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Age of Alcohol and Cannabis Use Onset Mediates the Association of Transmissible Risk in Childhood and Development of Alcohol and Cannabis Disorders: Evidence for Common Liability

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Abstract

Age at the time of first alcohol and cannabis use was investigated in relation to a measure of transmissible (intergenerational) risk for addiction in childhood and development of alcohol use disorder (AUD) and cannabis use disorder (CUD). It was hypothesized that age at the time of first experience with either substance mediates the association between transmissible risk and subsequent diagnosis of both disorders. The Transmissible Liability Index (TLI; (Vanyukov et al., 2009) was administered to 339 10- to 12-year-old boys ($n = 254$) and girls ($n = 85$). Age at the time of first alcohol and cannabis use, and diagnosis of AUD and CUD, were prospectively tracked to age 22. Each standard deviation unit increase in TLI severity corresponded to a reduction in age of alcohol and cannabis use onset by 3.2 months and 4.6 months, respectively. Age at the time of first alcohol use mediated the association of TLI with both AUD and CUD. Parallel results were obtained for cannabis. Whereas transmissible risk is congenious to both AUD and CUD, its magnitude was 7 times greater in youths who initiated substance use with cannabis. TLI predicts age of first use of alcohol and cannabis that is common to developing both AUD and CUD. The ramifications of these findings for prevention are discussed.

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Keywords

substance use disorder; transmissible risk; cannabis; alcohol; childhood

Initiating alcohol consumption at a young age is related to amplified risk for alcohol use disorder (AUD; Hingson, Heeren, & Winter, 2006; Pitkänen, Lyyra, & Pulkkinen, 2005). Most alcohol consumers do not, however, develop AUD. For example, 30-day prevalence of alcohol consumption is 52.1% among tenth-grade students (Johnston, O'Malley, Bachman, & Schulenberg, 2012), whereas only about 16% of the population qualifies for lifetime AUD by 65 years of age (Lin et al., 2011).

One factor that may distinguish youths who develop AUD from other alcohol users pertains to transmissible (intergenerational) risk. It has been shown, in this regard, that risk for AUD, manifest by age 22, is highly heritable (Chen et al., 2011; Cloninger, Bohman, & Sigvardsson, 1981). However, strong genetic correlations have also been documented between AUD and liabilities to other substance use disorders (SUDs; Kendler, Myers, & Prescott, 2007), reflective of general liability to addiction (GLA; Vanyukov et al., 2012). Consequently, GLA manifest in consumption initiated with one type of substance may culminate in SUD resulting from consumption of other compounds. For example, frequent consumers of hypercaffeinated ("energy") beverages are 3.5 times more likely than infrequent consumers to develop dependence on alcohol (Arria et al., 2011) and are more likely to subsequently use illicit drugs and prescription drugs without medical supervision (Arria et al., 2010).

The present study had the overarching goal of determining whether transmissible risk for SUD in childhood covaries with age of onset of alcohol and cannabis use, leading to AUD and CUD. Notably, Kirisci, Tarter, Ridenour, Reynolds, and Vanyukov (2012) report that boys who progress to CUD obtain a high score on a quantitative measure of transmissible risk (Vanyukov et al., 2012) before consumption onset that remains stable with increasing age. Cannabis-using boys who do not develop CUD, in contrast, exhibit a lower score before cannabis initiation that further declines with age. Based on these findings, it is hypothesized that age at the time of first use of alcohol and cannabis mediates transmissible risk in childhood and AUD and CUD manifest by young adulthood. As shown in Figure 1, the theoretical model guiding this investigation, transmissible risk for SUD is posited to covary negatively with age at the time of first exposure to both compounds, presaging diagnosis of AUD and CUD.

Furthermore, whereas youths often begin consuming alcohol before initiating cannabis use, the factors underlying this order remain controversial. Within the framework of the gateway hypothesis, a gateway drug is thought to promote the initiation of consumption of other substances, which, in aggregate, results in a sequence of drugs theorized to reflect a developmental process (Kandel & Yamaguchi, 1999). An alternative competing model asserts that the same general liability to addiction, albeit varying in magnitude, underlies consumption of all abusable compounds (Vanyukov, Kirisci, et al., 2003; Vanyukov, Tarter, et al., 2003; Vanyukov et al., 2012). Because youths who begin consumption with cannabis bypass alcohol, which is often more available, legal (for adults), and less severely sanctioned, it is also hypothesized that violation (cannabis use before alcohol) of the putative gateway sequence is associated with more severe transmissible risk in childhood. In view of recent research showing that deviant socialization mediates the association between transmissible risk in childhood and CUD in adulthood (Tarter et al., 2011), the hypothesis is therefore advanced that more severe transmissible liability increases the likelihood of skipping typical or "normative" experimentation with legal substances.

Confirmation of the two hypotheses advanced in this study informs etiology and potentially can improve prevention practice and effectiveness. Demonstrating that age at the time of onset of consumption of the most frequently used legal and illegal compounds is an indicator of their congenerous transmissible risk, leading to both types of SUD, underscores the importance of implementing intervention prior to first exposure to psychoactive compounds having abuse potential, including hypercaffeinated beverages, which are legally purchased and consumed by youths. In addition, showing that transmissible risk covaries negatively with age at the time of first use illustrates the need to temporally monitor risk magnitude in children for timely prevention. Furthermore, demonstrating greater transmissible risk in youths who initiate substance consumption with an illegal drug emphasizes the importance of aligning intervention intensity (“dose”) with severity of predisposing liability. Detecting vulnerable youth for timely prevention is an important public health concern, considering that habitual cannabis use impairs cognitive functioning, which does not fully recover with abstinence (Meier et al., 2012), and epidemiological data indicating that almost half the population of high school seniors have had lifetime exposure to this drug (Johnston et al., 2012).

Method

Subjects

The participants in this study were drawn from 775 families participating in a long-term longitudinal investigation directed at elucidating the etiology of SUD. Numerous studies conducted on this cohort have explored genetic, biochemical, physiological, psychological, and social contextual influences pertinent to the development of SUD between childhood and adulthood.¹ To qualify for participation in this study, the children (254 boys and 85 girls) were required to have had at least one lifetime experience with both alcohol and cannabis subsequent to the baseline assessment conducted when they were 10 to 12 years of age.

Recruitment procedures have been described in prior reports (Tarter, Kirisci, Ridenour, & Vanyukov, 2008; Tarter, Kirisci, Mezzich, et al., 2012). Briefly, the sample was accrued through biological fathers who qualified for SUD diagnosis consequent to use of an illegal drug (SUD+) or had no adult psychiatric disorder (SUD–). The SUD+ men were recruited using public service announcements, advertisements in print and electronic media, and random-digit dialing conducted by a market research firm. In addition, approximately 20% of the men were accrued through treatment facilities. Multiple recruitment methods were utilized, owing to the low prevalence in the population of SUD+ men who had a healthy 10- to 12-year-old biological child and current or past spouse (mother of the child) willing to participate in this long-term study. The children of the SUD– fathers were recruited using the same procedures, except that none of the men were obtained from treatment facilities. Follow-up evaluations of the children were conducted when they attained the ages of 12 to 14, 16, 19, and 22 years.

Attrition, defined as either a failure to locate the individual or his or her refusal to participate between baseline and the age-22 evaluation, was 23%. As shown in Table 1, participants who attrited were more likely to be female, have lower SES, and have lower Full Scale IQ, as measured by the Wechsler Intelligence Scale for Children WISC-III-R (1991). However, both retained and attrited participants scored in the normal range of intelligence. Importantly, the Transmissible Liability Index (TLI), the predictor variable, did not differ between retained and attrited participants. Frequency of externalizing diagnoses also did not

¹A complete list of publications can be found at www.pitt.edu/~cedar/publications.html.

differ between attrited and retained subjects. Thus, although the sample at the age-22 outcome evaluation contained proportionally fewer females and more participants having lower social status and intellectual capacity, their behavioral characteristics were not different from the attrited participants.

Instrumentation

TLI (age 10 to 12)—The TLI quantifies the component of SUD liability correlating across generations (Rice, Cloninger, & Reich, 1980; Vanyukov, Kirisci, et al., 2003; Vanyukov, Tarter, et al., 2003). It was derived from items contained in 24 psychological and psychiatric instruments administered to parents, teachers, and participants at the baseline (age 10 to 12) evaluation. Studies of twins have revealed that between 75% (Hicks, Iacono, & McGue, 2012) and 85% (Vanyukov et al., 2009) of TLI variance is genetic. At the outset, items were selected according to their face validity and assigned to constructs that have been documented in the empirical literature as associated with development of SUD (see Vanyukov, Tarter, et al., 2003, for review). Next, exploratory (EFA) and confirmatory (CFA) factor analysis documented construct validity of each factor. The items of constructs that discriminated children of SUD+ and SUD− fathers were then submitted to EFA and CFA. Lastly, item response theory (IRT) analysis was performed to obtain the threshold and discrimination parameter of each item and to derive the TLI. The items of the TLI, along with scoring criteria, informant, and reference source, are shown in the Appendix. As is shown, the TLI items are indicative of biopsychological self-regulation. Besides externalizing behaviors, the items pertain to thoughts about death during stress (#7), self-harm (#31), biting fingernails (#25), poor sleep (#32, 33), irregular appetite (#36), somatic distress (#29, 30), and adapting to new situations (#42, 43, 44). The diversity of these characteristics notwithstanding, the TLI has internal reliability exceeding .90 (Vanyukov et al., 2009). Moreover, it predicts SUD between childhood and adulthood (Kirisci et al., 2009) and all SUD categories in adults (Ridenour, Kirisci, Tarter, & Vanyukov, 2011).

Alcohol and cannabis use—The subjects were interviewed using the *Lifetime History of Alcohol Use* and *Lifetime Drug Use History* surveys (Center for Education and Drug Abuse Research, 1989a, 1989b) at each follow-up evaluation to document chronological age when alcohol and cannabis were consumed for the first time. The mean age of first alcohol and cannabis use was, respectively, 178.00 months ($SD = 25.03$) and 191.17 months ($SD = 28.64$), or 14.8 and 15.9 years, respectively, after birth.

Lifetime substance use—The self-report *Drug Use Chart* (Center for Education and Drug Abuse Research, 1989c) was completed at baseline and all follow-up evaluations. This checklist documents lifetime use of over 40 compounds having abuse potential.

AUD and CUD—The Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS) (Chambers et al., 1985) was administered when the participants were 10 to 12, 12 to 14, and 16 years of age. The Structured Clinical Interview for *DSM-III-R* (SCID; Spitzer, Williams, Gibbon, & First, 1990) was administered thereafter until age 22. The outcome variables, lifetime AUD and CUD (abuse or dependence), were present in 39.4% and 40.7% of the sample, respectively. This high rate of disorders is consistent with the high-risk family paradigm and the subject inclusion criterion requiring a history of consumption of alcohol and cannabis. The third edition of the *Diagnostic and Statistical Manual of Mental Disorders* (3rd ed., rev.; *DSM-III-R*; American Psychiatric Association, 1987) was used for diagnosis because this longitudinal project was initiated in 1989 prior to publication of the fourth edition of the *DSM* (text rev.; *DSM-IV-TR*; American Psychiatric Association, 2000).

Procedure

Written assent was obtained from the participants and written informed consent was obtained from the parents before commencing the research protocols. Beginning at age 18, the participants provided informed consent. Privacy was additionally protected by a certificate of confidentiality issued to the Center for Education and Drug Abuse Research by the National Institute on Drug Abuse. Once the youngster was deemed qualified to participate, an alcohol Breathalyzer test and urine screen were performed to ensure that the results were not confounded or biased by a substance-induced physiological state. A positive finding required rescheduling the participant. The measures were individually administered in sound-attenuating rooms in fixed order by experienced research associates. Following completion of each evaluation session, the participant was debriefed and compensated at the rate of approximately \$10/hr.

Statistical Analysis

At the outset, multiple logistic regression analysis was performed on the combined sample of children of SUD+ and SUD- parents to determine whether transmissible risk, respectively, predicts age of alcohol use and cannabis use as well as AUD and CUD. Mediation analysis was conducted to determine whether age of onset of alcohol and cannabis is a marker of transmissible risk for AUD and CUD. Significance of mediated paths was tested using Sobel's (1982) formula,

$$z = b_1 b_2 / \sqrt{b_1^2 \sigma_{b_1}^2 + b_2^2 \sigma_{b_2}^2},$$

where b_1 is the regression coefficient between the predictor and the mediator, b_2 is the regression coefficient between the mediator and dependent variables, and σ^2 is the square of the estimate of the standard error of the corresponding regression coefficient. Next, the common liability model was tested by examining whether age of alcohol use onset mediates the relationship between transmissible risk and CUD, and whether age of onset of cannabis use mediates the relationship between transmissible risk and AUD. A one-way ANOVA was then conducted to compare the magnitude of transmissible risk prior to substance use onset in youths who subsequently initiated alcohol use before and after first cannabis use, followed by Cox proportional hazard regression analysis to delineate the correspondence between TLI severity and age at the time of first alcohol and cannabis use. Furthermore, IRT methods were applied to the Drug Use Chart to delineate the probability of alcohol and cannabis use in relation to severity of overall substance use, taking into account 10 drug categories (alcohol, cannabis, crack/cocaine, opiates, amphetamines, sedatives, tobacco, hallucinogens, PCP, and inhalants; Kirisci, Vanyukov, Dunn, & Tarter, 2002). Item characteristic curves were derived to depict the probability of alcohol and cannabis use in relation to the person's overall severity of substance use. Lastly, it was determined whether the sequential order of alcohol use and cannabis use on a probability scale mediates the association of TLI with AUD and CUD.

Results

Both the TLI (OR = 1.32, $p = .02$, 95% CI [1.04, 1.69]) and age at the time of first alcohol use (OR = .78, $p < .001$, 95% CI [.68, .90]) predict AUD by age 22. Age at the time of first alcohol use mediates the association between TLI and AUD ($z = 2.23$, $p = .03$). Similarly, the TLI (OR = 1.59, $p < .001$, 95% CI [1.24, 2.05]) and age at the time of first cannabis consumption (OR = .85, $p < .001$, 95% CI [.79, .91]) predict CUD. Paralleling the results for alcohol, age at the time of first cannabis use mediates the association between TLI and CUD

($z = 3.06$, $p = .002$). These findings demonstrate that age of onset of alcohol and cannabis use presaging AUD and CUD is an indicator of transmissible risk for each disorder.

Furthermore, age at the time of first alcohol use predicts CUD ($OR = .88$, $p = .04$, 95% CI [.78, .99]) as well as mediates the association between TLI and CUD ($z = 2.17$, $p = .03$). Complementing this finding, age at the time of first cannabis use predicts AUD ($OR = .89$, $p < .001$, 95% CI [.83, .96]) and mediates the association between TLI and AUD ($z = 2.27$, $p = .02$). In effect, age at the time of first use of alcohol or cannabis is an indicator of nonspecific transmissible risk for both AUD and CUD.

Table 2 presents the mean TLI scores of participants, clustered according to temporal order of alcohol and cannabis use initiation. As illustrated, the most severe TLI scores were obtained by youths whose first substance was cannabis. Indeed, the TLI score is 7 times higher than youths whose consumption began with alcohol and 1.5 times higher in youths who began using alcohol and cannabis during the same month. Complementing these findings, the hazard rate related to age of first alcohol use increases by 11% ($HR = 1.11$, $p = .04$, 95% CI [1.002, 1.23]) for each standard deviation increase in TLI severity compared with 24% for cannabis use ($HR = 1.24$, $p = .007$, 95% CI [1.06, 1.45]). In practical terms, each standard deviation increase in TLI corresponds to lowering the age of alcohol use onset by 3.2 months (95% CI [-5.47, .45]) and cannabis use onset by 4.6 months (95% CI [-7.40, -1.69]).

Figure 2 depicts the item characteristic curves, showing the relationship between sequential order of alcohol and cannabis use initiation in relation to overall substance use involvement. As illustrated, alcohol use was more likely than cannabis use across all levels of severity of substance use involvement. As expected, the probability of alcohol use is related to AUD risk ($OR = 3.65$, $p < .001$, 95% CI [2.41, 5.54]) and the probability of cannabis use is related to CUD risk ($OR = 2.49$, $p < .001$, 95% CI [1.75, 3.52]). More importantly, however, the TLI predicts the probability of both alcohol use ($z = 2.94$, $p = .004$) and cannabis use ($z = 2.92$, $p = .004$). Furthermore, probability of alcohol use mediates the relationship between TLI and AUD ($z = 6.75$, $p < .001$) and cannabis use mediates the relationship between TLI and CUD ($z = 6.28$, $p < .001$). Confirmation of common liability was further obtained by the finding that probability of alcohol use predicts CUD ($OR = 2.75$, $p < .001$, 95% CI [1.89, 4.01]) and probability of cannabis use predicts AUD ($OR = 3.29$, $p < .001$, 95% CI [2.23, 4.85]). Indeed, even after taking into account differences in probability of consumption, alcohol use mediates the association between TLI and CUD ($z = 6.65$, $p < .001$) and cannabis use mediates the association between TLI and AUD ($z = 6.46$, $p < .001$).

Discussion

It is estimated that minors consume 16% of alcohol beverages sold in the United States (Miller, Levy, Spicer, & Taylor, 2006). The characteristics of the substantial portion of the population who subsequently develop AUD remain to be delineated. In view of the finding that development of AUD at a young age has high heritability (Chen et al., 2011; Cloninger et al., 1981), and evidence pointing to strong genetic correlation between liabilities for different SUDs (Kendler et al., 2007), it was posited that the score on a continuous measure of transmissible risk predicts age at the time of first exposure to alcohol and cannabis. In addition, it was hypothesized that greater transmissible risk is associated with increased likelihood of initiating substance consumption with cannabis. The results confirmed both hypotheses. Each standard deviation unit increase in the TLI is associated with the lowering of age at the time of alcohol initiation by 3.2 months and first cannabis use by 4.6 months. Furthermore, age at the time of first use of alcohol and cannabis mediates the relationship between transmissible risk and both AUD and CUD.

Youths who began consumption with cannabis scored 7 times higher on the TLI compared with youths whose first substance was alcohol. Thus, although transmissible liability is congenious to AUD and CUD, there is a marked difference in magnitude of risk among youths who begin substance use with cannabis. Considering that cannabis use is universally proscribed, whereas alcohol is proscribed for only minors, consumption of this illegal drug requires a more severe manifestation of the liability consistent with the finding that nonnormative socialization mediates the association between transmissible risk in childhood and CUD in adulthood (Tarter et al., 2011).

The finding that 23% of this sample used cannabis before alcohol contrasts with the widely held belief that the sequence of drug initiation invariably proceeds from legal to illegal drugs. Although this is the cornerstone assumption in the gateway hypothesis (Kandel & Yamaguchi, 1999), it is important to note that several studies have revealed that many youths begin using illegal drugs before legal drugs (Young et al., 1995; Golub & Johnson, 1994; Tarter et al., 2003). Furthermore, although order of initiation of different substances has garnered enormous interest, it is noteworthy that this variable does not improve prediction of SUD beyond transmissible liability (Tarter, Kirisci, Mezzich, et al., 2012).

The present findings have potentially important ramifications for prevention. Because liability phenotype measured by the TLI covaries with age of substance use onset, prevention should be directed at reducing motivation to commence consumption. Accordingly, five age-specific computer adaptive versions of the TLI have been validated to monitor risk status during development (Kirisci et al., 2012), thereby enabling identifying vulnerable youths for timely individualized prevention (Tarter, Kirisci, Ridenour, & Bogen, 2012).

This study has several limitations that warrant consideration. It is important to note that because the family high-risk paradigm was employed, the findings may not be representative of the general population. It is noteworthy, however, that results obtained in previous studies conducted on this sample concur with findings obtained by others pertaining to genetic, neurophysiological, and psychological antecedents of SUD (Habeych, Charles, Sciabassi, Kirisci, & Tarter, 2005; Vanyukov et al., 2004; Feske et al., 2008). In addition, it is important to point out that the outcomes in this study were confined to AUD and CUD. Furthermore, attrition occurred more frequently in females, the low SES segment of the sample, and participants having lower IQ (albeit still in the normal range). Hence, an attrition bias cannot be entirely ruled out. Lastly, AUD and CUD were evaluated only up to age 22. Whereas epidemiological (Le Strat, Grant, Ramoz, & Gorwood, 2010) and genetic (Chen et al., 2011) research indicates that age 22 is the optimum cutoff for manifesting the early onset variant of SUD, usually referred to as Type II (Cloninger et al., 1981) or Type B (Babor et al., 1992), the conclusions drawn herein may not be relevant to adult onset SUD.

In conclusion, the results obtained in this study demonstrate that magnitude of transmissible risk measured on a continuous scale covaries negatively with age at the time of first alcohol and cannabis use presaging AUD and CUD. The observation that age at the time of first substance use also fully mediates the association of transmissible risk and development of both disorders indicates that onset age is an indicator of magnitude of the individual's vulnerability predisposing to SUD. These findings underscore the importance of directing prevention at high-risk youths prior to first substance exposure.

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References

- Achenbach, TM. Manual for the Teacher's Report Form and 1991 profile. Burlington, VT: University of Vermont Department of Psychiatry; 1991.
- Achenbach, TM.; Edelbrock, C. Manual for the Child Behavior Checklist and Revised Child Behavior Profile. Burlington, VT: T. M. Achenbach; 1983.
- American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 3. Washington, DC: Author; 1987. rev
- American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4. Washington, DC: Author; 2000. text rev
- Arria AM, Caldeira KM, Kasperski SJ, O'Grady KE, Vincent KB, Griffiths RR, Wish ED. Increased alcohol consumption, nonmedical prescription drug use, and illicit drug use are associated with energy drink consumption among college students. *Journal of Addiction Medicine*. 2010; 4:74–80.10.1097/ADM.0b013e3181aa8dd4 [PubMed: 20729975]
- Arria AM, Caldeira KM, Kasperski SJ, Vincent KB, Griffiths RR, O'Grady KE. Energy drink consumption and increased risk for alcohol dependence. *Alcoholism: Clinical and Experimental Research*. 2011; 35:365–375.10.1111/j.1530-0277.2010.01352.x
- Babor TF, Hofmann M, DelBoca FK, Hesselbroch V, Meyer RE, Dolinsky ZS, Rounsaville B. Types of alcoholics, I. Evidence for an empirically derived typology based on indicators of vulnerability and severity. *Archives of General Psychiatry*. 1992; 49:599–608.10.1001/archpsyc.1992.01820080007002 [PubMed: 1637250]
- Center for Education and Drug Abuse Research. Unpublished manuscript. Pittsburgh, PA: Author; 1989a. Drug Use Chart.
- Center for Education and Drug Abuse Research. Unpublished manuscript. Pittsburgh, PA: Author; 1989b. Lifetime history of alcohol use.
- Center for Education and Drug Abuse Research. Unpublished manuscript. Pittsburgh, PA: Author; 1989c. Lifetime history of drug use.
- Chambers WJ, Puig-Antich J, Hirsch M, Paez P, Ambrosini PJ, Tabrizi MA, Davies M. The assessment of affective disorders in children and adolescents by semistructured interview. Test–retest reliability of the schedule for affective disorders and schizophrenia for school age children, present episode version. *Archives of General Psychiatry*. 1985; 42:696–702.10.1001/archpsyc.1985.01790300064008 [PubMed: 4015311]
- Chen YC, Prescott CA, Walsh D, Patterson DG, Riley BP, Kendler K, Kuo PH. Different phenotypic and genotypic presentations in alcohol dependence: Age at onset matters. *Journal of Studies on Alcohol and Drugs*. 2011; 72:752–762. [PubMed: 21906503]
- Cloninger CR, Bohman M, Sigvardsson S. Inheritance of alcohol abuse: Cross-fostering analysis of adopted men. *Archives of General Psychiatry*. 1981; 38:861–868.10.1001/archpsyc.1981.01780330019001 [PubMed: 7259422]
- Conners CK. A teacher rating scale for use in drug studies with children. *American Journal of Psychiatry*. 1969; 126:152–156.
- Feske U, Tarter R, Kirisci L, Gao Z, Reynolds M, Vanyukov M. Peer environment mediates parental history and individual risk in the etiology of cannabis use disorder in boys: A 10-year prospective study. *American Journal of Drug and Alcohol Abuse*. 2008; 34:307–320.10.1080/00952990802013631 [PubMed: 18428073]
- Golub A, Johnson B. The shifting importance of alcohol and marijuana as gateway substances among serious drug abusers. *Journal of Studies on Alcohol*. 1994; 55:607–614. [PubMed: 7990471]
- Habeych M, Charles P, Scabassi R, Kirisci L, Tarter R. Direct and mediated association between P300 amplitude in childhood and SUD outcome by young adulthood. *Biological Psychiatry*. 2005; 57:76–82.10.1016/j.biopsych.2004.09.028 [PubMed: 15607303]
- Hicks BM, Iacono WG, McGue M. Index of the transmissible common liability to addiction: Heritability and prospective associations with substance abuse and related outcomes. *Drug and Alcohol Dependence*. 2012; 123:S18–S23.10.1016/j.drugalcdep.2011.12.017 [PubMed: 22245078]

- Hingson RW, Heeren T, Winter MR. Age at drinking onset and alcohol dependence: Age at onset, duration, and severity. *Archives of Pediatric and Adolescent Medicine*. 2006; 160:739–746.10.1001/archpedi.160.7.739
- Johnston, LD.; O'Malley, PM.; Bachman, JG.; Schulenberg, JE. Monitoring the Future national results on adolescent drug use: Overview of key findings, 2011. Ann Arbor, MI: Institute for Social Research, University of Michigan; 2012.
- Kandel, D.; Yamaguchi, K. Developmental stages of involvement in substance use. In: Ott, P.; Tarter, R.; Ammerman, R., editors. *Sourcebook on substance abuse: Etiology, epidemiology, assessment, and treatment*. Boston, MA: Allyn & Bacon; 1999. p. 50-74.
- Kendler KS, Myers J, Prescott CA. Specificity of genetic and environmental risk factors for symptoms of cannabis, cocaine, alcohol, caffeine, and nicotine dependence. *Archives of General Psychiatry*. 2007; 64:1313–1320.10.1176/appi.ajp.160.4.687 [PubMed: 17984400]
- Kirisci L, Tarter R, Mezzich A, Ridenour T, Reynolds M, Vanyukov M. Prediction of cannabis use between childhood and young adulthood: Clarifying the phenotype and environment. *The American Journal on Addictions*. 2009; 18:36–47.10.1080/10550490802408829 [PubMed: 19219664]
- Kirisci L, Tarter R, Reynolds M, Ridenour T, Stone C, Vanyukov M. Computer adaptive testing of liability to addiction: Identifying individuals at risk. *Drug and Alcohol Dependence*. 2012; 123:S79–S86.10.1016/j.drugalcdep.2012.01.016 [PubMed: 22391133]
- Kirisci, L.; Tarter, R.; Ridenour, T.; Reynolds, M.; Vanyukov, M. Timing of first exposure and transmissible risk between childhood and adulthood. 2012. Which cannabis users will develop cannabis use disorder?. Manuscript submitted for publication
- Kirisci L, Vanyukov M, Dunn M, Tarter RE. Item response theory modeling of substance use: An index based on 10 drug categories. *Psychology of Addictive Behaviors*. 2002; 16:290–298.10.1037/0893-164X.16.4.290 [PubMed: 12503901]
- Lerner RM, Palermo M, Spiro A, Nesselroade AL. Assessing the dimensions of temperamental individuality across the life span: The dimensions of temperament survey. *Child Development*. 1982; 53:149–159.10.2307/1129647
- Le Strat Y, Grant BF, Ramoz N, Gorwood P. A new definition of early age at onset in alcohol dependence. *Drug and Alcohol Dependence*. 2010; 108:43–48.10.1016/j.drugalcdep.2009.11.011 [PubMed: 20018459]
- Lin JC, Karno MP, Grella CE, Warda U, Liao DH, Hu P, Moore AA. Alcohol, tobacco, and nonmedical drug use disorders in U.S. adults aged 65 years and older: Data from the 2001–2002 National Epidemiological Survey of Alcohol and Related Conditions. *The American Journal of Geriatric Psychiatry*. 2011; 19:292–299.10.1097/JGP.0b013e3181e898b4 [PubMed: 20808122]
- Meier MH, Caspi A, Ambler A, Harrington H-L, Houts R, Keefe RSE, Moffitt TE. Persistent cannabis users show neuropsychological decline from childhood to midlife. *Proceedings of the National Academy of Sciences of the United States of America*. 2012; 109:E2657–E2664.10.1073/pnas.1206820109 [PubMed: 22927402]
- Mezzich AC, Tarter RE, Giancola PR, Kirisci L. The dysregulation inventory: A new scale to assess the risk for substance use disorder. *Journal of Child & Adolescent Substance Abuse*. 2001; 10:35–43.10.1300/J029v10n04_04
- Miller TR, Levy DT, Spicer RS, Taylor DM. Societal costs of underage drinking. *Journal of Studies on Alcohol*. 2006; 67:519–528. [PubMed: 16736071]
- Orvaschel, H.; Puig-Antich, J. Schedule for Affective Disorder and Schizophrenia for School Age Children, epidemiological version: Kiddie-SADS-E (K-SADS-E). 4. Pittsburgh, PA: Western Psychiatric Institute and Clinic; 1987.
- Pelham WE Jr, Gnagy EM, Greenslade KE, Milich R. Teacher ratings of DSM-III-R symptoms for the disruptive behavior disorders. *Journal of the American Academy of Child and Adolescent Psychiatry*. 1992; 31:210–218.10.1097/00004583-199203000-00006 [PubMed: 1564021]
- Pitkänen T, Lyyra AL, Pulkkinen L. Age of onset of drinking and the use of alcohol in adulthood: A follow-up study from age 8 – 42 for females and males. *Addiction*. 2005; 100:652–661.10.1111/j.1360-0443.2005.01053.x [PubMed: 15847623]

- Rice J, Cloninger C, Reich T. General causal models for sex differences and the familial transmission of the multi-factorial traits: An application to human spatial visualizing ability. *Social Biology*. 1980; 26:36–47. [PubMed: 7292035]
- Ridenour TA, Kirisci L, Tarter RE, Vanyukov MM. Could a continuous measure of individual transmissible risk be useful in clinical assessment of substance use disorder? Findings from the National Epidemiological Survey on Alcohol and Related Conditions. *Drug and Alcohol Dependence*. 2011; 119:10–17.10.1016/j.drugalcdep.2011.05.018 [PubMed: 21715106]
- Sobel, ME. Asymptotic confidence intervals for indirect effects in structural equation models. In: Leinhardt, S., editor. *Sociological methodology*. San Francisco, CA: Jossey-Bass; 1982. p. 290-312.
- Spitzer, RL.; Williams, JBW.; Gibbon, M.; First, MB. User's guide for the structured clinical interview for DSM–III–R. Washington, DC: American Psychiatric Association; 1990.
- Tarter RE, Fishbein D, Kirisci L, Mezzich A, Ridenour T, Vanyukov M. Deviant socialization mediates transmissible and contextual risk for cannabis use disorder development: A prospective study. *Addiction*. 2011; 106:1301–1308.10.1111/j.1360-0443.2011.03401.x [PubMed: 21320228]
- Tarter RE, Kirisci L, Mezzich A, Cornelius J, Pajer K, Vanyukov M, Clark D. Neurobehavior disinhibition in childhood predicts early age onset substance disorder. *American Journal of Psychiatry*. 2003; 160:1078–1085.10.1176/appi.ajp.160.6.1078 [PubMed: 12777265]
- Tarter RE, Kirisci L, Mezzich A, Ridenour T, Fishbein D, Vanyukov M. Does the “gateway” sequence increase prediction of cannabis use disorder development beyond deviant socialization? Implications for procedure and policy. *Drug and Alcohol Dependence*. 2012; 123:S72–S78.10.1016/j.drugalcdep.2012.01.015 [PubMed: 22365896]
- Tarter RE, Kirisci L, Ridenour T, Bogen D. Application of person-centered medicine in addiction. *The International Journal of Person Centered Medicine*. 2012; 2:240–249.
- Tarter RE, Kirisci L, Ridenour T, Vanyukov M. Prediction of substance use disorder between childhood and adulthood using the internalizing and externalizing scales of the CBCL. *Journal of Psychopathology and Behavioral Assessment*. 2008; 30:272–278.10.1007/s10862-008-9083-3
- Tarter RE, McBride H, Buonpane N, Schneider D. Differentiation of alcoholics: Childhood history of minimal brain dysfunction, family history and drinking pattern. *Archives of General Psychiatry*. 1997; 34:761–768.10.1001/archpsyc.1977.01770190023002 [PubMed: 879973]
- Vanyukov MM, Kirisci L, Moss L, Tarter RE, Reynolds MD, Maher BS, Clark DB. Measurement of the risk for substance use disorders. Phenotypic and genetic analysis of an index of common liability. *Behavior Genetics*. 2009; 39:233–244.10.1007/s10519-009-9269-9 [PubMed: 19377872]
- Vanyukov MM, Kirisci L, Tarter R, Simkevitz H, Kirillova G, Maher B, Clark D. Liability to substance use disorders: 2. A measurement approach. *Neuroscience and Biobehavioral Reviews*. 2003; 27:517–526.10.1016/j.neubiorev.2003.08.003 [PubMed: 14599433]
- Vanyukov MM, Maher BS, Devlin B, Tarter RE, Kirillova GP, Yu L-M, Ferrell RE. Haplotypes of the monoamine oxidase genes and the risk for substance use disorders. *American Journal of Medical Genetics: Part B: Neuropsychiatric Genetics*. 2004; 125B:120–125.10.1002/ajmg.b.20105
- Vanyukov MM, Tarter RE, Kirillova GP, Kirisci L, Reynolds MD, Kreek MJ, Ridenour TA. Common liability to addiction and “gateway hypothesis”: Theoretical, empirical, and evolutionary perspective. *Drug and Alcohol Dependence*. 2012; 123:S3–S17. The URL is <http://dx.doi.org/10.1016/j.drugalcdep.2011.12.018>. 10.1016/j.drugalcdep.2011.12.018 [PubMed: 22261179]
- Vanyukov MM, Tarter RE, Kirisci L, Kirillova GP, Maher BS, Clark DB. Liability to substance use disorders: 1. Common mechanisms and manifestations. *Neuroscience and Biobehavior Review*. 2003; 27:507–515.10.1016/j.drugalcdep.2011.12.018
- Wechsler, D. Wechsler Intelligence Scale for Children. 3. The Psychological Corporation; 1991. Manual
- Young SE, Mikulich S, Goodwin M, Hardy J, Martin C, Zoccolillo M, Crowley T. Treated delinquent boys' substance use: Onset, pattern, relationship to conduct and mood disorders. *Drug and Alcohol Dependence*. 1995; 37:149–162.10.1016/0376-8716(94)01069-W [PubMed: 7758404]

Figure 1.
Theoretical model of age of alcohol and cannabis use onset mediates the association of transmissible risk in childhood and development of alcohol and cannabis disorders.

Figure 2. Item characteristic curves of alcohol and cannabis use depicting probability of consumption in relation to increasing severity of overall substance use.

Table 1

Baseline (Age 10 –12) Characteristics of Retained and Attrited Segments of the Sample

	Retained (n = 261)		Attrited (n = 78)		F	p
	Mean	SD	Mean	SD		
School grade	4.62	1.10	4.63	.91	.01	.93
Socioeconomic status ^a	41.37	13.53	36.77	14.00	6.83	.009
Full Scale IQ	107.36	16.43	100.19	14.87	11.91	.001
TLI (z-score)	.02	1.05	.14	.95	.79	.37

	n	%	n	%	χ^2	p
Male	188	72	66	84.6	5.06	.02
Female	73	28	12	15.4		
White	187	71	54	69.2	.17	.68
Black	74	29	24	30.8		
Conduct disorder	8	3.1	5	6.4	1.82	.18
ADHD	35	13.4	13	16.7	.52	.47
Opposition defiant disorder	32	12.3	11	14.1	.18	.67

Note. ADHD = attention-deficit hyperactivity disorder; TLI = Transmissible Liability Index.

^aHollingshead two-factor index.

Table 2

Transmissible Liability Index at Age 10 –12 in Relation to Subsequent Order of Substance Use Initiation

	Mean (SD)
Alcohol use preceded cannabis use ($n = 191$)	-.03 (.99)
Cannabis use preceded alcohol use ($n = 78$)	.18 (1.07)
Cannabis and alcohol use initiated at the same time ($n = 70$)	.12 (1.06)

Appendix

Items Comprising the Transmissible Liability Index at Age 10–12

Item	Response categories	Respondent	Source		
Characteristics of child prior to age 13					
1. Lying	1 = Yes	Parent	Childhood History Questionnaire (Tarter, McBride, Buonpane, & Schneider, 1997)		
2. Stealing	2 = No				
3. Impulsive					
4. Did you often annoy people on purpose to get even?	0 = No 1 = Yes	Child	K-SADS-E (Orvaschel & Puig-Antich, 1987)		
5. Did you often do things to annoy people like grabbing another child's hat?					
6. Did you blurt out answers to questions before they had been completed or did you get into trouble because you would rush into things without thinking?					
7. Were things so bad that you were thinking a lot about death or that you would be better off dead?		Parent	K-SADS-E (Orvaschel & Puig-Antich, 1987)		
8. Did he often do things to annoy people like grabbing another child's hat?	0 = No 1 = Yes				
9. Did he often annoy people on purpose to get even?					
10. Did he have difficulty staying in line in the supermarket or waiting for his turn while he was playing with other children?		Child	Dysregulation Inventory (Mezzich, Tarter, Giancola, & Kirisci, 2001)		
11. Did he blurt out answers to questions before they had been completed or did he get into trouble because he would rush into things without thinking?					
12. Did he get into trouble a lot for talking out of turn in school or talking without the teacher calling on him or for bothering people?					
13. Did he get into trouble because he would do things without thinking about them first, for example running into the street without looking?		Teacher	Conners's teacher questionnaire (Conners, 1969)		
14. I interrupt on people when they are speaking.	0 = Never true 1 = Occasionally true				
15. He/she interrupts on people when they are speaking.	2 = Mostly true 3 = Always true				
16. Excitable, impulsive best describes the child	0 = Not at all 1 = Just a little 2 = Pretty much 3 = Very much	Teacher	Disruptive Behavior Disorders Scale (Pelham, Gnagy, Greenslade, 1992)		
The behavior of the child is best described as ...					
17. ... often engages in physically dangerous activities without considering possible consequences (not for the purpose of thrill-seeking), e.g. runs into street without looking	0 = Not at all 1 = Just a little 2 = Pretty much 3 = Very much				
18. ... has difficulty awaiting turn in games or group situations		Parent	Child Behavior Checklist (Achenbach & Edelbrock, 1983)		
19. ... often blurts out answers to questions before they have been completed					
20. ... often interrupts or intrudes on others, e.g., butts into other children's games					
Describes your child now or within the past 6 months ...					
21. Impulsive or acts without thinking	0 = Not true 1 = Somewhat or sometimes true	Parent			

Item	Response categories	Respondent	Source
22. Destroys things belonging to his/her family or others	2 = Very true or often true		
23. Disobedient at school			
24. Steals at home			
25. Bites fingernails			
26. Picks nose, skin or other parts or body			
Describes the pupil now or within the past 2 months ...			
27. Impulsive or acts without thinking	0 = Not true 1 = Somewhat or sometimes true	Teacher	Teacher's Report Form of the Child Behavior Checklist (Achenbach, 1991)
28. Talks out of turn	2 = Very true or often true		
29. Aches or pains (not stomach or headaches, without known medical causes)			
30. Headaches (without known medical causes)			
31. Deliberately harms self or attempts suicide			
32. I move a great deal in my sleep.	1 = Usually false 2 = More false than true	Child	Dimensions of Temperament Survey-Revised (Lerner, Palermo, Spiro, & Nesselroade, 1982)
33. I don't move around much at all in my sleep. (reverse-coded)	3 = More true than false 4 = Usually true		
34. I get hungry about the same time each day. (reverse-coded)			
35. I usually eat the same amount each day. (reverse-coded)			
36. I eat about the same amount at supper from day to day. (reverse- coded)			
37. My appetite seems to stay the same day after day. (reverse-coded)			
38. My child moves a great deal in his/her sleep.	1 = Usually false 2 = More false than true	Parent	Dimensions of Temperament Survey-Revised (Lerner, Palermo, Spiro, & Nesselroade, 1982)
39. In the morning, my child is still in the same place as he/she was when he/she fell asleep. (reverse-coded)	3 = More true than false 4 = Usually true		
40. My child doesn't move around much at all in his/her sleep. (reverse-coded)			
41. It takes my child a long time to get used to a new thing in the home. (reverse-coded)			
42. It takes my child a long time to adjust to new schedules. (reverse- coded)			
43. Changes in plans make my child restless. (reverse-coded)			
44. My child resists changes in routine. (reverse-coded)			
45. Did you skip classes or school without an excuse?	1 = Yes 2 = No	Child	K-SADS-E (Orvaschel & Puig-Antich, 1987)

Note. K-SADS-E = Kiddie-Schedule for Affective Disorder and Schizophrenia-Epidemiological Version.