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## Depression and Nicotine Dependence from Adolescence to Young Adulthood

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### Abstract

**Introduction**—Despite the highly replicated relationship between depression and nicotine dependence, little is known about this association across both time and levels of lifetime smoking exposure. In the present study, we evaluate if symptoms of depression are associated with emerging nicotine dependence after accounting for smoking exposure and whether this relationship varies from adolescence to young adulthood and across increasing levels of smoking.

**Patients and Methods**—The sample was drawn from the Social and Emotional Contexts of Adolescent Smoking Patterns Study which measured smoking, nicotine dependence and depression over 6 assessment waves spanning 6 years. Analyses were based on repeated assessment of 941 participants reporting any smoking 30 days prior to individual assessment waves. Mixed-effects regression models were estimated to examine potential time and smoking exposure varying effects in the association between depression and nicotine dependence.

**Results**—Inter-individual differences in mean levels of depression and within subject changes in depression from adolescence to young adulthood were each significantly associated with nicotine

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dependence symptoms over and above lifetime smoking exposure. This association was consistent across both time and increasing levels of lifetime smoking.

**Discussion**—Depression is a consistent risk factor for nicotine dependence over and above exposure to cigarettes and this association can be demonstrated from the earliest experiences with smoking in adolescents through the establishment of more regular smoking patterns across the transition to young adulthood.

**Conclusion**—Depression remains a prominent risk factor for nicotine dependence, and youth with depression symptoms represent an important subgroup in need of targeted smoking intervention.

### Keywords

Tobacco; Depression Symptoms; Mixed-effects regression model

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## 1.0 Introduction

Depression is one of the most consistent risk factors implicated in both the etiology of smoking behavior as well as the subsequent developmental course of nicotine dependence. Supporting evidence for this relationship comes from longitudinal investigations in which both depression symptoms (1) as well as a diagnosis of major depression (2–4) have been shown to be associated with increased risk of future smoking, the progression to nicotine dependence among adolescents (5) and adults (6) and a decreased likelihood of successful smoking cessation (7).

Though it is consistently linked to several smoking related outcomes, one line of emerging evidence suggests that depression may in fact be uniquely associated with symptoms of nicotine dependence rather than with one's level of smoking per se. For example, evidence from a family study following adolescent smokers through the age of risk for smoking initiation and escalation showed that depression, as well as several other psychiatric disorders, was associated with the progression to nicotine dependence, but not with experimental or regular smoking in the absence of dependence (4). More recently, an investigation of young adult smokers from the National Epidemiologic Study of Alcohol and Related Conditions (NESARC) demonstrated that daily smokers with depression were at increased risk for nicotine dependence both after controlling for level of smoking and also when examining rates of nicotine dependence across the continuum of daily smoking behaviors (8). That is, individuals with a lifetime diagnosis of depression showed higher rates of nicotine dependence at each level of daily smoking, ranging from 1 to 5 cigarettes per day to well over a pack per day, compared to individuals without a history of depression.

A discussion of the mechanism that may help to explain the association between depression and nicotine dependence has, to date, largely focused on the role of depression (either through causal or shared effects) in elevating one's probability of smoking (i.e. increasing the likelihood of initiation, promoting earlier onset, and/or influencing the number of cigarettes or persistence of smoking), suggesting that it is the increased exposure that then causes physiological adaptations that lead to dependence symptoms (9). The aforementioned evidence independently linking depression to nicotine dependence, however, supports an

alternate hypothesis that recognizes depression as a sign or signal for nicotine dependence across a potentially wide range of smoking behaviors (8).

Yet, how wide might this range be? For example, is it inclusive of even the very first experiences with cigarettes? Further, does depression as a signal of nicotine dependence sensitivity necessarily function consistently across time and developmental stage? Available research has largely documented static, between-subjects relationships rather than exploring the developmental growth and change in the association between depression and nicotine dependence within individuals and across the period of greatest risk for both smoking initiation and escalation. The present study sought to begin to fill this gap by examining the dynamic, longitudinal relationships between depression and nicotine dependence. Specifically, we investigate whether there are time and smoking exposure variations in the association between symptoms of depression and emerging nicotine dependence from the earliest experiences with cigarettes through increasing levels of smoking exposure, and from adolescence into young adulthood. We ask: (1) Are symptoms of depression independently associated with emerging nicotine dependence after accounting for smoking exposure? (2) Does this relationship vary across levels of smoking from the earliest exposures through higher levels of smoking quantity and regularity? And; (3) Does the relationship vary across the transition from adolescence to young adulthood? To address these questions, we rely on data from an ongoing longitudinal sample recruited during adolescence and followed for 6 years through the transition to young adulthood.

## 2.0 Methods

### 2.1 Participants

The sample was drawn from the Social and Emotional Contexts of Adolescent Smoking Patterns (SECASP) Study, which has been described elsewhere (10). All 9th and 10th grade students at 16 Chicago-area high schools completed a brief screener survey of smoking behavior (N = 12,970). All students who reported 1) smoking in the past 90 days and smoking <100 cigarettes/ lifetime, 2) smoking in the past 30 days and smoking >100 cigarettes/lifetime, or 3) smoking <100 cigarettes/lifetime, but not smoking in the past 90 days, were invited to participate, as were random samples of never-smokers. Of the 3654 students invited, 1263 agreed to participate and completed the baseline measurement wave 2 months after screening.

Following the baseline assessment, 5 additional assessment waves that included identical measures of smoking, depression and nicotine dependence occurred at 6-, 15-, 24-, 60- and 72 months. All procedures received approval from the University of Illinois at Chicago IRB. Written informed consent was obtained from the parents or guardians of the adolescents and each adolescent provided their assent to participate in the study. For assessment following each participant's 18<sup>th</sup> birthday, informed consent was directly obtained. Retention at 72 months was 84.6% (N = 1068). The present analyses focused on participant level smoking observations across the multiple assessment waves that included reports of any smoking 30 days prior to each assessment (n = 941 participants, contributing 3077 smoking observations). The mean age of this sample when recruited for the study was 15.7 years (s.d.

0.62). Fifty-five percent (n=521) were male, 57.4% (n=540) White, 15.2% (n=143), Black and 18.5% (n=174) were Hispanic.

## 2.2 Measures

**Smoking**—Smoking behavior for the present analyses was measured at the baseline, 6-, 15-, 24-, 60- and 72-month assessment waves with two items. “About how many cigarettes have you smoked in your entire life (500 or more, 100 or more cigarettes, 26 to 99 cigarettes, 16 to 25 cigarettes, 6 to 15 cigarettes, 2 to 5 cigarettes, 1 cigarette, or 1 or more puffs, but never a whole cigarette)?” and “Have you ever smoked cigarettes on a daily basis (i.e. At least 30 days when you smoked every day or nearly every day)?”

**Nicotine dependence**—Nicotine dependence was assessed at the baseline, 6-, 15, 24-, 60- and 72-month follow-up assessments with a shortened version of the nicotine dependence syndrome scale (NDSS); (11), modified for use with adolescents. The full NDSS scale was reduced to 10 items based on psychometric analyses conducted on an adolescent sample (12), retaining those items reflecting mainly drive and tolerance from the original NDSS. Research supports the reliability, stability, construct validity, and predictive validity of the NDSS for use with adolescents (13, 14), and the modified version demonstrated strong internal consistency with the current sample (coefficient alpha = .93). Items in the current study were answered on a four-point Likert-type scale, ranging from 0 (not at all true) to 3 (very true), and were summed into a total NDSS score.

**Depression**—Symptoms of depression were measured at the baseline, 6-, 15, 24-, 60- and 72-month follow-up assessments with the Center for Epidemiological Studies-Depression Scale (CES-D) (15). Items were answered on a four-point Likert-type scale, ranging from 0 (never or rarely) to 3 (most of the time or all of the time), and were summed into a total CES-D score. The internal consistency of the CES-D has been reported to be in the 0.8–0.9 range (note: in the present sample, internal consistency ranged from .88 to .91 across each of the 6 waves) and test–retest stability has been reported to be 0.5–0.6 over follow-up periods, ranging from several weeks to several months (16).

**Other tobacco use**—Other tobacco use was measured at the baseline, 6-, 15, and 24-month follow-up assessments with the questions, During the past 30 days, on how many days did you (a) use chewing tobacco, snuff or dip; (b) smoke cigars, cigarillos or little cigars; (c) smoked bidis (small, thin, hand-rolled cigarettes wrapped in tendu or temburni leaf) or (d) smoked kreteks (cigarettes typically containing a mixture of tobacco and cloves)?. At the 60 and 72 month follow-up assessments, other tobacco use was measured by the questions, During the past 30 days, on how many days did you (a) use chewing tobacco, snuff or dip; (b) smoke cigars; (c) use snus (a moist powder, smokeless tobacco); (d) use e-cigarettes or (e) smoke a hookah? Responses at each assessment wave were dichotomized into any other tobacco use vs. no other tobacco use.

## 2.3 Analyses

Using nicotine dependence symptom scores from the NDSS as the outcome, between-subjects (static) effects and time-varying effects of depression and number of lifetime

cigarettes smoked at each assessment were examined, while controlling for time varying effects of daily smoking, other tobacco use, and subject-level effects of age, ethnicity (White vs. non-White) and gender measured at baseline. Mixed-effects regression models (i.e. HLM or multi-level models), which include both fixed effects of variables and random effects to account for the repeated measurements of participants over time, were run using SAS PROC MIXED. Random effects included the intercept (allowing individual differences in baseline nicotine dependence), time trends (allowing individual differences in the rate of change in nicotine dependence across follow-up waves), and smoking levels (allowing individual differences in the rate of change in nicotine dependence with varying exposure to smoking) with an unstructured covariance structure.

Nicotine dependence symptoms (outcome), depression, number of lifetime cigarettes smoked, daily smoking and other tobacco use were all time-varying, while age, ethnicity and gender were static and derived from the baseline reports. To disentangle the contribution of within-subjects changes in both smoking and depression and between-subjects variability in predicting nicotine dependence, mixed effects regression models were estimated to simultaneously account for both an individual's mean level of smoking and depression across time (i.e. between-subjects effects) as well as the difference at each assessment wave between an individual's mean level of smoking and depression and their current level of smoking and depression at each assessment (i.e. within-subjects effects) (17). Both time-varying and smoking exposure-varying effects were investigated by including interactions between depression and both time and lifetime smoking level. An interaction term between CES-D and gender was also included in the model. Effect sizes were calculated using Cohen's  $f^2$  as described elsewhere (18) and interpreted as small ( $f^2 = 0.02$ ), medium ( $f^2 = 0.15$ ), or large effects ( $f^2 = 0.35$ ) (19).

### 3.0 Results

More than half of the sample (58.5%,  $n=550$ ) started the study having smoked fewer than 100 cigarettes in their lifetime and increased their smoking behavior to reach 100 or more cigarettes by the 72 month follow-up assessment; 22.1% ( $n= 208$ ) increased their smoking but did not reach 100 cigarettes by 72 months; 8.5% ( $n=80$ ) started the study having smoked 100 or more cigarettes and increased their smoking to over 500 cigarettes; and the remaining 10.9% ( $n=103$ ) did not increase their smoking during the study period. Average lifetime smoking, depression and nicotine dependence symptom scores, at each assessment wave, are shown in Table 1. Positive linear trends characterize average lifetime smoking levels ( $b=3.89$ ,  $p=.0001$ ) and nicotine dependence symptom scores ( $b=.06$ ,  $p=.0001$ ) between baseline and 72 months. In contrast, mean depression symptom scores showed a negative quadratic trend ( $b= -.002$ ,  $p=.0001$ ) in which average scores decreased from baseline to 15 months, increased at 24 months and then decreased again at 60 and 72 months.

The results of the mixed-effects regression model are shown in Table 2. Depression symptoms were consistently associated with the nicotine dependence symptom score, after controlling for baseline measures of gender, age, and ethnicity and time varying measures of daily smoking and other tobacco use. That is, the between subjects measure of depression symptoms (mean depression across assessment waves) as well as the within-subjects

measure (the difference between mean depression and current depression at each wave) were significantly and positively associated with nicotine dependence symptom scores, indicating that individuals with consistently high levels of depression scored consistently higher on the NDSS, and that within individuals, increases in depression at a particular wave is associated with increases in nicotine dependence symptoms at that wave. Notably, the associations between depression and nicotine dependence were significant even after accounting for the between-subject and within-subject measures of lifetime smoking level, which were also found to be independently associated with nicotine dependence symptom scores.

The relationship between depression and nicotine dependence did not vary by time, smoking level or gender as was observed by the non-significant interactions in the mixed-effects model. The effect size for the association between depression and nicotine dependence was consistently of medium in size ( $f^2 = 0.20$ ) and comparable to the effect size for lifetime smoking exposure and nicotine dependence ( $f^2 = 0.13$ ).

## 4.0 Discussion

Despite considerable evidence supporting a depression-smoking link, the mechanisms underlying this association remain relatively unclear. The present study sought to investigate this relationship from the perspective of emerging nicotine dependence symptoms and within a developmental context including both the transition from adolescence to young adulthood as well as increasing lifetime cigarette exposure. Three major findings emerged. First, after statistical control for nicotine exposure (i.e. lifetime smoking, current daily smoking and other tobacco use), depression symptoms were positively and significantly associated with symptoms of nicotine dependence. Second, this association was significant when considering both between subject differences as well as within subject *changes* in depression and nicotine dependence symptoms across time. Third, this association between depression and nicotine dependence symptoms was consistent across time (i.e. from adolescence to young adulthood) and across lifetime smoking exposure (i.e. from earliest experiences with cigarettes to 500 plus cigarettes smoked).

The relationship between depression and the emergence of smoking behavior has been previously hypothesized to result from increased exposure to cigarettes stemming from the need to medicate negative affective experiences common to these types of disorders (20). The present findings, however, show depression symptoms to be directly linked to symptoms of nicotine dependence above and beyond smoking exposure. Thus, depression symptoms are a signal for nicotine dependence symptoms (8). This signal might be interpreted in several ways. Nicotine dependence and depression involve overlapping neurobiological underpinnings (21–23), and it is possible that the emergence of one type of symptoms involves a functional recalibration of the Central Nervous System (CNS) which causes the emergence of the other symptoms. Important causal processes might also occur at the behavioral level. For instance, an over-reliance on smoking to cope with depressive symptoms may prevent acquisition of more effective coping responses to counteract mood disturbance (24). Because we examined contemporaneous associations between dependence and depression symptoms, the current findings can neither implicate causal processes per se

nor specify the direction of any such effect. The signal could also reflect latent genetic and environmental factors common to both disorders (25, 26). Finally, the clustering of problems in particular individuals may not be specific to these two syndromes, but rather may be an instantiation of a broad vulnerability factor associated with risk for any form of psychopathology (27).

To our knowledge, this is the first study to demonstrate an association between changes in depression and nicotine dependence symptoms (i.e. within subject effects) across time, over and above level of smoking, an association that was significant from adolescence to young adulthood and from the earliest experiences with smoking to higher levels of use. Further, the significant association between lifetime smoking level and nicotine dependence symptoms independent of depression suggests that an individual's cumulative exposure to cigarettes across time, rather than time per se, also plays a significant role in development of nicotine dependence symptoms.

The current findings should be interpreted within the context of study limitations. First, our measures of other forms of tobacco use did not consider the level of use of other tobacco products, which could add considerable exposure to nicotine. Thus, it is also possible that variability in nicotine dependence symptoms at similar levels of smoking among those with different levels of depression symptoms may still be based on variability in levels of nicotine exposure not captured by the present measures of the construct. Alternately, findings may be driven by systematic differences in subjective evaluations of nicotine dependence symptoms rather than physiologic differences in sensitivity. That is, there may be biases in the way those with certain negative affective symptoms respond to questions about nicotine dependence. For example, those with depression symptoms may be more likely to answer questions more negatively and see themselves as more addicted. Evidence against this explanation however can be seen in recent findings that early emerging nicotine dependence symptoms, even those reported by adolescents smoking only a few cigarettes in their lifetime, significantly predict future daily smoking (10).

Because we were interested in the association between depression and nicotine dependence among smokers, data for these analyses included individual observations for youth who had smoked in the 30 days prior to an assessment wave. Thus, while the findings demonstrate that decreases in nicotine dependence are associated with decreases in depression and vice versa, we were unable to evaluate levels of depression and dependence among those who have quit smoking. Further, we do not provide evidence regarding the temporal association between depression and nicotine dependence (i.e. which comes first) given our focus on the time varying nature of the cross-sectional relationship between these two constructs. It should be noted that additional exploratory work with this sample demonstrated consistently strong cross-sectional effects, but non-significant longitudinal associations when controlling for level of smoking, a construct seldom included in models from previous literature.

Despite these limitations, the current study has a number of strengths. First, it is based on one of only a few longitudinal samples available to date that includes a large group of youth at the earliest stages of smoking exposure. Further, these findings are among the first to characterize the relationship between symptoms of depression and nicotine dependence

across time and level of smoking exposure. As such, the present study adds to accumulating evidence showing individual variability in nicotine dependence symptoms based on the number of depression symptoms, an association that was not better accounted for by smoking exposure.

As the major dependence producing agent in cigarettes, nicotine is believed to play the pivotal role in keeping smoking rates stable. While smoking is a necessary contributor, the present study adds to accumulating evidence showing individual variability in nicotine dependence symptoms based on symptoms of depression, an association that is not better accounted for by variability in smoking exposure (8). If causally associated, these findings would suggest that treatment of depression symptoms may prevent or reduce the early emergence of nicotine dependence symptoms. If instead, however, depression symptoms are a signal for nicotine dependence, best accounted for by a third variable, then adolescents with measurable depression represent an important subgroup that may benefit from intervention that directly targets this association (29).

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### Highlights

- We evaluate the association between depression and emerging nicotine dependence.
- Analyses were based on repeated assessment of 941 smokers between adolescence and young adulthood.
- Differences between depression levels are associated with nicotine dependence symptoms.
- Changes in depression within individuals are associated with nicotine dependence symptoms.
- Depression remains a prominent risk factor for nicotine dependence.

**Table 1**

Average lifetime smoking, nicotine dependence and depression symptom scores at each assessment wave

|          | Smoking           |        | CESD  |       | NDSS  |      |
|----------|-------------------|--------|-------|-------|-------|------|
|          | Mean <sup>1</sup> | s.d.   | Mean  | s.d.  | Mean  | s.d. |
| Baseline | 107.84            | 170.41 | 18.14 | 10.15 | 6.69  | 7.06 |
| 6 mo     | 158.22            | 200.99 | 17.55 | 10.40 | 7.76  | 7.62 |
| 15 mo    | 193.40            | 215.40 | 15.78 | 9.67  | 8.67  | 8.09 |
| 24 mo    | 233.06            | 219.33 | 20.42 | 7.44  | 9.41  | 7.96 |
| 60 mo    | 369.40            | 199.55 | 14.48 | 10.34 | 10.84 | 8.85 |
| 72 mo    | 392.89            | 185.75 | 13.65 | 10.24 | 11.10 | 8.65 |

<sup>1</sup> Mean of median value of the endorsed response category.

**Table 2**

Unstandardized fixed effects on nicotine dependence symptoms, based on results of a mixed-effects regression model.

| Effect                                    | Estimate | Standard Error | DF  | t Value | P value |
|---|----------|----------------|-----|---------|---------|
| Intercept                                 | 3.3293   | 3.5798         | 928 | 0.93    | 0.3526  |
| CESD ( <i>between subjects</i> )          | 0.1428   | 0.02038        | 426 | 7.01    | <.0001  |
| CESD ( <i>within subjects</i> )           | 0.06779  | 0.0126         | 428 | 5.38    | <.0001  |
| White vs. other                           | 0.01673  | 0.2935         | 426 | 0.06    | 0.9546  |
| Gender (male vs. female)                  | 0.4324   | 0.2925         | 426 | 1.48    | 0.1401  |
| Age                                       | -0.3236  | 0.2267         | 426 | -1.43   | 0.1543  |
| Other tobacco use                         | 1.1782   | 0.2014         | 426 | 5.85    | <.0001  |
| Smoking level ( <i>between subjects</i> ) | 0.02131  | 0.001061       | 426 | 20.1    | <.0001  |
| Smoking level ( <i>within subjects</i> )  | 0.009794 | 0.000869       | 488 | 11.27   | <.0001  |
| Daily smoking                             | 4.0152   | 0.2781         | 426 | 14.44   | <.0001  |
| time (baseline vs. 72 mo.)                | 0.2272   | 0.4314         | 426 | 0.53    | 0.5988  |
| time (6 mo. vs. 72 mo.)                   | 0.1635   | 0.4128         | 426 | 0.4     | 0.6922  |
| time (15 mo. vs. 72 mo.)                  | 0.724    | 0.3909         | 426 | 1.85    | 0.0647  |
| time (24 mo. vs. 72 mo.)                  | 0.1879   | 0.375          | 426 | 0.5     | 0.6166  |
| time (60 mo. vs. 72 mo.)                  | 0.1245   | 0.2848         | 426 | 0.44    | 0.6622  |