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Age of initiation and transition times to tobacco dependence: Early onset and rapid escalated use increase risk for dependence severity

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ABSTRACT

Background: Research indicates that early tobacco initiation increases risk for dependence, but despite this, early initiation is associated with slower transitions to escalated tobacco use. In contrast to these findings, other studies suggest that rapid escalated tobacco use is associated with increased dependence outcomes.
Methods: Our sample was comprised of 5668 twins (2834 twin-pairs, mean age: 26.89, *s.d* = 4.42, 53.67% female, 57.69% monozygotic) from Colorado and Minnesota twin cohorts. We assessed the associations between 1) age of tobacco initiation and the speed of transitions (*latency*) to tobacco problem use and dependence and the associations between 2) age of initiation and latencies to tobacco problem use and dependence with tobacco dependence symptom severity. To further understand the etiological unfolding of these processes, we conducted univariate twin models and causally informative co-twin control models.
Results: After adjustment for covariates, we found that early tobacco initiation was associated with a slower transition from initiation to problem use *but* a faster transition from problem use to dependence. Additionally, we found that earlier initiation and faster transitions to tobacco problem use and dependence predicted greater tobacco dependence severity within twin pairs (consistent with causal influences). The contribution of shared genetic and environmental factors was also evident for these relationships.
Conclusions: Our study further disentangles the role of early initiation with transition times to tobacco problem use and dependence. In addition to common risk factors, we found potential causal roles for early tobacco initiation and rapid escalated tobacco use with increased risk for tobacco dependence severity.

1. Introduction

Nearly one billion individuals around the world are daily tobacco smokers (GBD Collaborators et al., 2017), and tobacco use is the second leading cause of death worldwide (GBD Collaborators, T. et al., 2016). The United States (US) has observed decreases in the rates of tobacco use in previous decades; however, this trend has slowed in recent years (Agaku et al., 2014; Jamal et al., 2016). Further understanding the path to tobacco dependence may help reduce the tobacco disease burden.

Research indicates that early tobacco onset/initiation contributes to higher rates of tobacco use and dependence (Sharapova et al., 2018; Hu et al., 2005), but despite being at augmented risk, early users tend to demonstrate slower transitions to escalated tobacco use and dependence (Behrendt et al., 2009; Breslau et al., 1993). Early onset tobacco use is thought to *cause* increased dependence severity (Kendler et al., 2013), suggesting a formative time-window for addiction vulnerability. Do causal factors also govern the relationship between age of initiation and transition times to escalated use/dependence? Unraveling these processes may refine time-windows for preventative tobacco interventions.

Tobacco transition times, or the speed of escalated use *after* initiation, may also play a role in the addictive process. Previous studies suggest that rapid transition times for escalated tobacco use are associated with increased risk for dependence (Dierker et al., 2008, 2012). Investigating transition times for multiple stages of tobacco use affords the opportunity to capture changes in liability over the developmental period from first use to tobacco dependence. Additionally, this line of research may clarify how early tobacco initiators (who typically transition slowly) and rapid escalated tobacco users are both at increased risk for pathological dependence outcomes.

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Rapid transitions from initial symptoms to dependence onset are proposed to reflect a metric of addictive liability (Ridenour et al., 2005). This hypothesis would be supported if a quicker transition to dependence causes increases in dependence severity but would be inconsistent with findings suggesting that *common risk factors* explain this association. For example, if individuals who are genetically prone to quickly escalate to dependence were also at high genetic risk for dependence severity, these transition times may not directly relate to addiction vulnerability. Twin studies raise this possibility by providing evidence that genetic risk factors contribute to the etiology of tobacco dependence transition times (Huggett et al., 2018) and tobacco dependence severity (Broms et al., 2007).

One way to disentangle associations into 1) common risk factors (shared genetic/environmental influences) and 2) *potentially* causal (directly predictive) relationships is through co-twin control modeling (McGue et al., 2010). Co-twin control modeling enables the testing of causal hypotheses that would otherwise not be ethical in humans. Previously, co-twin control models have investigated the speed of escalated alcohol use (Deutsch et al., 2016) but these analyses have yet to be used for transition times of tobacco use.

Using two independent twin-samples, we investigated the etiological processes characterizing the path to escalated tobacco use and dependence. First, we assessed the univariate genetic and environmental contributions to three tobacco stages/milestones: age of initiation, speed of transition from initiation to problem use (problem use *latency*), and speed of transition from problem use to dependence (dependence *latency*). Then, we used co-twin control models to examine the role of age of initiation and transition times/latencies to problem tobacco use and dependence and test causal hypotheses that early initiation and rapid escalated tobacco use are direct risk factors for tobacco dependence severity.

2. Methods

2.1. Sample

Our study included a combined total of 5668 identical/monozygotic (MZ) and fraternal/dizygotic (DZ) twins (2834 twin-pairs). We aggregated twins across Minnesota (MN) and Colorado (CO) samples. To be included in our sample, we required twins to be of legal age to use tobacco (> age 18) at time of assessment (range: 18.03–45.15). All DZ twins from MN were same sex, but the CO sample included 252 opposite-sex DZ twin pairs.

MN twin cohorts were ascertained as a part of the longitudinal Minnesota Twin Center for Twin and Family Research. The two MN cohorts were either recruited during elementary school or late adolescence and were longitudinally assessed roughly every 3–4 years (Iacono et al., 2006). For both cohorts, we used data across four consecutive assessments starting in late adolescence (˜ age 18). We observed no appreciable differences in tobacco traits between MN cohorts and therefore collapsed them into one MN twin-sample.

CO twins were recruited as a part of the Center for Antisocial Drug Dependence. Twins were ascertained via CO birth records or school districts and were longitudinally assessed across three time points (waves) every ˜5 years (Rhea et al., 2013). 88.25% of CO twins were < age 18 at the first wave; thus, we used data from the last two waves of assessment.

2.2. Measures

For descriptive information on the variables used in our analyses, see Table 1. Three measures were coded as dichotomous, including: twin-sample (1 MN/-1 CO), sex (1 males/-1 females) and zygosity (0 MZs/1 DZs). Age was treated as continuous and was transformed into *z*-scores within each individual model. All tobacco traits collapsed across types of tobacco (cigarettes, cigars, pipe tobacco, snuff, chew, but not e-cigarettes).

Our analyses evaluated three sequential milestones of tobacco use: initiation, problem use and dependence. For both samples, onset ages for tobacco milestones were assessed via the Composite International Diagnostic Interview-Substance Abuse Module (CIDI-SAM; Cottler et al., 1989). Age of tobacco initiation (range: 3–29) was the age participants reported first using tobacco. Onset age of problem use was the year individuals endorsed their first DSM tobacco dependence criterion (DSM-IV: Diagnostic and Statistical Manual of Mental Disorders 4th edition; range: 7–30). Onset age of dependence (range: 10–30) was the age twins first reported 3 or more DSM-IV criteria for tobacco dependence. We computed problem use and dependence latencies by subtracting participants' onset ages between milestones. Specifically, *problem use latency* is the number of years from age of initiation to the onset age of first dependence symptom. *Dependence latency* is the number of years from problem use onset to dependence onset (see Supplementary Figure S1).221 participants reported older tobacco onset ages for preceding milestones than subsequent outcomes (e.g., initiation age > age at dependence). For these individuals, we sought to recover their onset age data via a within-assessment technique. Specifically, we selected the assessment time-point in which individuals first reported problem use and/or dependence to determine onset ages for all milestones (rather than use later assessments that rely on longer recall). This recovered data for 99 individuals. The remaining 122 participants were removed from analyses. In total, 72.16% of twins reported initiating tobacco, 35.48% were problem users, and 25.21% met DSM criteria for tobacco dependence.

Tobacco dependence severity was assessed with the CIDI-SAM and defined as the number of endorsed DSM-IV dependence criteria. MN and CO assessments differed regarding the minimal level of tobacco use required to survey participants about dependence. For MN twins, only those who used tobacco every day for 2 weeks were surveyed for tobacco dependence symptoms, whereas CO twins were only assessed if they used tobacco products 20 or more times in their lifetime. We did detect significant differences in tobacco dependence severity between MN and CO twin-samples, $p < 0.001$, see Supplementrary Figure S1. However, we no longer observed differences in dependence severity across twin-samples after excluding subjects with no symptoms of dependence, $p = 0.238$; see Table 1. This suggests survey procedure discrepancies between samples. To minimize the impact of these assessment differences, tobacco dependence severity analyses were limited to individuals with at least one or more symptoms of dependence. For analyses assessing sample and sex differences, see Supplementary Note.

2.3. Analyses

We conducted univariate twin models to estimate heritable (additive genetic; a^2) and non-heritable (shared environmental; c^2 and non-shared environmental; e^2) risk factors. MZ twin-pairs share 100% and DZ twin-pairs share on average ˜50% of their additive genetic influences. Therefore, if MZ twin-pairs were substantially more similar than DZ twin-pairs on a trait, twin models would indicate that this trait is heritable and allow one to quantify the extent to which genetic factors contribute to trait variance. First, we estimated MZ/DZ cross-twin (within-trait) correlations and then fit univariate twin models to the tobacco traits in the full sample and then separately by sample and sex using Mplus version 7.31 (Muten and Muten, 1998–2015). For more information on model fitting to determine genetic and environmental sex and/or sample differences, see Supplementary Note.

We used two separate models to assess the relationships between age of tobacco initiation with 1) problem use latency and 2) dependence latency. Initially, we fit Cox proportional hazard (CoxPH) ratio models but found that all of our CoxPH models violated the proportional hazards assumption, as detected via Schoenfeld residual tests, all $X^2 > 56.76$, all $p < 0.001$. Therefore, we elected to use an alternative

Table 1
Descriptive statistics by sample.

Descriptive information for variables used in our analyses: *M* (*s.d.*)

Variable	Total	Colorado	Minnesota	Females	Males
n	5668	2,584	3,084	3,042	2,626
Age	26.89 (4.42)	25.10 (2.90)	28.39 (4.90)	26.73 (4.08)	27.07 (4.79)
Sex [% Female]	53.67%	54.03%	53.38%	100%	0%
Zygosity [% MZ]	57.69%	49.07%	64.92%	58.32%	56.97%
Age of tobacco initiation (n = 4091)	16.01 (3.26)	15.75 (3.14)	16.22 (3.33)	16.39 (3.29)	15.69 (3.20)
% Heritable: Age of initiation	39.00%*	48.00%*	38.00%*	46.00%*	26.00%*
Onset age: Tobacco problem use (n = 2101)	17.92 (2.94)	17.66 (2.90)	18.13 (2.95)	17.98 (2.99)	17.87 (2.90)
Tobacco problem use latency	2.88 (2.95)	2.81 (2.69)	2.94 (3.16)	2.66 (2.90)	3.05 (2.98)
% Heritable: Problem use latency	24.00%*	11.00%	29.00%*	10.00%	28.00%*
Onset age: Tobacco dependence (n = 1429)	19.03 (3.07)	18.97 (2.99)	19.07 (3.13)	19.27 (3.25)	18.85 (2.91)
Tobacco dependence latency	1.76 (2.28)	2.02 (2.26)	1.55 (2.28)	1.91 (2.46)	1.65 (2.13)
% Heritable: Dependence latency	18.00%*	28.00%*	1.00%	5.00%	13.00%
Tobacco dependence severity (1+ Symptoms; n = 2101)	3.41 (1.60)	3.46 (1.75)	3.36 (1.44)	3.39 (1.60)	3.42 (1.59)
% Heritable: Tobacco dependence severity	37.00%*	36.00%*	35.00%*	13.00%	31.00%*

Tobacco problem users were defined as those who endorsed one or more symptoms of tobacco dependence. *Problem use latency* was defined as the number of years from initiation to onset of problem use and *dependence latency* was the number of years from problem use to dependence onset. Heritability was defined as the proportion of variance explained by additive genetic factors and * represents $p < 0.05$. See Supplementary Note for sample and sex differences among tobacco traits and Supplementary Table S3 for full univariate twin model results.

survival model that does not assume proportional hazards, the Aalen's additive regression model (Aalen, 1989). We fit Aalen's survival models via the *aareg* command in the survival package in R (Threanau, 2015), which estimates slopes, *z*-scores and *p*-values. To account for non-linear age of initiation effects and the nested structure of twin-pairs, our Aalen's survival models controlled for the main effects of age of tobacco initiation^2 and used Huber sandwich estimators on family ids using the *cluster* argument.

Next, using the lme4 package in R (Bates et al., 2014), we estimated linear mixed effects regression models to explore the relationships between age of tobacco initiation and tobacco latencies with tobacco dependence severity. To simultaneously control for tobacco onset age and transition times, we estimated a single model using age of initiation and the two latencies as predictors of dependence severity. To be included in these analyses, individuals were required to have tobacco dependence, as dependence latency was a predictor/covariate. We used Kenward-Rogers approximation (Kenward and Roger, 1997) to estimate *p*-values for linear mixed effects regression models via the pbkrtest package in R (Halekoh and Hojsgaard, 2014).

Co-twin control analyses were conducted to parse individual-level associations into between-twin pair (β_B) and within-twin pair (β_W) effects. Consider the relationship between age of tobacco initiation (predictor) and tobacco dependence severity (outcome). In this case the between-twin pair predictor is computed by averaging the age of tobacco initiation for each twin-pair and would represent an association attributable to common risk factors (i.e., shared genetic and environmental influences). The within-twin pair predictor is computed by taking the difference of the individual twins' age of tobacco initiation and their twin-pair mean. A significant within-twin pair effect would be un-confounded by shared genetic and environmental influences and would be consistent with a *possible* causal relationship.

To boost power, co-twin control analyses incorporated all MZ and DZ twins and included discordant and concordant twin-pairs as well as individual twins (e.g., one twin has dependence, their co-twin does not). But since DZ twins are not identically matched on their genotypes, differences among DZ twin-pairs could be attributed to or biased by genetic factors (McGue et al., 2010). To address this, we included interaction terms among all between/within-twin pair predictors with zygosity and also performed analyses separately for MZ and DZ twins. Co-twin control models adjusted for potential sex and zygosity interactions. DZ-specific analyses detected no significant interaction between zygosity and sex, all $p > 0.231$, indicating no substantial etiological differences and suggesting opposite sex DZ twin-pairs can be included in co-twin control models. For more information by zygosity and discordance rates for relevant tobacco milestones, see Supplementary Table S1

When possible, models controlled for the main effects of zygosity, sex, age (at assessment), age^2 and twin-sample (CO/MN). Previous research observed sex differences in tobacco latencies (Blitstein et al., 2003; Thorner et al., 2007). We tested for sex differences by including interaction term(s) between sex and all tobacco predictors. Analyses performed in the full sample included an analogous interaction term to test for discrepancies between twin-samples (tobacco trait*twin-sample), similar to other multi-cohort designs (Agrawal et al., 2017). To assess sensitivity of our results to specific initiation ages, we repeated all analyses for those reporting initiating tobacco after age 10 and after age 16. For all analyses, the criterion for statistical significance was set as a nominal *p*-value threshold of ≤ 0.05. All significant interactions were highlighted in tables or reported in text.

3. Results

3.1. Univariate twin models

Cross-twin correlations for tobacco traits tended to be larger for MZ twin-pairs than DZ twin-pairs (see Supplementary Table S2), indicating heritable components. We fit a series of univariate twin models to estimated heritable/genetic (a^2) and non- heritable/environmental (c^2 and e^2) sources of variation. We found no evidence for significant sex differences in genetic and environmental influences for all traits. We observed sample differences in genetic and environmental influences for tobacco problem use latency and tobacco dependence severity, although differences in parameter estimates were not large (see Supplementary Table S3). In the full sample, genetic and environmental factors significantly contributed to age of tobacco initiation ($a^2/c^2/e^2 = 0.39/0.15/0.46$), problem use latency ($a^2/e^2 = 0.24/0.74$), dependence latency ($a^2/e^2 = 0.18/0.82$) and tobacco dependence severity ($a^2/e^2 = 0.37/0.63$; see Table 1 or Supplementary Table S4).

3.2. Individual-level analyses

Fig. 1A shows the developmental risk periods for the onset of tobacco initiation, problem use and dependence. Ages 14–18 appeared to be a high-risk period for tobacco initiation, as 64.26% of all initiators reported their first use during this time. Among twins who developed problem use or dependence, 63.82%–67.36% reached these milestones between age 16 and 20. Fig. 1B further details the speed of transitions to tobacco problem use and dependence by specific ages of initiation.

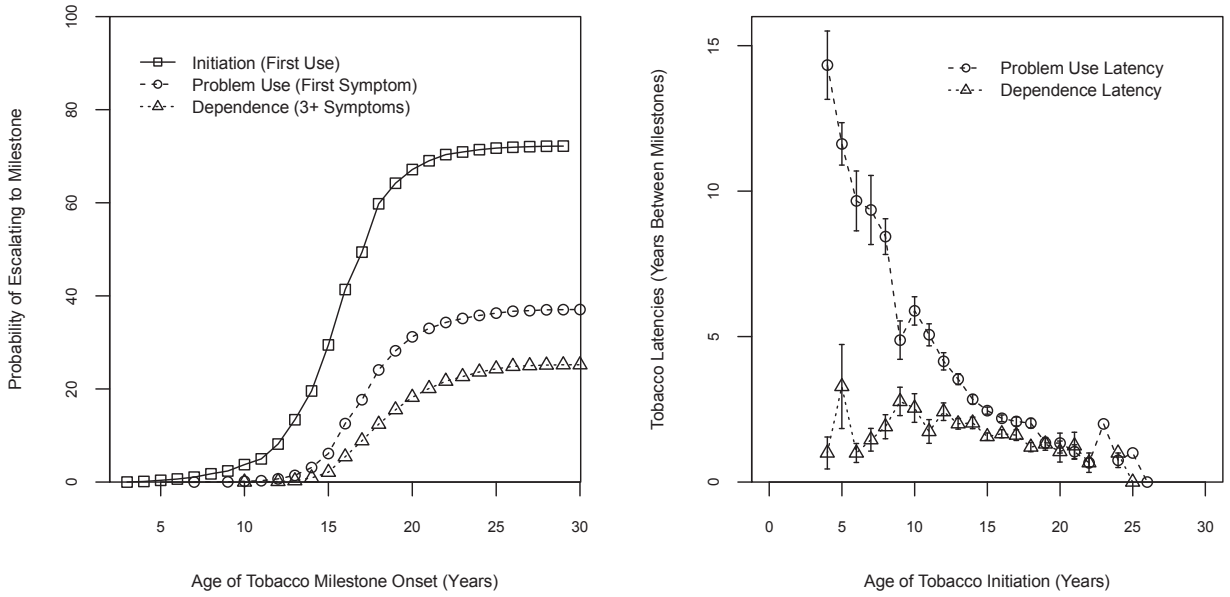

Fig. 1. Age of tobacco initiation and transition times to problem use and dependence in the full sample.
A) Prevalence and onset age of tobacco milestones.
Demonstrates the proportion of age-specific transitions to tobacco initiation, problem use and dependence in the full sample
B) Age of initiation predicts speed of escalated use (latency).
Shows mean (*s.e*) transition times from initiation to problem use (problem use latency) and transition times from problem use to dependence (dependence latency) by age of tobacco initiation in the full sample

We observed that tobacco initiation at age ten or less was associated with a particularly protracted latency to tobacco problem use (M = 7.49 years, $s.e$ = 0.35).

After adjustment for covariates, our individual-level Aalen's additive regression models indicated that earlier age of tobacco initiation was associated with a longer latency to tobacco problem use, $\beta = 0.08$, $Z = 5.10$, $p < 0.001$, but a shorter transition time from problem use to dependence, $\beta = -0.12$, $Z = -2.20$, $p = 0.028$. Earlier initiation was also associated with a longer latency to problem use for those initiating tobacco after age 10 but not after age 16 (see Supplementary Table S5). We found no significant association between age of tobacco initiation and tobacco dependence latency when using only subjects initiating tobacco after age 10 or after age 16 (see Supplementary Table S6).

Fig. 2A graphically illustrates the relationship between earlier tobacco initiation and higher tobacco dependence severity. We also observed that faster transitions/latencies to tobacco problem use and dependence tended to correspond with increased dependence severity (Fig. 2B). After adjusting for covariates, we found that early tobacco initiation and quicker latencies to problem use and dependence were all significantly associated with greater tobacco dependence severity, all $\beta <$ -0.06, all $s.e \leq 0.02$, all $p < 0.001$, with some interactions with sex and sample (see Supplementary Table S7). Associations between dependence severity and age of initiation and problem/dependence latencies remained significant for those initiating after age 10. However, only problem use latency predicted dependence severity for those initiating tobacco after age 16 (see Supplementary Table S8).

3.3. Co-twin control models

We then used co-twin control models to unravel the nature of our individual-level associations. First, we assessed the relationships between age of initiation and latencies to problem use and dependence. We found that twins who initiate tobacco earlier than their co-twin (within-twin pair effect) had significantly longer latencies to problem use, $\beta_W = 0.10$, $Z = 5.39$, $p < 0.001$, a finding that was consistent across twin-sample, sex, zygosity and ages of tobacco initiation > 10, but not ages of tobacco initiation > 16 (see Supplementary Tables S9 and S10). We also found significant between-twin pair effects for the relationships between age of initiation and tobacco problem use latency, $\beta_B = 0.07$, $Z = 4.00$, $p < 0.001$, and the relationship between age of initiation and the transition time from problem use to dependence, β_B = -0.13, $Z = 2.40$, $p = 0.016$ (see Supplementary Tables S11 and S12), indicating that shared genetic and environmental risk factors are contributing to these associations.

Table 2 displays the results from the co-twin control analyses predicting tobacco dependence severity. After controlling for covariates, we found significant within-twin pair effects for early tobacco initiation, rapid problem use and fast dependence latencies associated with increased tobacco dependence severity. These significant within-twin pair effects were consistent across twin-sample, sex and zygosity (see Supplementary Table S13) and are in accordance with potentially causal relationships. That is, the twin who initiates tobacco earlier than their co-twin and/or escalates their use quicker than their co-twin has more severe tobacco dependence. For those initiating after age 16, only fast tobacco problem use latency predicted increases in dependence severity within-twin pairs. We also detected significant between-twin pair effects such that the shared genetic and environmental risk factors influencing earlier tobacco initiation, faster latencies to problem use and dependence were also associated with higher tobacco dependence severity.

4. Discussion

Our study furthers the understanding of the roles of early tobacco initiation and rapid escalated use in the etiology of tobacco dependence and addresses paradoxical findings regarding the links between early initiation with slower transitions to escalated use, but greater risk for dependence. We found that early age of tobacco initiation is associated with a longer transition time (latency) from initiation to tobacco problem use but a shorter latency from problem use to dependence. Early tobacco initiation and fast latencies to problem use and dependence were also associated with increased tobacco dependence severity.

Co-twin control analyses identified that the twin initiating tobacco earlier than their co-twin had significantly slower transitions to

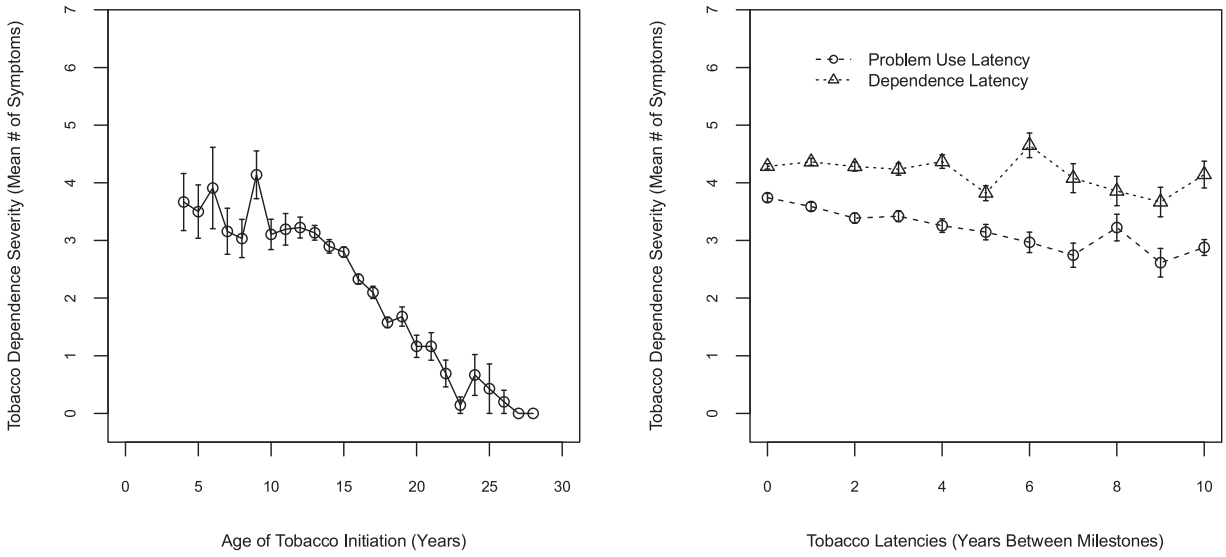

Fig. 2. Associations with tobacco dependence severity in the full sample.
A) Early initiation predicts higher dependence severity.
Illustrates the relationship of age of tobacco initiation with average (*s.e.*) dependence severity and includes everyone who reported every using tobacco.
B) Rapid escalated use predicts higher dependence severity.
Shows links between mean (*s.e.*) dependence severity with problem use and dependence latencies (speed of escalated use). *Note* tobacco problem use and dependence latencies were winsorized at 10 years and, by definition, only included problem users (1+ dependence symptoms) or those with tobacco dependence.

problem use (consistent with a potential causal relationship). Various social and contextual factors may preclude early tobacco initiators from prompt escalated use. For instance, peer tobacco use is a robust predictor of tobacco use trajectories (Bernat et al., 2008; Pollard et al., 2010), and previous research demonstrates that high (perceived) cigarette accessibility among initiators increases risk for the transition to regular cigarette use above and beyond parental smoking (Doubeni et al., 2008). In our study, tobacco problem use and dependence onset occurred approximately at ages 16–18 irrespective of various early initiation ages (see Table 3). Thus, longer problem use latencies (among early initiators) may be a *consequence* of delayed tobacco availability, which might complicate causal interpretations. Overall, our findings suggest that early age of tobacco initiation results in longer problem use latencies and that the emergence (or absence) of a smoking-supportive environment may be the crucial factor rather than age of onset per se.

Early tobacco initiation is not always associated with slower escalated use. Our analyses suggest that early initiation is associated with faster transitions from problem use to tobacco dependence. Co-twin control models detected that this relationship was non-causal and could be attributed to common genetic and environmental risk factors. High-risk, early onset users (≤ age 10) had rather unstable transition times to dependence and may possess very unique trajectories to pathological tobacco use. Perhaps early onset users are eager or primed to rush to dependence once equipped with the proper context/environment.

We detected small heritability estimates for tobacco latencies, which is similar to other twin research using continuous latency measures (Hines et al., 2015; Stallings et al., 1999). However, categorical substance use latencies seem to yield higher heritability estimates (Sartor et al., 2008a; Huggett et al., 2018) and could be capturing different sources of genetic and environmental variation by comparing

Table 2
Co-twin control analyses predicting dependence severity from age of intiation and tobacco latencies.

Co-twin control results by sample– Unraveling the roles for age of initiation and rapid escalated tobacco use with tobacco dependence severity: β (*s.e*)					
Variable	Full sample (n = 1429)	Colorado (n = 632)	Minnesota (n = 797)	Initiation age > 10 (n = 1311)	Initiation age > 16 (n = 330)
Zygosity	0.21 (0.46)$	−0.28 (0.71)$	0.60 (0.62)	−0.24 (0.53)$	−0.61 (1.76)
Sex	−0.07 (0.23)	0.20 (0.35)	−0.22 (0.32)	0.16 (0.26)	0.62 (0.85)
Age	0.12 (0.04)**	0.08 (0.05)	0.11 (0.05)*	0.11 (0.04)**	0.25 (0.08)**
Age$^{\sim 2}$	−0.02 (0.01)	0.00 (0.03)	−0.03 (0.02)	−0.02 (0.01)	−0.07 (0.03)*
Twin-sample (MN vs CO)	−0.69 (0.23)**	NA	NA	−0.73 (0.27)**	−0.91 (0.93)
β_W Age of tobacco initiation	−0.14 (0.03)***	−0.16 (0.06)**	−0.11 (0.04)**	−0.16 (0.04)***	−0.01 (0.08)
β_B Age of tobacco initiation	−0.11 (0.02)***&	−0.16 (0.03)***	−0.08 (0.02)**	−0.12 (0.02)***&	−0.03 (0.06)
β_W Tobacco problem use latency	−0.13 (0.03)***	−0.15 (0.06)*	−0.11 (0.03)***	−0.13 (0.04)***	−0.19 (0.07)*
β_B Tobacco problem use latency	−0.11 (0.02)***	−0.15 (0.04)***$	−0.08 (0.02)***	−0.11 (0.02)***	−0.19 (0.05)***
β_W Tobacco dependence latency	−0.06 (0.03)*	−0.03 (0.06)	−0.11 (0.04)**	−0.06 (0.03)&	−0.11 (0.07)
β_B Tobacco dependence latency	−0.06 (0.02)**&	−0.06 (0.04)	−0.08 (0.02)***	−0.06 (0.02)**	−0.07 (0.05)

Note. Co-twin control models assessed within-twin pair and between-twin pair predictors for: age of initiation, problem use latency and dependence latency. Analyses included full twin-pairs and also singleton twins with tobacco dependence.
β_W represents the within-twin pair effect (reflects potentially causal path).
β_B represents the between-twin pair effect (reflects common genetic and environmental risk factors).
& represents a significant interaction with sample ($p < 0.05$).
$ represents a significant interaction with sex ($p < 0.05$).
* represents $p < 0.05$, ** represents $p < 0.01$, *** represents $p < 0.001$.

Table 3
Relationships between age of tobacco initiation and tobacco milestones.

Onset and incidence of problem use and dependence by age of tobacco initiation				
Onset age: *M* (*s.e.*)			Escalated to milestone (% age adjusted)	
Initiation	Problem Use	Dependence	% Problem Users	% Dependent
3 (n = 1)	NA	NA	0.00%	0.00%
4) (n = 6)	18.33 (1.17)	19.40 (1.54)	99.92%	82.85%
5 (n = 15)	16.63 (0.73)	19.29 (1.48)	53.19%	45.85%
6 (n = 15)	15.67 (1.03)	16.13 (0.97)	59.91%	52.79%
7 (n = 23)	16.35 (1.19)	17.09 (1.30)	73.85%	47.49%
8 (n = 40)	16.44 (0.61)	18.24 (0.74)	62.37%	51.78%
9 (n = 36)	13.88 (0.69)	16.32 (0.43)	69.42%	60.97%
10 (n = 76)	15.89 (0.49)	18.48 (0.49)	68.41%	57.86%
11 (n = 70)	16.07 (0.38)	17.76 (0.52)	65.69%	59.85%
12 (n = 181)	16.15 (0.30)	17.94 (0.37)	65.73%	51.31%
13 (n = 296)	16.54 (0.19)	18.12 (0.24)	70.95%	55.76%
14 (n = 350)	16.86 (0.16)	18.46 (0.25)	66.58%	48.34%
15 (n = 561)	17.46 (0.12)	18.57 (0.17)	66.86%	46.96%
16 (n = 674)	18.19 (0.11)	19.31 (0.17)	58.64%	37.13%
17 (n = 457)	19.08 (0.15)	20.39 (0.24)	47.28%	28.96%
18 (n = 587)	20.02 (0.16)	20.46 (0.21)	37.31%	19.26%
19 (n = 251)	20.35 (0.19)	21.44 (0.28)	28.67%	17.86%
20 (n = 167)	21.34 (0.34)	21.80 (0.41)	20.95%	11.96%
21 (n = 107)	22.04 (0.24)	23.00 (0.51)	21.44%	10.90%
22 (n = 76)	22.67 (0.17)	23.33 (0.33)	11.82%	7.78%
23 (n = 31)	25.00 (NA)	NA	3.11%	0.00%
24 (n = 28)	24.75 (0.25)	25.00 (NA)	14.16%	2.90%
25 (n = 19)	26.00 (NA)	26.00 (NA)	5.14%	4.56%
26 (n = 10)	26.00 (NA)	NA	9.88%	0.00%
27 (n = 8)	NA	NA	0.00%	0.00%
28 (n = 5)	NA	NA	0.00%	0.00%
29 (n = 1)	NA	NA	0.00%	0.00%

Note. Age adjusted percentages were calculated with a linear model regressing out the effects of age.

non-users/progresses to those who escalate their use. The relatively small genetic contributions to tobacco latencies may suggest that transition times are malleable targets for tobacco interventions.

We observed a potentially causal relationship between early tobacco initiation and higher dependence severity, corroborating findings from other co-twin control research (Kendler et al., 2013). Rodent models complement these findings by revealing biological mechanisms proposing that early tobacco initiation alters the structural and functional development of executive-networks and reward systems in the brain (see Smith et al., 2015 for review), while also influencing neurochemical and behavioral responses to nicotine (Brielmaier et al., 2007; Cao et al., 2010; Placzek et al., 2009).

Common risk factors also contributed to the association between early age of initiation and increased tobacco dependence severity and may indicate a common genetic vulnerability. Recent large-scale genomics research identified a genetic correlation between age of smoking onset and cigarettes per day and implicates novel genes/loci involved in glutamate neurotransmission, neuronal excitability and reward learning (Liu et al., 2019).

Regardless of initiation age, twin sample, sex and shared genetic/environmental influences, we found that a faster transition from first use to problematic use is a risk factor for increased tobacco dependence severity. Our findings support the hypothesis that rapid transitions from initial symptoms to dependence are indicative of greater addiction liability (Ridenour et al., 2005), but tobacco problem use latency was the most robust risk factor. Approximately 11.3% of 18-34-year-olds in the US are rapid escalators of tobacco use, and these individuals tend to use cigarettes daily (Hair et al., 2017). In our study, 10.00% of tobacco initiators developed their first dependence symptom the same year they initiated tobacco use, and 76.04% of them progressed to tobacco dependence. Perhaps rapid escalated tobacco users have maladaptive disinhibition of reward learning or heightened tobacco salience promoting more severe dependence outcomes. Overall, our study suggests a novel, potentially causal role of rapid transition times on increased tobacco dependence severity.

In addition to potential causal factors, the relationship between quicker tobacco latencies and tobacco dependence severity was reflective of shared genetic and environmental risk factors. Parental tobacco use/dependence and pleasant initial tobacco experiences contribute to faster transitions to escalated tobacco use (Hair et al., 2017; Hu et al., 2012; Sartor et al., 2008b). Similarly, genetic risk among nicotine receptor and metabolism genes is associated with both quicker transitions from initiation to heavy smoking and increased rates of tobacco dependence (Belsky et al., 2013). It is possible that the familial landscape and/or genetic risk to nicotine responsiveness are contributing to both the speed of transition and severity of tobacco dependence.

The findings from this study should be interpreted in the context of the following limitations. Our study relied on retrospective reports to determine onset ages for tobacco milestones, which are prone to error (Bright and Soulakova, 2014). Age of initiation was defined as the age at first use of tobacco, which may capture etiologically distinct factors from research using alternative definitions of tobacco onset age (e.g., age of regular use). Our results should be considered in a developmentally sensitive framework, as not all findings remained significant across subsamples of initiation ages (> age 10/16). Late initiators may not have had enough time to transition to escalated tobacco milestones. However, over 84% of tobacco users that did not progress to problem use or dependence reported an age of initiation < 5 years from their most recent age at assessment.

Future research would benefit from delineating time-specific transitions for vaping products (Hair et al., 2018; Westling et al., 2017) as well as assessing additional tobacco milestones (e.g., cessation). With some notable exceptions, most research investigating tobacco onset ages and tobacco latencies have been conducted in the US, and more studies are warranted to explore these dynamics in other westernized societies such as Europe and Australia. Recent animal research has provided a model for escalated nicotine use (Cohen et al., 2012; Gilpin et al., 2014), but despite substantial individual variability for initial nicotine self-administration, these studies do not simultaneously analyze within-session dynamics (e.g., rate of escalated lever presses), making biological and mechanistic interpretations for tobacco latencies difficult. Ultimately, further characterizing tobacco transition times may outline a map to tobacco dependence and could be informative for interventions.

In conclusion, we found that early tobacco users are at higher risk for dependence but tend to transition slowly to problem/escalated use, tenably attributed to a delayed exposure to a tobacco-supportive environment. In addition to replicating potentially causal relationships between early tobacco use and subsequent tobacco dependence, our study provides novel evidence of a potentially causal role of fast tobacco transition times on increased dependence severity. Therefore, both early tobacco onset and rapid escalated tobacco use may increase risk for pathological tobacco use.

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Contributors

Spencer B Huggett was involved in data acquisition, cleaning the

data, performing statistical analyses and writing the initial draft of the manuscript. Matt McGue was involved in providing data access to the MN twin-sample. All remaining co-authors contributed by editing the manuscript and provided useful comments to improve the overall research project. All authors contributed to and approved the final version of the manuscript.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.drugalcdep.2019.04.027.

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