Brief Report

The Genetic and Environmental Influences Contributing to the Association between Electronic and Conventional Cigarette Initiation

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Abstract

Introduction: As the use of electronic cigarette (EC) continues to rise in the United States, especially among adolescents and young adults, it is necessary to better understand the factors associated with EC initiation. Specifically, it is unclear how genetic and environmental contributions influence the initiation of EC. Furthermore, the degree to which genetic and environmental influences are shared between EC initiation and conventional cigarette (CC) initiation is unknown.

Methods: A sample of young adult twins ages 15–20 ($N = 858$ individuals; 421 complete twin pairs) was used to estimate the genetic and environmental influences on the liability of initiation unique to EC and CC as well as the degree to which these factors are shared between the two. Approximately 24% of participants initiated the use of EC, 19% initiated the use of CC, and 11% initiated the dual use.

Results: Combined contributions of additive genetic and shared environmental influences were significant for CC ($A_{CC} = 0.19$ [95% confidence interval {CI} = 0–0.79], $p = 0.57$; $C_{CC} = 0.42$ [95% CI = 0–0.70], $p = 0.13$) and EC ($A_{EC} = 0.25$ [95% CI = 0–0.83], $p = 0.44$; $C_{EC} = 0.42$ [95% CI = 0–0.73], $p = 0.12$), whereas unique environmental influences were significant ($E_{CC} = 0.39$ [95% CI = 0.18–0.57], $p < 0.001$; $E_{EC} = 0.32$ [95% CI = 0.14–0.56], $p < 0.001$). Results also demonstrated a significant overlap of the unique environmental ($r_E = 0.87$, $p < 0.001$) and familial influences contributing to correlation between the two phenotypes in the bivariate analysis.

Conclusions: These preliminary results suggest that both genes and environmental influences are potential drivers of EC initiation among adolescents and young adults.

Implications: This article is the first to use a sample of twin to estimate the contributions of genetic and environmental influences toward EC initiation and estimate the potential for overlapping influences with CC initiation. This study has implications for future debate about the etiology of EC and CC use with respect to potential overlapping genetic and environmental influences.

Introduction

Electronic cigarette (EC) initiation is associated with conventional cigarette (CC) initiation in adolescents and young adults.^{1–4} A recent meta-analysis reported that individuals who engaged in any EC use were 3.5 times more likely to initiate CC use⁵ compared with those who did not use EC. Several factors associated with CC initiation have been identified,⁶ which have also been identified in EC initiation.⁷ The degree to which these factors are shared between EC and CC initiation remains unresolved.

Genetic Epidemiology of EC and CC Initiation

Prior studies on the genetic and environmental contributions on CC initiation indicate (1) significant additive genetic (ie, effect of alleles at every contributing locus) and shared environmental influences (ie, effect of environmental factors that increase similarity between members of twin pairs), (2) the magnitude of these influences change across development (ie, shared environmental influences have substantial contributions during adolescence and young adulthood which decreases into older adulthood), and (3) the presence of significant sex differences in genetic and environmental contributions.^{8–11}

Population-level studies indicate that more adolescents and young adults are using EC over CC.⁵ Although using one product increases the odds of using the other product, not every individual who uses ECs will use CCs.¹² Recent research has reported no association between polygenic risk scores of CC initiation and lifetime ever use of ECs¹²; however, these studies included predominantly adult samples (mean age = 45), which fails to examine the groups known to be at greatest risk of initiation and escalation, adolescents, and young adults. Thus, it remains unclear to what extent genetic and environmental factors contribute to liability to EC initiation, and whether these factors are the same or different from those contributing to liability to CC initiation. Furthermore, there are currently no known twin studies of EC use, which is a necessary to determine the need for further study of the genetic influence of this behavior. We address this knowledge gap in a twin study of adolescents and young adults. Specifically, we explore (1) the degree to which there is a correlation between EC and CC initiation, (2) the degree to which the correlation between EC and CC initiation is due to shared genetic and environmental influences, and (3) the degree to which genetic and environmental influences are specific to EC initiation.

Methods

Data and Study Population

Data were obtained from participants in the Adolescent and Young Adult Twin Study (AYATS), a longitudinal cohort study of twins residing in the United States, aged 15–20 (average age at Wave 1 = 17.22, SD = 1.28; Wave 2 = 19.23, SD = 1.33). Data were collected on 860 individuals via web-based questionnaires over two waves (Wave 1: March 2012–December 2016; Wave 2: May 2016–November 2019). A total of 858 individuals (421 complete twin pairs: 160 monozygotic [MZ] pairs, 261 dizygotic [DZ] pairs) who had tobacco use data were included in the analysis. The majority of the sample was female (56%), of European-American ancestry (>90%), had an average annual parental income greater than \$35 000 per year (60%), and most parents (68%) had earned a bachelor's degree or higher.

Tobacco Use Measures

Lifetime EC initiation was measured at both waves using a five-item ordinal variable, which asked, “On how many occasions, in your lifetime, have you used an e-cigarette (assume one use is about 15 puffs or lasts around 10 minutes)?” Participants could respond on a five-level ordinal scale (0 times [83.4%], 1–9 times [8.3%], 10–99 times [4.5%], 100–200 times [2.3%], more than 200 times [1.4%]). Participants indicating any level of use during Wave 1 or Wave 2 were considered to have initiated EC at some point in their lifetime and were coded as 1. Participants who did not initiate in Wave 1 and Wave 2 were considered not to have engaged in lifetime initiation and were coded as 0. Lifetime CC initiation was a binary variable which asked, “Do you currently or have you ever smoked cigarettes?” Participants indicating initiation during either Wave 1 or Wave 2 were considered to have initiated CC at some point in their lifetime and were coded as 1. Participants who did not initiate in Wave 1 and Wave 2 were coded as 0.

Statistical Analysis

The classical twin study design is based on the comparison of correlations between MZ and DZ twin pairs. MZ twins share 100% of their genes, whereas DZ twins share on average 50% of their segregating genes. This design can be used to estimate additive genetic influences (A —effects of alleles at every contributing locus); shared environmental effects (C —the influence of all the environmental effects shared by twin pairs); and unique environmental effects (E —the influence of all the environmental effects not shared by members of twin pair, which make the twins less similar and includes measurement error).¹³ In a univariate genetic analysis, the total variance underlying the liability (σ_p^2) of an outcome is decomposed as the sum of the genetic and environmental variances ($\sigma_p^2 = A + C + E$). The covariance between twins is parameterized as follows: $\text{cov}_{\text{MZ}} = A + C$ and $\text{cov}_{\text{DZ}} = 0.5A + C$. We also tested for the significance of sex differences in the magnitude and nature of genetic and environmental factors through: qualitative sex differences (ie, whether the same set of genes contributes to liability in males and females) and quantitative sex differences (ie, whether the magnitude of genetic and environmental influences is the same across the sexes).

A bivariate genetic model was implemented using a Cholesky factorization to determine how much of the covariance between EC and CC initiation could be explained by shared genetic and environmental factors by decomposing the genetic and environmental covariances¹³ (Figure 1). This is a method of triangular decomposition of the genetic and environmental sources of variance where the first variable is assumed to be influenced by a latent factor that also explains some or all of the variance in the second variable. Each variance component of the second variable is also explained by a latent factor that is uncorrelated with the first variable (path a_{22}). The diagonal elements in the genetic (eg, paths a_{11} and a_{22}) matrix in a Cholesky factorization estimate the variances due to a specific variable, whereas the off-diagonal element (path a_{21}) estimates the covariances shared between the variables. Due to the assumption that the latent variables are uncorrelated, a Cholesky factorization places few expectations on the temporal order of the relationship between variables.

Figure 1. Bivariate genetic model used to estimate genetic and environmental contributions. a_{11} and a_{22} represent unique sources of additive genetic variance for electronic cigarette and conventional cigarette initiation, respectively. a_{21} represents the amount of overlap in additive genetic variance.

Genetic and environmental correlations between EC and CC initiation were estimated to evaluate the degree to which genetic and environmental factors overlap between the initiation of EC and CC. Standardized genetic and environmental covariances were also estimated to detail the degree to which genetic or environmental factors contributed to the phenotypic correlation (r_p) between EC and CC initiation. The phenotypic correlation is equal to the sum of the standardized genetic (cov_A) and environmental (cov_C and cov_E) covariances.

The statistical significance of the genetic and environmental covariances was assessed by comparing the model fit of the full bivariate model to that of three submodels in which the genetic (cov_A) or environmental (cov_C or cov_E) covariances between EC and CC initiation were separately set to zero ($df = 1$). Under certain conditions, such differences are asymptotically distributed as a chi-square distribution with one degree of freedom.¹³ A fourth submodel tested the significance of the phenotypic correlation by setting all genetic and environmental covariances between EC and CC initiation to zero ($df = 3$).

All analyses were performed in R 3.4.1¹⁴ using the OpenMx package 2.8.3,¹⁵ and missing data were addressed using full-information maximum-likelihood estimation. We chose a priori to retain and report all parameters in the model. Estimates from a full ACE model will be more accurate than simplified models when analyzing discrete traits. Furthermore, attempts at parsimony result in oversimplification of the models rather than a simpler and more accurate representation of the data. Consequently, reporting a potentially oversimplified model might result in future research that may ignore an important source of variance.¹⁶

Results

Descriptive Statistics

Approximately 24% of the sample had initiated EC use, whereas 19% had initiated CC use, and 11% had initiated dual use or use of both EC and CC. Males had a significantly higher prevalence of CC (26.3%) and EC (31.5%) initiation compared with females (CC: 14.9% and EC: 19.0%). There was a moderate to large cross-twin correlation for EC initiation ($r_{MZ} = 0.65$, 95% confidence interval [CI] = 0.42–0.89; $r_{DZ} = 0.55$, 95% CI = 0.33–0.77). A similar pattern was observed for CC initiation ($r_{MZ} = 0.62$, 95% CI = 0.38–0.86; $r_{DZ} = 0.52$, 95% CI = 0.30–0.74).

Table 1. Standardized Genetic and Environmental Parameter Estimates for Electronic Cigarette and Conventional Cigarette Initiation

Parameter	Estimate (95% CI)	<i>p</i>
EC initiation		
A	0.25 (0–0.83)	0.44
C	0.42 (0–0.73)	0.12
E	0.32 (0.14–0.56)	<.001
CC initiation		
A	0.19 (0–0.79)	0.57
C	0.42 (0–0.70)	0.13
E	0.39 (0.18–0.57)	<.001
Overlap		
cov_A	0.23 (0–0.43)	0.74
cov_C	0.23 (0–0.52)	0.32
cov_E	0.31 (0.14–0.45)	<.001
r_g	0.76 (0–0.99)	0.74
r_c	0.68 (0–1.0)	0.32
r_e	0.87 (0.50–0.99)	<.001

cov_A = genetic covariance; cov_C = shared environmental covariance; cov_E = unique environmental covariance; r_g = genetic correlation; r_c = shared environmental correlation; r_e = unique environmental correlation; EC = electronic cigarette; CC = conventional cigarette; CI = confidence interval.

Genetic Analysis

No significant quantitative or qualitative sex differences were detected. However, significant differences in liability thresholds by sex were detected and as such all additional analyses included these influences. Common environmental influences accounted for a nonsignificant proportion of the variance in the liability of EC and CC initiation (EC: $C = 0.42$, 95% CI = 0–0.73, $p = 0.12$; CC: $C = 0.42$, 95% CI = 0–0.70, $p = 0.13$). In addition, the contribution of additive genetic influences on the initiation of both delivery systems was nonsignificant (EC: $A = 0.25$, 95% CI = 0–0.83, $p = 0.44$; CC: $A = 0.19$, 95% CI = 0–0.79, $p = 0.57$) (Table 1).

There was a strong phenotypic correlation between EC and CC initiation ($r = 0.77$, $p < 0.001$). This phenotypic correlation was due to nonsignificant common environmental covariance ($cov_C = 0.23$, $p = 0.32$), nonsignificant additive genetic covariance ($cov_A = 0.23$, $p = 1$), and significant unique environmental covariance ($cov_E = 0.31$, $p = 0.01$). The unique environmental correlation ($r_e = 0.87$, $p = 0.01$) was significant between both delivery systems (Table 1).

Discussion

This is the first study to investigate the genetic and environmental contributions to the liability for EC initiation and explore the degree to which genetic and environmental factors influencing EC initiation overlap with CC initiation. There was evidence for familial resemblance—likely a combination of additive genetic and shared environmental effects—on EC initiation. Additionally, there was substantial overlap of unique environmental factors shared between both delivery systems.

The prevalence of EC initiation (24%) was similar to others collected during a similar time frame (18.7% in 2014).⁴ However, the prevalence of CC initiation was higher compared with national estimates (19% vs an average prevalence of 9.9% during 2011–2015),¹⁵ and may reflect regional preferences for CC use (eg, Virginia, North Carolina). There was also a strong association between EC and CC initiation, which is supported by prior research which indicates that EC users are more likely to engage in CC use.^{1,3,5}

These analyses fit a bivariate Cholesky model (Figure 1), which models sources of variance that have effects on the first substance and the second substance (ie, the effect of *A* for EC initiation also has some effect on the initiation of CCs, path a_{21} in Figure 1). There are other ways to parameterize the twin model to fit different structural equation models.¹⁷ We chose to present results of a bivariate ACE model as a starting point for additional investigations with larger samples that would have sufficient power to discriminate between alternative explanation of the observed covariance between the liabilities of EC and CC initiation. Indeed, testing whether EC initiation has a direct causal effect on CC initiation or the reverse would be an obvious hypothesis to test. Future research, with higher powered samples, should consider multiple models, including those models with causal links between phenotypes, to describe the covariation between EC and CCs.

Genetic and Environmental Factors Influence EC as well as CC Initiation

The magnitude of the estimates for the genetic and environmental contributions on CC initiation were similar to those previously reported in a mega-study of adolescents.⁹ The magnitude of *A* from prior studies are generally smaller (range: 0.10–0.40) than estimates of *C* (range: 0.40–0.80).⁹ There was a similar pattern in the magnitude of genetic and environmental influences (*A* = 0.19 and *C* = 0.42) for CC as well as EC initiation (*A* = 0.25 and *C* = 0.42).

Additionally, although genetic and shared environmental correlations across EC and CC initiation were individually not significant, their combined effects were. Similarly, though estimates of *A* and *C* were nonsignificant, models that did not include both sources of variance fit significantly worse than models that did, suggesting that both *A* and *C* are important factors of EC and CC initiation. Molecular genetic research has also begun to examine the overlap between EC and CC use, with previous results reporting a polygenic risk score for cigarettes per day being significantly associated with lifetime use of ECs.¹⁴ However, there was no statistically significant association between a polygenic risk score for CC initiation and lifetime use of ECs, suggesting additional research should continue to characterize the overlap between these tobacco delivery systems.¹⁴

Unique Environmental Factors Influence EC Initiation and Have Overlap With CC Initiation

There were significant contributions of unique environmental factors specific to EC initiation, as well as significant overlap of unique

environmental factors contributing to EC and CC initiation. Possible factors include peer smoking and opinions toward nicotine products^{18,19} as well as exposure to tobacco marketing.²⁰ Consequently, unique environmental factors are important for tobacco initiation and may be shared across delivery systems.

These results should be evaluated in light of the following limitations. First, the majority of participants identified as European-American race/ethnicity and results from this study may not generalize to other racial/ethnic populations. Second, this study used self-report data, which may be subject to reporter bias. Third, we used measures of lifetime EC and CC initiation, which do not capture the complexities of long-term use (eg, quantity/frequency). Nevertheless, many genetic epidemiological studies have focused on CC initiation and have consistently identified similar results regarding the factors involved with this first step in nicotine dependence. Fourth, the power to detect significant additive genetic effects and genetic correlations was limited as a result of sample size and prevalence of EC/CC initiation. Consequently, the confidence intervals for *A* and *C*, as well as their covariances/correlations, were large resulting in imprecise estimates. This study was also unable to detect and distinguish quantitative versus qualitative sex differences for EC and CC initiation. Future research will require much larger sample sizes, which will help to increase statistical power to produce more precise estimates and allow for the testing of additional models, such as the detection of quantitative and qualitative sex differences.¹⁷ However, these results provide preliminary evidence for genetic and environmental influences involved in EC initiation and unique environmental as well as familial overlap between EC and CC initiation.

Supplementary Material

A Contributorship Form detailing each author's specific involvement with this content, as well as any supplementary data, are available online at <https://academic.oup.com/ntr>.

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Declaration of Interests

None declared.

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