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The Speed of Progression to Tobacco and Alcohol Dependence: A Twin Study

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Abstract

We investigated the etiological role of genetic and environmental influences for two milestones of tobacco and alcohol use: age of initiation, and speed of progression to dependence (latency). Study participants included 1352 monozygotic and 1422 dizygotic twins (mean age at assessment = 24.31). Earlier ages of initiation significantly increased the likelihood of developing dependence, but were associated with longer dependence latencies for tobacco and alcohol. Latencies to dependence were heritable traits for tobacco ($a^2 = 0.63$) and alcohol ($a^2 = 0.64$). Genetic influences contributing to early age of initiation were associated with faster latencies to dependence but sometimes were counteracted by environmental factors, the extent to which depended on substance and, sometimes, sex. Our findings may have important implications for public policy and add to the literature by characterizing the genetic and environmental contributions to the speed of progression to tobacco and alcohol dependence.

Keywords

Tobacco; Alcohol; Twins; Genetics; Age of Initiation; Dependence

Introduction

Every year over 6 million individuals worldwide die due to tobacco use (World Health Organization, 2015), and approximately 3.3 million die from alcohol related causes (World Health Organization, 2014). The United States spends approximately 170 billion dollars every year on health care due to tobacco use (Xu et al., 2015) and loses roughly 223.5 billion dollars annually from excessive alcohol use (Bouchery et al., 2011). Lifetime use of US citizens over the age of 11 is fairly high, with approximately 59% reporting ever using tobacco, and 82.1% endorsing ever using alcohol, but fewer individuals progress to problem

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Compliance with ethical standards

Conflict of Interest Dr. John Hewitt is an author on this paper, and is also the editor of the journal.

Human and Animal Rights All procedures of this study followed the ethical standards of the University of Colorado Institutional Review Board.

Informed Consent Informed consent or parental permission was obtained from each subject at each assessment time point.

use or dependence (National Survey of Drug Use and Health, 2015). Increased understanding of the development and transitions between milestones of tobacco and alcohol use may help reduce the tremendous health and financial burdens.

The etiology of substance dependency appears to be a stage-sequential process encompassing various milestones of escalated use (Heath et al., 2002; Hines et al., 2015; Sartor et al., 2009). Early age of initiation significantly increases the likelihood of progressing to dependence for both tobacco (Behrendt et al., 2009; Hu et al., 2006) and alcohol (Behrendt et al., 2008; Dawson et al., 2008; Dewit et al., 2000; Grant et al., 1997). For this reason, delaying age of initiation has been implemented in various prevention approaches intending to reduce risk for substance dependence (Pedersen & Skrondal, 1998; Spoth et al., 1999). Whether early use *causes* future substance use related problems or is attributed to a common liability remains controversial due to mixed findings in the literature (Prescott & Kendler, 1999; Grant et al., 2006; Kendler et al., 2013; Ystrom et al., 2014). Past research also indicates the importance of considering sex differences in the effectiveness of various substance use prevention programs (Graham, et al., 1990; Klepp et al., 1993; Kulis et al., 2007; Longshore et al., 2007; Vartiainen et al., 1997; Vigna-Taglianti et al., 2009).

Elucidating the factors that contribute to reaching a specific milestone in the addiction process is useful in assessing lifetime vulnerability, but this approach does not capture changes in liability over the developmental trajectory of the disorder (Sartor et al., 2008). Identifying factors contributing to the *speed* of transition (latency) between stages may provide a more comprehensive understanding of the developmental nature of addiction, and may indicate a more precise time window for targeted intervention. Interestingly, and almost paradoxically, younger initiation also tends to correspond to longer latencies to dependence (Behrendt et al., 2009; Blitstein et al., 2003; Breslau et al., 1993; Robinson et al., 2004; Sartor et al., 2006; Sartor et al., 2008), a phenomenon recently referred to as “telescoping” (Deutsch et al., 2016; Jackson et al., 2010), but historically investigated regarding sex differences in the latency of substance use problems (Lisansky, 1958).

Sex differences in latencies, which may depend on substance (Stallings et al., 1999), have been inconsistent with some studies reporting faster progression to tobacco and/or alcohol use in women (Gabrhelik et al., 2012; Piazza et al., 1989; Randall et al., 1999; Thorner et al., 2007), faster progression in men (Blitstein et al., 2003; Keyes et al., 2010; Stallings et al., 1999), or no effect of gender (Alvanzo et al., 2011; Hernandez-Avila et al., 2004), and there is sparse information indicating whether genetic and or environmental influences on latency milestones differ across sex. One way to evaluate genetic and environmental sex differences in tobacco and alcohol latencies is with biometrical twin modeling. Twin studies are a valuable and widely used approach that can partition etiological genetic and environmental influences by modeling differences between monozygotic (MZ) and dizygotic (DZ) twin pairs.

Twin studies have consistently demonstrated genetic influences on tobacco initiation (Han, et al., 1999; Kendler, et al., 2005; Koopmans, et al., 1999; Maes et al., 2004; Maes et al., 2017; McGue, et al., 2000), and, to a lesser extent alcohol initiation (Koopmans, et al., 1997; Pagan et al., 2006; Viken et al., 1999), which tends to have considerable influences from

shared environmental factors (Fowler et al., 2006; Stallings, et al., 1999). Genetic contributions have also been observed for age of initiation for both tobacco (Heath et al., 2002; Hardie et al., 2006) and alcohol (Pagan et al., 2006; Ystrom et al., 2014), but whether sex differences in genetic and or environmental influences occur for these milestones is less understood.

Substantial evidence also suggests genetic factors contribute to the progression to dependence for both tobacco and alcohol (Kendler et al., 1999; McGue et al., 2000; Prescott & Kendler, 1999; Vink et al., 2005), explaining roughly 30–80% of the variance in the liability to dependence. Genetic influences may also influence how quickly individuals make the transition to dependence. Twin studies assessing univariate genetic and environmental influences on tobacco and alcohol latencies, although often heterogeneous in both measurement and sample ascertainment have reported modest genetic, and substantial non-shared environmental contributions (Liu et al., 2004; Sartor et al., 2008; Stallings et al., 1999). Importantly, the aforementioned studies used chiefly older samples (Liu et al., 2004; Stallings et al., 1999), which are especially prone to recall bias, and were conducted on exclusively male (Liu et al., 2004), or female (Sartor et al., 2008) twin pairs, or combined sexes to increase power (Stallings et al., 1999).

To date, only one genetically informed study has evaluated sex differences for substance use latencies, reporting few sex differences in the genetic and/or environmental influences across latency milestones for alcohol (Deutsch et al., 2016). However, this study was unable to evaluate univariate genetic and/or environmental sex differences or differentiate between certain genetic and environmental factors due to their use of the discordant twin design. Thus, the degree to which distinct genetic and environmental sources of variation differ by sex in their contribution to tobacco and alcohol dependence latencies remains an open question.

Moreover, only one study has examined the degree to which specific genetic and environmental factors are unique or shared between age of initiation and dependence latency (Sartor et al., 2008). To extend these findings, which were performed exclusively on alcohol use in females, we evaluate the specific and overlapping genetic and environmental influences for alcohol and tobacco milestones (age of initiation and dependence latency), and determined the extent to which these influences differed by sex.

First, we assess phenotypic sex differences for age of initiation and dependence latencies for tobacco and alcohol. Next, we evaluate the associations between age of initiation and the progression (yes/no) and latency (how quickly one progresses) to dependence and the relationship between dependence latencies and dependence severity. Then, using biometrical twin models, we investigate quantitative and qualitative sex differences in the genetic and environmental contributions to age of initiation and dependence latency for tobacco and alcohol. Lastly, by conducting multivariate analyses, we evaluate the extent to which genetic and environmental factors are shared or specific to tobacco and alcohol milestones and whether there are sex differences in these influences.

METHODS

Sample

Our sample consisted of 2,774 twins including 1,422 dizygotic (DZ) twins (530 opposite sex twins or DZO), and 1352 monozygotic (MZ) twins. The sample was comprised of 53.2% females ($n = 1477$), and 46.8% males ($n = 1297$) with an average age of 24.31 ($s.d. = 3.59$, range = 16.02–34.37). The sample was mostly Caucasian, with approximately 87% of this sample identifying as being non-Hispanic White.

Twins were ascertained through the Colorado Longitudinal Twin Sample (LTS) and the Colorado Twin Sample (CTS; Rhea et al., 2013). Twins in the CTS and LTS were ascertained differently but both groups were assessed as part of the Center for the Genetics of Antisocial Drug Dependence (CADD; PI: Hewitt). CTS twins were recruited during adolescence (age 12 to 18) from both Colorado birth records, and Colorado school districts (Rhea et al., 2013). LTS twins were ascertained through birth records, made accessible by the Colorado Department of Health, recruited from infancy and longitudinally followed through their twenties. Both the CTS and LTS samples included multiple waves of assessment with roughly ~5 year gaps between the CADD assessments conducted in adolescence and young adulthood. We used all twins above the age of 16 from the CADD wave 1, 2 and 3 assessment time points, which had fairly high retention rates (75.2%). The mean ages at the three CADD assessments were 17.51 ($s.d. = 0.89$), 20.14 ($s.d. = 2.61$) and 25.51 ($s.d. = 2.70$), respectively.

Zygosity

For 92% of the subjects, DNA was extracted from buccal cells through saliva and/or cheek swab samples, and zygosity was determined by analyzing 11 highly polymorphic short tandem repeat polymorphisms (Rhea et al., 2006). For twins yet to provide DNA samples, zygosity was established via a 9-question survey (Nichols & Bilbro, 1966; see Rhea et al., 2013 for details).

Measures

Substance use measures were assessed via the Composite International Diagnostic Interview – Substance Abuse Module (CIDI-SAM; Cottler et al., 1989), a structured diagnostic interview, which quantified various substance use outcomes including: the onset age in which DSM-IV criteria for substance dependence was first met. Age of initiation was not assessed with this diagnostic instrument, but was ascertained via a CIDI-SAM supplement. Age of initiation was defined as how old the participant was the first time they used a drug. We focused our analyses on the ages of initiation and dependence latencies (age difference between initiation and dependence) for tobacco and alcohol.

Age of onset for initiation and dependence are subject to biases of retrospective report. Time between age of milestone onset and the age at interview has been shown to be a consistent and important source of error in individuals' retrospective reports (Bright & Soulakova, 2013; Shillington et al., 2012). To minimize these biases, we preferentially used data collected closest to the average age of milestone onset for age of initiation (wave1;

assessment ages 12–18) and dependence (wave2; assessment ages 17–23) for longitudinally assessed twins. If these participants did not reach a particular stage of use at a given assessment wave, data from subsequent waves were used to maximize sample size.

Variable Coding

Raw data for ages of initiation were roughly normally distributed for tobacco ($M = 14.78$, median = 15, s.d = 2.97), and alcohol ($M = 15.45$, median = 15, s.d = 2.52) (see Supplemental Figure 1). Similar to previous studies (Broms et al., 2006; Heath et al., 2002; Pagan et al., 2006), we treated ages of initiation as ordinal variables coding twins who had never used tobacco/alcohol as 0's, twins who reported initiating after age 15 as 1's (later onset), and if they reported initiating at age 15 or earlier as 2's (early onset). Binary measures of initiation have been shown to bias genetic and environmental correlations in bivariate designs. Heath et al. has shown that these biases can be minimized by operationalizing age of initiation as a 3-category ordinal variable (Heath et al., 2002) as we have done here.

Latency, defined as the speed with which individuals transition between stages, does not have a standard definition for slow versus rapid transitions (Sartor et al., 2014). Previous researchers have treated latency milestones as ordinal variables censoring individuals who do not progress to a certain stage of substance use (Sartor et al., 2008), which is an effective method to handle censored data in twin studies (Derks et al., 2005). Based on this approach, we calculated dependence latencies as difference scores between the age of initiation and age of dependence onset and binned the scores into 3 ordinal groups of transition speed: censored, slow, and fast.

Twins who initiated use of a drug but did not progress to dependence were coded 0 (censored) for dependence latencies. Censored individuals were required to have a test age (i.e., age at interview) five or more years greater than the reported age of initiation so that all censored individuals had not progressed to dependence for at least five years. This five-year cut-off was chosen based off the average time interval between waves of assessment and so that all censored twins were allowed a fixed amount of time to progress from initiation to dependence. Participants who did not progress to dependence and reported an age of initiation less than five years from their latest test date were coded as missing (tobacco: $n = 156$ [9.7% of initiators], alcohol: $n = 268$ [11.9% of initiators]). For these individuals, their progression (yes/no) to dependence status was considered unknown and were not included in subsequent analyses. We felt this conservative approach was necessary given the uncertainty of progression status for these individuals, rather than assuming a zero-liability for their dependence outcomes. However, transition times from initiation to tobacco/alcohol dependence often occur within 5 years (Behrendt et al., 2009). Therefore twin models were re-analyzed including these individuals (coding them as zeroes for dependence latencies) and results are described in the supplemental materials.

Dependence latencies were positively skewed for tobacco ($M = 4.48$, median = 4, s.d = 3.30) and alcohol ($M = 3.59$, median = 3, s.d = 3.25; see Supplemental Figure 2). Similar to operationalization of age of initiation, we used consistent definitions for dependence latency across drugs with scores adjacent to the median determining fast versus slow transition

times. That is, dependence latencies were coded as 1's (slow) if twins took 4+ years to escalate to dependence from initiation, and coded as 2's (fast) if the transition occurred within 0–3 years from initiation. Progressions to dependence were binary variables coding those who initiated but did not develop dependence as 0's and twins who did transition to dependence as 1's. Dependence phenotypes were contingent on initiation and thus had noticeably smaller sample sizes than initiation. Table 1 displays the cell size across tobacco/ alcohol initiations, and dependence latencies.

Analyses

First, we examined phenotypic sex differences for ages of initiation and dependence latencies for tobacco and alcohol. Descriptive statistics parsed by sex for ages of initiation, dependence onset and dependence latencies are displayed in Table 2. Phenotypic sex differences were tested with linear mixed effects models, which account for the nested structure of twin data and were computed by using the lme4 package in R (Bates et al., 2015).

Next, we investigated the relationship between early versus late age of initiation with the progression and latency to dependence for tobacco and alcohol. Odds ratios were computed via logistic mixed effects models, using the family = “binomial” command in R. Associations between early and late age of initiation with dependence latencies were modeled via cox proportional hazard (Cox PH) mixed effects regression, using the coxme package in R (Therneau, 2015). Cox PH mixed effects regression models estimate the cumulative probability of survival (progression to dependence), while accounting for the non-independence of twin pairs. Cox PH models were visualized via the survplot command from the kms package (Harrell Jr, 2017). Lastly, the relationships between tobacco and alcohol latencies and dependence severity were modeled using linear mixed effects regressions (lme4).

We used biometrical models to study the etiological influences of genetic and environmental factors on tobacco and alcohol use outcomes. Twin models assume that variation in traits can be partitioned into variance attributed to 4 latent factors: additive genetic effects (A), non-additive genetic effects such as genetic dominance (D), shared environment (C) including non-genetic influences that increase similarity between twins, and nonshared environmental factors (E) consisting of the unique environmental factors not shared by twin pairs which also includes measurement error. MZ twins have identical DNA and thus are correlated perfectly for A and D . DZ twins, on average, share half of their alleles identical by descent and thereby correlate 0.5 for A , and have a 1-in-4 chance of sharing both alleles identical by descent and thereby correlate 0.25 for D . By definition, C is set to correlate perfectly for both MZ and DZ pairs. Analyzing variation between MZ and DZ pairs yields estimates for how much each latent variable contributes to a trait. With twins reared together all four sources (A , C , D , and E) cannot be estimated simultaneously. Non-additive genetic variance can be estimated, by replacing shared environment (C) and fitting ADE models, but evidence for substantial nonadditive genetic effects has not been reported for substance-related behaviors (Stallings et al., 2016).

Structural equation modeling parameters and twin correlations were estimated via Mplus version 7.31 (Muthén & Muthén, 1998–2015) and allowed for sex specific thresholds. Cross-twin polychoric correlations were estimated for tobacco and alcohol milestones for all zygosity groups. Cross-twin cross-trait correlations between age of initiation and dependence latency were computed separately by drug for all zygosity groups and amongst the full sample. Given the lack of clear consensus of what defines early versus late initiation or fast versus slow dependence latency, sensitivity testing was performed for cross-twin and cross-twin cross-trait correlations and detailed in the supplementary materials. Specifically, twin correlations were re-run using two alternative definitions for early age of initiation (age of initiation < 15 or < 18) and one alternative definition for fast dependence latencies (< 3 years from initiation to dependence). Confidence intervals (CIs) for twin correlations were estimated via the CINTERVAL command in Mplus. Significant twin correlation differences may imply heterogeneous genetic/environmental etiologies for males and females. For instance, DZO and DZ same-sex twin pairs share half of their DNA and all of their shared environmental influences. Therefore, appreciably lower correlations in DZO twin pairs compared to DZ same-sex twin pairs would imply distinct, sex-specific genetic/environmental sources of variation for a trait (Neale & Cardon, 1992).

Univariate twin models were fit to estimate the degree to which genetic and environmental factors contribute to all traits independently. Subsequently, we arranged milestones by the sequential nature of substance use (i.e., initiation followed by dependence latency) and incorporated them into a two-stage bivariate Cholesky decomposition model for tobacco and alcohol. Cholesky decomposition models can determine the extent to which *A*, *C* and *E* influences are shared across substance use milestones (i.e., influence the correlation among milestones/stages), or are specific to milestones. We used this model to decompose the genetic and environmental variance and covariance among age of tobacco/alcohol initiation, and the latency to dependence.

Standard univariate and Cholesky decomposition models do not account for sex differences in the genetic and/or environmental etiology among traits. Therefore we fit a series of nested sex-limitation models to estimate *qualitative* and *quantitative* sex differences for all biometrical twin analyses. Qualitative sex differences examine whether the source of variance for a trait may arise from distinct genetic or environmental factors for males and females (i.e., sex-specific effects). Quantitative sex differences assess whether the same genetic and environmental factors differ in the magnitude of their effect across sex. When evaluating sex differences in multivariate analyses, it is assumed that the latent factors, which are the same in males and females, correlate equally across sex (Neale et al., 2006). One way to relax this assumption, is to fit a *modified Cholesky model*, which constrains correlations across these factors to be equal for males and females, but also allows parameter estimates to be computed separately by sex, as done previously (Baker et al., 2011). The modified Cholesky approach, however, could be susceptible to alterations in model fit depending on whether the sex-specific factor matrix is added to the males or females (Neale et al., 2006). Although this can be a concern, we found nearly identical results when applying the sex-specific factor(s) to males or females.

To investigate genetic and environmental sex differences in the speed of progression to dependence, we fit a series of nested and progressively reduced twin models. First *general* sex limitation models (full sex-limitation) were fit, which estimated common A , C and E parameters across sex allowing the magnitude of the effects to differ, while simultaneously estimating a single sex-specific A , D or C parameter (A' , D' or C'). We chose to estimate a sex-specific C' (arbitrarily loading specific to males) due to previous research indicating discrepant familial environmental influences for the etiology of tobacco and alcohol use (Becona et al., 2013; Choquet et al., 2007; Kelly et al., 2011; McArdle et al., 2002). Significant estimates of sex-specific C' parameters would be consistent with qualitative sex differences for a trait and would indicate distinct shared environmental etiologies for males and females. Subsequently, the *common effects* sex-limitation model was fit, which is identical to the general-sex limited model but it assumes no sex-specific variance (i.e., set C' to zero) and would be congruent with quantitative sex differences. Lastly, the *null* model was tested, which equates the magnitude of parameter estimates across sex and would assume no quantitative or qualitative sex differences.

Comparison of nested model fit was assessed via X^2_{diff} tests to determine the best-fitting model. Models were first tested whether thresholds could be constrained across sex. Subsequently, full (general) sex-limitation models were contrasted with common sex-limitation models. A significant X^2_{diff} value from this test would indicate that the common sex limitation model fit appreciably worse and should be rejected in favor of the general model. The resulting sex-limited model from this comparison was then tested against the null-model, which assumes no sex differences. If the X^2_{diff} value of this test was non-significant we would favor the null model because it offers the most parsimonious representations of the data without a significant decrement in model fit and thus would be considered the best fitting model. Note model fit comparisons were conducted via the DIFFTEST command in Mplus, which yield X^2_{diff} values not directly proportional to standard X^2_{diff} tests (i.e., fitting models to continuous data using maximum likelihood).

Since the omnibus chi-square (X^2) fit statistic is sensitive to sample size (Kline, 1998), we used the $\chi^2 < 2 \times \text{df}$ to establish adequate whole-model fit (Byrne, 1989) and verified the goodness of fit of our models with the root-mean-square error of approximation (RMSEA), which quantifies how closely the model-estimated correlations equate to the observed correlation structure. This criterion was selected because it accommodates model complexity by considering the degrees of freedom of the models (Hu & Bentler, 1998; Marsh & Hau, 1996). Good fit was confirmed if the RMSEA < 0.06, as proposed by Hu and Bentler (1998). The weighted least squares means and variance adjusted estimator, which has shown to appropriately accommodate categorical and nonmultivariate normal data (Asparouhov & Muthén, 2010), was used to determine all biometrical model parameters. Significance of individual model parameters were determined by one df X^2_{diff} tests, using a p -value threshold of < 0.05.

RESULTS

Phenotypic Analyses

No significant sex differences were observed for the mean age of tobacco initiation $F(1, 1604) = 0.14, p = 0.71$, nor tobacco dependence latency $F(1, 494) = 0.01, p = 0.91$. The average age of alcohol initiation was significantly earlier in males ($M = 15.23, s.d. = 2.57$) than females ($M = 15.66, s.d. = 2.46$), $F(1, 2254) = 16.57, p < 0.001$. We found marginally significant sex differences in the latency to alcohol dependence, potentially suggesting quicker transition periods for females ($M = 3.29, s.d. = 3.01$) than males ($M = 3.81, s.d. = 3.42, F(1, 434) = 2.75, p = 0.097$).

Twins who reported first using tobacco at age 15 or earlier were significantly more likely to develop dependence (OR = 1.63, 95% CI: 1.28–1.97, $p < 0.001$), see Table 3. Similarly, early initiators of alcohol were significantly more likely to progress to alcohol dependence (OR = 1.47, 95% CI: 1.14–1.79, $p < 0.001$), see Table 3. However, Cox PH mixed effects regression models revealed that early initiation was associated with longer latencies to dependence for tobacco ($_{exp}\beta = 0.29, SE = 0.15, Z = -8.49, p < 0.001$) and alcohol ($_{exp}\beta = 0.50, SE = 0.13, Z = -5.48, p < 0.001$), see Fig 1. Moreover, longer latencies were significantly associated with higher dependence severity for tobacco ($\beta = 0.04, SE = 0.02, p = 0.008$) and alcohol ($\beta = 0.08, SE = 0.02, p < 0.001$).

Twin Correlations

Cross-twin polychoric correlations for ordinal ages of initiation and dependence latencies are displayed in Table 4. All MZ correlations are larger than DZ correlations for both tobacco and alcohol milestones, indicating the presence of genetic influences. Cross-twin sex differences were observed only when comparing DZO to DZ same-sex pairs for age of tobacco initiation and trending for age of alcohol initiation, see Supplementary Table 1, suggesting sex-specific effects. No significant sex differences were observed amongst cross-twin correlations for dependence latencies, $X^2_{diffs}(1) < 1.74, p > 0.189$. Sensitivity testing of cross-twin correlations for alternative definitions of early initiation and fast dependence latencies were not appreciably different than their original estimates across all milestones and zygosity groups (see Supplementary Table 2).

Cross-twin cross-trait (i.e., between-milestones, within drug) polychoric correlations for tobacco and alcohol milestones are shown in Table 5, parsed by zygosity. Recall, these traits were censored and reverse coded (i.e., early initiation coded as 2's, fast dependence latencies coded as 2's etc.), thus we would expect positive correlations amongst age of initiation and dependence. Phenotypic cross-twin cross-trait correlations were modest, with full sample correlations less than or equal to 0.35. Cross-twin cross-trait correlations sometimes differed across sex for tobacco milestones, see Supplementary Table 3, suggesting multivariate genetic/environmental sex differences for tobacco but not alcohol. Similar to cross-twin correlations, sensitivity testing of cross-twin cross-trait correlations was conducted and not appreciably different than their original estimates across all zygosity groups for alternative definitions of early initiation (see Supplementary Table 4) or for fast dependence latency (see Supplementary Table 5). However, the MZ/DZ differences in cross-twin cross-trait

correlations appeared to be greater when defining early age of alcohol initiation as < 18 , suggesting that our multivariate alcohol model may be sensitive to trait operationalization.

Univariate Models

Results from univariate analyses are shown for tobacco in Table 6 and for alcohol in Table 7. Traits, model type and sex are listed on the left, standardized a^2 , c^2 , e^2 point estimates for variance components shown in the middle, and model fit information is presented on the right. The best fitting models were emphasized by reporting fit indices in bold and parameter estimates shown in black, whereas alternative (worse fitting or more complex) model parameter estimates and fit indices were shown in gray. For a graphical representation of univariate model fitting, see Supplementary Figure 3. Constraining thresholds across sex caused a significant decrease in model fit for all univariate analyses $X^2_{\text{diffs}}(2) > 8.42$, $p < 0.015$, except for tobacco dependence latency, $X^2_{\text{diff}}(2) = 3.94$, $p = 0.139$. Thus, for tobacco dependence latency thresholds were constrained to be equal for males and females but were allowed to vary across sex for other milestones. For brevity, only relevant parameter estimates ($p < 0.10$) from the best fitting univariate models were reported in text. All omnibus twin models demonstrated good fit with all $X^2 < 2 \times \text{df}$ and RMSEA values < 0.06 .

Tobacco - Univariate—Comparing the general sex limited model for age of tobacco initiation to the common or null model resulted in a significant decrement in model fit, $X^2_{\text{diff}}(1) = 4.50$, $p = 0.034$ and $X^2_{\text{diff}}(4) = 13.06$, $p = 0.011$, respectively. Thus, the general sex-limited model was favored as the best fitting model. Accordingly, common genetic and environmental sources of variation demonstrated significant contributions for age of tobacco initiation in females ($a^2 = 52\%$, $c^2 = 32\%$, $e^2 = 16\%$) and males ($a^2 = 28\%$, $c^2 = 9\%$, $e^2 = 21\%$), $X^2_{\text{diffs}}(1) > 3.87$, $p < 0.049$. Additionally, we found evidence of sex-specific shared environmental influences contributing to age of tobacco initiation in males ($c'^2_m = 42\%$), $X^2_{\text{diff}}(1) = 4.50$, $p = 0.034$, suggesting substantial etiological differences for males and females.

For tobacco dependence latency, contrasting the general with the common effects sex-limitation approach did not significantly decrease model fit, $X^2_{\text{diff}}(1) = 0.07$, $p = 0.787$. Subsequently, comparing the common effects sex-limited model with the null model did not significantly reduce model fit $X^2_{\text{diff}}(3) = 4.21$, $p = 0.240$, indicating no significant sex differences in genetic and environmental influences. Both additive genetic and non-shared environmental factors influenced the latency to tobacco dependence ($a^2 = 63\%$, $e^2 = 37\%$), $X^2_{\text{diffs}}(1) > 19.88$, $p < 0.001$, with no observable effects from shared environmental influences.

Alcohol - Univariate—For age of alcohol initiation, significant reduction in model fit was observed when comparing the general to the common effects sex-limitation models, $X^2_{\text{diff}}(1) = 4.25$, $p = 0.039$, suggesting a significant sex-specific parameter. However, the four df chi-square difference test comparing the general sex-limitation model with the null model did not significantly decrease model fit, $X^2_{\text{diff}}(4) = 4.70$, $p = 0.320$, suggesting no

substantial sex differences. For the null model, we detected significance from all genetic and environmental sources ($a^2 = 30\%$, $c^2 = 43\%$, $e^2 = 27\%$), $X^2_{\text{diffs}}(1) > 15.85$, $p < 0.001$.

For latency to alcohol dependence, reducing the general sex-limited model to only its common parameters did not significantly decrease model fit $X^2_{\text{diff}}(1) = 0.041$, $p = 0.840$, indicating no evidence for a sex-specific parameter. Similarly, contrasting the common effects sex-limited model with the null model did not significantly reduce model fit $X^2_{\text{diff}}(3) = 1.88$, $p = 0.598$, suggesting no genetic and environmental sex differences. Significant contributions to the latency of alcohol dependence were observed for the null model from additive genetic and non-shared environmental influences ($a^2 = 64\%$, $e^2 = 35\%$), $X^2_{\text{diffs}}(1) > 11.44$, $p < 0.001$, but not shared environmental influences.

Bivariate Models

We then fit the same series of nested models for the multivariate analyses bivariate Cholesky decomposition models for tobacco and alcohol milestones, see Supplementary Figure 4 for graphical representations. Similar to univariate analyses thresholds were tested to determine if they could be constrained across sex. Equating thresholds for males and females caused significant reductions in fit for tobacco and alcohol models, $X^2_{\text{diffs}}(4) > 29.25$, $p < 0.001$, and thus, were allowed to vary across sex. Subsequently, modified sex-limited Cholesky decomposition models were compared to more parsimonious sub models via multi-df X^2_{diff} tests to determine the best fitting model, which are shown in Fig. 2. The alternative sub models with their corresponding fit indices are shown in Supplementary Figure 5 for tobacco and Supplementary Figure 6 for alcohol, all of which demonstrated adequate fit.

Tobacco - Bivariate—Contrasting the general with the common effects sex-limitation model did not result in a significant decrease in model fit, although this effect was trending, $X^2_{\text{diff}}(3) = 6.30$, $p = 0.098$. Next, the common effects model was tested against the null sub model, which resulted in a significant reduction in model fit $X^2_{\text{diff}}(12) = 33.0$, $p = 0.001$. Therefore the common effects sex-limitation Cholesky decomposition model yielded the best fit to the data, $X^2(49) = 67.55$, $p = 0.041$, RMSEA = 0.037, indicating quantitative sex differences in the extent to which genetic and environmental influences are specific and/or shared for age of tobacco initiation and dependence latency. To no surprise, genetic and environmental influences specific to age of tobacco initiation mirrored those from univariate analyses for both sexes.

For females, we observed counteracting genetic and non-shared environmental influences between age of tobacco initiation and dependence latency. Additive genetic factors contributing to earlier age of initiation were associated with a faster latency to tobacco dependence, $X^2_{\text{diff}}(1) = 10.19$, $p = 0.008$. Non-shared environmental factors, however, contributing to an early age of initiation were significantly associated with a slower latency to tobacco dependence, $X^2_{\text{diff}}(1) = 13.08$, $p < 0.001$. These counteracting genetic and non-shared environmental influences between tobacco milestones might explain the relatively low cross-twin cross-trait phenotypic correlations observed in females. Even after accounting for the overlap between age of tobacco initiation and dependence latency, we

found significant milestone-specific additive genetic and non-shared environmental contributions to tobacco dependence latency, $X^2_{\text{diffs}}(1) > 4.51$, $p < 0.034$.

In males, common genetic and environmental influences (A , C and E) did not demonstrate significant overlap between age of initiation and tobacco dependence latency, $X^2_{\text{diffs}}(1) < 2.69$, $p > 0.101$. Rather, milestone specific non-shared environmental influences explained a significant amount of variance in tobacco dependence latency, $X^2_{\text{diff}}(1) = 18.94$, $p < 0.001$.

Alcohol Latency - Bivariate—Among alcohol milestones, comparing the general with the common effects sex-limitation model did not significantly worsen model fit, $X^2_{\text{diffs}}(3) = 3.78$, $p = 0.287$. We then tested the common sex-limited approach against the null model and found no significant reduction in model fit $X^2_{\text{diff}}(12) = 9.73$, $p = 0.640$. Therefore, the null model was considered the best-fitting model, $X^2(61) = 83.82$, $p = 0.003$, RMSEA = 0.037, suggesting no significant qualitative or quantitative sex differences in the genetic and environmental overlap/specificity amongst alcohol milestones. Once again, genetic and environmental factors specific to age of alcohol initiation explained analogous proportions of variance in the multivariate and univariate analyses.

In the null model, we found that shared environmental influences contributing to an earlier age of initiation were significantly associated with a faster latency to alcohol dependence, $X^2_{\text{diff}}(1) = 4.36$, $p = 0.037$. Whereas, non-shared environmental factors exhibited significant milestone-specific contributions to alcohol dependence latency, $X^2_{\text{diff}}(1) = 25.98$, $p < 0.001$, and there was a trending effect for additive genetic influences, $X^2_{\text{diff}}(1) = 3.29$, $p = 0.070$. These results suggest that the overlap between age of alcohol initiation and dependence latency could be attributed to shared environmental influences, while additive genetic and non-shared environmental influences might be specific to alcohol dependence latency.

Discussion

We add to the current body of literature suggesting that early age of initiation of tobacco and alcohol use significantly increases risk for the progression to dependence (Behrendt et al., 2009; Hu et al., 2005; Sartor et al., 2009). Furthermore, we replicated previous findings suggesting that early age of initiation is associated with slower latencies to dependence for tobacco and alcohol (Behrendt et al., 2008; Behrendt et al., 2009; Breslau, 1993; Jackson, 2010; Sartor et al., 2006; Sartor et al., 2008). Our results also suggest that longer transition times from initiation to dependence were associated with higher dependence severity for tobacco and alcohol, although these effects were small.

Genetic and environmental contributions to age of initiation yielded similar estimates as previous studies (Heath et al., 1999; Heath et al., 2002; Pagan et al., 2006; Ystrom et al., 2014) and significantly differed across sex for age of tobacco initiation, supporting other studies (Broms et al., 2006; Morley et al., 2007). Our results extend these findings by identifying sex-specific shared environmental etiologies for age of tobacco initiation, which was also observed for age of alcohol initiation, although this was not considered the best-fitting model. These results are consistent with previous research demonstrating distinct,

sex-specific familial contributions to age of initiation (Pederson & Skrondal, 1998). Latencies to tobacco and alcohol dependence did not demonstrate sufficient genetic and environmental sex differences from univariate analyses and demonstrated significant contributions from additive genetic and non-shared environmental influences, analogous to earlier reports (Liu et al., 2004; Sartor et al., 2008; Stallings et al., 1999).

Expanding upon these findings we conducted bivariate twin analyses to determine the extent to which genetic and environmental influences associated with age of initiation also contributed to the latency to dependence. Findings tended to differ by substance, and sometimes by sex.

Tobacco—For tobacco use, genetic and environmental influences contributing to both age of initiation and dependence latency significantly differed between males and females. Additive genetic factors associated with early age of initiation contributed to a faster latency to dependence in females, consistent with a common genetic liability. Similarly, high genetic risk of validated nicotine receptor and metabolizing genes amongst tobacco initiators has previously been associated with faster progression to heavy use and nicotine dependence (Belsky et al., 2013) and thus, genetic factors increasing risk for fast latencies to tobacco dependence might be operating through nicotine responsiveness once tobacco has been initiated. Why the genetic covariance between tobacco milestones is significant in females but not males remains unclear, but evidence is mounting regarding the temporally specific biological sex-differences for nicotine outcomes (for review, see Cross et al., 2017).

We also found evidence that non-shared environmental factors influencing early age of tobacco initiation tend to contribute to slower dependence latencies in females. These results are consistent with previous studies finding negative non-shared environmental influences from early tobacco initiation with subsequent tobacco outcomes (Heath et al., 2002; Morley et al., 2007). Different environmental influences have been proposed implicating substance availability for early stages of use and peer substance use for later stages (Hines et al., 2015), which may correlate negatively across phases of use. For instance, normative peer use and/or tobacco availability may be low during early tobacco initiation (e.g., initiation at age 12), but be more normative and accessible when initiation is later (e.g., age 17) facilitating escalation to dependence. Ultimately, our results suggest that additive genetic influences contributing to early age of tobacco initiation are conferring risk for an expedited latency to tobacco dependence, whereas non-shared environmental factors influencing earlier use are delaying the progression to dependence.

Notably, the bivariate *general* sex-limitation model suggested trending qualitative sex differences amongst tobacco milestones. Even though this was precluded as the best-fitting representation of the data due to a marginally significant decrease in model fit compared to the best-fitting model ($p = 0.098$), it still yielded adequate fit and may warrant interpretation since limiting discussion to reduced models may be susceptible to parameter indeterminacy (Keller & Coventry, 2005). In the general sex-limitation approach (see Supplementary Figure 5), shared environmental influences (common across sex) associated with early age of initiation corresponded to a trend for a longer latency to dependence in females, whereas *sex-specific* shared environmental influences contributing to early age of initiation were

associated (marginally significant) with a faster latency to tobacco dependence in males. These results are in accordance with previous research finding sex-specific associations between various familial influences and tobacco outcomes (Flay et al., 1998; Gutman et al., 2011; Sanchez et al., 2010; van Den Bree et al., 2004) and more broadly support the hypothesis that the associations with familial protective factors and substance use outcomes are more robust in females compared to males (Kumpfer et al., 2009). Cross-twin cross-trait correlations demonstrate that the origin of the overlapping genetic and environmental sex differences is likely driven by DZ twin comparisons. Taken together, we highlight the complexity and sex-dependent nature of the genetic and environmental etiologies contributing to the temporal and stage-sequential progression to tobacco dependence.

Alcohol—Common genetic liability between age of alcohol initiation and subsequent alcohol dependence latency was not found in our study ($p = 0.120$), in contrast to a study utilizing all female twin pairs (Sartor et al., 2008). Reasons for these discrepant findings may include: different model fitting techniques, lack of power, or our operationalization of alcohol milestones. In our best-fitting model we observed that shared environmental influences predicting earlier initiation of alcohol are associated with a faster latency to dependence, which have been observed to account for the overlap between early initiation and frequency of alcohol use (Pagan et al., 2006) and may implicate the familial environment as a risk factor. In line with our findings, earlier work has shown that lower parental monitoring among alcohol users predicts faster alcohol use trajectories (Barnes et al., 2006; Wichers et al., 2014). These findings suggest that the etiological overlap between earlier initiation and faster progression to alcohol dependence may be attributed to familial factors.

Analogous to Sartor et al. 2008, we found milestone-specific non-shared environmental contributions to alcohol dependence latency. We also discovered a trend indicating that sources of additive genetic variation exhibit milestone-specific contributions to alcohol dependence latency. Our results are in accordance with previous work finding milestone-specific loadings for genetic and non-shared environmental factors on alcohol use disorder/dependence after accounting for their overlap with age of initiation (Sartor et al., 2009; Ystrom et al., 2014). Similar to Deutsch et al., 2016, we found limited evidence of multivariate sex differences amongst familial/non-familial influences contributing to the speed of progression to alcohol dependence, as a model assuming no sex differences was deemed our best fitting model. However, multivariate sex-limitation models still yielded adequate fit and suggested trending positive and negative non-shared environmental associations between alcohol milestones for males and females, respectively. It is unclear why these cross-paths were trending in opposite directions across males and females, but sex differences in how peer, cultural, social and familial influences contribute to alcohol use and trajectories have been observed previously (see Schulte et al., 2009, for review). Ultimately considering the developmental, temporal and potentially sex divergent nature of alcohol trajectories in future research may facilitate the development of targeted intervention and prevention techniques.

Latency—This is the first genetically informed study that investigated sex differences in either tobacco or alcohol dependence latencies. Our findings do not replicate phenotypic sex differences in tobacco latencies (Blitstein et al., 2003; Gabrhelik et al., 2012; Thorner et al., 2007), nor suggest univariate genetic and environmental sex differences for tobacco dependence latency. Genetic and environmental influences did not differ by sex for alcohol use milestones. Phenotypic sex differences for alcohol dependence latency (commonly referred to as the “telescoping effect”) were trending, suggesting faster progression to escalated alcohol use in females, which has predominantly been found in older cohorts or clinical samples (Hernandez-Avila et al., 2004; Piazza et al., 1989; Randall et al., 1999; Ridneour et al., 2006; Schuckit et al., 1998; Schuckit et al., 1995).

A recent study suggests that the telescoping effect needs revision (Keyes et al., 2010). Perhaps a newer version of telescoping should incorporate the effect that earlier ages of initiation tend to correspond to significantly longer latencies to subsequent milestones, which has been widely replicated (Behrendt et al., 2009; Blitstein et al., 2003; Buchmann et al., 2009; Chou & Pickering, 1992; Deutsch et al., 2016; Dewit et al., 2000; Hu et al., 2006; Jackson et al., 2010; Sartor et al., 2009). Longer latencies for those who initiate earlier may be, at least partially, due to social-contextual factors (Hussong et al., 2008) such as normative peer use, parental monitoring and substance availability, which have shown to influence tobacco and alcohol latencies (Capaldi et al., 2009; Duncan et al., 1998; Komro et al., 2007; Li et al., 2002; Simons-Morton et al., 2004). Both sex and age of initiation are likely important considerations when analyzing the speed of progression to dependence. We extend these findings by estimating multivariate genetic/environmental influences amongst tobacco and alcohol milestones.

Individual differences in dependence latencies were explained in part by additive genetic sources, which sometimes yielded overlapping influences with age of initiation. Opposing influences between genetic and environmental factors blunted the association between milestones and tended to depend on sex and substance. For tobacco, genetic influences contributing to early ages of initiation are associated with an accelerated progression to dependence, an effect that was offset by environmental factors in females. Similarly in alcohol, non-shared environmental influences contributing to early age of initiation was associated (marginally significant) with slower latencies to dependence in males, although this was not considered the best-fitting model. If correct, our results suggest that prevention programs should tailor intervention strategies to be gender-sensitive and perhaps substance specific. Regardless of substance, model or sex, milestone-specific non-shared environmental effects were observed for dependence latencies, which could indicate the importance of accounting for both early and later stages of substance use. Importantly, early versus late initiators correspond to different developmental trajectories of substance use and may benefit from temporally and perhaps strategically distinct interventions.

Future Directions—The present study evaluates the latency to tobacco and alcohol dependence, but does not incorporate other latency outcomes such as rate of progression to regular/problem use, relapse, treatment, and/or cessation. Further disentangling the nature of the relationship between transition times and dependence severity might have clinically relevant implications. These analyses define latencies as a difference of years between time-

points. Perhaps applying this framework to a more precise time window (i.e., months) or an age of onset approach would yield different results. Also, it is unknown whether these findings will translate to other illicit substances, or to other samples with different age ranges. Examining, with confidence, the genetic and environmental sex differences for latencies to dependence will require adequately powered studies with larger samples. Tobacco and alcohol dependence latencies have demonstrated a consistent genetic liability across twin studies and therefore might be good traits for gene mapping analyses.

Limitations—Our findings should be interpreted considering the following limitations. Age of initiation was assessed via online self-report, whereas age of dependence was ascertained from a semi-structured interview, all of which involved retrospective self-report, and thus, are subject to recall biases (Johnson & Schultz, 2005; Shillington et al., 2012). However, self-reported ages of initiation for tobacco and alcohol have previously demonstrated sufficient reliability (Johnson & Mott, 2001). We used data closest to average substance milestone onset to accommodate for recall bias, which has previously been shown to alter age of substance milestone onset (Bright & Soulakova, 2013; Shillington et al., 2012). Therefore, our study may have less bias from retrospective report than previous published latency studies utilizing considerably older samples (Liu et al., 2004; Stallings et al., 1999).

To model multivariate genetic/environmental qualitative and quantitative sex-differences we elected to use of the modified Cholesky decomposition model. We chose the modified Cholesky method because its more parsimonious approach for testing qualitative sex differences relative to the correlated factors model, which tends to be difficult to interpret and is more useful at providing a description of the data than it is as a model testing the origin of these sex differences (Neale et al., 2006). However, the relative parsimony of the modified Cholesky model is restricted in its ability of detecting complex patterns of correlations compared to the correlated factors approach, and may have less desirable fit depending on the dataset (Neale et al., 2006). Another primary drawback of using the modified Cholesky model to analyze multivariate sex differences is the overall fit may depend on the ordering of the variables, a limitation, which is circumvented in our data due to the temporal ordering of substance use milestones. Regardless, both aforementioned models are adequate ways to model multivariate genetic and environmental sex differences and have been applied in the literature (Baker et al., 2011; Neale et al., 2006; Morley et al., 2007).

Operationalization of substance use milestones may be an important consideration to make when interpreting our results. We found that our multivariate alcohol model parameters were sensitive to the categorization of age of initiation. That is, defining early age of alcohol initiation as < 18 increased the magnitude of differences between MZ/DZ of cross-twin cross-trait correlations between milestones, which would be consistent with the common genetic liability found by Sartor et al., 2008. This may imply restricted generalizability and suggest future multivariate twin studies to carefully assess the definition of early initiation. We used a data-driven approach (median split) to define early age of initiation as ≤ 15 in order to distribute similar sample sizes across categories and substances. Twins that did not progress to dependence and had a test date less than five years from their age of initiation

were coded as missing and might instill a selection bias for our results. For instance, someone with late initiation may be more likely to be treated as missing than early initiators, rather than given the chance to be slow or censored. However, our analyses show that late initiators are more likely to rapidly progress to dependence - conceivably reducing this selection bias. For reassurance, we reran analyses including censored individuals and yielded similar conclusions (results from these analyses are shown in Supplementary Table 5 and Supplementary Figures 7 & 8).

Dependence outcomes were contingent on initiation, limiting our sample size and power, but this is characteristic of all stage-transition analyses. Low sample size may be particularly important for our ability to detect genetic and/or environmental sex differences for tobacco and alcohol dependence latencies, which appeared to have appreciable, yet nonsignificant, differences in univariate twin models. Lastly, negative non-shared environmental cross paths between milestones could represent correlated measurement error. However, this would not explain the negative shared environmental correlation trend observed amongst tobacco milestones. Future research is warranted investigating the etiological underpinnings for tobacco and alcohol dependence latencies.

Conclusion—This is the first genetically informed study incorporating a multivariate approach for both tobacco and alcohol dependence latencies. We corroborate previous findings suggesting that early age of initiation is associated with increased risk for developing dependence, but a slower trajectory to dependence. Our findings suggest a strong genetic liability for the speed of progression (latency) to tobacco and alcohol dependence. Genetic factors contributing to early age of initiation tend to confer risk for an expedited latency to dependence, which are sometimes being counter-acted by environmental factors that slow the progression to dependence. Ultimately, this study outlines a developmental representation of how genetic and environmental factors contribute to the speed of progression to tobacco and alcohol dependence.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.

Survival plot showing early age of initiation are associated with longer latencies to dependence for tobacco (left) and alcohol (right). 95% confidence intervals are shaded in gray, with early initiators (age of initiation < 15)

Fig. 2.

The best fitting bivariate Cholesky Decomposition models for tobacco (left) and alcohol (right) milestones. Constrained models were presented with a single point estimate per parameter, whereas sex-limited models show two point estimates (one for males and females) for each A , C , E and C' path. Male parameter estimates are displayed without brackets on top of female estimates, which are shown in brackets. Solid black lines or * indicate significant ($p < 0.05$) and dotted lines or # represent marginally significant ($p < 0.10$) parameter estimates, whereas gray lines/numbers denote non-significant effects, as determined by one df X^2_{diff} tests.

Table 1

Number of participants in each ordinal category for tobacco and alcohol milestones

Age of Initiation			
	Censored (0)	Late (1)	Early (2)
<i>Tobacco</i>	1166	657	951
<i>Alcohol</i>	516	1119	1139

Latency to Dependence			
	Censored (0)	Slow (1)	Fast (2)
<i>Tobacco</i>	954	277	221
<i>Alcohol</i>	1552	179	259

Ordinal tobacco and alcohol milestones are contingent on the previous stage. Thus, those who do not initiate tobacco and/or alcohol are excluded from latency to Dependence. Also, these traits are reverse coded, such that, twins who are late initiators and transition slowly to dependence are coded as 1's and those that initiate early or have a fast latency to dependence are coded as 2's.

Table II

Descriptive statistics of tobacco and alcohol milestones

Progression Prevalence (% reaching subsequent stage)						Mean (s.d.)
Substance	Sex	Initiation	Dependence	Age of Initiation	Age of Dependence	
Tobacco	Female	734 (49.7%)	247 (33.7%)	14.69 (2.93)	17.94 (2.80)	4.47 (3.32)
	Male	874 (67.4%)	251 (28.7%)	14.86 (3.0)	18.14 (2.93)	4.49 (3.30)
	Total	1608 (58%)	498 (31%)	14.78 (2.97)	18.04 (2.86)	4.48 (3.31)
Alcohol	Female	1188 (80.4%)	186 (15.7%)	15.66 (2.46)	17.42 (2.77)	3.29 (3.01)
	Male	1070 (82.5%)	252 (23.6%)	15.23 (2.57)	18.19 (2.84)	3.81 (3.42)
	Total	2258 (81.4%)	438 (19.4%)	15.45 (2.52)	17.86 (2.83)	3.59 (3.26)

Total sample size is 2712. Left side of the table shows the number of twins who progress to each stage of substance use, with the proportion of individuals progressing to the next milestone conditional on the previous stage shown in parentheses. Right side of the table shows average age for each milestone, with standard deviations reported in parentheses.

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Table III
Odds ratios for early age of initiation and progression to problem use and dependence

Early Initiation Increases Odds of Developing Dependence	
Substance	Odds of Developing Dependence
Tobacco	OR = 1.63 [1.28, 1.97], $p < 0.001$
Alcohol	OR = 1.47 [1.14, 1.79], $p < 0.001$

Early age of initiation is defined as twins reporting trying either substance at age 15 or younger. 95% confidence intervals are shown in brackets.

Cross-twin polychoric correlations parsed by zygosity for age of initiation and dependence latency

Table IV

Cross-Twin Correlations: Age of Initiation and Dependence Latency					
Zygosity		Tobacco		Alcohol	
Twin Group	Age of Initiation	Dependence Latency	Age of Initiation	Dependence Latency	
rMZF	0.84 [0.79; 0.88]	0.68 [0.57; 0.79]	0.74 [0.70; 0.79]	0.60 [0.47; 0.73]	
rDZF	0.57 [0.46; 0.67]	0.04 [−0.27; 0.35]	0.63 [0.54; 0.71]	0.48 [0.24; 0.72]	
rMZM	0.78 [0.73; 0.84]	0.61 [0.47; 0.74]	0.71 [0.65; 0.77]	0.69 [0.58; 0.79]	
rDZM	0.65 [0.56; 0.74]	0.26 [0.02; 0.49]	0.61 [0.53; 0.70]	0.32 [0.11; 0.54]	
rDZO	0.35 [0.24; 0.47]	0.09 [−0.15; 0.34]	0.47 [0.37; 0.57]	0.21 [−0.01; 0.44]	

Correlations across twin pairs for tobacco traits are shown on the left, while correlations for alcohol are shown on the right. 95% confidence intervals are displayed in brackets. DZ = dizygotic; MZ = monozygotic; F = female; M = male; O = opposite sex.

Cross-twin cross-trait correlations between age of initiation and dependence latency for tobacco and alcohol

Table V

Cross-Twin Cross-Trait Correlations		
Group	Tobacco	Alcohol
<i>r</i> MZF	0.29 [0.20; 0.38]	0.36 [0.24; 0.49]
<i>r</i> DZF	0.04 [−0.10; 0.18]	0.33 [0.15; 0.50]
<i>r</i> MZM	0.39 [0.27; 0.50]	0.40 [0.27; 0.53]
<i>r</i> DZM	0.34 [0.21; 0.49]	0.31 [0.16; 0.45]
<i>r</i> DZO	0.21 [0.08; 0.34]	0.32 [0.19; 0.44]
<i>Total</i>	0.27 [0.07; 0.18]	0.35 [0.29; 0.41]

Cross-twin cross-trait correlations were computed with ordinal, reverse coded age of initiation and latency variables. 95% confidence intervals are shown in brackets. DZ = dizygotic; MZ = monozygotic; F = female; M = male; O = opposite sex.

Table VI
Univariate Analyses of Tobacco Milestones: Age of Initiation and Dependence Latency

Proportion of Variance in Tobacco Phenotypes Accounted for by a^2 , c^2 and e^2									
Trait	Model	Sex	a^2	c^2	e^2	c'^2	c_m^2	χ^2	df p RMSEA
Age of Initiation	General	Female	0.52*	0.32*	0.16*	-	-	23.18	18 0.19 0.032
	Common	Male	0.28*	0.09*	0.21*	0.42*			
		Female							
		Male							
	Null	Constrained							
Dependence Latency	General								
	Common								
	Null	Constrained	0.63*	0	0.37*	-	-	22.27	22 0.44 0.008

Bold model fit statistics represent results from best fitting models

* signifies $p < 0.05$, and # represents $p < 0.1$ & $p > 0.05$ as determined by one df χ^2 difference tests.

Note $c'm^2$ represents sex-specific shared environmental influences for males that were only estimated in general sex-limitation models.

Table VII

Bold model fit statistics represent results from best fitting models

Note $c'm^2$ represents sex-specific shared environmental influences for males that were only estimated in general sex-limitation models.