



Published in final edited form as:

Prev Med. 2017 March ; 96: 73–78. doi:10.1016/j.yjmed.2016.12.034.

## Bi-directional associations of electronic and combustible cigarette use onset patterns with depressive symptoms in adolescents

William V. Lechner<sup>a,\*</sup>, Tim Janssen<sup>a</sup>, Christopher W. Kahler<sup>a</sup>, Janet Audrain-McGovern<sup>b</sup>, and Adam M. Leventhal<sup>c</sup>

<sup>a</sup>Center for Alcohol and Addiction Studies, Brown University, School of Public Health, Providence, RI USA

<sup>b</sup>Department of Psychiatry, University of Pennsylvania, Perelman School of Medicine, PA, USA

<sup>c</sup>Department of Preventive Medicine, University of Southern California, Keck School of Medicine, Los Angeles, CA, USA

### Abstract

Whether well-documented patterns of mental health comorbidity with adolescent combustible cigarette use extend to e-cigarette use is unclear. Demonstrating associations between e-cigarette and combustible cigarette use with mental health symptomatology across adolescence may be important for promoting accurate perceptions of populations at risk for and potential consequences of tobacco product use. Adolescents ( $N = 2460$ ; mean age at baseline = 14.1; 53.4% female; 44.1% Hispanic) who had never previously used combustible or e-cigarettes were assessed at baseline, and 6- and 12-month follow-ups in Los Angeles, CA (2013–2014). Logistic regression was used to examine associations between baseline depressive symptoms and onset of e-cigarette and cigarette single product and dual use at follow-ups. Latent growth modeling was used to examine associations between sustained use of either product (vs. non-use) and changes in depressive symptoms over 12-months. Higher baseline depressive symptoms predicted subsequent onset of cigarette (OR = 1.024, 95% C.I. = 1.009–1.055), e-cigarette (OR = 1.015, C.I. = 1.003–1.023), and dual use of both products (OR = 1.021, C.I. = 1.003–1.043). Sustained use of e-cigarettes over the 12-month observation (vs. non-use) was associated with a greater rate of increase in depressive symptoms over time ( $b = 1.272$ , SE = 0.513,  $p = 0.01$ ). Among those who sustained use of e-cigarettes, higher frequency of use was associated with higher depressive symptoms at the final follow-up ( $B = 1.611$ ,  $p = 0.04$ ). A bi-directional association of depressive symptoms with e-cigarette use onset across mid adolescence was observed. Further research on the causal nature, etiological underpinnings, and intervention implications of mental health and tobacco product use comorbidity is warranted.

\*Corresponding author at: Brown University, School of Public Health, 121 South Main St. 4th Floor Office 214, Providence, RI 02906, USA. william\_lechner@brown.edu (W.V. Lechner).

#### Disclosures

The authors report no potential conflicts of interests.

#### Author contributions

WVL and TJ conducted primary data analyses with advisement from CWK and AML WVL conceptualized and wrote the majority of the manuscript text. CWK, AML, JAM, and TJ aided in conceptualization and contributed significantly to revision.

## Keywords

Electronic cigarettes; E-cigarettes; Depression; Depressive symptoms; Adolescents; Developmental; Structural equation modeling; Growth curve model

---

## 1. Introduction

The association between (combustible) cigarette smoking and depressive symptoms has been well documented in adolescent populations and appears to be bi-directional. Depressive symptoms predict onset and escalation of smoking, and smoking predicts increasing levels of depressive symptoms over time (Brown et al., 1996; Chaiton et al., 2009; Wang et al., 1996; Windle and Windle, 2001). The recent emergence of e-cigarettes as a dominant form of tobacco product use in adolescent populations (Leventhal et al., 2015; Johnston et al., 2015a; Corey et al., 2013) raises questions regarding whether associations with depressive symptoms extend to e-cigarette use. The extent to which the bi-directional association of depressive symptoms with e-cigarette use parallels with or departs from the well-studied association of depressive symptoms and cigarette smoking has implications for understanding whether: (a) e-cigarette use is confined to vulnerable subpopulations with risk factors, such as depressive symptoms, or has appeal to a wider cross-section of the adolescent population including those with no or low levels of depressive symptoms; and (b) if poor mental health is a potential consequence of adolescent e-cigarette use. Given recent reports indicating that e-cigarettes may have a lower risk-profile in terms of acute physical harm (Hajek et al., 2014; Goniewicz et al., 2014; Polosa et al., 2014), documenting associations between prolonged e-cigarette use and negative associations with mental health may be particularly important in creating an accurate perception of the overall harm associated with these products.

Adolescents with higher depressive symptoms have been shown to be at greater risk of smoking due to heightened motivation to derive nicotine's rewarding (Audrain-McGovern et al., 2012) or negatively reinforcing effects (Audrain-McGovern et al., 2009; Laje et al., 2001) and greater association with peers who smoke (Audrain-McGovern et al., 2009) or engage in other deviant or risky behaviors. Prolonged nicotine exposure can cause abnormal cerebral dopamine transmission (Rademacher et al., 2016), dysregulate neural pathways underlying emotional processing (Parrott, 2015), amplify stress sensitivity (Kassel et al., 2003; Sinha, 2007), and interfere with the development of adaptive coping strategies that buffer against the onset of depressive symptoms (Leventhal and Zvolensky, 2015), particularly during adolescence when the developing brain is more vulnerable to nicotine-induced neurobiological insults (Holliday and Gould, 2016).

Some but not all of these aforementioned mechanisms underlying the link between cigarette smoking and depressive symptoms may extend to a possible coupling of depressive symptoms with e-cigarette use. Greater social acceptability (Kong et al., 2015) and ubiquitous use of e-cigarettes in comparison to conventional cigarettes in adolescent populations (Johnston et al., 2016), may result in e-cigarette use being less confined to peer groups saturated with high-risk youth with vulnerabilities such as depression. Or, e-

cigarettes may be seen as less risky products (Wills et al., 2015) and thus initiated by adolescents with less mental health vulnerability who may normally be deterred from initiating riskier products, like combustible cigarettes. Some adolescents report using e-cigarettes without nicotine (Miech et al., 2016). Additionally, nicotine absorption and effects may differ based on the type and generation of e-cigarette used (Farsalinos et al., 2014a; Lechner et al., 2015), thus effects of nicotine on the neural circuitry underlying depressive symptoms may be more variable as compared to cigarettes which may deliver nicotine more reliably.

Research on the association of depressive symptoms and e-cigarette use in adolescents is scant and entirely cross-sectional. One such study of psychiatric comorbidity among adolescent ever cigarette smokers, ever e-cigarette users, dual users of both products, and never users of either product found that e-cigarette users had a level of depressive symptoms midway between adolescents who had not used either product and adolescents who had smoked or were dual users (Leventhal et al., 2016). Thus, while the association of depressive symptoms with e-cigarette use is present and may be less pronounced than the corresponding relation with combustible cigarettes, whether such relationships extend to longitudinal designs and follow bi-directional patterns is unknown.

To provide the first longitudinal evidence on the association of e-cigarette use and depressive symptoms in adolescents, this study examined bi-directional associations of depressive symptoms with onset and sustained use of e-cigarettes over a 12-month period in adolescent's who had never used cigarettes or e-cigarettes at baseline. We hypothesized that elevated baseline depressive symptoms would predict onset of e-cigarette use over the follow-up period. We also hypothesized that teens who onset and then sustained use of e-cigarettes during the 12-month follow-up period (as compared to non-users of either tobacco product) would report higher concurrent increases in depressive symptoms across the 12 months. Furthermore, given the data reviewed above indicating that e-cigarette users may have less pronounced risk factors than combustible cigarette users, we also examined the bi-directional associations of depressive symptoms with combustible cigarette, and dual use. Examining these relationships will provide information on mental health risk factors for e-cigarette use and aid in understanding the overall harm associated with these products.

## 2. Method

### 2.1. Participants and procedure

Data were drawn from a longitudinal study (baseline [wave 1], 6-month follow-up [wave 2], and 12 month follow-up [wave 3]) of substance use and mental health among high school students in the Los Angeles, CA metropolitan area between 2013 and 2014. At each wave students completed surveys in their classrooms; those absent during data collection completed phone or web surveys. All procedures were approved by the University of Southern California Institutional Review Board.

The first wave of data collection commenced when participants were enrolled in ninth-grade coursework; all English-speaking students not in special education were eligible to participate (N = 4100). Of the assenting students (N = 3874; 94.5%), 3396 (87.7%) returned

parental consent, from whom data was collected for 3383 (99.6%), 3293 (97.0%), and 3282 (96.6%) participants, at baseline and 6- and 12-month follow-ups, respectively. The sample for the current report included 2460 adolescents who completed measures within the current analyses for all 3 waves, and reported never using combustible or electronic cigarettes, in their lifetime, at the baseline assessment. The analytic sample had a baseline mean age = 14.1 (SD = 0.41) and was ethnically heterogeneous (53.4% female, 44.1% Hispanic, 19.0% Asian, 16.2% White, 5.6% Bi-ethnic or Bi-racial, 4.8% African-American, 4.1% Native-American/Pacific-Islander, 5.5% other); 71.5% of students' parents attained a level of education of high school diploma or higher.

## 2.2. Measures

**2.2.1. E-cigarette and cigarette use**—Using items derived from the Youth Behavior Risk Surveillance (Eaton et al., 2010) and Monitoring the Future Surveys (Johnston et al., 2015b), lifetime and past 6-month use of e-cigarettes (described as “electronic cigarettes, personal vaporizers”) and combustible cigarettes were measured at each wave (yes/no). Frequency of e-cigarette use and cigarette use within the last 30 days (scored as a 6-level variable: 0 = 0 days, 1 = 1–2 days, 2 = 3–5 days, 3 = 6–9 days, 4 = 10–14 days, 5 = 30 days) was assessed only at wave 3. For analyses of the association of baseline depression with the onset of tobacco product use, we defined four mutually exclusive groups: (1) tobacco non-users (no-use of either tobacco product across waves); (2) onset of only combustible cigarette use at wave 2 or 3 (any onset within 12 months of baseline); (3) onset of only e-cigarette use at wave 2 or 3; (4) onset of dual use of both products at wave 2 or 3. For analyses of the trajectories of depressive symptoms associated with tobacco product use over time, e-cigarette use and combustible cigarette use were separately categorized as non-use (no use at wave 2 or 3), non-sustained use (use at wave 2 or 3 but not both), or sustained use (use at both wave 2 and wave 3). We did not model onset of dual use as a separate classification for these analyses due to small cell sizes.

**2.2.2. Depressive symptoms**—The 20-item Center for Epidemiologic Studies — Depression Scale (CES-D) was used to obtain self-reports of recent depressive symptom level. Questions are phrased as self-statements (e.g., “I felt sad”, “I had crying spells”). Sum past week frequency rating was utilized for the current analysis (score range for each item: 0 [rarely or none of the time; 01 day] to 3 [most or all of the time; 5–7 days]). The CES-D has been shown to have good internal consistency and adequate psychometric properties in adolescent populations (Garrison et al., 1991).

**2.2.3. Covariates: demographics, other tobacco use, alcohol use**—Variables peripheral to a putative pathway by which tobacco product use may be directly associated with depressive symptoms were selected a priori as covariates based on the previous literature. Sociodemographic characteristics including age, gender, ethnicity/race, and highest parental education were assessed using self-report responses to investigator-selected forced choice items. Family living environment was measured with the item, “Who do you live with most of the time?” (both biological parents vs. other) (Covey and Tam, 1990). Other tobacco and alcohol use was measured at each wave, using items based on the YRBS (Eaton et al., 2010) and MTF (Johnston et al., 2015b) assessing lifetime and past 6-month use

(yes/no) of full-size cigars, little cigars/cigarillos, hookah water pipe, blunts (“marijuana rolled in a tobacco leaf or cigar casing”), and frequency alcohol use in the past 30 days.

### 2.3. Analytic strategy

To examine the prospective relationship between baseline level of depressive symptoms and likelihood of subsequent tobacco product use onset (during the 12-month follow-up), logistic regression analyses were conducted using SPSS version 21.0. Each logistic regression analysis compared the likelihood of inclusion into one of the tobacco use onset groups (e-cigarette only, cigarette only, dual use) vs. the non-use group reference category (no use of both products) over the 12-month follow-up, as a function of baseline depressive symptoms adjusted for covariates described above. Follow-up post-hoc tests compared each tobacco product use group to one another (e.g., e-cigarette only vs. cigarette use, and e-cigarette use vs. dual use), and are considered exploratory due to the smaller frequencies and reduced power of these tests.

To test how combustible cigarette and e-cigarette use onset patterns were related to individual differences in changes in symptoms of depression over time controlling for baseline depression and other covariates, latent slopes of depressive symptoms were regressed on dummy-coded variables (described in measures section) representing non-sustained and sustained use for e-cigarette and combustible cigarette use separately (with non-use of each respective product at both follow-ups set as the referent) in a single model using Mplus version 7.3.(Muthen et al., 2002; Muthen and Asparouhov, 2015; Muthen, 2003). First, fit of identified unconditional growth model was assessed to ensure optimal representation of linear change over time (latent intercept being represented with intercept loadings fixed at 1 for all time points, latent linear change being represented by fixing factor loadings of depression scores at 0 for baseline, 1 for the 6-month assessment, and at 2 for the 12-month assessment) as described further in the Results. Maximum likelihood estimation was utilized under assumption of MAR for missing CES-D depressive symptom data across waves (missing data = 1.3%) and independent variables with missing data were removed list-wise (N = 270). Given that adding interaction terms between the dummy-codes representing combustible cigarette and e-cigarette use patterns of the main effects did not significantly improve fit(  $\chi^2 = 3.63$ ,  $df = 4, 0.56$ ) and due to small cell size for dual sustained use, only main effects were included in the final model.

Lastly, in order to provide additional insight into the relationship between tobacco product use and depressive symptoms, we examined how the frequency of tobacco product use was related to depressive symptoms. Linear regressions were conducted with frequency of use within the past 30 days set as the independent variable and depressive symptoms set as the dependent variable. This regression analysis included the same covariates as all other analyses and was performed for both e-cigarette use among sustained e-cigarette users and for cigarette use among sustained smokers. Frequency of use in the past 30 days of e-cigarettes was not collected until wave 3; therefore, this test is only performed for wave 3 variables.

## 3. Results

### 3.1. Descriptive analyses

Descriptive statistics for demographic characteristics and CES-D scores at each wave of the sample by product use group are listed in Table 1. The current sample included 347 (14.1%) individuals who initiated e-cigarette use within 12-months after baseline, 33 (1.3%) individuals who initiated cigarette use within 12-months of baseline, and 69 (2.8%) individuals who initiated dual use; these groups were mutually exclusive. Regarding patterns of e-cigarette use initiation, 104 (4.2%) individuals sustained e-cigarette use through waves 2 and 3 (6 and 12-month follow-up) and 312 (12.7%) engaged in a non-sustained use pattern (use at wave 2 or 3 but not both). Regarding cigarette use initiation patterns, 14 (0.6%) sustained cigarette smoking through waves 2 and 3 and 88 (3.6%) engaged in a non-sustained use pattern. These groups were not mutually exclusive. Mean frequency score of use in the past 30 days for the sustained e-cigarette use group was 1.48 (SD = 1.79), indicating use of e-cigarettes between 1 and 5 days in the past month. Similarly, smoking frequency score in the past 30 days for the sustained cigarette use group was 1.52 (SD = 1.83). Mean CESD depression score for the overall sample at wave 1 was 13.65 (SD = 11.26), wave 2 mean = 14.48 (SD = 12.1), and wave 3 mean = 14.56 (SD = 12.23). Information regarding correlates of attrition in the full study sample have been published previously (Leventhal et al., 2015); students completing follow-up vs. those not completing follow-up did not differ by baseline tobacco use or any sociodemographic characteristic with the exception of age, with those not completing follow-up date being older.

### 3.2. Tobacco use and depressive symptoms

**3.2.1. Logistic regression of baseline depressive symptoms predicting tobacco use onset**—As illustrated in Table 2, higher levels of baseline depression predicted increased likelihood of combustible cigarette use onset (OR = 1.024, C.I. = 1.009–1.055), e-cigarette use onset (OR = 1.015, C.I. = 1.003–1.023), and dual use onset (OR = 1.021, C.I. = 1.003–1.043), as compared to non-use of the tobacco products over the follow-up period in covariate adjusted logistic regression models. These results can be interpreted as reflecting that each increase in one SD unit across the distribution of baseline depressive symptom levels in the sample was associated with 36%, 12%, and 26% increase in odds of combustible cigarette, e-cigarette, and dual use onset, respectively. Models comparing likelihood of onset of cigarette use vs. e-cigarette use, as well as each product compared to dual use, were non-significant (see Table 2).

**3.2.2. Growth curve model of regressing depressive symptoms over time on tobacco use onset patterns**—An unconditional latent growth model including only depressive symptom growth parameters (intercept and linear change over time) demonstrated adequate fit, AIC = 57,473, SRMR = 0.009, CFI = 0.999, RMSEA = 0.042. The unconditional growth model showed that participants on average demonstrate significant linear increase in depressive symptoms over time ( $b = 0.414$ ,  $SE = 0.107$ ) and significant between-subject variance on the slope factor (estimate: 14.45,  $SD = 1.9$ ), indicating that individual differences in growth in depressive symptoms could be meaningfully predicted by exogenous variables (i.e., tobacco product use).

The full conditional model including paths from exogenous variables (i.e., tobacco product use onset and covariates) to depressive symptom growth demonstrated adequate fit: AIC = 45,898, SRMR = 0.032, CFI = 0.920, RMSEA = 0.051. Results revealed that sustained electronic cigarette use (versus non-use) was associated with a greater rate of increase in depressive symptoms over time ( $b = 1.272$ ,  $SE = 0.513$ ). Sustained combustible cigarette use (versus non-use) did not significantly predict depressive symptom trajectories; however, standard error for this effect was large as the cell size of sustained combustible smokers was small ( $N = 14$ ; see Table 3). Effects of non-sustained use of either product (vs. non-use) were also non-significant (see Table 3).

**3.2.3. Association between frequency of e-cigarette and cigarette use with depressive symptoms at wave 3**—Linear regression analysis of sustained e-cigarette users demonstrated a positive association of frequency of e-cigarette use score in the last 30 days with depressive symptoms at wave 3 ( $b = 1.611$ ,  $SE = 0.782$ ), indicating that increased frequency of use was associated with increased depressive symptoms. Linear regression analysis examining effects of frequency of cigarette use score in past 30 days on depressive symptoms among sustained cigarette users yielded sizeable parameter estimates, however, the standard error was large and the effect was not significant ( $b = 3.618$ ,  $SE = 2.545$ ).

## 4. Discussion

The current study provides new evidence indicating a potentially bi-directional prospective relationship between depressive symptoms and e-cigarette use in adolescents. These findings suggest that the prospective relationships observed in previous studies between combustible cigarettes and depressive symptoms are also present for e-cigarettes.

While teens with higher baseline depressive symptoms were at increased odds of starting e-cigarette use, smoking, and dual use of both products over the 12 month follow up, baseline depressive symptoms did not significantly predict differential likelihood of initiating e-cigarette compared to cigarette and dual use in post-hoc comparisons. We interpret these non-significant comparisons with caution due to somewhat limited power for these analyses and evidence of lower unadjusted baseline depressive symptom scores for those who initiated e-cigarettes vs. other products (see Table 1). Several recent studies have reported higher levels of mental health problems or other behavioral risk factors, measured in cross-section, for cigarette vs. e-cigarette using adolescents (Wills et al., 2015; Leventhal et al., 2016) with results in line with the observed mean difference in the current study and suggestive non-significant evidence in the post-hoc contrasts from regression models. One interpretation of the extant cross-sectional evidence is that e-cigarettes may be drawing in a new population of ‘lower-risk’ teens with moderate (but not severe) levels of mental health and behavioral problems (Leventhal et al., 2016) who may be attracted to e-cigarettes because they are socially acceptable and perceived to be a less-risky product. This paper advances our understanding by examining this relationship prospectively, and demonstrating that differences in at least one aspect of mental health (i.e. depressive symptoms) clearly predicts onset of e-cigarette and dual use, and opens the door for further research on whether mental health differentially predicts onset of e-cigarette vs. cigarette use.

Sustained electronic cigarette use across the 12 months of follow-up was associated with an acceleration of growth in depressive symptoms over time compared to non-use of the tobacco products. Among teens who use e-cigarettes containing nicotine, this association could reflect nicotine's dysregulating effects on mood (Rademacher et al., 2016; Parrott, 2015). Among the overall population of teens who use e-cigarettes with or without nicotine, the association of sustained e-cigarette use and increases in depressive symptoms could be explained by one of several mechanisms. Teens who use e-cigarettes may fail to develop adequate coping strategies to buffer against affective triggers (e.g., problem solving, communication and reach out to social support) by relying on e-cigarette use as a (maladaptive) coping mechanism (Leventhal and Zvolensky, 2015) that provides transitory relief but not long-term mental health benefits. It is also possible that instead of engaging in healthy pro-social recreational activities that prevent depression and enhance well-being (being part of clubs after school, sports, etc.) (Audrain-McGovern et al., 2011), teen e-cigarette users opt to use e-cigarettes as a primary source of recreation, which could leave them vulnerable to depressive symptoms. Another possibility is that a separate risk variable not accounted for in the current analysis explains the association observed. Future studies collecting data on the type of e-cigarette product and nicotine content of e-liquid used (or ideally a biological measure of absorbed nicotine), and a measure of coping strategies will help to elucidate important mediators of the relationship between prolonged e-cigarette use and depressive symptoms.

Most prior reports on the possible health correlates of e-cigarette use have focused on toxins in e-cigarettes and their potential acute respiratory, cardiovascular, and carcinogenic effects, which appear to be favorable compared to combustible cigarettes but not without harm (Hajek et al., 2014; Goniewicz et al., 2014; Polosa et al., 2014; Britton et al., 2014). Here, we show that sustained e-cigarette use over a 12-month period of adolescence (vs. no use) is associated with a disproportionate worsening of emotional health over this timeframe. Such a result highlights the need to consider not only the physical, but also the mental health correlates of e-cigarettes when evaluating harm and promoting accurate perceptions of potential harm associated with these products. The reported estimate (1.272) indicates the difference in rate of change on the CESD per observational period, thus the increase in CESD score was 2.55 points higher for sustained e-cigarette users, compared to non-users, over the one year period in the current study. A longer follow-up period may be required to observe larger changes in depressive symptoms. If future studies demonstrate that this rate of increase among sustained e-cigarette users is consistent over several years, it would represent clinically significant change in depressive symptoms.

The measure of e-cigarette use was highly sensitive for detecting at least a very low threshold of use (i.e., any e-cigarette use over the prior 6-month period) but inadequate for distinguishing frequent patterns of use. Consequently, we conducted a supplemental analysis showing that among teens with a sustained onset e-cigarette use pattern, those who used e-cigarettes more frequently reported higher depressive symptoms at the 12-month follow-up. This result suggests that perhaps a subgroup of more frequent sustained e-cigarette users disproportionately account for the accelerating depressive symptoms in this group and raises questions about a possible 'dose-response' relation between more frequent e-cigarette use and more frequent depressive symptom that warrants further inquiry.



The association of sustained combustible cigarette use with trajectory of depressive symptoms over time was not significant nor were the associations of cigarettes smoking frequency with depressive symptom level among sustained smokers. However, it is important to note these tests were under-powered to adequately detect differences in depressive symptoms over time due to small cell size ( $N = 14$ ), and thus must be interpreted with caution as the standard error of the estimates were large.

The current study has several limitations. First, the nature of the observational design used within the current study precludes direct causal inferences. Thus, unobserved individual-level characteristics may influence the main outcome variables examined. Further attempts to replicate these findings, using alternate designs, like increased frequency of measurement, longer duration of follow-up, and other methods, will help to determine the generalizability of the associations demonstrated herein. Additional work is also needed to examine whether these associations extend to other age ranges and geographic regions. The current study did not measure the level of nicotine used in e-cigarettes nor the frequency (within each wave) of e-cigarette use; thus, the analyses are limited in terms of interpreting mechanisms for the association observed between sustained e-cigarette use and depressive symptoms. Frequency of tobacco product use data in the last 30 days was available for wave 3, however, the single time point only allowed for cross-sectional analyses which carry limitations. Additionally, previous research indicates a strong relationship between internalizing behaviors (e.g. depressive symptoms) and externalizing behaviors; a measure of externalizing behaviors was not included in the current study, which could result in model misspecification. The current study utilized the CES-D; a clinical diagnosis of Major Depressive Disorder obtained through structured interview may provide additional information whether e-cigarette use is associated with clinical depression. Lastly, while the study was adequately powered to compare e-cigarette vs. non-users, small group sizes limited power for contrasts to combustible cigarette and dual use patterns; future studies with larger sample sizes will be necessary to examine individual differences in gender or race between tobacco use and symptoms of depression.

In conclusion, this analysis of Los Angeles area high school students showed that elevated symptoms of depression predicted subsequent initiation of both cigarettes and e-cigarettes, as well as dual product use, and found that sustained e-cigarette use was associated with an acceleration of growth in depressive symptoms over time. Further research on the causal nature, etiological underpinnings, and intervention implications of adolescent mental health and tobacco product use comorbidity is warranted. Future work aimed at examining the causal nature of the relationship between prolonged e-cigarette use and depressive symptoms may be particularly important given that many individuals who use e-cigarettes believe they are less harmful than combustible cigarettes or are completely harmless (Farsalinos et al., 2014b; Tackett et al., 2015; Berg et al., 2015a; Berg et al., 2015b; Berg et al., 2015c).

## Acknowledgments

### Funding

This research was supported by National Institutes of Health Grants R01-DA033296, T32-DA016184; the funding agency had no role in the design or execution of the study.

## References

- Audrain-McGovern J, Rodriguez D, Kassel JD. Adolescent smoking and depression: evidence for self-medication and peer smoking mediation. *Addiction*. Oct; 2009 104(10):1743–1756. [PubMed: 19549056]
- Audrain-McGovern J, Rodriguez D, Rodgers K, Cuevas J. Declining alternative reinforcers link depression to young adult smoking. *Addiction*. Sep 15; 2011 106(1):178–187. [PubMed: 20840206]
- Audrain-McGovern J, Rodriguez D, Rodgers K, Cuevas J, Sass J, Riley T. Reward expectations lead to smoking uptake among depressed adolescents. *Drug Alcohol Depend*. Sep 15; 2012 120(1–3):181–189. [PubMed: 21855235]
- Berg CJ, Haardoefer R, Escoffery C, Zheng P, Kegler M. Cigarette users' interest in using or switching to electronic nicotine delivery systems for smokeless tobacco for harm reduction, cessation, or novelty: a cross-sectional survey of US adults. *Nicotine Tob Res*. 2015a; 17(2):245–255. [PubMed: 24951496]
- Berg CJ, Stratton E, Schauer GL, et al. Perceived harm, addictiveness, and social acceptability of tobacco products and marijuana among young adults: marijuana, hookah, and electronic cigarettes win. *Subst Use Misuse*. 2015b; 50(1):79–89. [PubMed: 25268294]
- Berg CJ, Romero DR, Pulvers K. Perceived harm of tobacco products and individual schemas of a smoker in relation to change in tobacco product use over one year among young adults. *Subst Use Misuse*. 2015c; 50(1):90–98. [PubMed: 25338288]
- Britton J, Bogdanovica I, Ashcroft R, McNeill A. Electronic cigarettes, smoking and population health. *Clin Med (Lond)*. Aug; 2014 14(4):334–337. [PubMed: 25099828]
- Brown RA, Lewinsohn PM, Seeley JR, Wagner EF. Cigarette smoking, major depression, and other psychiatric disorders among adolescents. *J Am Acad Child Adolesc Psychiatry*. Dec; 1996 35(12):1602–1610. [PubMed: 8973066]
- Chaitin MO, Cohen JE, O'Loughlin J, Rehm J. A systematic review of longitudinal studies on the association between depression and smoking in adolescents. *BMC Public Health*. 2009; 9:356. [PubMed: 19772635]
- Corey C, Wang B, Johnson SE. Centers for Disease Control and Prevention. Notes from the field: electronic cigarette use among middle and high school students: United States, 2011–2012. *MMWR Morb Mortal Wkly Rep*. 2013; 62(35):729–730. [PubMed: 24005229]
- Covey LS, Tam D. Depressive mood, the single-parent home, and adolescent cigarette smoking. *Am J Public Health*. Nov; 1990 80(11):1330–1333. [PubMed: 2240299]
- Eaton DK, Kann L, Kinchen S, et al. Youth risk behavior surveillance — United States, 2009. *MMWR Surveill Summ*. 2010; 59(5):1–142.
- Farsalinos KE, Spyrou A, Tsimopoulou K, Stefopoulos C, Romagna G, Voudris V. Nicotine absorption from electronic cigarette use: comparison between first and new-generation devices. *Sci Rep*. 2014a; 4:4133. [PubMed: 24569565]
- Farsalinos KE, Romagna G, Tsiapras D, Kyrzopoulos S, Voudris V. Characteristics, perceived side effects and benefits of electronic cigarette use: a worldwide survey of more than 19,000 consumers. *Int J Environ Res Public Health*. 2014b; 11(4):4356–4373. [PubMed: 24758891]
- Garrison CZ, Addy CL, Jackson KL, McKeown RE, Waller JL. The CES-D as a screen for depression and other psychiatric disorders in adolescents. *J Am Acad Child Adolesc Psychiatry*. Jul; 1991 30(4):636–641. [PubMed: 1890099]
- Goniewicz ML, Knysak J, Gawron M, et al. Levels of selected carcinogens and toxicants in vapour from electronic cigarettes. *Tob Control*. 2014; 23(2):133–139. [PubMed: 23467656]
- Hajek P, Etter JF, Benowitz N, Eissenberg T, McRobbie H. Electronic cigarettes: review of use, content, safety, effects on smokers and potential for harm and benefit. *Addiction*. Nov; 2014 109(11):1801–1810. [PubMed: 25078252]
- Holliday E, Gould TJ. Nicotine, adolescence, and stress: A review of how stress can modulate the negative consequences of adolescent nicotine abuse. *Neurosci Biobehav Rev*. Apr 8.2016 65:173–184. [PubMed: 27068856]
- Johnston, LD., Miech, RA., O'Malley, PM., et al. Use of alcohol, cigarettes, and number of illicit drugs declines among US teens. 2015a. <http://www.monitoringthefuture.org/data/14data.html>

- Johnston, LD., O'Malley, PM., Miech, RA., Bachman, JG., Schulenberg, JE. Overview: Key Findings on Adolescent Drug Use. Institute for Social Research, The University of Michigan; Ann Arbor, MI: 2015b. Monitoring the Future National Survey Results on Drug Use 1975–2014.
- Johnston, LD., O'Malley, PM., Miech, RA., Bachman, JG., Schulenberg, JE. Monitoring the Future National Results on Adolescent Drug Use: Overview of Key Findings 2015. Institute for Social Research, the University of Michigan; Ann Arbor, Mich: 2016.
- Kassel JD, Stroud LR, Paronis CA. Smoking, stress, and negative affect: correlation, causation, and context across stages of smoking. *Psychol Bull.* Mar; 2003 129(2):270–304. [PubMed: 12696841]
- Kong G, Morean ME, Cavallo DA, Camenga DR, Krishnan-Sarin S. Reasons for electronic cigarette experimentation and discontinuation among adolescents and young adults. *Nicotine Tob Res.* Jul; 2015 17(7):847–854. [PubMed: 25481917]
- Laje RP, Berman JA, Glassman AH. Depression and nicotine: preclinical and clinical evidence for common mechanisms. *Curr Psychiatry Rep.* Dec; 2001 3(6):470–474. [PubMed: 11707160]
- Lechner WV, Meier E, Wiener JL, et al. The comparative efficacy of first-versus second-generation electronic cigarettes in reducing symptoms of nicotine withdrawal. *Addiction.* 2015; 110(5):862–867. [PubMed: 25639148]
- Leventhal AM, Zvolensky MJ. Anxiety, depression, and cigarette smoking: a transdiagnostic vulnerability framework to understanding emotion-smoking comorbidity. *Psychol Bull.* Jan; 2015 141(1):176–212. [PubMed: 25365764]
- Leventhal AM, Strong DR, Kirkpatrick MG, et al. Association of electronic cigarette use with initiation of combustible tobacco product smoking in early adolescence. *J Am Med Assoc.* 2015; 314(7):700–707.
- Leventhal AM, Strong DR, Sussman S, et al. Psychiatric comorbidity in adolescent electronic and conventional cigarette use. *J Psychiatr Res.* 2016; 73:71–78. [PubMed: 26688438]
- Miech R, Patrick ME, O'Malley PM, Johnston LD. What are kids vaping? Results from a national survey of US adolescents. *Tob Control.* Aug 25.2016 2016
- Muthen B. Statistical and substantive checking in growth mixture modeling: comment on Bauer and Curran (2003). *Psychol Methods.* Sep; 2003 8(3):369–377. discussion 384–393. [PubMed: 14596497]
- Muthen B, Asparouhov T. Growth mixture modeling with non-normal distributions. *Stat Med.* Mar 15; 2015 34(6):1041–1058. [PubMed: 25504555]
- Muthen B, Brown CH, Masyn K, et al. General growth mixture modeling for randomized preventive interventions. *Biostatistics.* 2002; 3(4):459–175. [PubMed: 12933592]
- Parrott AC. The psychobiological problems of continued nicotine dependency in e-cigarette 'vapers'. Commentary: "Electronic cigarettes". *Front Psychol.* 2015; 6:123. [PubMed: 25762953]
- Polosa R, Morjaria J, Caponnetto P, et al. Effect of smoking abstinence and reduction in asthmatic smokers switching to electronic cigarettes: evidence for harm reversal. *Int J Environ Res Public Health.* 2014; 11(5):4965–4977. [PubMed: 24814944]
- Rademacher L, Prinz S, Winz O, et al. Effects of smoking cessation on presynaptic dopamine function of addicted male smokers. *Biol Psychiatry.* 2016; 80(3):198–206. [PubMed: 26803340]
- Sinha R. The role of stress in addiction relapse. *Curr Psychiatry Rep.* Oct; 2007 9(5):388–395. [PubMed: 17915078]
- Tackett AP, Lechner WV, Meier E, et al. Biochemically verified smoking cessation and vaping beliefs among vape store customers. *Addiction.* 2015; 110(5):868–874. [PubMed: 25675943]
- Wang MQ, Fitzhugh EC, Turner L, Fu Q, Westerfield RC. Association of depressive symptoms and school adolescents' smoking: a cross-lagged analysis. *Psychol Rep.* Aug; 1996 79(1):127–130. [PubMed: 8873796]
- Wills TA, Knight R, Williams RJ, Pagano I, Sargent JD. Risk factors for exclusive e-cigarette use and dual e-cigarette use and tobacco use in adolescents. *Pediatrics.* Jan; 2015 135(1):e43–e51. [PubMed: 25511118]
- Windle M, Windle RC. Depressive symptoms and cigarette smoking among middle adolescents: prospective associations and intrapersonal and interpersonal influences. *J Consult Clin Psychol.* Apr; 2001 69(2):215–226. [PubMed: 11393599]

**Table 1**

Demographic characteristics and depressive symptoms by tobacco product use group.

	No onset of either product	Any use onset		Sustained and non-sustained use patterns					
		E-cigarette use	Cigarette use	Dual use	Non-sustained e-cigarette use	Sustained e-cigarette use	Non-sustained cigarette use	Sustained cigarette use	
Total N (2460)	2011	347	33	69	312	104	88	14	
Age, M (SD)	14.05 (0.41)	14.09 (0.41)	14.14 (0.45)	14.12 (0.42)	14.09 (0.42)	14.11 (0.40)	14.11 (0.38)	14.25 (0.62)	
Female %	55.6%	55.6%	60.6%	49.3%	56.4%	49.0%	54.5%	42.9%	
Ethnicity/race, %									
Hisp/Latinos	44.3%	58.0%	48.4%	50.0%	59.0%	50.0%	46.5%	69.2%	
African Americans	5.3%	2.3%	6.1%	0.0%	1.6%	2.9%	2.3%	0.0%	
Asians	20.6%	8.5%	9.1%	10.6%	8.5%	9.8%	10.5%	7.7%	
American Indian	0.9%	1.2%	0.0%	3.0%	1.6%	1.0%	2.3%	0.0%	
Native Hawaiian	4.0%	4.7%	12.1%	1.5%	4.6%	2.9%	4.6%	7.7%	
Whites	17.0%	17.8%	15.2%	15.2%	14.7%	25.5%	16.3%	7.7%	
Bi-racial	6.4%	6.7%	9.1%	18.2%	8.8%	7.9%	16.3%	7.7%	
Other	1.5%	0.8%	0.0%	1.5%	1.2%	0.0%	1.2%	0.0%	
Parent's education < GED (%)	10.9%	16.8%	23.3%	17.9%	16.8%	17.6%	20.5%	15.4%	
CES-D wave 1, M (SD)	13.65 (11.26)	15.65 (12.04)	20.11 (15.45)	17.01 (11.17)	15.93 (11.8)	15.82 (12.77)	17.49 (12.53)	20.09 (14.74)	
CES-D wave 2, M (SD)	14.48 (12.1)	-	-	-	17.12 (13.13)	16.77 (13.65)	20.55 (14.45)	21.78 (14.54)	
CES-D wave 3, M (SD)	14.56 (12.23)	-	-	-	16.7 (12.7)	17.59 (14.04)	19.12 (15.7)	19.78 (15.08)	

Students in the Los Angeles metropolitan region participating in the USC Happiness & Health Study (2013–2014). N = 2640 for this analysis. GED = General Education Diploma, High School Education Equivalency.

**Table 2**

Odds ratios for association of baseline depressive symptoms with tobacco product use onset across the 12-month follow-up.

	<i>Wald</i>	<b>OR</b>	<b>Lower 95%</b>	<b>Upper 95%</b>
Relative to non-use referent group				
Cigarette use only onset vs. non-use	5.208	1.024	1.009	1.055
E-cigarette use only onset vs. non-use	7.382	1.015	1.003	1.023
Dual-use onset vs. non-use	3.904	1.021	1.003	1.043
Post-hoc pairwise contrasts				
Cigarette only vs. e-cigarette only use onset	2.210	1.025	0.992	1.060
Cigarette only vs. dual use onset	0.641	1.019	0.973	1.068
E-cigarette only vs. dual use onset	3.277	0.977	0.952	1.002

Students in the Los Angeles metropolitan region participating in the USC Happiness & Health Study (2013–2014). N = 2306 for this analysis. Results from logistic regression of baseline CESD as a regressor and tobacco product use onset group as an outcome adjusted for age, gender, race, ethnicity, school, living situation, parental education, use of alcohol and other tobacco products including hookah, little/big cigar, and smokeless tobacco use. CESD = Center for Epidemiologic Studies — Depression Scale.

**Table 3**

Growth curve model estimates for associations of dummy coded variables representing sustained and non sustained tobacco product use onset patterns with depressive symptom slopes across the 12-month follow-up.

	Estimate	S.E.	Est./S.E.	p
Intercept	13.670	0.240	6.981	0.00
E-cigarette onset pattern variable				
Sustained electronic cigarette use	1.272	0.513	2.479	0.01
Non-sustained e-cigarette use	0.133	0.108	1.230	0.22
Non-use	(Referent)			
Cigarette onset pattern variable				
Sustained cigarette use	1.359	1.867	0.728	0.83
Non-sustained cigarette use	0.071	0.186	0.384	0.70
Non-use	(Referent)			

Students in the Los Angeles metropolitan region participating in the USC Happiness & Health Study (2013–2014). N = 2190 for this analysis. Parameter estimates for paths from e-cigarette use (non-use vs. non-sustained vs. sustained) and Cigarette use (non-use vs. non-sustained vs. sustained) to linear latent slope of CESD score across waves 1 through 3 in a structural equation model adjusted for age, gender, race, ethnicity, school, living situation, and parental education, use of alcohol and other tobacco products including hookah, little/big cigar, and smokeless tobacco use. CESD = Center for Epidemiologic Studies — Depression Scale.