RESEARCH ARTICLE

REVISED E-cigarette use and onset of first cigarette smoking among adolescents: An empirical test of the 'common liability' theory [version 3; peer review: 2 approved]

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Abstract

Background: E-cigarettes have become the most commonly used tobacco products among youth in the United States (US) recently. It is not clear whether there is a causal relationship between e-cigarette use and the onset of cigarette smoking. The "common liability" theory postulates that the association between e-cigarette use and cigarette smoking can be attributed to a common risk construct of using tobacco products. This study aims to investigate the relationship between ever e-cigarette use and cigarette smoking onset in the US using a structural equation modeling approach guided by the "common liability" theory.

Methods: The study population is non-institutionalized civilian adolescents living in the US, sampled in the longitudinal Population Assessment of Tobacco and Health study. Information about tobacco product use was obtained via confidential self-report. A structural equation modeling approach was used to estimate the relationship between e-cigarette use at wave 1 and the onset of cigarette smoking at wave 2 after controlling for a latent construct representing a "common liability to use tobacco products."

Results: After controlling for a latent construct representing a "common liability to use tobacco products", ever e-cigarette use does not predict the onset of cigarette smoking (β=0.13, 95% CI= -0.07, 0.32, p=0.204). The latent "common liability to use tobacco products" is a robust predictor for the onset of cigarette smoking (β=0.38; 95% CI=0.07, 0.69; p=0.015).

Conclusions: Findings from this study provide supportive evidence for the 'common liability' underlying observed associations between e-cigarette use and smoking onset.

Keywords
Adolescents, e-cigarette, cigarette smoking, common liability theory

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REVISED **Amendments from Version 2**

We have made a few amendments based on reviewers' comments. Specifically, we enhanced the consistency in the description of statistically non-significant estimates, added a new citation, relabelled model numbers, and revised the title of Table 2.

Any further responses from the reviewers can be found at the end of the article

Introduction

The prevention of underage cigarette smoking is an essential component to curtail the substantial disease burden associated with cigarette smoking[1]. The prevalence of underage cigarette smoking has been declining in the US over the past two decades[2]. E-cigarettes (or e-vapor products) were introduced to the market as potentially reduced-harm alternatives to combustible cigarettes and have gained popularity since they became generally accessible around 2009[3,4]. In the US, the prevalence of youth e-cigarette use increased sharply between 2011 and 2015 and, after a brief decline, increased again in 2018 and 2019[3,4]. Multiple national surveys have shown that the majority of e-cigarette use is infrequent or experimental[4–6]. Despite this, the existence of exclusive e-cigarette users who do not use other tobacco products raises concerns about whether e-cigarettes may play a causal role in the uptake of cigarette use and, therefore, offset the decline in underage cigarette use.

A review of existing literature revealed some inconsistencies in evidence about the relationship between e-cigarette use and cigarette smoking. The largest body of literature comes from individual-level observational studies showing a consistent positive association linking e-cigarette use with a higher risk of cigarette smoking onset, even after adjusting for a range of variables known to be associated with cigarette smoking in a generalized linear regression framework[7–11]. Nonetheless, in the context of observational studies, it is almost impossible to control for an exhaustive list of confounders; the positive relationship can be attributed to unmeasured confounders associated with e-cigarette use, which would produce a spurious relationship between e-cigarette use and cigarette smoking without the presence of a causal relationship[11–13]. Propensity scoring is a statistical method to reduce biases due to confounding in observational studies to provide more robust evidence for causal inference[14]. Recent studies using propensity scoring method have found either null or *inverse* association between e-cigarette use and smoking among youth[15,16].

To infer causality, studies with an experimental design arguably provide the best evidence. Nonetheless, a randomized controlled trial of e-cigarette use among nonusers is not feasible[12]. In this context, Vasiljevic and colleagues evaluated the impact of exposure to advertisements promoting e-cigarettes on appeal and susceptibility of tobacco smoking using an experimental design. They found no differences in appeal, susceptibility, or perceived harm of cigarette smoking between youth who were randomized to the exposure group and the control group[17]. Despite the lack of direct behavioral measures, this study suggests that the exposure to e-cigarette advertisement had no acute effect on the measures related to cigarette smoking.

Ecological prevalence trends are inconsistent with the notion that e-vapor use increases cigarette smoking. At the country level, e-cigarettes emerged and gained popularity during the period when the sharpest decline in adolescent cigarette smoking was observed in the US and other countries[5,18,19]. Total nicotine use have remained stable since the introduction of e-cigarettes[20]. In an interrupted time series analysis, Dutra and Glantz found no difference in the rate of decline in ever (p=0.57) or current (p=0.23) cigarette smoking before and after 2009, when e-cigarette became available in the US market[2]. In another study, Levy and colleagues found strong inverse associations between the prevalence of e-cigarette use and the prevalence of cigarette smoking among adolescents and young adults, which confluence with all US national surveys identified via a systematic literature search[21]. Similar findings have been documented in a recent study by Foxon and Selya[20]. Similarly, a few studies that compared youth cigarette smoking prevalence between states with and without regulations to prohibit sales of e-cigarettes to minors have produced inconsistent findings with two studies documenting lower youth cigarette smoking in states without an e-cigarette age restriction[22,23], and one study documenting the opposite[24].

One potential explanation of the consistently observed association between e-cigarette use and cigarette smoking from individual observational studies is the "common liability" theory, which postulates that any observed relationships between e-cigarettes and combustible tobacco cigarettes is attributed to the "liability" to use tobacco products of the individual; once this "common liability" is controlled for, there is no causal relationship between e-cigarette use and cigarette smoking[25–28]. This 'common liability' that encompasses a range of genetic and behavioral factors may not be directly observable but gives rise to the use of various tobacco products (various psychoactive substances in the original theory). Several lines of evidence align with the "common liability" theory. First, the relationship is not unique to e-cigarettes. Various studies showed that the use of any type of tobacco products (e.g., cigar, hookah, etc.) and/or other substances (e.g., alcohol and cannabis) predicted cigarette smoking onset (e.g., 9,10,28,29). Moreover, the risk of cigarette smoking onset increases with the number of types of tobacco product used[9]. Findings from a recent study using a propensity scoring approach found supportive evidence that the frequently observed association between e-cigarette use and smoking is largely attributed to shared risk factors, using data from Monitoring the Future, a national school survey of 8th, 10th, and 12th graders[15], Kim and Selya found that the association between e-cigarette use and current smoking became null after taking into account a range of variables encompassing demographic characteristics, use of other psychoactive substances, perceived peer cigarette use, risk-taking, socially maladaptive behaviors, attitude toward smoking, and parental education using propensity scoring[15]. Another study using data from NYTS, another national school survey, found inverse relationships linking e-cigarette use and subsequent cigarette smoking after propensity score matching

(i.e., evidence of 'gateway out')[16]. Second, the relationships between cigarette smoking and e-cigarette use are often recipro-cal. Numerous studies have documented that cigarette smoking is associated with higher risk of e-cigarette use[10,30–32]. Indeed, a few studies have found that smoking is a stronger predictor for e-cigarette use compared to e-cigarette use as a predictor for cigarette smoking[10,16]. Third, e-cigarette use predicts the onset of a range of other substance use behaviors, not limited to cigarette smoking[8,29]. These lines of evidence sup-port the notion that the relationship is not limited or specific to e-cigarettes, and common risk factors may underlie the use of various tobacco products[33].

Poorer inhibitory control and elevated impulsivity are phenotypes of externalizing problems, which has been linked to precocious use of various substances[34–37]. A study found similar levels of inhibitory control and impulsivity between youth e-cigarette users who never smoked a cigarette and youth smokers who never used an e-cigarette. Both groups showed poorer inhibitory control and elevated impulsivity compared to youth not using any tobacco products[38].

Given this background and guided by the 'common liability' theory, the aim of this study is to estimate the prospective relationship between e-cigarette ever use and the onset of cigarette smoking after controlling for a "common liability" to use tobacco in US adolescents using a structural equation modeling approach. In essence, we first created a unidimen-sional construct to represent the 'liability' to use tobacco prod-ucts, and then regressed the onset of cigarette use on antecedent e-cigarette use taking into account the latent 'liability' to use tobacco products.

Methods
Study population and sample
The study population consisted of non-institutionalized civilian adolescents 12–17 years of age living in the US, sampled in the longitudinal Population Assessment of Tobacco and Health (PATH) study. A multi-stage sampling method was used to draw nationally representative samples after Institutional-Review-Board-approved parent consent and youth assent[39]. In contrast to school surveys of adolescents, the PATH sample includes young people irrespective of school attendance, and its sampling frame includes college dormitories and children of active-duty military living in the US. More details about the PATH methodology is provided elsewhere[39].

In this study, PATH wave 1 (2013–2014) and wave 2 (2014–2015) data were used. Participation levels were 54% at the house-hold level and 78% at the individual level for the youth survey at wave 1. Wave 2 follow-up rate was 88% for youth. Because the outcome in this study is the onset of cigarette smoking, the study sample consists of wave 1 never smokers who were followed up at wave 2. We did not include "aged-up" adolescents (i.e., those who became 18 at wave 2) to retain a sample relevant for underage smoking (n=9,045).

Assessments
PATH confidential assessments were audio computer assisted self-interviews (ACASI), with standardized multi-item modules

on use of various tobacco products, including cigarettes, e-cigarettes, cigars (including traditional cigars, cigarillos, and fil-tered cigars), smokeless tobacco, snus, hookah, pipe, dissolvable tobacco, bidis, and kretek. Survey questions about ever use of these tobacco products are typically in the format of "Have you ever smoked/used …, even one or two puffs/times?" In this study, the outcome is the onset of ever cigarette smoking at wave 2, which is defined as smoking cigarettes (even one or two puffs) for the first time between wave 1 and wave 2 assess-ments among adolescents who had never smoked cigarettes at wave 1. PATH also assessed lifetime history (i.e., ever use) of alcohol, cannabis, Ritalin® or Adderall®, Painkillers/sedatives/tranquilizers, cocaine, stimulants, and other drugs, respectively.

Sex (male or female) and age categories (12–14 or 15–17 years of age at baseline) were included as covariates. (The PATH Pub-lic Use File only included a binary variable for age.) Information about these covariates is from survey items in the Demographics module. When these items are missing, information from the household screening roster is drawn. Other covariates include race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispan-ics, and non-Hispanic others), availability of tobacco products in the household (yes/no), and a measure of novelty seeking ("agree" or "strongly agree" to the question "I like new and exciting experiences, even if I have to break the rules. Do you…"), participant's self-rated health (excellent/non-excellent), harm perception of cigarettes ("a lot of harm" to the question "How much do you think people harm themselves when they smoke cigarettes"), and participant's school performance (mostly A's or A's and B's vs. others).

Analysis approach
Guided by the "common liability" theory, we used a structural equation modeling approach to test whether there is a specific association between e-cigarette ever use at wave 1 and the onset of first cigarette smoking at wave 2 holding constant a latent construct for the "liability to use tobacco products."

Structural equation modeling is a collection of statistical tech-niques that allows simultaneous estimation of relationships of various independent and dependent variables. Compared to conventional single-equation linear models, SEM has several major advantages including a) the flexibility to incorporate vari-ous direct and indirect paths simultaneously based on theories or hypotheses, b) the ability to construct latent variables, c) evalua-tion of how well the specified model fits data via model fit indices, and d) minimization of measurement error via the construction of the latent construct. SEM has been used in tobacco research and yielded valuable insights[40,41]. It is particularly useful when a certain condition (e.g., depression, addiction, or, in this study, the liability to use tobacco products) cannot be directly observed but can be derived from a set of observable behaviors that often happen as a cluster because of the underlying condition. We con-sider SEM a suitable method to evaluate the common liability theory because the common liability is hypothesized as a latent construct that encompasses various genetic and environmental causes for tobacco use.

in the first analysis steps, we built a latent construct for the common liability to use tobacco products using confirmatory

factor analysis methods. The observed variables were lifetime ever use of specific tobacco products. All tobacco products assessed in PATH wave 1 were included to create the latent construct. Snuff and chewing tobacco, snus, and dissolvable tobacco products were combined to create a "smokeless tobacco products" variable due to the considerations that a) youth participants may not differentiate these oral tobacco products well, and b) low occurrence of dissolvable tobacco use (n=9) and high correlation between smokeless tobacco use and snus use (i.e., 69% of snus users had also used smokeless tobacco). All observed variables were treated as categorical variables. The variance of the latent construct was fixed to one in order to obtain factor loading and threshold estimates for each observed variable. After ensuring a good fit of the measurement model (as described in the next paragraph), we built the structural portion of the model to assess the relationship between e-cigarette ever use at wave 1 and the onset of first cigarette smoking at wave 2. Specifically, we drew a path from the latent construct to the onset of first cigarette smoking as well as a direct path from e-cigarette ever use to the onset of first cigarette smoking. Figure 1 provides a conceptual description of the model. If the direct path from e-cigarette to cigarette smoking is statistically robust, it provides evidence that e-cigarettes plays a role for cigarette smoking onset over and beyond the common liability to use tobacco products. If not, it supports the notion that the frequently observed association between e-cigarettes ever use and smoking is attributed to a common liability to use tobacco products.

A series of models were fit to explore the sensitivity of the main model. First, we expanded the measurement model to include other substances measured in PATH (i.e., alcohol, cannabis, prescription Ritalin and Adderall, cocaine/crack, stimulants, and other drugs (heroin, inhalants, solvents, and hallucinogens) in order to further test the model with a latent construct for the liability for use of psychoactive substances (as was originally proposed by the 'common liability theory'). Second, we included additional sociodemographic and individual characteristics variables related to tobacco use in the model as covariates, including race/ethnicity, availability of tobacco products in the household, a measure of novelty seeking, participant's self-rated health, harm perception of cigarettes, and participant's school performance. In the last step of exploratory analyses, we repeated the main model with PATH wave 2 and 3 data as PATH wave 3 data became available soon after the initial analysis was conducted.

Several model fit indices were used to assess the goodness of fit of the measurement and the final structural models. These fit indices include root mean square of approximation (RMSEA)[42], comparative fit index (CFI)[43], and Tucker-Lewis index (TLI) . A RMSEA<0.08 and CFI/TLI > 0.90 are considered as indications of reasonably good model fit[44,45].

Analysis weights were used to adjust for selection probability, nonresponse patterns, possible deficiencies in the sampling frame, and attrition. The PATH User Guide provides details about the calculation of weights[39]. A robust weighted least square mean and variance (WLSMV) adjusted estimator, which uses a full weight matrix, was used to accommodate categorical variables and complex survey design. For all tobacco use variables, there were <3% missing values. None of wave 1 never smokers had missing values in all tobacco use variables, so we are able to include all never smokers in the main model. Balanced repeated replication method was used to generate standard errors and 95% confidence intervals (CI). Analyses were conducted using Stata 15.0 (StataCorp, College Station, Texas, USA) and Mplus 8.1 (Muthén & Muthén, Los Angeles, CA, USA).
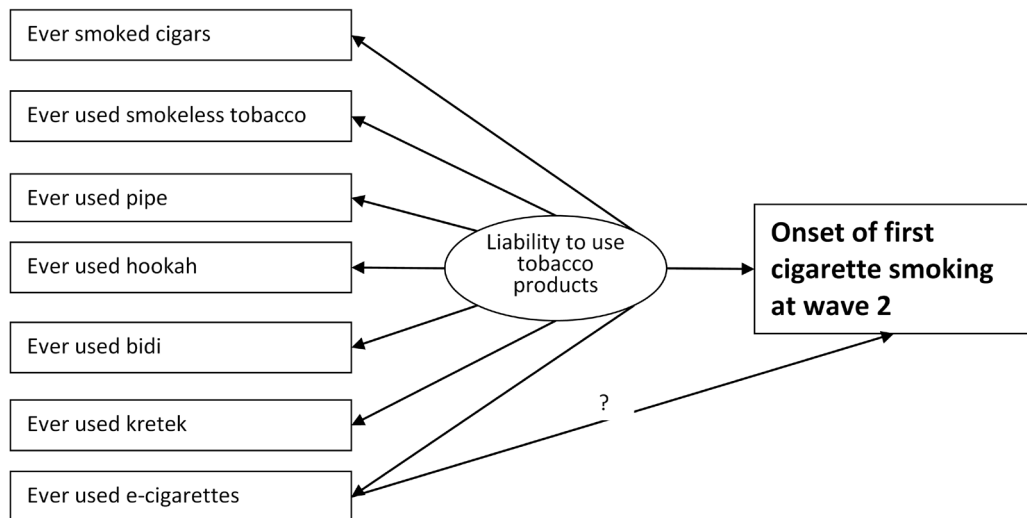

Figure 1. Depiction of a conceptual structural equation model to predict the onset of first cigarette smoking by e-cigarette use adjusting for a latent 'liability to use tobacco' construct.

Results

Among 13,651 participants at wave 1, there were 11,792 never smokers, among whom 9,045 remained youth (12–17 years of age) and were followed up for wave 2 assessment. Of the 9,045 participants, 51% were males; 64% were 12–14 years of age at wave 1; and 54% were non-Hispanic whites. Table 1 presents the estimated ever use of tobacco products as well as factor loadings and thresholds from confirmatory factor analysis among youths who had never tried a cigarette at wave 1 (n=9,045). Among the sample of youth never smokers, e-cigarette was the most common tobacco product ever tried (3.7%), followed by hookah (2.5%), with bidi and kretek being the least common tobacco products ever tried (0.1%). The measurement model fits reasonably well (RMSEA=0.019, 90% CI=0.014, 0.024; CFI=0.963; TLI=0.945); all factor loadings were greater than 0.4 and statistically significant (p<0.001). Each individual's factor score, a score reflecting the latent liability to use tobacco products, was calculated based on both the threshold and the loading of each item. Therefore, an individual who used

bidi, kretek, or pipe (items with greater thresholds) would have a higher factor score compared to an individual who used e-cigarette or hookah only (items with lower thresholds). An individual who used multiple products would generally have a higher factor score than an individual who used a single product. This factor score represents an individual's liability (unobserved) to use tobacco products.

Of the 9,045 never cigarette smokers at wave 1 assessment, 338 adolescents smoked a cigarette for the first time between wave 1 and wave 2 assessments (weighted incidence= 3.8%). The structural equation model shown in Figure 1 fits data well (RMSEA=0.015, 90% CI=0.011, 0.020; CFI=0.969; TLI=0.954). The model shows that after accounting for the general liability to use tobacco products, the association between e-cigarette ever use at wave 1 and cigarette onset at wave 2 is not statistically significant (M1 in Table 2: β=0.13; 95% CI= -0.07, 0.32; p=0.204). The latent general liability variable is positively associated with wave 2 onset of ever cigarette

Table 1. Estimated occurrence (%) of lifetime ever use of tobacco products, alcohol, cannabis, and other psychoactive drugs at wave 1, factor loadings, and thresholds from confirmatory factor analysis among never smokers. Data from Population Assessment of Tobacco and Health wave 1 and 2, 2013–2015[46]. (Unweighted n=9,045 12–17 Year Olds[a]).

Ever use of	Weighted %	Tobacco-only measurement model		All psychoactive substance measurement model	
		Standardized factor loading[d]	Unstandardized threshold	Standardized factor loading[d]	Unstandardized threshold
E-cigarette	3.7	0.76	2.75	0.70	2.49
Cigar	1.3	0.71	3.16	0.72	3.16
Pipe	0.3	0.88	5.83	0.70	3.84
Hookah	2.5	0.62	2.51	0.68	2.68
Smokeless tobacco products[b]	1.2	0.63	2.85	0.59	2.74
Bidi	0.1	0.45	3.63	0.46	3.87
Kretek	0.1	0.68	4.49	0.76	5.01
Alcohol	29.1			0.60	0.69
Cannabis	4.8			0.84	3.13
Prescription Ritalin and Adderall	1.1			0.53	2.69
Cocaine/crack	0.1			0.81	5.08
Stimulants	0.1			0.79	4.80
Other drugs[c]	0.2			0.65	3.87
	Selected demographic characteristics				
Male	51.3				
12–14 years of age	63.7				
Non-Hispanic whites	53.8				

[a]Analytical sample consists of youths who had never smoked a puff of cigarette at wave 1 and followed up and remained youths at wave 2. [b]smokeless tobacco includes smokeless tobacco, snus, and dissolvable tobacco products. [c]Other drugs include heroin, inhalants, solvents, and hallucinogens.
[d]Factor loadings are standardized based on the variances of the continuous latent variables as well as the variances of the outcome variables.

Table 2. Estimated relationships linking e-cigarette use and common liability latent construct to onset of ever cigarette smoking from structural equation models. Data from Population Assessment of Tobacco and Health.

PATH waves	n[a]	Model description[b]	β (95% CI) for e-cigarette →smoking	β (95% CI) for common liability → smoking
1 & 2	9045	M1: Main model	0.13 (-0.07, 0.32)	0.38 (0.07, 0.69)
		M2: M1+ Sex & age	0.16 (-0.03, 0.35)	0.33 (0.04, 0.61)
		M3: M1 + Other psychoactive substances	0.13 (-0.002, 0.27)	0.44 (0.28, 0.61)
		M4: M3 + sex and age	0.14 (-0.002, 0.29)	0.43 (0.25, 0.60)
		M5: M1 + additional covariates	0.16 (-0.04, 0.35)	0.31 (0.01, 0.61)
		M6: M5 + additional covariates	0.16 (-0.04, 0.35)	0.30 (-0.02, 0.62)
2 & 3	8668	M1	0.15 (-0.06, 0.35)	0.34 (-0.03, 0.71)
		M3: M1 + Other psychoactive substances	0.13 (-0.03, 0.30)	0.42 (0.16, 0.68)

[a]Unweighted sample size.

[b]M1 is the model depicted in Figure 1. M5 includes the following covariates: race/ethnicity, availability of tobacco products in the household, and novelty seeking. M6 includes the following additional covariates: self-rated health, harm perception of cigarette smoking, and school performance.

smoking (β=0.38; 95% CI=0.07, 0.69; p=0.015). Because sex and age are the two most important exogenous variables that are related to tobacco use behaviors, they were introduced as covariates in the next step to assess any potential changes in estimates and statistical inference. Including sex and age as covariates introduced little change in estimates, and statistical inference remained the same (M2 in Table 2: β=0.16; 95% CI= -0.03, 0.35; p=0.095; for the e-cigarette to cigarette onset path; β=0.33; 95% CI= 0.04, 0.61; p=0.025; for the 'liability to use tobacco' latent construct to cigarette onset path).

In the first exploratory step, we expanded the measurement model to include other substances measured in PATH (see Table 1 for factor loading and thresholds). The expanded measurement and structural equation models both have good fit (RSMEA= 0.015, 90% CI=0.012, 0.017; CFI=0.948, TLI=0.938 for the model without sex and age; RSMEA=0.016, 90% CI=0.015, 0.018; CFI=0.922, TLI=0.905 for the model out sex and age as covariates). Similar to results from the tobacco liability model shown above, the e-cigarette-specific path is not statistically significant (M3 in Table 2: β=0.13; 95% CI= -0.002, 0.27; p=0.053 without adjusting for sex and age; M4 in Table 2: β=0.14; 95% CI= -0.002, 0.29; p=0.054 with adjusting for sex and age), and the latent 'liability' construct is a robust predictor of cigarette smoking onset (β=0.44; 95% CI=0.28, 0.61; p<0.001 without adjusting for sex and age; β=0.43; 95% CI=0.25, 0.60; p<0.001 with adjusting for sex and age).

In the next exploratory step, we included two sets of socio-demographic and individual characteristics variables related to tobacco use in the model as covariates. First, we included race/ethnicity, availability of tobacco products in the household, and a measure of novelty seeking as covariates in the

model. Inclusion of these covariates introduced little change in estimates, and statistical inference remained the same (M5 in Table 2). Next, we additionally included participant's self-rated health, harm perception of cigarettes, and participant's school performance. Again, inclusion of these additional covariates introduced little change in estimates (M6 in Table 2).

In final exploratory analysis steps, we repeated the main structural equation model with PATH wave 2 and 3 data as PATH wave 3 data became available soon after the initial analysis was conducted. Fit indices indicate that the model fit the data well (RSMEA=0.010, 90% CI=0.004, 0.015; CFI=0.992, TLI=0.988). Estimates are similar to those in the wave 1 and wave 2 model. That is, after accounting for the general liability to use tobacco products, the association between e-cigarette ever use at wave 2 and cigarette onset at wave 3 was not statistically significant (β=0.15; 95% CI= -0.06, 0.35; p=0.157). Possibly due to a reduced sample size of never smokers at wave 2 (n=8,668), the association leading from the latent general liability variable to wave 2 onset of ever cigarette smoking became statistically non-significant (β=0.34; 95% CI=-0.03, 0.71; p=0.074), although the point estimate is similar to that from the corresponding model using wave 1 and wave 2 data. As shown in Table 2, estimates for the e-cigarette-to-cigarette path is highly consistent across the series of models that we tested, which highlights the robustness of these structural equation models.

Discussion
In this study, we found that the latent 'common liability to use tobacco products' construct is sufficient to explain later onset of smoking among US adolescents. In our exploratory analysis, we included various sets of covariates that have been shown to be associated with smoking onset. Estimates from these exploratory

analyses are almost identical to the estimate from the main model, providing evidence that the model and the latent 'common liability' construct are robust.

Interpretation of findings, implications, and future directions

A few hypotheses have been developed to provide theoretical grounds and underlying mechanisms for the relationship between e-cigarette use and subsequent cigarette smoking among youth. Here, we highlight three main theories as cited by the Academies of Sciences Engineering Medicine: the 'diversion theory', 'catalyst theory', and 'common liability theory'[47]. In brief, the 'diversion theory' hypothesizes that e-cigarette deters tobacco cigarette use by diverting 'high-risk' individuals to e-cigarette from combustible cigarettes[26,48]. The 'catalyst theory' postulates that e-cigarette use increases the risk of combustible cigarette use by first attracting 'low-risk' individuals to e-cigarettes, as a reduced-harm product, and then increasing proclivity to try combustible tobacco cigarettes[49]. The 'common liability theory' proposes that any observed relationships between e-cigarettes and combustible tobacco cigarettes is completely attributed to shared risk factors such as impulsivity and novelty-seeking (e.g., common liability to use tobacco products;[25–28]). If the 'diversion theory' is true, e-cigarette use should decrease the onset of cigarette smoking (or accelerate the declining trend of smoking); if the 'catalyst theory' is true, e-cigarette use should increase the onset of cigarette smoking; if the 'common liability' theory is true, a null relationship should be observed. Our findings provide supporting evidence for the 'common liability' theory for the US youth population as a whole. Recent studies using propensity scoring methods found supportive evidence that the observed association between e-cigarette use and current cigarette smoking was attributed to shared risk factors for tobacco use[15,16]. In this study, we found converging evidence using a different approach (i.e., SEM vs. propensity scoring), which accentuates the possibility that shared causes give rise to both e-cigarette use and cigarette smoking. Nonetheless, it is possible that different hypotheses apply to heterogeneous groups of individuals or contexts. For example, e-cigarettes may provide an alternative to cigarette smoking for some adolescents, whereas they may expose some other adolescents to a more smoking-prone environment. The onset of cigarette smoking is a complex interplay between micro-, meso-, and macro-level factors. Future studies with assessments of a breadth of these relevant factors and due attention to potential heterogeneities may provide more insights about the role of e-cigarette in smoking onset to guide targeted prevention and intervention efforts among youth. Applications of similar approaches in other cultures will help assess the reproducibility and consistency of the evidence, which is required for causal inference. It is noteworthy in this context that tobacco use behaviors in youth are often experimental and highly dependent on the availability of tobacco products[6,50–52], and an infrequent use pattern (1–2 days during the past 30 day) is more pronounced among exclusive e-cigarette users compared to youths who use other tobacco products concurrently[51]. In this context, future studies incorporating the frequency of e-cigarette use and examining the relationship between e-cigarette use and the progression to more established cigarette smoking will provide useful insights about the e-cigarette-use-and-smoking relationship.

Limitations and strengths

This study's findings should be interpreted in light of the following limitations.

First, this study is observational in nature. Although we included multiple covariates in this study, unmeasured heterogeneity is possible (variables not accounted for by the latent 'liability' construct and other covariates not included in this study), and no definitive evidence for a causal relationship is warranted. Nonetheless, we observed high consistency in the estimates across models with different configurations, which supports the robustness of the model. Second, the assessment was based on self-report information. There is possible under-reporting of tobacco and other drug use due to socially desirable responding[53]. The use of audio computer assisted self-interviews can help ameliorate this limitation. Measures for ever use of tobacco products have been shown to have good validity based on self-reported information[54]. Third, the response level at the household screening is moderate. Nonetheless, it is comparable to other modern national household surveys in the US[55], and post-stratification was applied to bring the sample into balance with the US adolescent population.

Strengths of this study include a) the prospective design provides clear temporal relationship, and is less prone to differential recall as compared to cross-sectional surveys; b) compared to prevalence-based measures, newly incident cigarette use focuses on the onset process without any interference of the persistence process[56]; c) by using nationally representative data, our results are generalizable to the general US adolescent population; and d) the use of audio computer assisted self-interviews and relatively low attrition in PATH enhances internal validity by reducing potential socially desirable responding and bias associated with attrition. In this study, we observed a much smaller point estimates for the e-cigarette-to-smoking relationship compared to estimates for the common-liability-to-smoking relationship. Together with the fairly large sample size of PATH (which grants reasonable statistical power), it suggests that the "common liability to tobacco use" is sufficient to explain the onset of cigarette smoking among adolescents.

Our approach is driven by the "common liability" theory. To the best of our knowledge, this is the first study to use a structural equation modeling approach to create a latent unidimensional 'liability' variable, which is consistent with the conceptualization of "liability", which denotes "a latent (unobservable) quantitative trait that, when measured, 'would give us a graded scale of the degree of affectedness or of normality'[27,57]."

Tobacco products use is the result of complex genetic-environment interplay. Under the "common liability" conceptualization, the sequence of tobacco product use is opportunistic and depends upon various environmental factors including accessibility, local policies, and social norms. Therefore, the threshold for each product may change from one culture to other. For example, in a cigar-prone culture, the threshold for cigar use may be lower than that for e-cigarettes. The latent 'liability' construct is capable of accommodating these types of environmental variations.

Data availability

Underlying data

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Open Peer Review

Current Peer Review Status: ✓ ✓

Version 3

Reviewer Report 16 July 2020

✓
Arielle Selya (iD)

[1] Behavioral Sciences Group, Sanford Research, Sioux Falls, USA
[2] Pinney Associates, Inc., Pittsburgh, PA, USA

The authors have addressed all of my concerns.

Competing Interests: After my second review of this manuscript, I became employed by Pinney Associates, which provides consulting services on tobacco harm minimization to JUUL Labs, Inc. I performed the first two reviews of this manuscript prior to starting this employment relationship.

Reviewer Expertise: Behavioral science, esp. nicotine use and dependence among adolescents

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 2

Reviewer Report 02 June 2020

✓
Alexa Gallagher (iD)
Ramboll, Amhurst, USA
Sandra I. Sulsky (iD)
Ramboll US Corporation, Amherst, MA, USA

We were pleased to review the revised version of the Cheng *et al.* (2019) manuscript. The authors made several changes that strengthened and clarified the manuscript including a re-organization of the introduction with additional information on Kim *et al.* (2019) and a very recently published study by Shahab *et al.* (2020) and an explanation of the common liability theory. The methods section now includes more background information on SEM, which will be helpful to readers not familiar with this type of modeling. We were also pleased to see sensitivity analyses using PATH Wave 3 data as well as analyses including a broader set of covariates (age, sex, race/ethnicity, tobacco product availability in the household, novelty seeking, self-rated health, cigarette smoking harm perception, school performance). The authors provided detail about how missing information was handled. The results section now includes some basic demographic information, revisions to the tables, and additional results based on the new sensitivity analyses described in the methods.

We have a few minor suggestions:
- On page 5, the first letter of the first complete paragraph needs to be capitalized.
- Table 2 provides results for models M1 to M6 using PATH waves 1 and 2 data. The written results describe models M1 and M2 followed by M5 and M6. Models M3 and M4 are described last. Why not change the order of the models in the table so they are described in sequence in the results?
- Please revisit the title of table 2. You present estimates for e-cigarette use and onset of ever cigarette smoking as well as estimates for the liability to use tobacco and the onset of ever cigarette smoking. The title only explains the e-cigarette piece.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Epidemiology

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 18 Jun 2020

Hui Cheng, Altria Client Services, Richmond, USA

We are delighted to see that reviewers are happy about the revision. We appreciate reviewers' constructive comments which have helped us improve the manuscript.
We have made additional adjustments based on reviewers' comments. Specifically, we have changed the model labels, and we have changed the title of Table 2 to "**Estimated relationships linking e-cigarette use and common liability latent construct to onset of ever cigarette smoking from structural equation models.** Data from Population Assessment of Tobacco and Health survey".

Competing Interests: No competing interests were disclosed.

Reviewer Report 26 May 2020

? **Arielle Selya** (iD)

1 Behavioral Sciences Group, Sanford Research, Sioux Falls, USA

2 Pinney Associates, Inc., Pittsburgh, PA, USA

The authors have done an excellent job responding to my concerns. I agree that a latent factor for nicotine
use would make sense as a single latent factor, and that additional covariates would add complications.
However, the additional exploratory analyses which include such covariates show that the findings are
robust. I have a few remaining comments:

- My biggest concern is that the authors should be careful not to conclude *no relationship* between
  e-cigarettes and later cigarette use. Using the significance testing here, that cannot be concluded.
  A couple specific points:
    - Such results should be worded as, e.g. "not significantly associated with" instead of "not
      associated with" (p. 6).
    - Though the Beta coefficient does not reach statistical significance, it does look like it's
      trending towards a small but positive value (~0.13) based on most of the confidence interval
      being above 0. It is possible then, that with larger sample sizes, this could become
      significant.
    - Therefore it might be helpful to also phrase this as, "common liability is sufficient to explain
      later cigarette use" if this is backed up by your results.
    - In this vein, it might be valuable to do something like a nested model test of M1 vs. a model
      where the path from e-cigarettes to later cigarette use is removed; if the model fit does not
      substantially worsen, then this would support e-cigarettes not having any additional
      explanatory power in addition to that of the latent factor.
    - An inconsistency with respect to how p-values are treated: in one place, p=.054 is
      interpreted as "not statistically significant"; but in another place, p=.074 is interpreted as
      "marginally associated." This highlights the importance of interpreting the effect sizes as
      well (e.g. Beta coefficients).

- It would be more appropriate to use "nicotine" rather than "tobacco" in most instances, as
  e-cigarettes contain nicotine but not tobacco.

- Another recent paper may be relevant in the literature review on common liability: Foxon & Selya,
  2020, *Addiction*[1], which shows that total nicotine use trends (i.e. the use of any nicotine product)
  has not changed after the introduction of e-cigarettes.

References

1. Foxon F, Selya A: Electronic cigarettes, nicotine use trends and use initiation ages among US
adolescents from 1999 to 2018. *Addiction*. 2020. Publisher Full Text

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Behavioral science, esp. nicotine use and dependence among adolescents

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 18 Jun 2020

Hui Cheng, Altria Client Services, Richmond, USA

We thank the reviewer for the positive response. We have amended the manuscript based on reviewer's comments.

To address the reviewer's comment about non-significant relationships, we have made the following revisions to the manuscript: (1) we have changed description of null associations to "not statistically significant…"; (2) we have changed the first sentence in the Discussion section to "In this study, we found that the latent 'common liability to use nicotine products' construct is sufficient to explain later onset of smoking among US adolescents."; (3) we have used consistent description for p-values and highlighted the importance of the beta coefficients (last paragraph of Results) and; (4) we have added the following language in the Discussion section "In this study, we observed a much smaller point estimates for the e-cigarette-to-smoking relationship compared to estimates for the common-liability-to-smoking relationship. Together with the fairly large sample size of PATH (which grants reasonable statistical power), it suggests that the "common liability to nicotine use" is sufficient to explain the onset of cigarette smoking among adolescents."

We agree with the reviewer that a test of nested models would help make the point that the e-cigarette-to-cigarette path does not substantially improve the model fit. Regrettably, the use of replicate weights (to properly calculate the variance) precludes such formal comparisons of model fit. Nonetheless, as we mentioned above, we have added language emphasizing the effect size estimates.

With respect to the reviewer's comment about using 'nicotine' instead of 'tobacco,' we thank the reviewer for pointing it out. The point is well taken. Nonetheless, we decided to retain the term 'tobacco products' for the following reasons: (1) although e-cigarettes do not contain natural tobacco, they typically contain tobacco-derived nicotine; (2) the FDA has deemed and regulates e-cigarettes as tobacco products, (3) other nicotine products (e.g., nicotine replacement therapy or novel oral tobacco-derived nicotine products) are not included in this study. We hope these reasons are sufficient to justify our use of 'tobacco' products in this manuscript.

We thank the reviewer to bring the recent paper to our attention. We have cited the paper in the Introduction section of the revised manuscript (reference #20).

Competing Interests: No competing interests were disclosed.

Version 1

Reviewer Report 28 January 2020

? **Alexa Gallagher** iD
Ramboll, Amhurst, USA
Sandra I. Sulsky iD
Ramboll US Corporation, Amherst, MA, USA

Cheng *et al.* (2019) examines the association between e-cigarette use and onset of cigarette smoking in youth between the ages of 12 and 17 years in the U.S. They utilize nationally representative and publicly available data from the PATH study. The research was guided by "common liability" theory, which "postulates that any observed relationship between e-cigarettes and combustible tobacco products is attributed to the liability to use tobacco products of the individual; once this common liability is controlled for, there is no causal relationship between e-cigarette use and cigarette smoking." The authors report that they are the first study to use structural equation modeling to answer this question.

Introduction
- Cheng and colleagues ask an interesting and timely research question. They include a series of recent publications in their background as they lay out their justification. The introduction, however, is rather long and somewhat unfocused.

- I would lead the discussion of the existing literature with the paragraph starting, "The largest body of literature comes from individual-level observational studies showing a consistent positive association…" The Vasiljevic study looking at exposure to e-cigarette advertisements does not seem directly relevant. Although I understand that it utilizes an experimental design, it could be cut to shorten the rather long introduction.

- The authors' reference #26 should be discussed more fully in the introduction and discussion sections, as it identifies the components of common liability to use tobacco products and could shed light on the proper covariates to include in the SEM.

- The discussion of ecological studies is lengthy and could be shortened.

- Common liability theory should be introduced and described in the introduction, as it underlies the whole project. What is it, how is it measured, why is it appropriate for this project?

Methods
- SEM is not that commonly used by epidemiologists. The paper would be more accessible if it included a brief introduction to SEM, including model selection, model evaluation, and how to interpret the results. The authors should explain why SEM is the right way to analyze a hypothesis based in common liability theory.

- The authors used data from Wave 1 (2013-2014) and Wave 2 (2014-2015) of the PATH study. Were PATH Wave 3 (2015-2016) data available and considered? If available but not included, why not?

- Are the questions the same in Wave 2 for those who are 18? If so, have you considered running a sensitivity model that includes the 18-year-olds? Have other authors made this same decision to exclude them? How many Wave 1 youth were excluded because they had aged up by Wave 2? It may make less sense for future studies to make this cut-off considering changes in the minimum legal age to purchase tobacco products.

- The authors ran two sets of models, one limited to tobacco products and a second, which they call the 'expanded liability model', that includes tobacco products and psychoactive substances. This expanded liability model is not introduced until the results section. It should be described in the methods.

- Sex and age were included as covariates. Were any of the other risk factors for smoking available in PATH, such as were identified in authors' reference 26? If so, why not use those?

- Please provide additional information on missing information. The only mention of it is as it relates to the covariates of age and sex. The authors report that this information was obtained from the Demographics module, which if missing was taken from the household screening roster. Was there missing information for the questions related to tobacco products, alcohol, cannabis, and other psychoactive drugs. If so, provide numbers and describe how it was handled. If there was limited missing information, that could be noted as a strength. Also, was there evidence that the data were, or were not, missing systematically? This can be assessed by comparing the available information for respondents who answered the substance use questions vs. those who did not.

Results
- Please provide the number of eligible participants at Wave 1 and Wave 2 and report numbers and reasons for any that were excluded. This could be done in the form of a figure ending with the final number included in your analysis.

- Also, please include a baseline table that provides basic demographic information. This could also be described in text.

- The titles for tables 1 and 2 indicate that that data is from Wave 1 and Wave 2. We are interested in ever use of the products listed in the table at Wave 1 and ever use of cigarettes at Wave 2. Please clarify what is provided in the table and update the table titles/descriptions.

- In fact, perhaps tables 1 and 2 could be combined to include demographic data from Wave 1; ever use of e-cigarette, cigar, pipe, hookah, SLT, bidi, alcohol, cannabis, prescription Ritalin and Adderall, cocaine/crack, stimulants, and other drugs at Wave 1; and ever cigarette use at Wave 3.

- I'd suggest placing the model results described in the text in a table.

Discussion
- The authors conclude that "after accounting for the latent 'common liability to use tobacco products' construct, ever e-cigarette use does not predict the onset of smoking among US adolescents." This statement is supported by the results provided, assuming that the variables considered by the authors reasonably captured the common liability they hypothesized exists. This point – whether or not the covariates included were sufficient – needs further explanation and justification.

- The authors identify several appropriate limitations and strengths. However, the limitations should address more explicitly the availability of data to describe smoking propensity, as defined in

reference 26 or elsewhere. The authors identify lack of recall bias as a strength of the study, but the interval between waves in PATH is quite short, so recall bias is not a major concern.

- The discussion section should place the current results into context of what is already known about smoking initiation in youth. The authors note that their findings are in line with a study by Kim *et al.* (2019) and they should discuss this reference more fully. Several other observational studies are referenced in the introduction and further description of these observational studies might be useful here as well.

Thank you for the opportunity to be a reviewer of this study. It is my recommendation that this paper be approved with reservations.

Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Epidemiology

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however we have significant reservations, as outlined above.

Author Response 22 Apr 2020
Hui Cheng, Altria Client Services, Richmond, USA

Dr. Gallagher and Dr. Sulsky comments

Cheng et al. (2019) examines the association between e-cigarette use and onset of cigarette smoking in youth between the ages of 12 and 17 years in the U.S. They utilize nationally representative and publicly available data from the PATH study. The research was guided by "common liability" theory, which "postulates that any observed relationship between e-cigarettes and combustible tobacco products is attributed to the liability to use tobacco products of the individual; once this common liability is controlled for, there is no causal relationship between e-cigarette use and cigarette smoking." The authors report that they are the first study to use

structural equation modeling to answer this question.

1. Introduction

1.1 Cheng and colleagues ask an interesting and timely research question. They include a series of recent publications in their background as they lay out their justification. The introduction, however, is rather long and somewhat unfocused.

Authors response: We thank the reviewer for recognizing the value of the research question. We have amended the introduction to make it more focused based on reviewers' helpful comments as follows.

1.2 I would lead the discussion of the existing literature with the paragraph starting, "The largest body of literature comes from individual-level observational studies showing a consistent positive association…" The Vasiljevic study looking at exposure to e-cigarette advertisements does not seem directly relevant. Although I understand that it utilizes an experimental design, it could be cut to shorten the rather long introduction.

Authors response: We have reorganized the discussion of existing literature in the revised manuscript. It now begins with observational studies, followed by the experimental study by Vasiljevic and colleagues, and then ecological evidence. The description of the Vasiljevic study has been shortened.

1.3 The authors' reference #26 should be discussed more fully in the introduction and discussion sections, as it identifies the components of common liability to use tobacco products and could shed light on the proper covariates to include in the SEM.

Authors response: We have added more details of reference #26 (now reference # 15) in the revised manuscript (the middle of the 5th paragraph in the Introduction and the middle of the second paragraph in Discussion). During the revision, another study using similar method has been published. In this study, an inverse association was found between e-cigarette use and subsequent cigarette smoking using data from NYTS. We have added this study in the revised manuscript (ref. #16).

1.4 The discussion of ecological studies is lengthy and could be shortened.

Authors response: We have shortened the discussion about ecological studies in the revised manuscript.

1.5 Common liability theory should be introduced and described in the introduction, as it underlies the whole project. What is it, how is it measured, why is it appropriate for this project?

Authors response: In the revised manuscript, we have added more details about the common liability theory (the beginning of the 5th paragraph of the Introduction).

2. Methods

2.1 SEM is not that commonly used by epidemiologists. The paper would be more accessible if it included a brief introduction to SEM, including model selection, model evaluation, and how to interpret the results. The authors should explain why SEM is the right way to analyze a hypothesis based in common liability theory.

Authors response: We have added a brief introduction of SEM and why we think SEM is appropriate for this analysis based on the common liability theory (2nd paragraph under Analysis Approach).

2.2 The authors used data from Wave 1 (2013-2014) and Wave 2 (2014-2015) of the PATH study. Were PATH Wave 3 (2015-2016) data available and considered? If available but not included, why not?

Authors response: PATH wave 3 data were not available when we started this project. During the course of the project, they became available. We did repeat the analysis using wave 2 and 3 data, and the results are similar. We have added estimates using wave 2 and 3 data in the Results section of the revised manuscript and in the new Table 3.
Nonetheless, we consider wave 1 and 2 data our primary focus because it is what we set out to do. Also, PATH wave 1 is the true baseline cohort, which is a representative sample of youth. Wave 2 is a follow-up of the wave 1 cohort with 'shadow' youth (those younger than 12) sampled at wave 1. In addition, for longitudinal studies like PATH, attrition occurs at each follow-up. When using wave 2 and 3 data, attrition may play a larger role.

2.3 Are the questions the same in Wave 2 for those who are 18? If so, have you considered running a sensitivity model that includes the 18-year-olds? Have other authors made this same decision to exclude them? How many Wave 1 youth were excluded because they had aged up by Wave 2? It may make less sense for future studies to make this cut-off considering changes in the minimum legal age to purchase tobacco products.

Authors response: We did discuss whether we should include aged-up youth in the analysis, and we decided not to because the focus of this study is on youth smoking onset. During wave 1 and 2 data collection (2013-2015), cigarettes were legal for 18-year-olds to purchase in most places. Risk profiles and mechanisms may differ for underage smoking from of-age smoking. We wanted to retain a focus on youth smoking onset and, therefore, did not include 18 year olds in the current study.

2.4 The authors ran two sets of models, one limited to tobacco products and a second, which they call the 'expanded liability model', that includes tobacco products and psychoactive substances. This expanded liability model is not introduced until the results section. It should be described in the methods.

Authors response: We have added a paragraph in the Method section to describe a series of models to explore the sensitivity of the main model results, including the model with additional

psychosocial covariates and the model with wave 2 and wave 3 data, as suggested by the reviewers (fourth paragraph in the Analysis section).

2.5 Sex and age were included as covariates. Were any of the other risk factors for smoking available in PATH, such as were identified in authors' reference 26? If so, why not use those?

Authors response: We have added additional covariates in the series of exploratory analysis described in the revised manuscript. Please see our response to reviewer #1's comment #2 for a detailed explanation.

2.6 Please provide additional information on missing information. The only mention of it is as it relates to the covariates of age and sex. The authors report that this information was obtained from the Demographics module, which if missing was taken from the household screening roster. Was there missing information for the questions related to tobacco products, alcohol, cannabis, and other psychoactive drugs. If so, provide numbers and describe how it was handled. If there was limited missing information, that could be noted as a strength. Also, was there evidence that the data were, or were not, missing systematically? This can be assessed by comparing the available information for respondents who answered the substance use questions vs. those who did not.

Authors response: We have added a sentence in the revised manuscript to indicate that for all tobacco use variables, there were <3% missing values. In addition, we specified a robust weighted least square mean and variance adjusted estimator which uses a full weight matrix. Therefore, a participant is included in the model unless the participant has missing values in all indicator variables (i.e., tobacco use and substance use variables). None of wave 1 never smokers had missing values in all of these variables, so we are able to include all never smokers in our model. We have added this information in the last paragraph of the Methods section in the revised manuscript.

3. Results

3.1 Please provide the number of eligible participants at Wave 1 and Wave 2 and report numbers and reasons for any that were excluded. This could be done in the form of a figure ending with the final number included in your analysis.

Authors response: In the revised manuscript, we added a sentence about the number of participants included in the current study:
Among 13,651 participants at wave 1, 11,792 were never smokers, among whom 9,045 remained youth (12-17 years of age) and were followed up for wave 2 assessment.
The sampling procedure of PATH is described in detail in PATH User's Guide (ref. #39)

3.2 Also, please include a baseline table that provides basic demographic information. This could also be described in text.

Authors response: In the revised manuscript, we have added basic demographics of the sample in Table 1 and a sentence in the first paragraph of the Results section:
Of the 9,045 participants, 51% were males; 64% were 12-14 year olds; and 54% were

non-Hispanic whites.

3.3 The titles for tables 1 and 2 indicate that that data is from Wave 1 and Wave 2. We are interested in ever use of the products listed in the table at Wave 1 and ever use of cigarettes at Wave 2. Please clarify what is provided in the table and update the table titles/descriptions.

Authors response: We have adjusted the titles of Table 1 and Table 2 to reflect the estimates are among wave 1 never smokers.

3.4 In fact, perhaps tables 1 and 2 could be combined to include demographic data from Wave 1; ever use of e-cigarette, cigar, pipe, hookah, SLT, bidi, alcohol, cannabis, prescription Ritalin and Adderall, cocaine/crack, stimulants, and other drugs at Wave 1; and ever cigarette use at Wave 3.

Authors response: In the revised manuscript, we have combined the previous Table 1 and 2 into one table (new Table 1).

3.5 I'd suggest placing the model results described in the text in a table.

Authors response: We have added Table 2 which contains model results.

4. Discussion

4.1 The authors conclude that "after accounting for the latent 'common liability to use tobacco products' construct, ever e-cigarette use does not predict the onset of smoking among US adolescents." This statement is supported by the results provided, assuming that the variables considered by the authors reasonably captured the common liability they hypothesized exists. This point – whether or not the covariates included were sufficient – needs further explanation and justification.

Authors response: As we indicated above, we have added additional covariates in the model in our exploratory analyses, and the estimates were very similar to the one from the main model. We think these additional results suggest a certain degree of robustness of the latent 'common liability' construct and the main model overall. We have added this information and related discussion in the revised manuscript.
Please also see our response to comment 2.5 and to reviewer #1's comment #2 for more details.

4.2 The authors identify several appropriate limitations and strengths. However, the limitations should address more explicitly the availability of data to describe smoking propensity, as defined in reference 26 or elsewhere. The authors identify lack of recall bias as a strength of the study, but the interval between waves in PATH is quite short, so recall bias is not a major concern.

Authors response: Regarding concerns about other covariates, we have conducted additional exploratory analyses to incorporate additional covariates related to smoking onset based on previous literature. Please also see our response to comment 2.5 and to reviewer #1's comment #2.
Regarding recall bias, we understand that the follow-up interval is only a year; however, there has been literature showing inconsistencies in the reporting of tobacco use as well as alcohol drinking behaviors in the youth population. In a cross-sectional setting, a smoker may be more likely to

recall other tobacco use and vice versa because they can be correlated behaviors. Therefore, we think it is a noteworthy strength of the current study.

4.3 The discussion section should place the current results into context of what is already known about smoking initiation in youth. The authors note that their findings are in line with a study by Kim *et al.* (2019) and they should discuss this reference more fully. Several other observational studies are referenced in the introduction and further description of these observational studies might be useful here as well.

Authors response: We have revised both the Introduction and Discussion to provide fuller details of previous studies and their relevance to the current study to help put findings from the current study into context.

In closing, we thank all three reviewers for their helpful and constructive comments. We hope we have provided sufficient information and revision to make the work acceptable for publication.

Competing Interests: No competing interests were disclosed.

Reviewer Report 08 January 2020

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?   **Arielle Selya** (iD)

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This manuscript focuses on the controversial question of whether e-cigarettes causally lead to later cigarette smoking among adolescents, or whether the use of both conventional cigarettes and e-cigarettes are due to a common liability. The paper uses structural equation modeling to model the pre-existing likelihood of e-cigarette use as a latent factor, finds that e-cigarettes do *not* have a causal effect on later conventional smoking over and above the latent factor. This paper uses an innovative method to address a complicated statistical question. The paper is well-written, and the implications are important.

Major comments:
- The introduction has an excellent literature review that makes a convincing case for the common liability hypothesis, even using papers that at face value support the "gateway" hypothesis of e-cigarettes but identifying interesting counterpoints in the analyses of these papers.

- My main concern is about the choice to include only substance use variables in the latent factor representing liability to use tobacco products. Propensity to use tobacco products includes a variety of other factors as well (socioeconomic, personality characteristics, risk perception, peer group and family substance use, mental health, etc). Are these other variables available in the

PATH study, and if so what was the rationale to restrict only to behavioral tobacco use measures? What would the results look like if other covariates were also included?

- I would recommend a re-organization of the Discussion, to discuss interpretation of findings, implications, and relation to existing literature first, followed by limitations and strengths.

Minor comments:

- I think a brief description of "standardized threshold" (which appears first in Table 1) would be helpful.

- On p. 6, last paragraph, why are exact values not reported for the fit measures ("RMSEA <0.02, CFI and TLI > 0.90") as they are elsewhere?

- What does the acronym ACASI mean (p.7)?

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Behavioral science, esp. nicotine use and dependence among adolescents

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 22 Apr 2020
Hui Cheng, Altria Client Services, Richmond, USA

Dr. Selya's comments

General comments:

- This manuscript focuses on the controversial question of whether e-cigarettes causally lead to later cigarette smoking among adolescents, or whether the use of both conventional cigarettes and e-cigarettes are due to a common liability. The paper uses structural

equation modeling to model the pre-existing likelihood of e-cigarette use as a latent factor, finds that e-cigarettes do *not* have a causal effect on later conventional smoking over and above the latent factor. This paper uses an innovative method to address a complicated statistical question. The paper is well-written, and the implications are important. <u>Authors response:</u> We thank the reviewer for recognizing the significance and novelty of the work and the helpful comments. We have revised the original manuscript based on these comments as detailed below.

Major comments:

- 1. The introduction has an excellent literature review that makes a convincing case for the common liability hypothesis, even using papers that at face value support the "gateway" hypothesis of e-cigarettes but identifying interesting counterpoints in the analyses of these papers.

<u>Authors response:</u> We thank the reviewer for recognizing the value of the research question.

- 2. My main concern is about the choice to include only substance use variables in the latent factor representing liability to use tobacco products. Propensity to use tobacco products includes a variety of other factors as well (socioeconomic, personality characteristics, risk perception, peer group and family substance use, mental health, etc). Are these other variables available in the PATH study, and if so what was the rationale to restrict only to behavioral tobacco use measures? What would the results look like if other covariates were also included?

<u>Authors response:</u> We agree with the reviewer that the propensity to use tobacco products is multifaceted, including important factors mentioned by the reviewers.

In this study, we were guided by the 'common-liability' theory and hypothesized that the use of various tobacco products is driven by an unobserved latent liability to use tobacco products. That is, a single-dimension latent variable (i.e., the liability to use tobacco products) gives rise to the use of different tobacco products. This latent liability to use tobacco products likely varies by socioeconomic, personality characteristics, risk perception, peer influence, and familial history of substance use, mental health etc., which can be precedents, consequences, or both (feedback loops) of tobacco use. That is, our expectation is that the latent variable, which represents an individual's liability to use tobacco products, is correlated with these other variables. Practically, one complexity to include various other factors in the structural equation framework is that these variables are not necessarily manifestations of a single dimension, which complicates the structure of the measurement model. Due to the above theoretical and practical reasons, we chose to take a simpler theory-driven approach to define the latent construct by tobacco use behaviors and only included sex and age as covariates because they are exogenous to the liability-and-smoking-onset relationship. In an exploratory step, we further expanded the model to include other substances because it has been shown that adolescent substance use is highly opportunistic and tobacco use is highly correlated with other substance use among adolescents in the original submission.

That said, the reviewer's concern is well taken. We have expanded the model to include aforementioned variables as covariates to the extent that they were assessed in PATH wave 1 survey. Specifically, we took a two-step approach to include additional covariates. <u>First,</u> we added race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanics, and non-Hispanic others), availability of tobacco products in the household (yes/no), and a measure of novelty seeking ("agree" or "strongly agree" to the question "I like new and exciting experiences, even if I have to break the rules. Do you…"). <u>In the second step,</u> we additionally included participant's self-rated health (excellent/non-excellent), harm perception of cigarettes ("a lot of harm" to the question "How much do you think people harm themselves when they smoke cigarettes"), and participant's grade

(mostly A's or A's and B's vs. others) because these variables are more likely to have feedback loops with tobacco use. These covariates were modeled to correlate with the latent liability construct and to predict the onset of cigarette smoking at wave 2.

The inclusion of these variables induced little change in estimates, although the latent-liability-to-smoking-onset path became marginally significant statistically, possibly due to the loss of precision associated with the additional covariates. Nonetheless, e-cigarette did not predict smoking onset in either model (Additional model 1: β=0.16; 95% CI= -0.04, 0.35; p=0.109; Additional model 2: β=0.16; 95% CI= -0.03, 0.35; p=0.102), and the latent liability of tobacco use predicted smoking onset in the first additional model (β=0.31; 95% CI= 0.01, 0.61; p=0.047) as well as in additional model 2 (β=0.31; 95% CI= 0.01, 0.61; p=0.047).

We observed little change in estimates for the e-cigarette-to-smoking relationship as well as the liability-to-smoking relationship across the four models (no covariates, sex-and-age as covariates, additional model 1, and additional model 2 described above), which suggests that the model is robust to variations of covariates.

In the revised manuscript, we have added this additional information in the Results section and revised the Discussion section accordingly.

- 3. I would recommend a re-organization of the Discussion, to discuss interpretation of findings, implications, and relation to existing literature first, followed by limitations and strengths.

Authors response: We thank the reviewer for the suggestion. We have moved the 'Limitation and strengths' section to the end of the manuscript.

Minor comments:

- 1. I think a brief description of "standardized threshold" (which appears first in Table 1) would be helpful.

Authors response: We thank the reviewer for bringing it to our attention. After further consideration, we think the unstandardized thresholds are more meaningful than the standardized threshold. In the revised version, we have changed the standardized thresholds to unstandardized thresholds, which represents the 'difficulty parameter' of items. We have also added the following footnote for "standardized loading" in Table 1:

"Factor loadings are standardized based on the variances of the continuous latent variables as well as the variances of the outcome variables."

- 2. On p. 6, last paragraph, why are exact values not reported for the fit measures ("RMSEA <0.02, CFI and TLI > 0.90") as they are elsewhere?

Authors response: In the revised version, we have added exact values for these fit indices in the revised version as follows,

"RSMEA=0.015, 90% CI=0.012, 0.017; CFI=0.948, TLI=0.938 for the model without sex and age; RSMEA=0.016, 90% CI=0.015, 0.018; CFI=0.922, TLI=0.905 for the model out sex and age as covariates"

We did not report the exact values in the previous version because we considered the expanded model a post-estimation exploratory step and the results are similar to those of the main model.

- 3. What does the acronym ACASI mean (p.7)?

Authors response: ACASI stands for audio computer assisted self-interviews. It was defined at first appearance under "Assessment." Since it only appeared three times in the manuscript, we have replaced the acronyms with its full name in the revised version.

Competing Interests: No competing interests were disclosed.

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