expression of daily stress self-organizes across time consistent with stress functioning as a dynamical regulatory system (Brooks et al., 2021). Second, in adolescents and emerging adults with T1D, day-to-day diabetes-related stress was also observed to function as an attractor state that was coordinated with other daily diabetes management processes including in the family system (J. E. Butner et al., 2018; Munion et al., 2020). Aligned with these findings, the current study is the first to show that everyday life stress in adolescents with T1D was also represented by a regulatory system. Further research is needed to clarify the everyday life stress regulatory system including what components comprise the everyday life stress regulatory system and which of those components might function as a control parameter to guide intervention research to support reducing everyday life stress in adolescents with T1D.

In contrast, this study did not observe a relationship between everyday life stress and mean blood glucose at either the linear or systems level. While these results contrast past findings linking stress and blood glucose levels at the daily level (Hilliard et al., 2016), there are some inconsistencies in the literature. Specifically, multiple studies only observed a relationship between blood glucose and everyday life (or general stress) through other mechanisms, e.g. treatment engagement (Farrell et al., 2004) or diabetes-specific stress (Rechenberg et al., 2017). Taken together, these findings suggest that both linear and systems models of everyday life stress might need to focus on the transactional associations of treatment engagement and diabetes-specific stress. Still, other studies have also failed to find a linear association between stress and blood glucose levels (Baucom et al., 2015; Hilliard et al., 2016) or only found the association for a small subset of the study sample (Halford et al., 1990; Kramer et al., 2000; Riazi et al., 2004). Less is known about whether exploring everyday life stress and blood glucose levels nonlinearly may help explain the relationship between everyday life stress and blood glucose regulation. In particular, given we did not find support for daily blood glucose level as a control parameter of the everyday life stress regulatory system, it will be important to examine if this association might occur at a more micro-level than day-to-day cycles or only for some adolescents with T1D, perhaps those with highly elevated stress. Future research should continue to utilize dynamic systems modeling and other nonlinear means to aid in understanding how daily blood glucose regulation relates to the regulation of everyday life stress.

Limitations

There are multiple limitations to this study that may also contribute to the findings. First, the results of this study are limited by a small sample size and the occurrence of missing data. Only 44 of the original 79 participants recruited participated in the daily diary portion of the study. Increasing the sample size would increase power and our ability to detect smaller associations between everyday life stress and glucose levels, especially in the context of moderation analyses. Although the use of daily diary data increases power compared to single time-point analyses, the limited sample size remains a concern. In addition, of the 39 participants analyzed, only approximately 77% of participants completed all seven days of the daily diary. Estimations are made to predict around days adolescents did not complete a diary via full information maximum likelihood estimation, but the reliability of this approach diminishes with fewer data available. Ultimately, a larger sample size will likely increase power and reduce the impacts of missing data on future studies examining daily life stress and glucose levels.

Second, an association between everyday life stress and mean blood glucose may not have been observed because on average, the sample in this study endorsed low levels of stress that decreased across the daily diary period. Thus, it is important to consider possible reporter and sampling bias in this study. For reporter bias, day of daily diary was a near significant predictor of decreasing everyday life stress across time. That is, the act of reporting on everyday life stress each night may have impacted adolescents' perception of their stress on the following day. In addition to reporter biases, characteristics of the sample itself may have also contributed to low levels of stress on average. The adolescents completed the daily diary upon returning to school for the new school year and it is possible that this time period was a less stressful one for diabetes management. It may also be that the adolescents who chose to participate in the daily diary phase of the study were overall a less distressed group compared to those who did not participate in the daily diary phase. In addition, a majority of the adolescents in this study (92%) used both an insulin pump and a CGM, and all of the adolescents used at least one piece of technology to assist with managing their diabetes. Research suggests that the use of both of these devices highly reduces stress (Benjamin, 2021). Future studies should consider using samples that better represent low technology users or samples of high-risk individuals, such as adolescents with T1D and high family conflict or psychopathology to ensure representation of variability of everyday life stress scores across the spectrum of diabetes management experiences.

Third, multiple barriers in the measurement of everyday life stress and blood glucose regulation may have also contributed to the present findings of this study. As discussed, low levels of everyday life stress were observed from the current sample on average. Rather than this finding being the result of reporter or sampling bias, low stress levels could be due to limitations in how everyday life stress was measured. Specifically, the Daily Stress Scale was designed as a brief measure of both general and diabetes-specific stress (Baucom et al., 2015), and the general stress subscale only consisted of five stressful situations. It is possible that other unmeasured stressful situations could have contributed to increased stress for the adolescents, including those associated with finances, transportation, respect/disrespect, and receiving bad news (Almeida et al., 2002). Further, the Daily Stress Scale was also unable to capture factors that have been found to highly correlate with stress levels including sleep quality (Hirotsu et al., 2015), level of social support (Lee & Goldstein, 2016), and nutrition (Bremner et al., 2020). Similarly, the current measurement of blood glucose regulation may have also limited the results of this study. Although mean blood glucose levels are a good metric of blood glucose regulation and outcomes (Suh & Kim, 2015), they do not account for blood glucose variability. Standard deviation blood glucose can be used as a measure of variability from limited self-report data points but can be skewed towards hyperglycemia due to individuals having fewer incidences of low blood glucose levels (Gonder-Frederick et al., 2016). Instead, many researchers opt for calculating a “time in range” or “risk range score” that takes into account differences in high and low blood glucose levels per individual. For example, the Average Daily Risk Range (Patton & Clements, 2013) metric mathematically transforms given blood glucose levels to give equal weight to episodes of hyper-and hypoglycemia. Metrics such as these are better able to capture individual differences in glucose regulation that might impact everyday life stress compared to utilizing mean blood glucose only but require all participants to provide CGM data. Overall, an alternative measure of everyday life stress and glucose regulation may be warranted for future studies.

In addition to barriers within the measurement of the constructs examined in this study, the frequency of sampling is also a factor that may contribute to the findings. Participants only completed the everyday life stress measure once daily at the end of the day. Although this data is useful for comparing everyday life stress across days, it does not allow for the assessment of how everyday life stress may fluctuate throughout a single day. Prior research has found that stress fluctuates by state multiple times in a given day (Brooks et al., 2021). However, the current measurement of everyday life stress makes it impossible to determine if within-day fluctuations in blood glucose may correspond to the timing of fluctuations in stress. Similarly, blood glucose was also measured infrequently throughout the week when adolescents did not provide downloads from their CGMs. Although adolescents reported their blood glucose readings from six time points during each day, an individual’s highest or lowest scores from the day may not have been captured in any of the six entries. One potential solution is to analyze data captured directly from CGMs. For example, the use of patients' CGM data provides continuous information about blood glucose levels throughout the day, increasing the number of readings used to calculate a mean blood glucose score and a wider variety of measures of blood glucose regulation (Gonder-Frederick et al., 2016). Future research should consider assessing everyday life stress at multiple time points per day and collecting more thorough continuous blood glucose data to capture potential shifts in stress and blood glucose levels within days.

Finally, additional variables not included in this study may better explain how everyday life stress changes over time. For example, time spent on treatment tasks may also contribute to increased everyday life stress. Many adolescents view the completion of diabetes tasks to be a significant burden on their lives and cause problems in aspects of daily living that are already a significant source of stress (Guttmann-Bauman et al., 1998; Ingersgaard et al., 2021; Seiffge-Krenke & Stemmler, 2003). There is evidence suggesting that adolescents with T1D often struggle to prioritize treatment engagement and instead let other activities in their lives (such as those associated with school and friends) take priority (Ingersgaard et al., 2021). In addition, diabetes-specific stress may also play a role in the daily fluctuation of everyday life stress in adolescents with T1D. Unlike everyday life stress, diabetes-specific stress is that which is experienced during the process of managing T1D and the related symptoms and health outcomes associated with the disease (Berlin et al., 2012). Research on the contagion effect of stressful experiences suggests that a specific form of stress is subject to either "spilling over" or "crossing over" onto other forms (Bolger et al., 1989). Thus, additional factors, including treatment engagement and diabetes stress as they related to everyday life stress and its regulatory system should be explored further in future studies.

Conclusions

The present study found that everyday life stress in adolescents with T1D functions as a regulatory system. It was also found that the relationship between mean blood glucose and everyday life stress was not explained by either a linear or a systems approach. In particular, these associations need further exploration in larger samples that have more frequent and thorough measurement of each variable and a sample that includes adolescents with T1D who are experiencing higher levels of distress. Reducing everyday life stress, a common experience for adolescents with T1D, remains a critical area to target to improve quality of life outcomes for these youth, and continued research that uses non-linear dynamic systems approaches to study the stress regulatory system is needed to guide and support intervention development.

Tables

Table 1: *The linear association between everyday life stress and mean blood glucose (Aim 1)*

		Estimate	S.E.	Est./S.E.	P-Value	95% CI
Within	ELS on					
	MBG_W	0.003	0.005	0.560	0.576	[-0.006, 0.016]
	Day	-0.408	0.089	-4.562	0.000***	[-0.555, -0.178]
	Residual Variances					
	ELS	7.481	0.741	10.100	0.000***	[6.262, 9.388]
Between	ELS on					
	MBG_B	0.003	0.009	0.377	0.706	[-0.011, 0.026]
	LengthDx	-0.039	0.097	-0.405	0.685	[-0.199, 0.210]
	Gender	0.883	0.711	1.243	0.214	[-0.286, 2.714]
	Age	-0.529	0.302	-1.749	0.080	[-1.026, 0.250]
	Race	-0.401	0.645	-0.621	0.535	[-1.462, 1.261]
	Intercepts					
	ELS	11.708	5.119	2.287	0.022*	[3.288, 24.892]
	Residual Variances					
	ELS	2.540	0.853	2.979	0.003**	[1.137, 4.736]

Table 2: *Everyday life stress as a self-regulatory system (Aim 2)*

		Estimate	S.E.	Est./S.E.	P-Value	95% CI
Within	ELS_Chg on					
	ELS	-0.847	0.076	-11.168	0.000***	[-0.972, -0.652]
	Day	-0.290	0.113	-2.560	0.010**	[-0.477, 0.002]
	Residual Variances					
	ELS_Chg	6.440	0.736	8.746	0.000***	[5.229, 8.337]
Between	Means					
	ELS_Chg	2.952	0.576	5.127	0.000***	[2.005, 4.435]
	Residual Variances					
	ELS_Chg	2.085	0.921	2.263	0.024*	[0.569, 4.459]

Table 3: *The nonlinear relationship between everyday life stress and mean blood glucose (Aim 3)*

		Estimate	S.E.	Est./S.E.	P-Value	95% CI
Within	ELS_Chg on					
	ELS	-0.753	0.221	-3.411	0.001**	[-1.116, -0.184]
	MBG	0.002	0.006	0.285	0.776	[-0.008, 0.018]
	ELSxMBG	-0.001	0.001	-0.454	0.650	[-0.002, 0.003]

	Day	-0.283	0.118	-2.396	0.017*	[-0.477, 0.021]
	Residual Variances					
	ELS_Chg	6.539	0.754	8.676	0.000	[5.299, 8.480]
Between	ELS_Chg on					
	LengthDx	0.002	0.084	0.029	0.977	[-0.136, 0.220]
	Gender	0.661	0.651	1.014	0.310	[-0.411, 2.338]
	Age	-0.415	0.279	-1.484	0.138	[-0.874, 0.305]
	Race	-0.341	0.586	-0.583	0.560	[-1.304, 1.167]
	Intercepts					
	ELS_Chg	8.719	4.767	1.829	0.067	[0.878, 20.997]
	Residual Variances					
	ELS_Chg	1.727	0.837	2.063	0.039*	[0.350, 3.884]

Figures

Figure 1: *Daily mean blood glucose and daily everyday life stress (Aim 1) for Example Participant A*

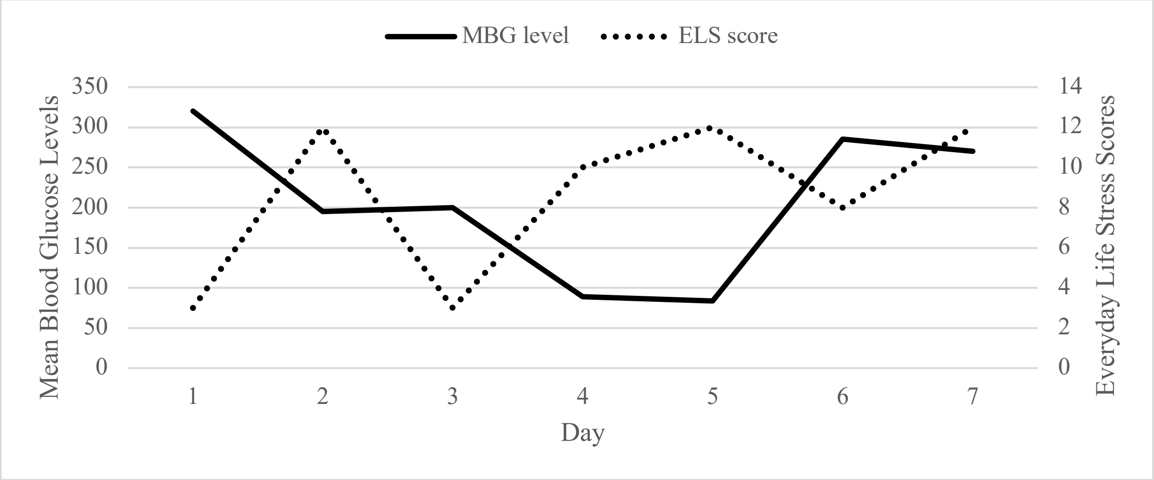
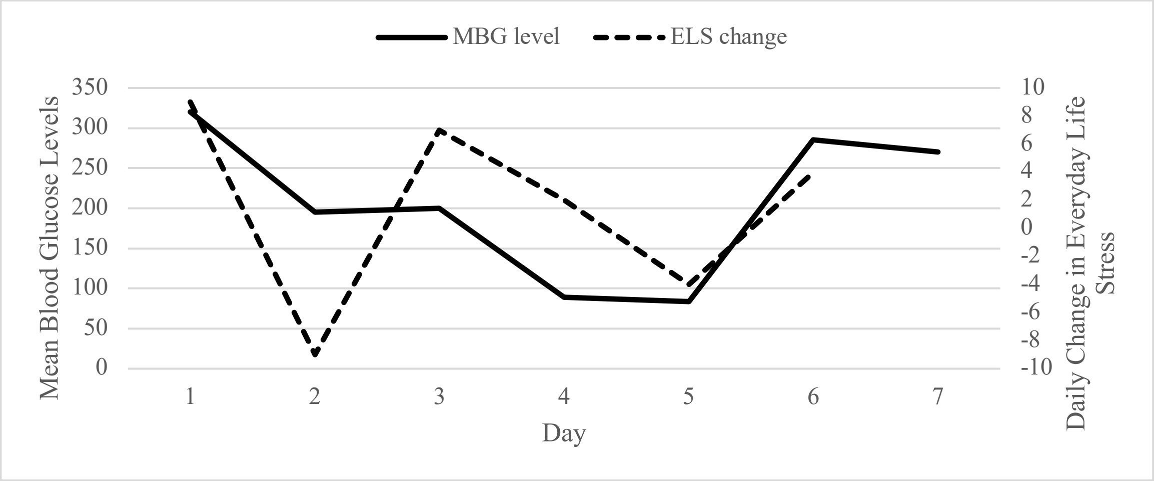


Figure 2: *Daily mean blood glucose and daily change in everyday life stress (Aim 3) for Example Participant A*



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