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Depressive symptoms, negative urgency and substance use initiation in adolescents

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Abstract

Background—Studies show depressive symptoms are associated with substance use in adolescents, but the mechanism underlying this association is still unclear. This study investigated negative urgency – the disposition to rash action during emotional states – as a factor explaining relations between depressive symptoms and use of several substances.

Methods—In this cross-sectional study, 476 adolescents (mean age 14.5 years) completed self-report surveys. Regression models and products of coefficient analyses examined the overall relation of depressive symptoms to substance use and negative urgency as a statistical mediator of this association

Results—Depression levels associated with increased likelihood of lifetime use of cigarettes, other forms of tobacco, marijuana, alcohol, inhalants, prescription painkillers, and any substance. Relations between depression levels and lifetime use of alcohol, inhalants, and any substance were accounted for (i.e., statistically mediated) by negative urgency. In adolescents endorsing lifetime use, depression levels associated with younger age of first use of other forms of tobacco and alcohol as well as use frequency of cigarette, alcohol, and composite frequency. Negative urgency accounted for the covariance between depression level and age of first use of alcohol, but did not for other forms of tobacco or frequency of use of any substances.

Conclusions—Depression levels are associated with lifetime use of a variety of substances in early adolescence and targeting this risk factor with preventive efforts may be useful in reducing

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risk. Negative urgency may be an important target for interventions aimed at alcohol and inhalant use.

Keywords

Urgency; Depressive symptoms; Lifetime substance use; Adolescents

1. Introduction

Adolescent substance use remains remarkably prevalent in the general population (Substance Abuse and Mental Health Services Administration and Quality, 2013). Alcohol and drug use in adolescence greatly increases risk of substance use disorders in adulthood (Englund et al., 2008; Grant and Dawson, 1997; Lynskey et al., 2003) as well as poorer educational outcomes, lower income, greater welfare dependence and unemployment and lower relationship and life satisfaction (Fergusson and Boden, 2008). Thus, efforts toward understanding of processes associated with initiation of adolescent substance use may help inform substance use prevention efforts and ultimately reduce the public health burden of substance use disorders.

In adolescent samples there is evidence that higher level of depressive symptoms associate with an increase in smoking uptake and progression (Audrain-McGovern et al., 2011, 2012) and increased risk for early life initiation of alcohol or illicit drug use (Tang and Orwin, 2009). However, the mechanisms that account for the covariation between depressive symptoms and substance use initiation are unclear. Identifying whether depressive symptoms associate with initiation of use of specific substances and elucidating factors that link depressive symptoms and teen substance use initiation could shed light on the development of prevention interventions that target these mediational processes and ultimately perhaps buffer substance use risk channeled by depressive symptoms.

Dispositions towards mood-based rash action (i.e., trait urgency) may be an underlying mechanism linking depressive symptoms and substance use initiation. Urgency is a personality construct that reflects the tendency to act rashly without considering consequences specifically during emotional states and can be separated into rash actions during extreme positive states (i.e., positive urgency) and rash actions during periods of extreme negative emotion (i.e., negative urgency; Cyders and Smith, 2008). Empirical evidence shows that urgency is psychometrically and conceptually distinct from other impulsive traits such as the tendency to seek out novel and thrilling experiences (i.e., sensation seeking) and the tendency to act without thinking and inability to remain focused on a task (i.e., deficits in conscientiousness; Cyders and Smith, 2008; Smith et al., 2007).

In considering mechanisms accounting for depression-substance use relations, negative urgency may be particularly relevant trait within the overarching cluster of impulsivity-relevant constructs because of its link to both affect and rash actions. We purport that depressive symptoms may generate an accumulation of affective disturbance that may ultimately cloud one's judgment and engender greater opportunities for rash actions in negative affect states (i.e., negative urgency). Specifically, depressive symptoms such as agitation/restlessness, crying, and other negative states as well as difficulty concentrating

may interfere with one's ability to inhibit methodical decision-making. One such expression of rash action may be the decision to overlook the long-term negative consequences of substance use and experiment with substances. Indeed, negative urgency has been shown to associate with amount of use of alcohol, cigarettes, and illicit drugs (i.e., marijuana, cocaine, LSD, heroin, ecstasy, other illegal drugs, and misuse of prescription drugs; Kaiser et al., 2012; Settles et al., 2012). Furthermore, negative urgency associates with depression in adolescence and children (d'Acremont and Van der Linden, 2007; Marmorstein, 2013) and one study showed negative urgency partially mediated relations between depression and problematic drinking in college students (Gonzalez et al., 2011). Yet, a sizable proportion of substance users initiate in adolescence prior to entering young adulthood (Substance Abuse and Mental Health Services Administration and Quality, 2013). Furthermore, age of initiation may also be an important factor with studies suggesting that earlier onset of use of a substance results in poorer alcohol (Hingson and Zha, 2009; Kang et al., 2014) and marijuana (Ellickson et al., 2004) related outcomes. Thus, understanding processes surrounding initiation is important and current research on risk factors related to substance use in young adulthood may inadequately capture these processes.

This cross-sectional study is the first to our knowledge that investigates negative urgency as a mediator of associations between depressive symptoms and onset of use of various substances in early adolescence (mean age 14.5). We hypothesized that depressive symptoms would be associated with increased likelihood of substance initiation, and that this relation would be accounted for (i.e., statistically mediated by) negative urgency. As secondary outcomes we examined, among the subsample of substance initiators, retrospective reports of age of use onset as well as use frequency within past 30 days. Here, we hypothesized that higher depressive symptoms, higher negative urgency, and their mediational relations would associate with earlier age of onset and greater use frequency. Given the prior scant literature on this topic, we did not propose hypotheses regarding which particular substances might be associated by the aforementioned mediational relationships. Nonetheless, assessment of a variety of different substances, which often has not been addressed in prior work in this area, allows us to make wider spanning generalizations to drug use etiology and prevention programs targeting multiple substances.

2. Method

2.1. Participants

The current report is a secondary analysis of 9th grade participants enrolled in one of two public high schools in the Los Angeles metropolitan area participating in a study on the relation between personality, psychopathology, health behavior, and substance use. All students were eligible to participate with the exception of those in either special education or English as a second language programs. A total of 807 students were eligible. Of the 689 (85%) who provided assent, 585 (82%) provided parental consent, enrolled in the study, and were administered the study survey. The IRB at the University of Southern California approved all procedures used in this study.

2.2. Procedure

Students completed paper-and-pencil surveys assessing urgency, substance use, depression, and other constructs within the domain of emotion and health behavior administered on-site at schools across two mandatory 40-min class periods in May, 2013. Data collectors clearly explained that responses would be confidential and not shared with teachers, parents, or school staff, per a certificate of confidentiality from federal government and the institutional review board.

2.3. Measures

2.3.1. Substance use questionnaire—Substance use measures from the Youth Behavior Risk Surveillance Survey (YBRS) and the Monitoring the Future Questionnaire (MTF), which have been extensively validated in adolescents (Eaton et al., 2010; Johnston et al., 2010), were used to assess lifetime and past 30 days use frequency for a variety of illicit and licit prescription substances. These questionnaires instruct respondents that use refers to use "without a doctor's notice/order" for substances that can be prescribed. Small sips of alcohol for religious purposes were explained to not count towards alcohol use.

2.3.1.1. Lifetime use and age of onset: Initiation (yes/no; any lifetime use) and age of first use (8, 9–10, 11–2, 13–14, 15–16, or 17 years old) were collected for the following 20 drug classes: A whole cigarette; other forms of tobacco (e.g., cigars, cigarillos, e-cigarettes, flavored tobacco); smokeless tobacco; one full drink of alcohol; marijuana; inhalants; cocaine; methamphetamine; psychedelics (e.g., LSD, mushrooms, or other psychedelics); ecstasy; heroin; salvia; prescription painkillers to get "high"; barbiturates, tranquilizers or sedatives; cold/cough medicine to get "high"; diet pills; prescription stimulants to get "high"; antihistamines to get "high"; and any other pill or illegal drug to get "high". An "any lifetime substance use" composite variable (yes/no) was coded which denoted students who endorsed use of any of the 20 substances assessed in the study. A similar variable denoting "age of onset of any substance" was coded which noted the earliest age of use of any of the 20 substances.

2.3.1.2. Past 30 day use: Frequency of use in the past 30 days (0=no days, 1=1–2 days, 2=3–5 days, 3=6–9 days, 4=10–14 days, and 5=15–30 days) was assessed for six substances: alcohol, tobacco, marijuana, illicit stimulants (e.g., methamphetamine, cocaine), prescription stimulants (e.g., Adderall, Ritalin), and prescription painkillers (e.g., Oxycontin, Vicodin). Choice of the six substances to include when asking about frequency of past 30 day use was based off of prior literature of indicating higher lifetime use prevalence rates in national samples (Johnston et al., 2014) and in prior studies in the target location (Unger, 2014) relative to the other substances, as well as conceptual interests that these substances may be particularly related to emotion disturbance. Given the low variance in individual use for illicit substances, a composite frequency of use variable was created by summing the frequencies reported across all six substances.

2.3.2. UPPS impulsive behavior scale (UPPS-P) negative urgency subscale—

The UPPS-P Impulsive Behavior Scale (Whiteside and Lynam, 2001), which has been used in adolescent samples (Robinson et al., 2014), has a subscale tapping negative urgency (12

items; e.g., "When I feel bad I will often do things I regret later to make myself feel better now" and "When I'm upset I often act without thinking"). Participants rate statements on a 4-point Likert scale from "disagree strongly" (1 point) to "agree strongly" (4 points) with higher scores indicating higher levels of urgency. An average score per item was computed for the negative urgency subscale. Negative urgency has been linked to addictive behaviors (Coskunpinar and Cyders, 2012; Dir et al., 2013; Settles et al., 2012; Spillane et al., 2012) and has been shown to have good discriminant validity from other impulsivity constructs (Smith et al., 2007).

2.3.3. Center for epidemiologic studies depression scale (CESD)—The CESD is a 20-item measure of how often over the past week feeling and behaviors associated with depression (e.g., "I felt sad" and "I felt that everything I did was an effort") were experienced. Participants rate statements on a 4-point likert scale from "rarely or none of the time" (0 points) to "most or all of the time" (3 points) with higher scores indicating higher levels of depressive symptoms. An average score for all questions was computed to give a total mean score. The CESD has shown good reliability (Chabrol et al., 2002) and validity in adolescent samples (Garrison et al., 1991; Radloff, 1991).

2.4. Data analysis

2.4.1. Preliminary analyses—Preliminary analyses involved reporting sample descriptive, correlations among key measures, demographics, and substance use. To ensure adequate frequencies of individual substance type variables for analyses and avoid potential type-I errors due to multiple testing of outcomes that were rare, we analyzed substances only with at least 5% use prevalence (in addition to the "Any substance" use which concatenated use of any of the 20 total substances). Of 20 substances assessed, 6 substances (cigarette, other forms of tobacco, alcohol, marijuana, inhalants, and prescription painkillers) had at least 5% of our sample reporting lifetime use and were included in substance-specific lifetime analyses.

2.4.2. Primary analyses—First, we ran linear regression models examining CESD predicting negative urgency. Next, we ran logistic regression models in which CESD total mean score served as the predictor and use of a particular substance served as the binary outcome (no use = 0; use = 1). For substances in which CESD significantly predicted use, we moved on to a meditational model to explore whether the relation of depressive symptoms to use of that substance was mediated by negative urgency. In these models, CESD was input as the predictor, negative urgency as the mediator, and the outcome was lifetime use of a substance. Mediational paths were analyzed by computing the product of the coefficients from two regression models: (a) the "a path" which examined the relation between the predictor to the mediator using linear regression and controlling for demographics; and (b) the "b path" which examined the relation of the mediator to the outcome using logistic regression and controlling for variables in the "a path". Both the "a path" and "b path" needed to show significance to be considered a mediational effect. The product of the coefficients served as the indicator of the strength of the indirect effect, for which significance was determined using PRODCLIN to estimate asymmetric confidence intervals (CIs) around the meditational effect (Tofighi and MacKinnon, 2011). In this

approach, the indirect effects are significant if the CI does not include 0. To determine the remaining direct effect of the predictor after controlling for the mediator, logistic regression models were run with the covariates that significantly correlated with the predictor (CESD) and/or the mediator (urgency). Results of regression models are reported as parameter estimates using standardized variables (M=0, SD=1; β s). Significance was set to .05 (two-tailed) for each analysis.

2.4.3. Supplemental analyses—We explored the meditational pathway of depression to negative urgency to age of first use and frequency of use over the past 30 days using linear regression models using the same strategies as described above, but inputting age of first use or frequency over the past 30 days as the outcome in the b path. Only the subsamples of individuals expressing lifetime use of a substance were included in these analyses and analyses for composite scores (any substance use and composite frequency) were restricted to individuals reporting lifetime use of any substance; hence, we were underpowered to detect effects and therefore consider these supplemental exploratory results.

3. Results

3.1. Preliminary analyses

The adolescent sample [mean age = 14.5 (SD =0.54)] was 51.3% female, largely Hispanic/ Latino (48.3%) and white (24.1%), with some representation from those reporting being American Indian/Alaska Native (.9%), Asian (6.0%), Black/African American (1.9%), Native Hawaiian/Pacific Islander (2.2%), or some Other ethnic or multi-racial category (16.6%). The highest parental education was as follows: 8th or less (4.4%), Some high school (6.3%), High school graduate (17.2%), Some college (22.9%), College graduate (26.3%), Advanced degree (13.9%), and Don't know (9.0%). Depressive symptom level and negative urgency were significantly positively correlated (r = .40, p < .001). There was a significant relation between gender and CESD scores (p < .05) and between highest parental education and negative urgency (p = .04); thus gender and highest parental education were controlled for in all models. Other demographics were not associated with depressive symptoms or negative urgency.

The following was reported percentage lifetime use of the 20 substances we looked at: A whole cigarette (12.3%); other forms of tobacco (17.7%); smokeless tobacco (1.8%); one full drink of alcohol (41.6%); marijuana (25.3%); inhalants (9.7%); cocaine (1.0%); methamphetamine (.9%); psychedelics (1.7%); ecstasy (.3%); heroin (1.0%); salvia (3.5%); prescription painkillers to get "high" (5.7%); barbiturates (0%), tranquilizers or sedatives (3.5%); cold/cough medicine to get "high" (4.2%); diet pills (1.7%); prescription stimulants to get "high" (2.6%); antihistamines to get "high" (.5%); and any other pill or illegal drug to get "high" (.9%). In our sample, 49.7% reported use of at least one substance.

3.2. Primary analyses

In individual regression models, depressive symptoms predicted negative urgency ($\beta = .37, p < .001$), and lifetime use of cigarettes ($\beta = .50, p < .001$), other forms of tobacco ($\beta = .43, p$

< .001), alcohol (β = .30, p < .01), marijuana (β = .58, p < .001), inhalants (β = .71, p < . 001), and prescription painkillers (β = .48, p < .05), and any substance (β = .39, p < .001).

Separate mediational models illustrated that negative urgency significantly mediated the relation of depressive symptoms to lifetime use of alcohol (β [95% CI] = .11 [.03–.21]), inhalants (β [95% CI] = .16 [.04–.30]), and use of any substance (β [95% CI] = .12 [.05–. 21]). After controlling for urgency, the remaining direct effect of depression score on lifetime alcohol use was no longer significant, but remained significant for lifetime use of inhalants and any substance (see Table 1). Hence, the results suggest a remaining direct effect over and above the meditational process for lifetime use of inhalants and any substance (i.e., partial mediation), but complete mediation for lifetime alcohol use.

3.3. Supplemental analyses

After limiting analyses to subsamples expressing use of a particular substance, depressive symptoms predicted age of first use for other forms of tobacco ($n = 102 \ \beta = -.25$, p < .05) and alcohol ($n = 239 \ \beta = -.16$, p < .05). Mediational models showed that negative urgency significantly mediated the relation of depressive symptoms to earlier age of first use of alcohol (β [95% CI] = .04 [.01–.09]). After accounting for negative urgency, the remaining direct effect of depression score on age of alcohol use was no longer significantly predict age of first use for variables in the 'a' path, negative urgency did not significantly predict age of first use for other forms of tobacco (see Table 1); thus further meditational testing was not warranted.

After limiting analyses to subsamples expressing lifetime use of a particular substance, depression scores predicted frequency of use of cigarettes (n = 66; $\beta = .25$, p < .05), alcohol (n = 231; $\beta = .18$, p < .05), and any use of at least one of the 6 substances measured for frequency (n = 284; $\beta = 26$, p < .001). Depression scores did not predict frequency of use of marijuana (n = 141) or prescription painkillers (n = 32). After adjusting for variables in the 'a' path, negative urgency did not significantly predict frequency of use for any substance (see Table 1) and further mediational models were not warranted.

4. Discussion

This study found that depressive symptom level associated with the lifetime use of cigarettes, other forms of tobacco products, marijuana, alcohol, inhalants, prescription painkillers, and any substance in an adolescent sample. This is consistent with previous research showing depressive symptoms associate with lifetime cigarette use (Audrain-McGovern et al., 2011, 2012), earlier onset of use of alcohol (Cerda et al., 2013), and literature showing associations between depression and use of a other substance categories (Harrington et al., 2011; O'Neil et al., 2011).

The results of this study also indicate that the covariance between depression scores and lifetime use of alcohol, inhalants, and any substance was accounted for by shared variance in negative urgency. This is consistent with previous reports showing that negative urgency associates with lifetime alcohol use in adolescents (Robinson et al., 2014) and extends these findings to suggest that negative urgency could act as a factor that channels risk for alcohol

use in individuals experiencing emotional symptoms, albeit this causal interpretation should be interpreted with caution given the cross-sectional design. Additionally, this is the first study to our knowledge to show that negative urgency associates with inhalant use and use of any substance along a meditational pathway from depression. Visual inspection of the pattern of meditational effects across substances suggested comparatively larger effect for alcohol versus other substances. Some potential reasons why the relations were strongest for alcohol are that alcohol is the most commonly used substance in this age range (Johnston et al., 2014) or that urgency differentially influences initiation of alcohol vs other substances (Robinson et al., 2014).

Analyses in adolescents reporting lifetime use of a particular substance showed that depression levels associated with age of first use of other forms of tobacco and alcohol and frequency of use of cigarettes, alcohol, and use of any substance. Negative urgency associated with relations between depression levels and age of first use of alcohol. These results are consistent with the results of the primary analyses suggesting that the pathways between depression levels and negative urgency may be strongest for alcohol use. After controlling for depression levels, negative urgency did not associate with frequency of use of any of the substances investigated. This is surprising given the extant literature showing urgency relates to problematic use of alcohol and other substances (King et al., 2011; Stautz and Cooper, 2013a, b). However, power was greatly limited in these secondary analyses, given the smaller sample sizes due to restricting our analyses to current users. Another possibility is relations with use frequency develop during later adolescence or young adulthood, and our sample was too young to reflect such processes (Stautz and Cooper, 2013a, b). Lastly, there is the possibility that negative urgency has no additional relation to frequency over and above depression, which was a powerful correlate of frequency in this study.

The results of this study need to be interpreted in the context of its limitations. For one, the cross sectional nature of this study precludes temporal and causal inferences. This may be particularly important as some studies suggest a bidirectional linkage between depression and substance use (Bulloch et al., 2012) or even suggest that substance use causes depression (Kenneson et al., 2013). Future prospective longitudinal cohort studies should be performed to further clarify the predictive nature of these variables. Also, the correlational nature of the study leaves open the possibility that an unmeasured extraneous variable explains the relations demonstrated in this paper, although we statistically controlled for demographic factors that are possible confounders. Additionally, this study only included self-report measures and did not include other forms of impulsivity. Future studies could include additional measures of impulsivity outside of urgency. Hence we cannot elucidate whether urgency has incremental associations with substance use over and above other impulsive traits (e.g., lack of premeditation, sensation seeking), which would be important to address in future work. While the creation of combined substance use scales increased the power to detect effects, it does leave open the possibility that the associations between depression, negative urgency, and substance use could be driven a single (or smaller set) of substances and may not reflect a propensity towards any type of substance use or polysubstance use. Given the proportionally higher prevalence of alcohol use compared to other substances in this study and the comparatively more robust substance-specific findings

for alcohol variables, relations to any substance use in this study could have been dramatically influenced by alcohol use. Future studies with larger samples of use of substances other than alcohol could have greater power to test specific effects of substances as well as address the associations of these variables with initiation of any substance use. Lastly, this study utilized only two schools in a restricted geographic region, which could limit the generalizability of the results.

Despite these limitations, this study expands the literature on depression levels and substance use in adolescence in several ways. The current study suggests that emotional vulnerability increases the likelihood of trying a number of different substances in early adolescence. This suggests that addressing depressive symptoms in adolescents may be an effective strategy in preventing the onset of many of the commonly used substances in early adolescence. This is important knowledge because preventing substance use in adolescence should reduce the amount of individuals moving on to substance use disorders in adulthood. Furthermore, this is the first study examining a mechanism linking depression and negative urgency to the onset of substance use in adolescence, which is important in advancing theory on motivational processes underlying substance use onset among individuals with psychological vulnerability factors. Pending replication and extension to a longitudinal design, the current research suggests that negative urgency may be a specific target for interventions designed to buffer the risk of use of alcohol and inhalants in depressed adolescents. Interventions that reduce urgency and provide other coping mechanisms during emotionally vulnerable states may be useful in preventing the onset of use of alcohol and inhalants.

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Table 1

Interrelations between depressive symptoms, negative urgency, and lifetime substance use, age of first use and past 30-day frequency of use.

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Outcome	M (SD) or %	Predicto	r			Mediation: CES	$\mathbf{D} \rightarrow \mathbf{NU} \rightarrow \mathbf{Use}$
		CESD		NU		Indirect Effect	Remaining Direct Effect
		ß	þ	βı	ß	β	ßł
NU	2.00 (.62)	.40 ^{***}	.37***				
Cigarettes							
Lifetime use	12.3%	.46***	.50***	.40**	.22	ı	ı
Age first use	12.63 (1.83)	01	18	01	.03	ı	
Frequency of use	2.50 (6.13)	.21	.25*	.02	.02	I	ı
Other forms of tobacc	0						
Lifetime use	17.7%	.36**	.43***	.34**	.23	ı	ı
Age first use	13.21 (1.49)	13	25*	16	17	ı	ı
Alcohol							
Lifetime Use	41.6%	.35***	.30**	.43***	.35***	.11**	.12
Age first use	12.77 (1.87)	14*	16*	26***	25**	.04*	04
Frequency of use	1.75 (3.64)	.22	.18*	.18*	60.	I	ı
Marijuana							
Lifetime use	25.3%	.50***	.58***	.35**	.17	ı	ı
Age first use	12.80 (1.45)	06	14	-00	11		,
Frequency of use	4.51 (7.10)	.12	.10	.17	.14		,
Inhalants							
Lifetime use	9.7%	.75***	.71***	.65***	.43**	$.16^{**}$.55**
Age first use	12.00 (1.74)	.23	.19	.15	.07	ı	1
Prescription painkille	rs						
Lifetime Use	5.7%	.51**	.48*	.40	.12	ı	
Age first use	13.33 (1.78)	.02	10	.01	08		,
Frequency of use	2.50 (4.78)	.19	.17	05	05	1	ı

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Outcome	M (SD) or %	Predicto	r			Mediation: CES	$D \rightarrow NU \rightarrow Use$
		CESD		NU		Indirect Effect	Remaining Direct Effect
		ßı	þ	Ъ	æ	¢¢	₿ł
Any Substance							
Lifetime use	49.7%	.42**	.39***	.45***	.33**	.12**	.24*
Age first use	12.27 (2.02)	10	12	18**	19**	ı	ı
Frequency of use	1.07 (2.05)	.23***	.26***	.14*	.08	ı	I
<i>Note</i> : Across lifetime u	se analyses, samp	ples sizes r	ange from	575 to 585	across due	e to missing data. If	either the a path (effect of CES)

 $D \rightarrow NU)$ or b path (effect of NU \rightarrow use controlling for CESD) did not show a significant effect, meditational analyses were not performed for that particular substance outcome (indicated by a dash). Age of first use and frequency of use only includes individuals reporting use of the particular substance. Mean and standard deviation for frequency of use is coded as 0 = no days, 1-2 days = 1.5, 3-5 days = 4.6-9 days = 7.5, 10-14 days = 12, 15-30 days = 22.5. All continuous variables were standardized (M = 0, SD = 1). CESD = Center for Epidemiologic Studies Depression Scale. UPPSP = UPPS Impulsive Behavior Scale.

^aUnadjusted regression parameter.

 $^{b}{\rm Adjusted}$ regression parameter after controlling for highest parental education and gender.

^cAdjusted regression parameter after controlling for the predictor (CESD), highest parental education and gender.

 d Adjusted regression parameter after controlling for highest parental education, gender, and negative urgency.

* P<.05. ** P<.01.

 $^{***}_{P<.001.}$