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Biopsychosocial pathways linking subjective socioeconomic disadvantage to glycemic control in youths with type I diabetes

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ABSTRACT

Older adolescent and young adults (OAYA) with type 1 diabetes (T1D) living in contexts of socio-economic disadvantage (SED) suffer disproportionately from poor glycemic control and related health complications. Although SED may convey a variety of risks, it may exacerbate diabetes-related stress levels, which in turn may account for observed disparities in health outcomes. The primary goal of the present study was to investigate the relationship between subjective SED, diabetes-related perceived stress, and diurnal cortisol secretion in urban OAYA with T1D. A secondary goal was to determine if cortisol was related to measures of blood glucose (HbA1c and mean blood glucose). Analyses were conducted among OAYA ages 17–20 years ($n = 61$) affected by T1D, who provided daily saliva samples for four days, measures of glycemic control (i.e., HbA1c and mean blood glucose assessed via Continuous Glucose Monitor), and completed psychosocial questionnaires. We found that subjective SED was associated with a flatter diurnal cortisol rhythm via diabetes-related stress. Flattened cortisol rhythm was, in turn, associated with higher levels of HbA1c, but not with mean blood glucose assessed via Continuous Glucose Monitor. These results represent some of the first empirical evidence on how distal social factors (i.e., subjective SED) and proximal psychological processes (diabetes-related perceived stress) are connected to condition-relevant biological mechanisms (i.e., elevated HbA1c), via broad biological pathways implicated in health (i.e., flatter cortisol slope).

1. Introduction

Older adolescents and young adults (OAYA) with type 1 diabetes (T1D) are more likely to experience adverse health status than either younger children or older adults, marking this as a high risk developmental period (Wood et al., 2013). Furthermore, OAYA with chronic poor metabolic control are more likely to come from disadvantaged groups such as those of lower socioeconomic status, those who hold public insurance, single-parent headed households, and members of minority groups (Harris et al., 1999; Wang et al., 2011). African-American OAYA in particular have been found to be at significantly higher risk for problems with treatment adherence and metabolic control (Palta et al., 1997; Wang et al., 2011) and also for post-diagnostic diabetic ketoacidosis (DKA) admissions (Frey et al., 2007). Such outcomes may be accounted for by a clustering of risk factors among minority OAYA. These include higher numbers of single-parent families where parents must juggle diabetes care with multiple other demands and have fewer resources for supervising adolescents' diabetes care (Beyers et al., 2003). Social disadvantage is also a marker for other community factors that may play a role in poor diabetes management, such as lack of access to healthy foods in neighborhood stores (Kipke et al., 2007).

One plausible explanation for disparities in health outcomes in OAYA with T1D living under conditions of socioeconomic disadvantage (SED) is increased psychological stress, the feeling of strain that emerges when an individual appraises environmental threats as taxing and unmanageable. The relationship between SED and higher levels of stress is well established in general population samples (Baum et al., 1999). Further, individuals affected by chronic conditions such as diabetes face unique stressors, such as the need to engage in daily management of a complex self-care regimen, coping with fluctuations in blood glucose levels that result in physical symptoms (e.g., fatigue and trouble concentrating), and facing stigma associated with their condition (Delamater et al., 1987; Chao et al., 2015). Some of these challenges, such as fitting in with

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peers, are particularly salient during adolescence and young adulthood, which may explain why OAYA with T1D, despite their more advanced diabetes management skills and disease knowledge, display poorer glycemic control than younger children (Thomas et al., 1997). Diabetes-related stressors have been shown to be even more common in the context of SED (Mühlhauser et al., 1998), likely because of the additional burden associated with material resources scarcity and the exposure to negative social experiences (e.g., discrimination based on social class). It is thus plausible that perceived stress could act as a psychological intermediary between SED and disparities in diabetes-related health (Viner et al., 1996; Lloyd et al., 1999). Evidence to support the possibility that stress can explain the relationship between SED in OAYA with T1D and poorer glycemic control also comes from research among individuals affected by other chronic conditions. For example, among youth with asthma, perceived stress has been shown to account for the detrimental effect of SED on asthma-relevant immunological mechanisms (Chen et al., 2003; Chen et al., 2006). Such studies also indicate that psychological stress may be associated with worse disease progression among high SED individuals with asthma.

In the current study we tested whether perceived diabetes-related stress acts as an intermediate psychological factor connecting SED to diurnal cortisol secretion. Disruptions in the hypothalamic pituitary adrenal (HPA) axis are associated with increased risk of infectious disease and inflammatory diseases, including type 2 diabetes (T2D) (Schoorlemmer et al., 2009; Nefs et al., 2015). In T2D, cells are compromised in their ability to properly respond to insulin, a condition known as insulin resistance. Insulin resistance, in turn, leads to high levels of blood glucose. In T1D, pancreatic islet beta-cells, which are responsible for the synthesis and release of insulin, are attacked and destroyed by the immune system, leading to extremely low or absent levels of endogenous insulin. Cortisol, the end product of the HPA axis, contributes to gluconeogenesis, hinders peripheral glucose uptake, and thus offsets the effects of insulin. Because cortisol is not only responsive to metabolic challenges (e.g., fasting, illness), but also psychological stressors, it is plausible that increased cortisol secretion is a direct pathway through which stress impairs glucose control (Barglow et al., 1984; Mazziotti et al., 2011) in persons with T1D. Cortisol secretion follows a diurnal rhythm, with higher levels at awakening followed by a gradual decline throughout the day. Cortisol slope corresponds to the rate of decline of cortisol throughout the day. Broadly, a flatter cortisol slope is indicative of sustained levels of cortisol during waking hours and is a stronger predictor of poor health outcomes (Matthews et al., 2006; Kumari et al., 2011) than other diurnal cortisol parameters, such as the cortisol awakening response (CAR).

Previous studies showed that exogenous disruptions of the cortisol diurnal pattern (Plat et al., 1999) as well as stress-related increases in cortisol secretion (Rosmond et al., 1998) lead to glucose metabolism abnormalities typical of people affected by T2D. Further, among T2D subjects, elevated cortisol is related to diabetes complications (Chiodini et al., 2007). Lastly, recent work has also shown that a flatter diurnal cortisol slope (less "healthy") was prospectively associated with T2D onset (Hackett et al., 2015). Taken together, these findings suggest that stress can have downstream effects on glucose metabolism through disruptions of diurnal cortisol rhythm (e.g., via a flatter diurnal cortisol slope).

In T1D subjects, cortisol levels are higher compared to matched control groups (Radetti et al., 1994) and, because cortisol acts in opposition to exogenous insulin, elevated cortisol is related to impaired glycemic control (Couch, 1992). Psychological stress, which activates the HPA axis (Miller et al., 2007), is also associated with poor glycemic control (Aikens et al., 1992; Goldston et al., 1995; Viner et al., 1996; Lloyd et al., 1999) (for similar findings in non-human animals, see Radahmadi et al., 2006). Despite these complementary lines of evidence, empirical support in favor of diurnal cortisol fluctuations as a mechanism for the link between diabetes-related psychological stress and impaired glycemic control among T1D patients is lacking. Further, studies that have established the relationship between psychological stress and increased blood glucose levels (Kramer et al., 2000) have not demonstrated that cortisol dysregulation is the mechanism through which this occurs.

In the current study, we tested two hypotheses concerning the effects of psychological stress on the HPA activity of OAYA with T1D. First, we hypothesized that high-SED OAYA would report more diabetes-related stress, which in turn would predict a flatter diurnal cortisol slope (i.e., higher SED → higher diabetes-related stress → flatter diurnal cortisol slope). Second, we investigated whether cortisol dysregulation resulting from SED and psychological stress would influence critical markers of health among people with diabetes such as glycemic control. Two measures of glycemic control were implemented, HbA1c and mean blood glucose assessed via Continuous Glucose Monitor (CGM). Thus, we tested whether cortisol disruption (i.e., flatter cortisol slope) resulting from SED and diabetes-related stress would be ultimately associated with higher levels of glycemic control (i.e., higher SED → higher diabetes-related stress → flatter diurnal cortisol slope → poorer glycemic control).

Table 1
Descriptive Statistics.

Descriptive variables	M or%	SD
Female	32.8%	–
Ethnicity		–
African American/Black	45.9%	–
White	45.9%	–
Other	8.2%	–
Education (some college)	16.4%	–
Age	18.30	0.99
Employed	49.2%	–
Living with Parents	86.9%	–
Diabetes insulin regimen		–
Mixed short and intermediate acting via injection	9.8%	–
BBT via injection	77.0%	–
Insulin Pump	13.1%	–
BMI	23.22	3.30
Diabetes Duration (years)	7.29	4.36
SSED	0.60	0.58
DSQ	1.97	0.60
Cortisol (ng/mL)	4.42	1.86
HbA1c (%)	9.58	2.22
Blood Glucose from CGM (mg/dL)	208.85	55.13

Note: BBT = Basal Bolus Therapy, BMI = Body Mass Index, DSQ = Diabetes Stress Questionnaire, CGM = Continuous Glucose Monitor.

2. Methods

2.1. Participants

A total of 68 OAYA between the ages of 17 and 20 and affected by type 1 diabetes (i.e., diagnosed for at least 6 months) took part in the current study. Of the larger sample of 68 OAYA, sixty-six provided saliva samples for cortisol analyses. Among these 66 individuals, five reported endocrine disorders other than diabetes and were therefore excluded for analyses concerning diurnal cortisol secretion. Thus, the final sample comprised sixty-one OAYA (32.8% female, 54.1% non-black, age, $M = 18.30$ years, $SD = 0.99$ years, see Table 1 for detailed descriptive statistics). All procedures were subject to review and prior approval by the Institutional Review Board at Wayne State University.

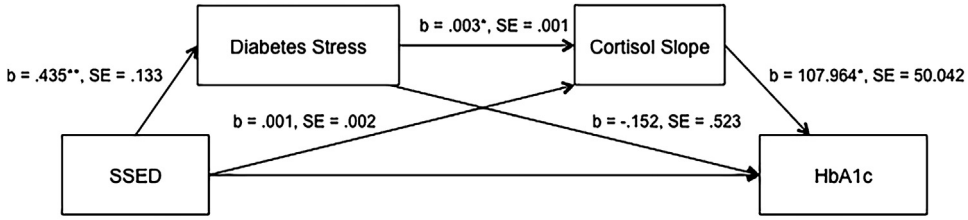

Fig. 1. Multiple mediation model linking socioeconomic disadvantage to HbA1c via diabetes-related stress and cortisol slope. $^{**}p < 0.01$, $^{*}p < 0.05$. Any differences between the beta coefficients reported in the figure and in the text reflect the fact that diabetes-related stress levels and cortisol slope were centered during multiple mediation analyses.

2.2. Procedure

Participants were recruited from the diabetes clinic in an urban tertiary care children's hospital located in a large Midwestern city. This diabetes clinic serves a largely low income, ethnically diverse population of OAYA up to the age of 21. Individuals were eligible to participate if they were between 16 and 20 years old, had been diagnosed with Type 1 diabetes for at least six months, and could speak, read, and write in English. Exclusion criteria for the current study were: 1) conditions that could potentially compromise data integrity including thought disorders, autism spectrum disorder, developmental delay, and suicidality 2) presence of a comorbid medical condition that resulted in atypical diabetes management, such as cystic fibrosis, or that required taking an oral steroid medication and 3) presence of an endocrine disorder such as hypothyroidism that might affect cortisol production. After potential participants were identified by electronic medical record review, they were contacted by telephone by research assistants to assess interest, describe the study, and confirm eligibility. Written assent and/or consent were obtained from the OAYA and/or their parent once eligibility and interest were established.

Data were collected in the home by a study nurse and a trained research assistant over the course of six days. After obtaining consent to participate, a demographic questionnaire was completed. The second visit was completed the following day. The participant was instructed in how to collect saliva specimens for cortisol assay and additional questionnaires were completed. Finally, a third visit was completed 5–6 days following the first visit. At this time, saliva specimens were collected, the CGM was removed and a final set of questionnaires was completed. Height and weight were also obtained and blood was collected by fingerstick to measure glycemic control.

Participants were instructed to collect saliva samples for diurnal cortisol assessment on two weekend days and two weekdays. Samples for diurnal cortisol assessment were collected four times per day: immediately at wakeup, 30 min after wakeup, at dinnertime, and at bedtime (MacArthur Foundation Network on SES and Health, 2000). Saliva was obtained using a Salivette (Sarstedt 1534, Sarstedt Inc., Newton, NC), consisting of a sterilized cotton swab that the participant placed in his/her mouth for 2 min and then stored in a small beaker contained in a plastic tube. Participants were instructed to abstain from eating, drinking, smoking, brushing their teeth, and exercising before collecting of saliva samples. At each sampling time, they were also asked to report whether they engaged in any of these activities within the past 30 min. Participants were asked to refrigerate these samples at home immediately and were given ice packs and cold bags to use if they were outside of the home during saliva collection. Compliance with the timing of saliva sampling was ensured in a number of ways. First, participants withdrew Salivettes from a small plastic vial that was capped with a lid containing a microchip that recorded each opening of the vial (MEMS track cap; Aardex, Denver, CO). Second, participants received daily reminder via phone calls and/or text messages. Third, participants received a bonus research payment of $25 if they collected the saliva according to the instructions provided. One hundred and twenty-one saliva samples (12.4%) had either CAR compliance issues (i.e., deviated by 15 min or more from the requested 30-min interval), were not received, or were received empty. Thus, cortisol was available for 855 observations out of the potential 976. The total possible payment for participation in the six-day research protocol was $125 ($100 for questionnaires and HbA1c, $25 for cortisol collection).

2.3. Psychosocial measures

2.3.1. Subjective socioeconomic disadvantage (SSED)

A 14-item monetary problems subscale was constructed ($M = 0.60$, $SD = 0.58$). Sample items, which were rated on a 4-point Likert scale (0 = Never or did not occur, 3 = Extremely severe), included "Concerns about money for emergencies" and "Not enough money for basic necessities" ($\alpha = 0.90$). Participants were asked to report the severity with which the various hassles had occurred in the past week. Mean replacement was used to replace one missing value on this scale. Similar measures of subjective SSED have been used in previous studies (e.g., Gruenewald et al., 2012; Zilioli et al., 2017) and found to reliably predict biological risk; furthermore, subjective measures of financial hardship have been found to be better predictors of health outcomes such as mortality than traditional measures of SES (Singh-Manoux et al., 2005; see also, Tucker-Seeley et al., 2009).

2.3.2. Diabetes stress questionnaire (DSQ)

The DSQ (Delamater et al., 2013) is a self-report instrument designed to measure day-to day stressors encountered when managing diabetes. The instrument measures stress related to worries about diabetes, peer and family interactions, diabetes management responsibilities, and impact of symptoms such as hypo- and hyperglycemia. Eight items from the original scale that were not applicable to current diabetes management practices were dropped (e.g., "watching brothers or sisters eat foods that I should not") leaving a total of 45 items. In addition, since the measure was originally designed for use with young adolescents rather than OAYA, items referring to stressors "at school" were reworded to "at school or work" since some older youth participating in the study did not attend school. Participants indicated how stressful each situation was on a 4-point Likert scale (1 = Not at All, 4 = Very Much). Sample items included "Disagreements with family members about taking my insulin on time", "Having to live my life around a schedule of blood tests, meals and insulin" ($\alpha = 0.96$). The measure was scored by calculating the mean of the values of all the items. Higher scores indicated higher diabetes-related stress. Scores ranged from 1 to 3.56 ($M = 1.97$, $SD = 0.60$).

2.3.3. Salivary cortisol

Saliva samples were stored at −20 °C until assayed using commercially available enzyme-linked immunoassay kits (DRG International, Springfield, NJ SLV-2930). Before assay, saliva sam-

ples were allowed to thaw at room temperature and were then centrifuged at 3000 rpm for 10 min. All samples were assayed in duplicate and the average of the duplicates was used in all analyses. Optical densities were read at 450 nm using a plate reader (Perkin Elmer Victor 1 microplate reader). Concentrations (ng/mL) were interpolated from the calibration curve using a 4-parameter logistics curve fit. The mean intra-and inter- assay coefficients of variation were below 3%. Cortisol values were log-transformed to correct for positive skew in the distribution (Adam and Kumari, 2009). To ensure that all transformed scores were positive, we added a constant of 1 before the transformation. Six cortisol observations were more than 3 standard deviations above the mean and were therefore winsorized (e.g., Doane and Van Lenten, 2014)

2.3.4. Glycemic control

HbA1c is an indirect and retrospective measure of average blood glucose levels over the prior two to three months. HbA1c levels were obtained using the Accubase A1c test kit from Diabetes Technologies (AccuBase A1c™ Test Kit, 2004). This kit uses a capillary tube blood collection method rather than a venipuncture method, making it suitable for home-based collection. Previous research has compared these two methods of collection, finding that the capillary tube method is comparable to the venipuncture method in a sample of pediatric patients (AccuBase A1c™ Test Kit, 2004). The blood sample was analyzed via high performance liquid chromatography (HPLC), with a reagent solution containing 1 ml of EDTA and 0.023 mom/l KCN to preserve the sample. Because mean blood glucose obtained from continuous blood glucose monitor (CGM) strongly correlated with HbA1c (r = 0.624, $p < 0.001$), linear regression was used to replace one missing value for HbA1c (M = 9.58%, SD = 2.22).

2.3.5. Continuous glucose monitor

Data on daily glycemic control during a four-day window was obtained from a CGM, which was inserted at the first home visit by a study nurse. While HbA1c provides a retrospective measure of overall glycemic control over the past 2–3 months, it does not capture day-to-day blood glucose levels. The CGM used in the current study was the Medtronic iPro2 system, which is a blinded system developed for use by physicians to assess glycemic control rather than for home diabetes management. Therefore, participants did not have real-time access to blood glucose values, ensuring that they were not able to use information obtained from the CGM to make changes in diabetes management during the study period. From the CGM, we obtained a mean daily blood glucose level during the four-day cortisol collection period. Linear regression was used to replace six missing values for CGM mean blood glucose (M = 208.85 mg/dL, SD = 55.13).

2.3.6. Demographic covariates

Demographic covariates included ethnicity (54.1% nonblack), age (M = 18.30, SD = 0.99), BMI (M = 23.22, SD = 3.3), gender (33.0% female), and diabetes duration (M = 7.29 years, SD = 4.36). Further, for analyses concerning cortisol we controlled for day of the week (0 = weekday, 1 = weekend) and wake-up time at the daily level. Lastly, at the cortisol level, we created an additional covariate based on participants' self-report eating, drinking, smoking, brushing teeth, and exercising within the past 30 min before saliva collection (0 = compliant, 1 = non-compliant). Diabetes duration and BMI were extracted from patients' clinic medical records. All of these variables are standard demographic covariates in diurnal cortisol studies (Adam et al., 2006).

2.4. Statistical analyses

Hierarchical Linear Modeling (HLM) was used to model diurnal cortisol. Following prior diurnal cortisol research (Adam and Kumari, 2009), Time Since Waking, Time Since Waking-squared, and CAR (dummy coded 0 or 1) were modeled at Level-1 to provide estimates of each participant's diurnal cortisol rhythm, while at Level-3 (person-level), we first ran models with SSED as the main predictor, and then with SSED and diabetes-related stress as the main predictors. The 95% confidence interval for the indirect effect linking SSED to cortisol parameters via diabetes-related stress was estimated using Monte Carlo simulation (Preacher and Selig, 2012).

In order to test our second hypothesis that cortisol dysregulation resulting from diabetes-related stress would predict glycemic control and that diabetes related-stress and cortisol slope would explain the link between SSED and glycemic control (HbA1c and mean blood glucose assessed via CGM), we ran two-step mediation analyses (for a graphical representation, see Fig. 1). Specifically, using PROCESS (Hayes, 2013), we tested three indirect pathways: 1) one from SSED to glycemic control via diabetes-related stress (*a1b1*); 2) one running from SSED to glycemic control via cortisol slope (*a2b2*); and, 3) one running from SSED to glycemic control via both diabetes-related stress (first) and cortisol slope (second) (*a1a3b2*). Bootstrapping was used to derive indirect 95% confidence interval (CI) for all indirect effects. Individual differences in cortisol slope were measured using empirical Bayes residuals obtained from an HLM model predicting cortisol with all Level 1 variables included (Time Since Waking, Time Since Waking-squared, CAR, and compliance), wake-up time and day of the week at Level-2 for a similar approach, see Browning and Cagney (2002), and no predictors at Level-3. Continuous predictors at Level-2 and Level-3 were grand-mean centered and analyses were run with and without controlling for covariates.

3. Results

Bivariate correlations among study variables are reported in Table 2. SSED was positively associated with diabetes-related stress (r = 0.430, p = 0.001), the cortisol slope (i.e., higher SSED was associated with flatter cortisol slopes) (r = 0.286, p = 0.026), and HbA1c (r = 0.250, p = 0.052). Higher levels of diabetes stress were associated with flatter cortisol slopes (r = 0.390, p = 0.002), but not with higher blood glucose levels assessed via CGM (r = 0.219, p = 0.089). Flatter cortisol slopes were associated with higher levels of HbA1c (r = 0.369, p = 0.003), but not with blood glucose levels assessed via CGM (r = 0.228, p = 0.077), though the association was in the expected direction.

3.1. SED, diabetes-related stress, and diurnal cortisol

HLM analyses showed that greater SSED was associated with a flatter cortisol slope (β = 0.004, SE = 0.002, p = 0.049; β = 0.005, SE = 0.002, p = 0.014, without controlling for covariates). No direct association was found between SSED and morning cortisol (β = −0.001, SE = 0.044, p = 0.974; β = 0.006, SE = 0.054, p = 0.915, without controlling for covariates) or CAR (β = −0.010, SE = 0.031, p = 0.751; β = −0.013, SE = 0.030, p = 0.670, without controlling for covariates). Next, diabetes-related stress was introduced in the analyses. Individuals with higher diabetes-related stress experienced a flatter cortisol decline than individuals with lower diabetes-related stress (β = 0.005, SE = 0.002, p = 0.010; β = 0.006, SE = 0.002, p = 0.005 without controlling for covariates) (Fig. 2). Next, we tested whether the association between SSED and the cortisol slope was partially explained by diabetes stress. Regression analyses showed that SSED positively predicted diabetes-related

Table 2
Bivariate Correlations Between Study Variables.

Descriptive variables	1	2	3	4	5	6	7	8	9	10
1. Female	1	−0.198	0.182	0.147	−0.190	0.073	0.006	0.072	0.088	0.146
2. Non-Black		1	−0.159	−0.04	−0.046	−0.264*	−0.182	−0.261*	−0.421**	−0.121
3. Age			1	−0.163	0.288*	0.311*	0.001	0.095	0.193	0.142
4. BMI				1	0.052	−0.062	−0.138	−0.165	−0.048	0.004
5. Diabetes Duration					1	−0.047	−0.244†	0.040	−0.091	−0.183
6. SSED						1	0.430**	0.286*	0.250†	0.061
7. DSQ							1	0.390**	0.192	0.219†
8. Cortisol Slope								1	0.369**	0.228†
9. HbA1c									1	0.639**
10. Blood Glucose from CGM										1

Note: BMI = Body Mass Index, DSQ = Diabetes Stress Questionnaire, CGM = Continuous Glucose Monitor.
† $p < 0.10$.
* $p < 0.05$.
** $p < 0.01$.

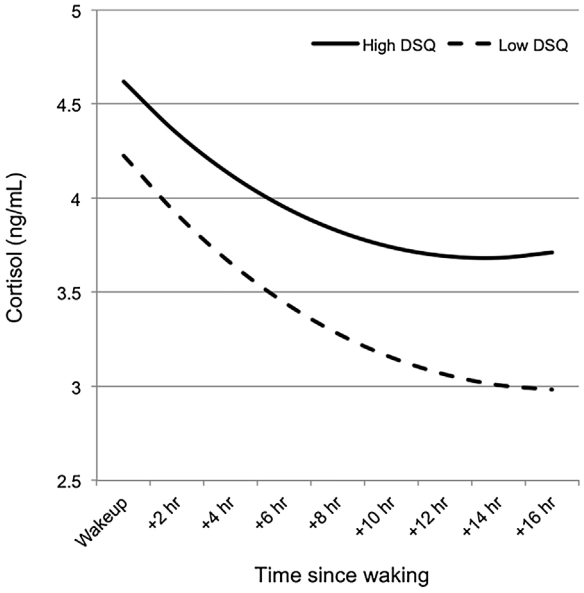

Fig. 2. Associations between diabetes related stress and diurnal cortisol. Cortisol levels (ug/mL) are graphed as a function of time since waking, separately for OAYA that reported low (1 SD below the mean) and high (1 SD above the mean) diabetes related stress.

stress (b = 0.435, *SE* = 0.133, $p = 0.002$; without controlling for covariates: b = 0.448, *SE* = 0.123, $p = 0.001$). Monte Carlo analyses showed a significant indirect effect of SSED on the cortisol slope via diabetes stress, 95% CI = [0.0004, 0.0047] (without controlling for covariates: 95% CI = [0.0006, 0.0049]), which indicates that high SSED was linked to a flatter cortisol slope via high diabetes stress.

3.2. SSED, diabetes-related stress, cortisol slope, and HbA1c

Regression analyses controlling for covariates revealed an association between cortisol slope and HbA1c (b = 107.964, *SE* = 50.042, $p = 0.036$; b = 122.113 *SE* = 50.046, $p = 0.018$), such that flatter slopes were associated with higher levels of HbA1c. Further, we found evidence for the hypothesis that diabetes-related stress and cortisol slope sequentially explained the relationship between SSED and HbA1c (i.e., SSED → diabetes-related stress → cortisol slope → HbA1c) [95% CI: 0.0117, 0.6634; 95% CI: 0.0405, 0.5415, without controlling for covariates]. Interestingly, diabetes-related stress alone (i.e., SSED → diabetes-related stress → HbA1c) [95% CI: −0.8333, 0.3053; 95% CI: −0.5948, 0.4709, without controlling for covariates] did not explain the effect of SSED on HbA1c. Similarly, cortisol slope alone did not explain the effect of SSED on HbA1c [95% CI: −0.1686, 0.8094; 95% CI: −0.1517, 0.6859, without controlling for covariates] (Fig. 1).

3.3. SSED, diabetes-related stress, cortisol slope, and mean CGM blood glucose

Regression analyses controlling for covariates revealed no significant effect of cortisol slope on mean CGM blood glucose (b = 1,835.50, *SE* = 1,340.94, $p = 0.177$; b = 1,630.32, *SE* = 1,286.89, $p = 0.210$). No evidence was found for the hypothesis that diabetes-related stress and cortisol slope sequentially explained the relationship between SSED and mean CGM blood glucose (i.e., SSED → diabetes-related stress → cortisol slope → mean CGM blood glucose) [95% CI: −0.6812, 16.8947; 95% CI: −0.4953, 11.3304, without controlling for covariates]. Diabetes-related stress alone (i.e., SSED → diabetes-related stress → mean CGM blood glucose) [95% CI: −5.2840, 25.7655; 95% CI: −5.8369, 25.1977, without controlling for covariates] and cortisol slope alone (i.e., SSED → cortisol slope → mean CGM blood glucose) [95% CI: −2.9983, 21.4227; 95% CI: −1.8317, 15.5784, without controlling for covariates] did not explain the effect of SSED on mean CGM blood glucose.

3.4. Testing alternative indirect effects models

Our measure of glycemic control (HbA1c) reflects blood glucose during the period 2–3 months prior to the cortisol data collection, posing the problem of temporal precedence in our indirect effects models. Cortisol slope shows higher levels of stability over time than other cortisol parameters (Wang et al., 2014), making it plausible for trait individual differences in diurnal decline to be predictive of stable individual differences in measures of metabolic control for a similar approach, see Rosmond et al. (1998). However, we also chose to empirically test an alternative indirect effects model to rule out the possibility that HbA1c would predict cortisol. For this reason, we tested whether diabetes-related stress and HbA1c sequentially explained the relationship between SSED and cortisol slope (i.e., SSED → diabetes-related stress → HbA1c → cortisol slope). No evidence was found in favor of a significant indirect effect [95% CI: −0.0003, 0.0006; 95% CI: −0.0002, 0.0007, without controlling for covariates]. These results lend support to the directionality of the cortisol-glucose pattern of covariation.

4. Discussion

Despite the well-established links between socioeconomic status and health disparities among OAYA with T1D, the specific causes of poorer diabetes health status in OAYA living in conditions of socio-economic disadvantage remain unclear. The current study

explored the effects of SSED on stress related to living with diabetes and, in turn, the potential of such stress to result in cortisol dysregulation with associated downstream effects on glycemic control. We found that perceived diabetes-related stress indirectly explained the link between SSED and flatter cortisol slope. The effect was constrained to cortisol slope and did not involve morning cortisol or CAR, possibly because youth encounter and cope with most of diabetes worries, diabetes management responsibility, and symptoms (e.g., increase thirst and hunger, tiredness) during daytime hours. This finding is consistent with the broader literature on the modulatory effects of psychosocial stressors on daily cortisol decline among adults (Liao et al., 2013; Stafford et al., 2013) and children (Bruce et al., 2002; Slatcher and Robles, 2012; Lippold et al., 2016), including children affected by chronic health conditions (Wolf et al., 2008).

Second, we found that flatter cortisol slopes resulting from diabetes-related perceived stress were associated with poorer glycemic control (i.e., higher HbA1c). SSED was ultimately associated with poorer glycemic control via an indirect effect linking SSED to higher perceived diabetes stress, higher perceived diabetes stress to dysregulated cortisol, and dysregulated cortisol to elevated HbA1c. Previous studies have linked psychosocial stress, including diabetes-related stress (Farrell et al., 2004), to glycemic control in T1D adults (Aikens et al., 1992; Lloyd et al., 1999) and children (Goldston et al., 1995; Viner et al., 1996; Helgeson et al., 2010). For example, Viner and collaborators found that a comprehensive measure of family stress positively predicted HbA1c in a cross-sectional study among forty-three children with T1D. Similarly, in a five year longitudinal study, Helgeson and colleagues (Helgeson et al., 2010) found that life stressful events were associated with poor glycemic control and that this association was partially mediated by poor illness management (but see, Aikens et al., 1992; for a direct effect of stress on glycemic control that was not mediated by illness management). Despite this literature, no prior studies have shown that increased in diabetes-related psychological stress associated with SSED in this population can account for poorer health outcomes. In addition, since prior studies assessed only perceptions of psychological stress, the direct effects of stress via dysregulation of the HPA axis have not previously been demonstrated. The idea that cortisol fluctuations might act as a mechanism through which psychosocial stress affects metabolic control is plausible when considering HPA axis sensitivity to psychosocial stressors and the link between increased cortisol and impaired glycemic control among T1D (Couch, 1992). Further, support for this idea comes from studies conducted among T2D patients. In contrast to T1D, T2D involves resistance to endogenously produced insulin. Elevated cortisol levels lead to increased glucose production via increased gluconeogenesis and reduced insulin sensitivity (i.e., insulin resistance) in the liver as well as inhibition of glucose uptake and glycogen synthesis in muscles (McMahon et al., 1988). In addition to the well-established effect of cortisol on glucose availability through insulin modulation (McMahon et al., 1988), experimental evidence shows that induced cortisol elevation later in the day (vs. morning) lead to severe increases in glucose levels and insulin resistance (Plat et al., 1999). The proposed chain of indirect effects is also strengthened by previous work conducted among non-diabetic individuals showing that stress-related cortisol secretion lead to glucose metabolism abnormalities typical of people affected by T2D (Rosmond et al., 1998). Lastly, it is also remarkable that the scenario in which HbA1c predicted cortisol slope was not supported by our statistical analyses.

Notably, the proposed serial mediation model did not significantly predict blood glucose assessed via CGM. One reason behind this null finding could be that other CGM measures (e.g., daily glycemic variability) may be more related to psychosocial stress and related cortisol fluctuations than average CGM blood glucose. This possibility could be addressed by future studies. Lastly, mean CGM blood glucose, despite being assessed concurrently with cortisol, reflects average glucose over a much shorter time window (i.e., four days) than HbA1c (i.e., three months) and, for this reason, it might be more susceptible to daily spikes. Thus, it is possible that this measure of metabolic control is less sensitive than HbA1c when trying to correlate it to measures of psychological and physiological stress.

Our study opens up other promising avenues for research on diabetes-related psychological stress and glycemic control among T1D patients. For example, although previous studies showed an association between laboratory-induced acute stressors and glycemic control in T1D adults (Wiesli et al., 2005), no study has looked at the same association in the daily life of OAYA. Our study underlines the importance of assessing cortisol reactivity as a potential mechanism for the diabetes-related stress/glycemic control link. Additional studies in this area could shed light on mechanisms by which individual differences in stress appraisal and coping in T1D affect metabolic control (Delamater et al., 1987; Hägglöf et al., 1993). Lastly, psychological intervention studies (for a review, see Winkley et al., 2006; Hood et al., 2010) could benefit from including measures of diabetes-related stress and physiological measures, such as those used in our study, to discern with more specificity the biopsychological pathways responsible for the beneficial effects of stress management interventions on glycemic control among T1D patients.

One limitation of the current study was the use of only subjective measures of SED. Despite empirical evidence suggesting that measures of subjective SES are better predictors of health than objective indicators (Singh-Manoux et al., 2005), future studies would benefit from testing the hypotheses here reported including more standard indicators of SES, such as education and income. A second limitation concerns the relatively small sample size, which was partially due to the difficulties associated when working with a very specific population (i.e., OAYA with T1D with no additional endocrine disorders such as hypothyroidism). Thus, future larger and longitudinal studies are required to corroborate the current findings, which, regardless of these limitations, provide one of the first multilayered biopsychosocial accounts for diabetes-relevant biology. In this respect, the proposed pathway is one of the first empirical examples on how distal social factors (i.e., SSED) and proximal psychological processes (i.e., perceived diabetes stress) are connected to condition-specific biological mechanisms (i.e., elevated glucose), via broad biological pathways implicated in health (i.e., flatter cortisol slope). A more comprehensive elaboration of the various biobehavioral pathways by which social status inequalities influence diabetes health outcomes in OAYA also highlights the need to develop interventions that specifically target stress management in high risk populations with T1D.

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