7

Trajectories of Tobacco Use from Adolescence to Adulthood: Are the Most Informative Phenotypes Tobacco Specific?

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The relationship between developmental trajectories of smoking and other substance use may provide clues for a genetic vulnerability to nicotine dependence, which, in turn, may inform smoking phenotypes for genetic analysis. This chapter examines the evidence base for linkages between substance-use trajectories as well as the results of an original empirical study examining smoking and alcohol use over time across a cohort group of male twins from Finland. Areas discussed include

- *Common versus specific liability to substance-use disorders*
- *Covariate relationships between smoking and other substance-abuse trajectories*
- *Conjoint trajectories of smoking and other substances, including alcohol, marijuana, and polysubstance use*

Available evidence points to the possible existence of general underlying factors for substance-use and tobacco-specific pathways, both of which may link to genetic phenotypes. Moreover, the cohort study examined in this chapter supports the existence of heritable genetic traits for general substance-abuse trajectories on the basis of comparisons between monozygotic and dizygotic twins. The link between such trajectories and a genetic basis for nicotine dependence remains an area for further study.

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Introduction

As described in chapter 5 of this volume, an unresolved question is whether phenotypic information is best conceptualized as tobacco specific or as describing a broader spectrum of substance use or disinhibition. Accordingly, the goal of this chapter is to examine the utility of considering joint trajectories of tobacco and other substance use, drawing on trajectories of tobacco and alcohol use as an empirical example. Moreover, as discussed in chapters 5 and 6, almost no empirical work exists on the heritability of these trajectories. After a review of the literature, joint trajectories of alcohol and tobacco use with a genetically informative (twin) sample are characterized, and the extent to which these trajectories overlap across substance is described. Findings from the empirical example will have implications regarding the extent to which trajectories are unique to tobacco or whether they can be conceptualized as general pathways of substance use.

Resolving the question of tobacco-specific phenotypes versus general substance use is critical for identifying key etiological and maintaining processes, developing theory-based prevention programs, and allocating resources for prevention activities. Broad, substance-general phenotypes could reflect underlying shared individual vulnerability factors (e.g., affective dysregulation, impaired self-control, reward seeking, conventionality) or common environmental influences (peer affiliation, substance availability) on use. Individual and environmental factors might act alone or may operate in combination for promoting or inhibiting multiple forms of substance use. In contrast, tobacco-specific phenotypes could reflect individual differences in sensitivity to the rewarding and punishing effects of nicotine (and associated variables inherent in smoking) alone and in interaction with cultural variables and tobacco control and prevention policies.

Importance of Studying Substance-Use Comorbidity

A wealth of literature supports the high concurrent use of nicotine with other substances. This is particularly true for cigarette smoking and alcohol use,[1–4] but also for use of tobacco with marijuana and other drugs.[5–7] During adolescence, smoking is highly associated with use of other substances such as alcohol, marijuana, and other drugs,[8–17] and tobacco use often precedes both alcohol-use[18] and substance-use disorders, including alcohol dependence.[19]

By using a nationally representative sample, onset and persistence of drinking and smoking in adolescence were each predicted by prior use of the other substance.[20] This smoking-drinking association persists into emerging adulthood.[21–23] One nationally representative college student sample revealed that over 98% of smokers reported prior-year drinking, and those who initiated regular smoking at an early age were at greatest risk for drinking. Likewise, current smoking and regular smoking were overrepresented among those who drank, particularly at high or risky levels.[24] Compared with nonsmokers, young adults with tobacco dependence and nondependent smokers had increased odds of being diagnosed with an alcohol or illicit drug disorder.[25]

The health consequences of tobacco use in conjunction with other substance use can be severe. Concurrent use of tobacco and alcohol acts synergistically to produce greater health risks than expected from the additive effects of each substance,[2] including elevated rates of esophageal,[26,27] laryngeal,[28–30] and oral cancers.[29,31,32]

Although the case for considering tobacco use in conjunction with other substance use for estimating health risks

(i.e., consequences) is now well established, consideration of tobacco use in the context of other substance use may be just as important for understanding etiological processes. Extant research has suggested several possible mechanisms underlying substance-use comorbidity. Directional (perhaps causal) associations include cross-tolerance and cueing as well as reciprocal antagonism; for example, individuals may use nicotine to counteract alcohol's debilitating effects on cognitive skills.[33,34]

Alternatively, a common-vulnerability model suggests that different substances share important third-variable precursors and hence are likely to co-occur. Using prospective data, Jackson and colleagues[35] demonstrated that the prospective association between tobacco- and alcohol-use disorders could be explained by a general traitlike tendency to use both substances as opposed to directional associations between the two. Such underlying tendencies to use both substances appear

Phenotypes Based on Comorbidity and Course

Comorbidity has traditionally been viewed as a cross-sectional phenomenon—that is, the existence of two or more conditions occurring at a single point in time (even when sequencing information is used to classify one condition as "primary" and the comorbid condition as "secondary."[a] Implicit in the traditional approach is that each comorbid condition is adequately characterized as a static entity. Subsequent data (described elsewhere in this chapter), however, emphasize the importance of the course of single disorders or conditions, suggesting that comorbidity should be viewed in the context of the longitudinal course of each co-occurring condition. Despite the surge of longitudinal research on comorbidity, however, "too little attention has been given to the implications of diagnostic course…both singly and across related disorders."[b(p.956)]

Although the explicit diagnostic criteria sets introduced in the third edition of the *Diagnostic and Statistical Manual of Mental Disorders* and subsequent revisions[c,d,e] represent a major advance in psychiatric phenotype definition by rejuvenating the Kraepelinian approach to diagnosis, these criteria represent only a partial embrace of a Kraepelinian approach that equally emphasized syndrome description by using specific behavioral indicators and longitudinal course.[b] To a large extent, formal diagnostic nosology has not kept up with either developmental theory or data that highlight the importance of considering both longitudinal course and co-occurring comorbidity as informative phenotypes. Corresponding (e.g., parallel) courses suggest similar developmental timing of use across substances. Developmental transitions such as change in living situation or attainment of traditional roles associated with career and family may exert common influence on use of different substances. Understanding the extent to which pattern of use of different substances overlap can provide the foundation for understanding factors contributing to substance use, abuse, and dependence and can suggest the existence of particular subtypes that may benefit from targeted prevention or treatment efforts.

[a]Schuckit, M. A., R. M. Anthenelli, K. K. Bucholz, V. M. Hesselbrock, and J. Tipp. 1995. The time course of development of alcohol-related problems in men and women. *Journal of Studies on Alcohol* 56 (2): 218–25.

[b]Widiger, T. A., and L. A. Clark. 2000. Toward DSM-V and the classification of psychopathology. *Psychological Bulletin* 126 (6): 946–63.

[c]American Psychiatric Association. 1980. *Diagnostic and Statistical Manual of Mental Disorders: DSM III.* 3rd ed. Washington, DC: American Psychiatric Association.

[d]American Psychiatric Association. 1987. *Diagnostic and Statistical Manual of Mental Disorders: DSM-III-R.* 3rd rev. ed. Washington, DC: American Psychiatric Association.

[e]American Psychiatric Association. 1994. *Diagnostic and Statistical Manual of Mental Disorders: DSM-IV.* 4th ed. Washington, DC: American Psychiatric Association.

to be, at least partially, genetic in origin. Given the high statistical association between tobacco and alcohol use and the finding that there appears to be a shared, genetically transmitted vulnerability to use both substances, it is possible and perhaps even likely that the most informative smoking phenotypes for genetic analysis will be those that simultaneously consider smoking and other substance use as associated features.

Common Versus Specific Liability to Substance-Use Disorders

Models Supporting a Common Underlying Substance-Use Factor

An influential model of substance use—the gateway theory—suggests that use of tobacco, alcohol, and drugs follows a progressive sequence of involvement from licit to illicit substances. In general, the sequence starts with use of alcohol and/or tobacco products, followed by marijuana use, proceeding to other illicit drug use (see Kandel[36] for a review). Thus, the idea that tobacco use is comorbid with use of other substances is refined whereby tobacco serves as a "gateway" to use of other drugs; that is, smoking is necessary but not sufficient for subsequent substance use. This sequencing is robust to gender, ethnicity/culture, and age of initiation, and has been demonstrated in numerous cross-sectional and prospective analytic approaches, including prevention trials.[36] Research demonstrating that early smoking[18,37–39] leads to subsequent alcohol and drug use also supports the gateway theory. However, some research has led to conclusions that a common-factor model based on propensity and opportunity to use substances serves as a more parsimonious alternative.[40]

In contrast to the gateway theory, a body of research suggests that the associations among smoking, drinking, and marijuana and other substance use are a function of a common factor of substance-use vulnerability. This idea has received attention from various camps, initially by Jessor and Jessor in their problem behavior theory (PBT).[41] PBT conceptualizes substance use as one of a number of behaviors (also including delinquency and precocious sexual activity) associated with a deviant lifestyle in rejection of the conventional values of society. This theory stands up to replication using different samples[42,43] and long-term follow-up.[44] Applications of this theory show robust support for PBT.[45,46]

A number of researchers have added to the evidence that a common factor underlies substance use and other problem behaviors. A body of studies by Krueger and colleagues using both quantitative[47,48] and behavior-genetic[48,49] approaches support a common externalizing dimension underlying substance dependence, antisocial behaviors, and a disinhibited personality. This work, however, only considers alcohol, marijuana, and other drug dependence; information regarding the degree to which smoking loads on a common externalizing factor is lacking. Consistent with the work by these authors, McGue and colleagues suggest that a common trait of disinhibition underlies use of alcohol, tobacco, and illicit drugs as well as other problem behaviors.[50,51] Supporting this idea, indices of behavioral undercontrol (e.g., constraint, novelty seeking, psychoticism,[52,53] as well as conduct disorder and attention deficit hyperactivity disorder [ADHD][54,55] increase the risk of alcohol, tobacco, and marijuana use in adolescents. King and colleagues[56] demonstrated prospective relationships between childhood externalizing disorders (conduct disorder, oppositional defiant disorder, ADHD), internalizing disorders (major depressive disorder, and for girls

only, overanxious disorder and separation anxiety disorder), and substance use in early adolescence. Externalizing psychopathology predicted having tried alcohol, nicotine, and marijuana by 14 years of age as well as regular and advanced experience with these substances. Internalizing disorders showed much weaker effects, with only major depression at 11 years of age showing a significant relationship with substance use at 14 years of age. Hence, a large and growing body of empirical literature implicates the existence of general mechanisms linking adolescent problem behavior and disinhibitory psychopathology in adulthood.

Further, Lynskey and colleagues[57] presented evidence that much of the association between smoking, drinking, and marijuana use in adolescence could be explained by a factor representing individual vulnerability to substance use. Newcomb and colleagues[58] demonstrated that alcohol, marijuana, and other drug use are indicators of a common substance-use factor, and the influence of risk factors on use of these substances is mediated through the common factor. This factor was also evident across different developmental stages.[59] In addition, Vanyukov and colleagues[60] showed that a substantial proportion of the variance in liability to use substances is shared between substances.

Finally, the idea of a common substance-use factor is supported by models of substance-use behavior that have been shown to generalize across different types of substances. These include Petraitis and colleagues'[61] integrative theory of triadic influence (see also Flay and Petraitis[62]) and the social development model of Catalano, Hawkins, and colleagues[63,64] as well as West's[65] synthesis of different models of addiction.

However, some research has failed to identify a common factor that underlies substance use and other problem behaviors.[66,67] Willoughby and colleagues[68] identified a substance-use factor distinct from other problem behaviors such as delinquency and aggression. Likewise, White and Labouvie[69] showed in a community sample that substance use (including alcohol, tobacco, and illicit drug use) and delinquency represented two dimensions of problem behavior. In addition, in contrast to work suggesting a common underlying substance-use factor, several studies suggest that use of different types of substances may be better represented by separate (but correlated) factors. These studies demonstrate that use of alcohol loads on a factor separate from smoking[70] or drug use,[71,72] although Zhang and colleagues[72] demonstrated that drinking, drug use, and delinquency loaded strongly on a higher-order deviance factor. Likewise, Dembo and colleagues[73] noted some specificity of alcohol use beyond a general deviance factor that included marijuana use (as well as delinquency).

Osgood and colleagues[74] proposed that associations between various deviant behaviors can be attributed to general deviance during adolescence at a point at which behaviors such as substance use and sexual activity are much less normative; however, as youth age, behaviors become more acceptable and show greater specificity. The finding by Resnicow and colleagues[75] that substance use loaded on the same factor as carrying a weapon and stealing, but not more normative school problems and (low) positive behaviors, supports this notion. White[76] noted that certain problem behaviors cluster at different developmental periods. White suggested that youth experiment with different problem behaviors across adolescence but that many of these behaviors do not become established behavior patterns. In summary, there appears to be a strong general factor indicating susceptibility to varied forms of substance use, but there remains

considerable substance-specific residual vulnerability, and evidence for overlap with other problem behaviors is more limited.

Shared Genetic Risk

Consistent with the phenotypic work supporting a common general dimension of substance use and evidence for common correlates across substances, a good portion of genetic risk for substance-use disorders is carried through one major common factor.[77] Twin data provide ample evidence for a general underlying genetic risk factor that increases liability to use tobacco and alcohol, including measures of alcohol volume,[78–81] intoxication,[82] and alcohol dependence.[83] Comparable findings have been shown for tobacco dependence and alcohol dependence[84,85] (also see Volk and colleagues[86] for evidence of specificity of genetic effects). Extending this work further, there is evidence for a common genetic influence mediating concurrent tobacco, alcohol, and marijuana use[87] and problem use,[88] with tobacco and marijuana showing the strongest genetic overlap. In a study by Yoon and colleagues,[89] P3 amplitude, shown to be highly heritable in adolescent boys, is associated with various indices of use of different substances (e.g., early use, frequency of use, maximum use across cigarettes, alcohol, and illicit drugs). This finding extends the work demonstrating that a common genetic vulnerability underlies substance use in general.

Also consistent with the problem behavior theory, although not directly relevant to understanding smoking phenotypes, some studies have documented common genetic factors underlying alcohol and drug dependence.[49,90–92] In general, Hettema and colleagues[79] noted that common genetic liability may be attributable to variation in genetically influenced personality traits (e.g., sensation seeking) or variation in biological substrates, which may include genetic influences on variation in the reward system.[93] Consistent with evidence for a common genetic influence, genetically informed family studies also show familial transmission of smoking, alcohol use, marijuana use, and illicit drug use.[94–96]

Approaches to Research on Substance-Use Prevention

Evidence of a common externalizing factor suggests the design of relatively generic prevention strategies that target multiple problem behaviors.[51] Numerous studies that have adopted a general approach in prevention of adolescent substance use show evidence of reduced use of alcohol, tobacco, and marijuana across multiple community, school-based, and high-risk populations[97–103] and reduced use of illicit drugs;[104] however, see Brown and colleagues[105] for failure to detect program effects specifically for smoking.

However, it is important to note that several macro-level environmental factors can influence the availability and social acceptability of specific substances. Local and cultural social norms can differ across substances. For example, for the last several decades in the United States, the college environment has promoted heavy episodic drinking but not regular smoking as a normative behavior.[106] Moreover, formal alcohol and tobacco prevention and control policies (e.g., taxation, minimum age laws, advertising bans) can be applied to both substances in a roughly equal manner or differentially, and the nature of this balance presumably has implications for overall comorbidity and the relative degree of common versus unique environmental influence across substances. Other substance-control policies for tobacco use (e.g., smoking bans; see Hopkins and colleagues[107]) and alcohol use (e.g., social host and dram shop liability laws, zoning of outlets; see Wagenaar and colleagues[108]) are substance specific and presumably unique. This larger environmental context

highlights the importance of considering a range of environmental variables that might condition both manifest comorbidity and the relative contribution of genes, environments, and their interaction within a given population.

Review of Trajectory Literature

Chapter 5 of this volume reviews the literature on smoking trajectories; consequently, this literature is summarized here only to the extent that it is relevant to this discussion. First, the large and growing literature on trajectories of alcohol and marijuana/drug use is described in greater detail. Then, literature characterizing the associations between trajectories of one substance and use of other substances is reviewed, considering associations with time-invariant substance use as well as course of co-occurring substance use.

Trajectories of Alcohol Involvement

Consistent with theoretical work on course of alcohol involvement[109–111] and complementing a wide body of subtyping literature in the alcohol field,[112] a large number of studies have characterized the developmental course of drinking over adolescence and young adulthood. Although results with respect to the specific characterization of course and associated prevalences vary somewhat from study to study, investigations are consistent in identifying four broad classes that vary in age of onset, magnitude and direction of slope, and severity of use: a nonuser/stable low-user course, a chronic high-use course, a decreasing course, and an escalating course. Not unexpectedly, trajectories derived from adolescent samples tend to detect courses typified by escalation, whereas samples that include young adults reveal decreasing courses. For example, studies that follow adolescent drinking often show two groups of escalators that differ in age of onset and slope.[113–116] In contrast, studies examining drinking in young adult samples are more likely to detect a decreasing or "developmentally limited" course.[117–119] Some studies assessing a sample across the developmental transition from adolescence to young adulthood also identify a "fling" or "time-limited" trajectory,[118,120,121] which, in studies using a younger or older sample, may manifest itself as an increasing or a developmentally limited course.

Although most of these studies have focused on a broad developmental span covering a number of years, a few studies have explored alcohol involvement over the course of a single year[122–124] to resolve more-fine-grained changes in drinking behavior over shorter intervals. These fine-grained studies identify patterns of use primarily characterized by slope (e.g., stable behavior versus behavior that escalates or declines over time).

Drinking course has been defined along indices of alcohol involvement such as heavy/binge drinking,[113,115,116,118–121,125] quantity/frequency,[114,126,127] problem drinking,[128,129] alcohol dependence,[130] or a composite of drinking items.[131] Subsequent work examined congruence of trajectories across different indices of alcohol involvement (alcohol-use disorder, alcohol dependence, alcohol consequences, heavy drinking, and alcohol quantity/frequency[117]). Consistent with the existing body of literature, there was similarity in trajectory shapes (i.e., courses) across diverse indices, although predicted prevalences varied across measure.

Trajectories of Marijuana Involvement

Far fewer studies have characterized developmental course for frequency of

marijuana use,[132–136] but findings have generally been consistent with regard to course shape and prevalence, with the majority of individuals being classified as abstainers/nonusers (ranging from 41% to 82%, with higher rates among adolescent samples). All studies identified a chronic high group marked by early onset and heavy use. A later-onset, escalating course was observed in three of the five studies. Not surprisingly, this group was the largest in the study with the longest time frame (covering ages 13–23 years). Additional groups were marked either by moderate occasional use or by reduced use.

Trajectories of Polysubstance Use

Some researchers assume but do not explicitly test comparability of substance-use course by using indices based on a composite of multiple substances at the point of trajectory identification. Using a large adolescent sample, Wills and colleagues[137] classified substance-use trajectories by using a composite of frequency of alcohol use, heavy alcohol use, tobacco use, and marijuana use. Although one-half of the sample consisted of nonusers, there were sizable subgroups characterized by experimentation and varying degrees of escalation. Clark and colleagues[138] identified course of substance-use-disorder symptoms based on retrospective report by using a sample of young adult males diagnosed with a substance-use disorder. Trajectories of substance-use problems varied across severity and onset age, with groups ranging from early-onset, severe, to improved (decrease), to mild or minimal problems. In addition, on the basis of indices of onset and intensity, Labouvie and White[139] detected three substance-specific trajectories (heavy smoking, heavy alcohol use, and heavy drug use) as well as a common-substance, adolescent-limited course, suggesting both specificity and commonality across courses of different types of substance use.

Associations between Substance-Use Trajectories and Other Substance Involvement

A number of studies indicate that smoking courses can be differentiated as a function of involvement with other substances (alcohol, marijuana, and other drug use) as measured at a single time point (e.g., as a baseline correlate or as an outcome), and smoking behavior (measured at a single time point) can differentiate alcohol and marijuana courses. These studies advance comorbidity research by considering the dynamic nature of at least one of the substances, but the arbitrary nature of which variable to consider as primary, and which as covariate, highlights the need for a true multivariate (i.e., multisubstance) approach to deriving trajectories.

Smoking Trajectories with Alcohol and Marijuana Use

Smoking behavior that is characterized by early onset and heavy use is robustly associated with marijuana use and, to a less consistent degree, with alcohol involvement. This is true when looking at substance-use correlates at baseline, as outcomes, or as time-varying covariates that track the smoking courses. White and colleagues[140] demonstrated that smokers endorsed more frequent alcohol, marijuana, and other drug use at baseline than did nonsmokers, although substance use did not differentiate between heavy/regular smoking and occasional smoking. Wills and colleagues[141] showed that both (heavy) drinking and marijuana use tracked smoking frequency during early- to mid-adolescence. That is, those smokers characterized by early onset showed greatest use, and nonsmokers the lowest use, with experimenters showing

low but still elevated rates compared with nonsmokers. In addition, Brook and colleagues[142] found that early-onset smokers with continuous use over adolescence and emerging adulthood were more likely to be diagnosed with alcohol dependence and illicit drug dependence than nonsmokers and smokers who had later onset of smoking or who showed reduced use over time. Moreover, late-starting smokers were more likely to be diagnosed with drug dependence than were nonsmokers. Finally, Juon and colleagues[143] showed that drug abuse/dependence during adulthood was highest for those assigned to a smoking class on the basis of reported use and age of onset and was lowest for those classified as nonsmokers.

After identifying four courses of smoking in adolescence (early adopters, late adopters, experimenters, and never smokers), Audrain-McGovern and colleagues[144] examined lifetime alcohol and marijuana use both as baseline predictors and as time-varying covariates. All smoking courses differed from never smokers on alcohol and marijuana use, and both early and late adopters showed greater use of marijuana (and alcohol for late adopters only) than did experimenters. For the most part, early and late adopters did not differ from one another as a function of other substance use.

Orlando and colleagues[145] characterized courses defined by smoking frequency over adolescence and emerging adulthood. They also tracked heavy drinking and marijuana over the study interval. No differences were observed in heavy drinking at 13 or 18 years of age, but at 15 years of age both the stable high and early, increasing courses showed greater drinking than did all other groups. Drinking rates were lowest for nonsmokers, with rates for late increasers and experimenters ("triers") falling between nonsmokers and those with declining smoking rates. A similar pattern was observed for marijuana use, but it was more consistently associated with smoking across time (at 13, 15, and 18 years of age). Early adulthood alcohol and drug problems showed similar patterns, with those characterized by a stable high smoking course and by an early-onset, increasing course most likely to report substance-use problems (by 23 years of age) and nonsmokers or triers least likely to report problems. Using the same data, but limiting the sample to women and extending outcomes to 29 years of age, revealed the same patterns.[146]

Soldz and Cui[147] identified the extent to which substance use tracked courses of adolescent past-month smoking quantity. They portrayed a pattern of marijuana use that very closely paralleled smoking, with similar findings for alcohol use. Continuous smokers had the highest rates of marijuana and alcohol use, and early-smoking escalators also started at low or moderate levels but escalated rapidly to high rates of drinking and marijuana use. Experimenters and late escalators were also similar, both showing escalating use of marijuana and alcohol toward the end of high school. In addition, smoking quitters showed more substance use than did nonsmokers but only minimally so (indicating a pattern of experimentation).

Finally, using data from the prospective Dunedin sample, Stanton and colleagues[148] showed that alcohol and marijuana use tracked smoking patterns over preadolescence and adolescence, with highest rates of substance use among rapid escalators. Again, indicators of alcohol use (past-month drinking, intention to get drunk) were less associated with smoking than was marijuana use. In sum, those with smoking trajectories characterized by early initiation or elevated use tend to report greater baseline substance use and subsequent problems or abuse/dependence.

Drinking Trajectories with Smoking and Marijuana/Drug Use

Few of the many studies characterizing course of alcohol involvement examine smoking or marijuana-use correlates. Windle and colleagues[121] showed an association with heavy drinking course for men only; moderate or high heavy drinking (but not very high heavy drinking) was associated with heavier baseline smoking. Men with high or very high drinking also were more likely to report marijuana use at baseline. In contrast, women were more likely to report baseline marijuana use if they belonged to an infrequent or time-limited drinking course. D'Amico and colleagues[123] showed that adolescents who were consistently heavy drinkers over the course of a year reported higher rates of smoking and marijuana use and initiated smoking, regular smoking, and marijuana use at a younger age than did nonheavy drinkers or individuals whose drinking increased over the course of the year.

Hill and colleagues[115] demonstrated that those whose heavy drinking began early and was persistently high were more likely to use drugs in early adolescence; likewise, reported lifetime history of drug use obtained during adolescence was higher for those with courses marked by early drinking experience.[113] In addition, those with increasing rates of heavy drinking were most likely to be diagnosed subsequently with drug-use disorder,[115] whereas non-heavy-drinking individuals were less likely than any heavy drinking group to develop subsequent drug abuse.[113] Finally, Schulenberg and colleagues[119] showed that time-varying measures of illicit drug use very closely paralleled heavy drinking trajectories, and Wiesner and colleagues[149] found that regular drinkers (those with chronic high alcohol use) were overrepresented with regard to marijuana and other drug use.

Marijuana Trajectories with Smoking and Alcohol Use

Studies characterizing marijuana trajectories suggest that those with an early onset show increased likelihood of being diagnosed with a lifetime alcohol-use disorder,[136] as well as increased alcohol use at study outset[134,136] or study end[132] and hard drug use at study end.[132,133] These studies also were more likely to report early onset for drinking and smoking.[134] Correspondingly, the low- or nonusing marijuana groups showed the lowest rates of smoking and drinking. Alcohol involvement was also high among those whose marijuana use declined over time. Occasional users tended to fall in the middle for drug use,[133] and those whose marijuana use increased to a high rate reported heavy drinking at study end.[132] Although not formally testing concordance between the two courses, Schulenberg and colleagues[135] demonstrated that both frequency of smoking and binge drinking closely tracked courses of marijuana during the developmental period (ages 18–24 years) under consideration.

Modeling Conjoint Trajectories of Substance Use

Researchers have begun exploring the extent to which various risk behaviors or disorders "travel together" over time, with an emerging literature that uses a developmental framework to examine co-occurrence of use of different substances. The available body of work is described, with acknowledgment that this is a rapidly evolving field. Table 7.1 presents characteristics of this literature, describing for each study the nature of the sample, the developmental period under investigation, the number of waves, the measures from which trajectories were

derived, the trajectory group structure and prevalence, and the type of analytic model.

Tobacco and Alcohol

Four studies were found that have modeled trajectories of both smoking and drinking. Orlando and colleagues[155] extracted five classes (and an a priori nonusing class) from indicators of drinking and smoking frequency when the two substances were modeled together in a single model. They demonstrated that, for the most part, smoking and drinking during adolescence and emerging adulthood tracked one another. A large group of normative users was observed (consisting of experimental smokers and moderate drinkers). Additional groups included those who exhibited chronic high use of both tobacco and alcohol, two groups whose substance use increased over time, and those who maintained their alcohol use but quit smoking. There was no evidence for a group of smokers whose drinking remitted, suggesting that smoking may be an indicator of a more severe form of drinking. Belonging to an early substance-use class was predicted by factors such as disrupted nuclear family, lower parental education, poor grades, and being white. In addition, nonusers and normative users revealed better overall health and life satisfaction, higher college graduation rates, fewer delinquent and violent behaviors, and fewer alcohol and drug problems.

A similar study was conducted using panel data from the Monitoring the Future project.[154] Group membership was identified on the basis of both smoking and (heavy) drinking. Perhaps because the large sample size ($N > 32{,}000$) permitted identification of classes with relatively low prevalence, seven groups were identified, including nonusers, chronic high users, those who smoked but did not drink, those who consumed alcohol but did not smoke, and three classes whose drinking was moderate but whose pattern of smoking differed (moderate, late onset, or decreasing). Hence, unlike the Orlando and colleagues study,[155] a group of individuals who smoked but did not drink was observed. This may be due to the age under investigation, with the Orlando study targeting individuals earlier in adolescence (13 years of age versus 18 years) and tracking behavior until 23 years of age (versus 26 years); drinking rates tend to drop off in mid-adolescence but smoking tends to be more stable. Jackson and colleagues[154] demonstrated that some risk factors were relatively unique to the substance being predicted (e.g., parent education, gender, and race) and may exhibit additive effects in predicting smoking and drinking. In contrast, religiosity was a risk factor common to both smoking and drinking. Perhaps of greatest interest, alcohol expectancies and delinquency showed a "masked" effect whereby their association with smoking could be attributed to smoking's association with drinking.

Using a high-risk college sample, Jackson and colleagues[35] identified five classes derived on the basis of both tobacco and alcohol involvement (specifically, tobacco dependence and alcohol-use disorders). Consistent with the Orlando study[155] and Jackson and colleagues,[154] an earlier study by Jackson and colleagues[35] observed a chronic high class for both substances, a class characterized by alcohol involvement but not tobacco involvement, and a nondiagnosing class. In addition, as in their later study,[154] Jackson and colleagues[35] observed a group diagnosed with tobacco dependence but not with alcohol-use disorder. Of note, a second class of individuals who were alcohol involved but not diagnosed with tobacco dependence was identified; however, diagnoses with alcohol-use disorders declined over time, consistent with a "maturing out" effect that has been observed in young adulthood. Predictors that were common to both substances included a family history of

Table 7.1 Overview of the Literature on Conjoint Trajectories of Substance Use

Study	Sample	Developmental period	Number of waves	Measures	Number and characteristics of class	How is conjoint substance use characterized?
Jackson et al. 2000[35]	*N* = 449 college student sample	Young adult (ages 18–24 years)	5	Tobacco dependence (TD) Alcohol-use disorder (AUD)	Nondiagnosers (60%) Chronic AUD (6%) Developmentally limited AUD (16%) Chronic TD (11%) Comorbid AUD and TD (7%)	Dual-trajectory model
White et al. 2000[127]	*N* = 1,380 community sample	Adolescence/ early adulthood (ages 15–28 years)	4	Smoking volume Alcohol volume (volume = frequency × quantity)	Smoking: Low (52% female/56% male) Moderate (36%/37%) Heavy (12%/7%) Alcohol: Low (18% female/17% male) Late/increase (27%/25%) Moderate (38%/35%) Heavy (17%/23%)	No explicit comparison but evidence for common predictors
Guo et al. 2002[150]	*N* = 786 children in Seattle Social Development Project	Adolescence/ early adulthood (ages 10–21 years)	5	Frequency of smoking Frequency of binge drinking Frequency of marijuana use Frequency of illicit drug use	Tobacco: Chronic smokers 1% Escalators 8% Late onsetters 11% Experimenters 7% Nonsmokers 73% Alcohol: Chronic bingers 3% Escalators 4% Late onsetters 23% Nonbingers 70% Marijuana: Early high 3% Escalators 4% Late onsetters 4% Nonusers 89% Illicit drug: Early onsetters 7% Late onsetters 4% Nonusers 89%	No explicit comparison but evidence for common outcomes

Study	Sample	Developmental period	Number of waves	Measures	Number and characteristics of class	How is conjoint substance use characterized?
Chassin et al. 2004[151]	*N* = 586 community sample	Adolescence/ early adulthood (ages 13–23 years)	6	Alcohol volume (volume = frequency × quantity) Frequency of smoking Frequency of drinking	Growth mixture model: 3 classes (plus a priori abstainers, 11%): low (light drinking/ rare drug use; 24%); moderate (moderate drinking/experimental drug use; 45%); heavy (heavy drinking/heavy drug use; 20%)	Dual-trajectory model
Chung et al. 2004[152]	*N* = 110 outpatient treatment sample (aged 16–25 years)	Course over a single year posttreatment Compute monthly abstention rates based on timeline follow-back technique	12	Number of consecutive abstinent days per month for drinking and other drug use	Alcohol: High abstinence (53%) Decreasing abstinence (10%) Increasing abstinence (16%) Low abstinence (21%) Other drug: High abstinence (59%) Decreasing abstinence (12%) Increasing abstinence (14%) Low abstinence (15%)	Cross-classification: $\chi^2(9, N = 110) = 80.74$, $p < .001$ ($\kappa = .49$)
Flory et al. 2004[153]	*N* = 481 Project DARE	Adolescence/ early adulthood (age 12 through age 19–21 years)	6	Frequency of drinking Frequency of marijuana use	Alcohol: Early onset (17% men/25% women) Late onset (64%/57%) Nonusers (19%/18%) Marijuana: Early onset (6% men/12% women) Late onset (56%/42%) Nonusers (39%/46%)	Cross-classification: $\chi^2(4, N = 236) = 78.82$, $p < .001$ (men; 61% on diagonal) $\chi^2(4, N = 234) = 69.37$, $p < .001$ (women; 50% on diagonal)
Jackson et al. 2005[154]	*N* = 32,087 Monitoring the Future panel data	Late adolescence/ early adulthood (ages 20–26 years)	4	Smoking quantity Frequency of binge drinking	Nondrinker/nonsmoker (56%) Chronic (6%) Chronic drinker (14%) Chronic smoker (8%) Moderate drinker/developmentally limited smoker (5%) Moderate drinker/late onset-smoker (5%) Moderate drinker/smoker (6%)	Dual-trajectory model

Table 7.1 Overview of the Literature on Conjoint Trajectories of Substance Use *(continued)*

Study	Sample	Developmental period	Number of waves	Measures	Number and characteristics of class	How is conjoint substance use characterized?
Orlando et al. 2005[155]	*N* = 5,608 school-based substance program for substance abuse prevention	Adolescence/ early adulthood (ages 13–23 years)	6	Frequency of smoking Frequency of drinking	A prior nonusing class (4%) Normative users (55%) Smoking quitters/drinking maintainers (6%) Steady increasers (13%) Early increasers (12%) Early, high (9%)	Dual-trajectory model
Tucker et al. 2005[156]	*N* = 4,245 (smoking) *N* = 3,889 (drinking) *N* = 3,185 (marijuana) school-based program for substance abuse prevention	Adolescence/ early adulthood (ages 13–23 years)	6	Frequency of smoking Frequency of binge drinking Frequency of marijuana use	Tobacco: Abstainers (28%) Persistent light use (55%) Stable high use (26%) Decreasers (9%) Steady increasers (14%) Early increasers (9%) Alcohol: Abstainers (32%) Persistent light use (54%) Early, high (22%) Steady increasers (23%) Increase/decrease (bingers/fling) (13%) Marijuana: Abstainers (45%) Persistent light use (53%) Stable occasional light users (17%) Early, high (5%) Steady increasers (25%)	Cross-classification: greatest overlap among abstainers

Study	Sample	Developmental period	Number of waves	Measures	Number and characteristics of class	How is conjoint substance use characterized?
Jackson et al. 2008[157]	$N = 32,087$ Monitoring the Future panel data	Late adolescence/ early adulthood (ages 20–26 years)	4	Smoking quantity Frequency of binge drinking Frequency of marijuana use	Tobacco: Nonheavy smoker (69%) Chronic (12%) Developmentally limited (6%) Late onset (5%) Moderate (8%) Alcohol: Nonheavy drinker (64%) Chronic (12%) Developmentally limited (16%) Late onset (7%) Marijuana: Nonheavy user (81%) Chronic (7%) Developmentally limited (9%) Late onset (3%)	Cross-classification: Tobacco vs. alcohol: $\chi^2(12, N = 31,853) = 2,474.41, p < .001, \Phi = .28$, Cramer's V = .16 Tobacco vs. marijuana: $\chi^2(6, N = 31,872) = 3,683.51, p < .001, \Phi = .34$, Cramer's V = .20 Alcohol vs. marijuana: $\chi^2(9, N = 31,869) = 4,172.32, p < .001, \Phi = .36$, Cramer's V = .21
Audrain-McGovern et al. Forthcoming	$N = 998$ high school students	Late adolescence (age 14–20 years)	6	Smoking categories (based on frequency and quantity) Frequency of marijuana use	Regular users (11%) Late escalators (8%) Slow escalators (23%) Fast escalators (2%) Cigarettes only (21%) Abstainers (33%)	Sequential process model

alcoholism and expectancies about the effects of alcohol (suggesting the possibility of common expectancies across substance). However, being male and exhibiting behavioral undercontrol was a predictor that was specific to alcohol-use disorders, and childhood stressors only predicted comorbid tobacco dependence and alcohol-use disorder.

Muthén[159] reanalyzed the same data by using a different analytic technique (general growth mixture modeling versus the use of latent class analysis). Muthén identified three classes of alcohol-use disorders and three classes of tobacco dependence and estimated joint probabilities between the classes. The results of these analyses corresponded to the findings in Jackson and colleagues[35]: the five trajectory groups in Jackson and colleagues[35] were represented by the five most prevalent joint probabilities in Muthén.[159]

Although White and colleagues[127] modeled the developmental course of both smoking and drinking over adolescence and young adulthood, they did not explicitly compare concordance across the two substances. Both smoking and drinking showed low, moderate, and heavy courses; in addition, for drinking, a later-onset course made up one-quarter of the sample. The authors found evidence for both common (parental warmth) and specific (parental smoking, for tobacco use; parental drinking, for alcohol use) predictors of smoking and drinking. In conclusion, these four studies show that tracking trajectories of multiple substances not only illustrates the pattern of concurrent substance use over adolescence and young adulthood but also can permit better understanding of mechanisms that are common versus unique to use of a given substance.

Tobacco and Marijuana Use

Using a sequential process model, Audrain-McGovern and colleagues[158] characterized conjoint trajectories of smoking and marijuana use over adolescence and emerging adulthood. With the exception of a class characterized by smoking only, courses of cigarette and marijuana use tracked one another; these were marked by abstention, regular use, or slow, fast, or late escalation. Of interest to this chapter, the regular smokers and the fast escalators tended to have greater marijuana use than did the other groups.

Tobacco, Alcohol, and Marijuana/Other Drugs

Several studies have extended the analysis of conjoint substance-use course by also considering marijuana or other drug use. Unlike the work focusing on only tobacco and alcohol use, these studies have each modeled course of each substance separately and then examined concordance between substances to ascertain the extent to which patterns of substance use change together.

Again using the Monitoring the Future panel data, Jackson and colleagues[157] examined smoking, (heavy) drinking, and marijuana use and identified similar classes across substance that included nonusers, chronic high users, later-onset users, and decreasing users; for smoking only, there was also a class of moderate users. Smoking, drinking, and marijuana use tracked each other over time, with concordance between trajectories of marijuana and tobacco use as high as the association between tobacco and alcohol use. Early users of alcohol and marijuana were most likely to smoke moderately or heavily, even for those whose drinking decreased over young adulthood, underscoring the highly addictive nature of smoking. Delinquency and alcohol expectancies were the strongest predictors of general comorbidity; gender, race, religiosity, and parent education emerged also as significant predictors. Delinquency and alcohol expectancies both accounted for configurations of comorbid chronic high use, although expectancies failed to explain

combinations of smoking and marijuana use, supporting some specificity of expectancies to alcohol use. That delinquent behavior accounts for combinations of comorbidity characterized by early onset and persistently high use corroborates research suggesting common vulnerability underlying substance use.

Building on their earlier work, Tucker and colleagues[156] compared trajectories of smoking, (heavy) drinking, and marijuana use over adolescence and emerging adulthood. The greatest overlap was among abstainers but also among those characterized by increasing or early high use. Adult psychosocial and behavioral functioning was associated with class membership similarly across substances. Nonusers were at lowest risk for adverse outcomes (e.g., stealing, violence), and those whose substance use increased steadily to very high use were at greatest risk. However, in contrast to smoking, those who began using marijuana early but declined over time were not distinguishable from those with steady increasing use.

Using indices of cigarette smoking, (heavy) drinking, marijuana use, and illicit drug use, Guo and colleagues[150] tracked each substance over early to late adolescence. Each substance showed a large nonusing class and groups with onset either early or at a later point. In addition, chronic users were observed for smoking, drinking, and marijuana use, and an additional class of experimenters was observed for smoking only. Although explicit comparisons between substances were not conducted, the extent to which associations between course and sexual risk-taking behaviors at 21 years of age were common versus unique to substance was examined. Chronic and later-onset alcohol and marijuana use, but not cigarette or hard drug use, were associated with risky sexual behavior, whereas early cigarette and alcohol use, but not early marijuana or hard drug use, increased risk, suggesting greater specificity than might be expected from theories of general adolescent problem behavior.

Alcohol and Marijuana/Other Drugs

Although not directly relevant to this chapter, work examining trajectories of alcohol and marijuana/drug use provides additional evidence that longitudinal phenotypes of substance use are relatively common across substances. Chassin and colleagues[151] demonstrated that trajectories of alcohol/drug use in adolescence and young adulthood tracked concurrent alcohol- and drug-use disorders such that those with heavy use were most likely to be diagnosed with a substance-use disorder. Likewise, Flory and colleagues[153] demonstrated substantial overlap among courses of alcohol and marijuana use, although a number of alcohol users were nonusers of marijuana. Etiological correlates and young adult outcomes were common to both substances, with little evidence of specificity. Finally, using retrospective reports of days abstinent in a clinical sample of adolescents and young adults, Chung and colleagues[152] documented moderate concordance ($\kappa = .49$) between courses of alcohol and drug use in the year following treatment whereby change in alcohol use typically paralleled change in drug use, although there was evidence that some individuals abstained from one substance but not the other.

Review of Results

On the basis of findings from studies that jointly model course and comorbidity, several conclusions can be advanced. First, despite the diverse course shapes and different course prevalences that were identified by each study, it is reassuring that in each case, relatively high concordance was observed between corresponding

trajectories (e.g., chronic high smoking with chronic high drinking), as were common correlates of course across substance.

Second, both common and specific factors that underlie concurrent substance use were observed. As noted by Jackson and colleagues,[154] identifying risk factors that distinguish among courses of comorbidity can provide construct validity for the trajectories and can not only illuminate the nature of comorbidity but also can provide a better understanding of each substance. For example, one could compare risk factors for courses characterized by heavy use of one substance and low use of the co-occurring substance. Jackson and colleagues[154] identified different patterns of association between risk factors and paths of co-occurring tobacco and alcohol use that suggested additive effects, synergistic effects, and masked (confounded) effects.

Third, it is apparent from this work that individuals who remit from alcohol and marijuana use frequently remain smokers. This may be, in part, because tobacco is so highly physically and psychologically

Why Might It Be Useful to Use Course as a Phenotype?

Developmental course might serve as a valuable phenotype for biometric models. Researchers have been using latent growth modeling[a,b] to model developmental course by using genetically informative (twin) data. Although work conducted in 1986 by McArdle[c] and Plomin[d] introduced the idea of capturing the heritability of developmental change, 20 years passed before the heritability of latent variables reflecting level (intercept) and growth was demonstrated by applying latent growth models to the study of genetic influences.[e,f] Carlson and Iacono[e] suggested that intercept and slope factors may serve as developmental phenotypes that indicate the extent of genetic vulnerability for continuity or change in a given behavior. However, although this work is informative with regard to the heritability of initial level (at a given age) and change from that level over an extended observation period, these parameters do not capture individuals who are particularly "at risk" by virtue of membership in a developmental course that is marked by both high initial level and chronic continued use. A latent variable that characterizes membership in some developmental course could be a valuable phenotype in that it classifies individuals by their level of and change in substance use as well as the timing of onset or initiation. The integration of mixture models into genetic models is under way,[g] although thus far this work considers only a single behavior (i.e., alcohol use). Determining the degree to which these phenotypes are substance specific represents a logical next step in the genetic study of addictive behavior.

[a]Curran, P. J., and A. M. Hussong. 2003. The use of latent trajectory models in psychopathology research. *Journal of Abnormal Psychology* 112 (4): 526–44.

[b]Muthén, B. 2001. Latent variable mixture modeling. In *New developments and techniques in structural equation modeling,* ed. G. A. Marcoulides and R. E. Schumacker, 1–33. Mahway, NJ: Lawrence Erlbaum.

[c]McArdle, J. J. 1986. Latent variable growth within behavior genetic models. *Behavior Genetics* 16 (1): 163–200.

[d]Plomin, R. 1986. Multivariate analysis and development behavioral genetics: Developmental change as well as continuity. *Behavior Genetics* 16 (1): 25–43.

[e]Carlson, S. R., and W. G. Iacono. 2006. Heritability of P300 amplitude development from adolescence to adulthood. *Psychophysiology* 43 (5): 470–80.

[f]Finkel, D., C. A. Reynolds, J. J. McArdle, and N. L. Pedersen. 2005. The longitudinal relationship between processing speed and cognitive ability: Genetic and environmental influences. *Behavior Genetics* 35 (5): 535–49.

[g]Muthén, B., T. Asparouhov, and I. Rebollo. 2006. Advances in behavioral genetics modeling using Mplus: Applications of factor mixture modeling to twin data. *Twin Research and Human Genetics* 9 (3): 313–24.

addictive; it also may be that once an individual has reached adulthood, alcohol and marijuana use are much less compatible with day-to-day adult responsibilities.

Finally, although several courses for tobacco and alcohol use were not associated with risk factors or adverse outcomes (e.g., escalating and decreasing courses), it appears that membership in any course indicating marijuana use increases risk of many negative correlates of substance-use behavior, suggesting some specificity to substances, at least with regard to those that are licit versus illicit.

Empirical Example of Modeling Co-Occurring Courses of Substance Use

In this section, an empirical example is presented of the modeling of conjoint use of multiple substances by using data from the Finn Twin16-25 study.[160] For simplification, only two substances are considered: cigarette smoking and alcohol consumption; models can be extended to consider more than two substances.[150,156,157]

Because this is only an illustration of the methodological approach, some simplifying decisions and assumptions were made: (1) Analysis was limited to data from twin brothers so that gender moderation was not an issue. Finnish girls mature earlier and initiate drinking at earlier ages than do boys in matched birth cohorts,[161,162] and environmental contributions to individual differences in pubertal development differ across genders.[163] Limiting the analysis to males attenuates the differential effects of pubertal maturation. (2) Trajectory analyses were conducted on the full sample of twins as individuals without consideration of the twin design. As such, the standard errors of parameters are underestimated, and confidence intervals are narrower than if the sampling design were taken into account. However, the actual parameter estimates are not biased.* Furthermore, prior studies suggest that it is reasonable to generalize from twin to nontwin samples.[164,165] (3) Finally, although analytic techniques permit missing data under the assumption that data are missing at random, missing data were not modeled to facilitate model convergence. Ascertainment of Finnish twins at the baseline of 16 years of age was essentially exhaustive and unbiased,[166] and individual response rates were ≥ 90% through the third assessment at 18 years of age.[167] But compliance declined at the fourth wave of assessment and more so among adult male twins. Consequently, it is acknowledged that generalization to the general population is constrained in this regard.

Method

Participants and Procedure

Finn Twin16-25 is a population-based, longitudinal twin study that includes five twin birth cohorts obtained from the Finnish national population registry and consists of all twins born in Finland between the years 1975 and 1979,[166,168] with both co-twins alive and resident in Finland at 16 years of age. Within 90 days of their 16th birthday, 3,065 twin pairs received mailed questionnaires. They were then followed up at the ages of 17 years, 18.5 years (age range 18–19 years), and 25 years (age range 23–27 years; response rate 83%); this final assessment generally corresponds to a period of maturing out/cessation of alcohol and tobacco use. Zygosity was

*Although it is possible to correct for dependence in Mplus by using the complex statement, the parameters do not change, and in fact, including this statement did not change the trajectory prevalence or structure.

determined from validated questionnaires completed by both co-twins and parents at baseline.[168] Data on smoking and drinking, across all four waves of assessment, were available for 1,132 male twins from brother-brother twin pairs of known zygosity; after deleting twins missing some data from their co-twins, 970 twins remained, forming 485 male twin pairs: 213 monozygotic and 272 dizygotic. This sample of twin brothers was used for all analyses.

Measures

Baseline questionnaires assessed frequency of alcohol use and frequency of smoking as well as other measures of substance use (including age at initiation, experimentation with cigarettes, and number of cigarettes smoked so far) and other health behaviors. The measures of drinking and smoking frequency were used in the analyses reported here.

Smoking

At 16 years of age, frequency of smoking was assessed with a single measure that asked, "Which of the following best describes your present smoking habits?" Response options included (1) I smoke once or more daily; (2) I smoke once or more a week, but not every day; (3) I smoke less often than once a week; (4) I am trying to or have quit smoking; and (5) I have never smoked. At the later ages, the set of five alternatives was expanded to six options (17 years of age) or seven options (ages 18 and 25 years) to better distinguish individual differences in density of smoking. To derive consistent measures over the four assessments, variables were recoded into the following four response options: (0) I have never smoked; (1) I smoke less than once a week or am trying to quit; (2) I smoke once or more a week but not daily; and (3) I smoke once or more daily. Items were rescored so that high scores indicate frequent smoking. Figure 7.1 (top) shows smoking prevalence over the four waves.

Alcohol Use

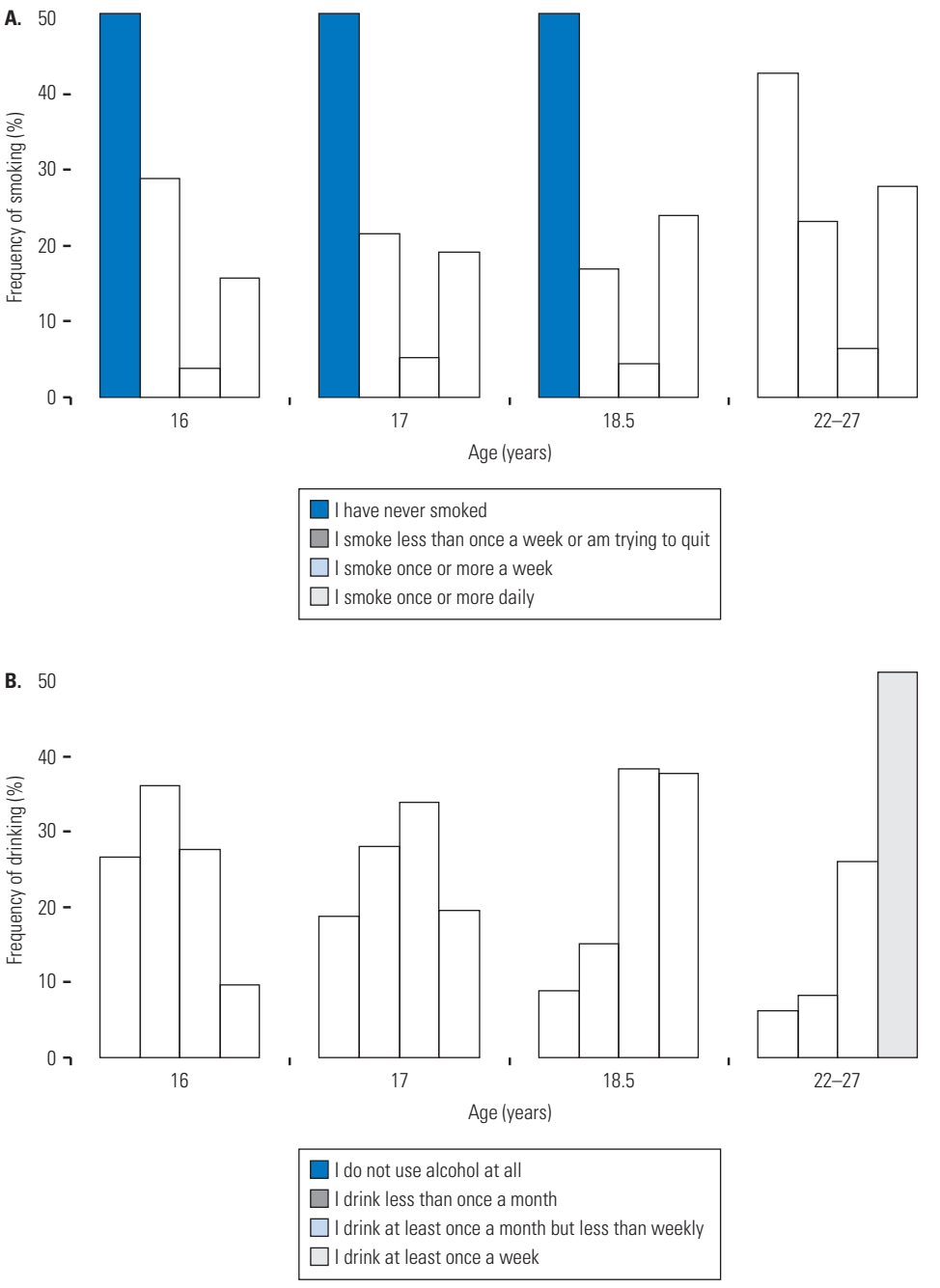
Frequency of drinking was assessed at all waves using a single measure asking how often the respondents use alcohol. Response options included (1) daily, (2) couple of times a week, (3) once a week, (4) a couple of times a month, (5) about once a month, (6) about once every two months, (7) 3–4 times a year, (8) once a year or less, and (9) I don't drink any alcohol. For consistency with the smoking items, variables were recoded into four response options: (0) I do not use alcohol at all, (1) drink less than once a month, (2) drink at least once a month but less than weekly, and (3) drink at least once a week. Items were rescored so that high scores indicate frequent drinking. Figure 7.1 (bottom) shows the prevalence of drinking over the four waves.

Analytic Procedure

To identify trajectories, a mixture modeling procedure—general growth mixture modeling/models (GGMM)—was used.[15,159,169,170] GGMM is a form of latent growth modeling, but it includes an unobserved categorical variable that models variability around the latent growth factors via discrete homogeneous classes of individuals (versus representing variability with a parameter, as in growth modeling). Basically, these models combine the continuous nature of a latent growth curve model with the categorical nature of group membership in a single estimation procedure. Rather than obtaining a trajectory of drinking for each individual in the study, as might be observed via latent growth modeling, multilevel modeling, or generalized estimating equations, GGMM groups individuals into meaningful "clusters" or "classes."

Typical latent growth curve models assume that respondents come from the same population, with the same basic

Figure 7.1 Prevalence of Smoking (A) and Drinking (B) across the Four Study Waves



Note. Analyses for the four study waves are based on these collection dates: age 16, Wave 1, 1991–1995; age 17, Wave 2, 1992–1996; age 18.5, Wave 3, 1994–1998; age 22–27, Wave 4, 2000–2003.

growth function with respect to starting point (intercept) and growth (slope; with individual variation represented by the intercept and slope factor variances). GGMMs, however, allow for different populations to have unique intercepts and slopes. In essence, GGMM estimates a unique latent growth curve (with individual variability) for each underlying population. This technique has some important advantages over other techniques used to derive developmental courses of substance use (e.g., cluster analysis, latent class analysis) in that it treats group membership as a latent (error free) variable (unlike cluster analysis) and accounts for the temporal ordering of prospective data (unlike traditional latent class analysis). Although GGMM is the model used here, other techniques can model change (e.g., regime switching[171] and latent transition analysis).[172] For example, in regime switching, individuals transition (or "switch") among groups. For the purposes of this example, the more frequently applied trajectory-analysis technique of GGMM is used.

The GGMMs were based on a basic latent growth model. The base model included intercept and both linear and quadratic slopes. The intercept was centered at time 1 (by virtue of a zero loading on the slope factors at time 1). Linear and quadratic slope factor loadings were set according to the interval between assessments (roughly 0, 1, 2.5, and 8.8). For the sake of a simplified example, no within-class variability was permitted.* The smoking and drinking variables were treated as four-level ordinal variables. Models were estimated with automatically generated random start values with 100 initial-stage random sets of starting values and 10 final stage optimizations. All models were estimated using Mplus 4.10.[173]

Two sets of analyses were conducted. The first was to model smoking and drinking independently. That is, a GGMM was estimated for smoking and, in a separate analysis, a GGMM was estimated for drinking. Then, the association between the trajectories of smoking and drinking was examined. In the second set of analyses, smoking and drinking were modeled simultaneously in a multivariate procedure. Figure 7.2 portrays the underlying GGMM for the two sets of analyses. The top panel shows two GGMMs for drinking and smoking; the bottom panel shows the multivariate procedure.

Results

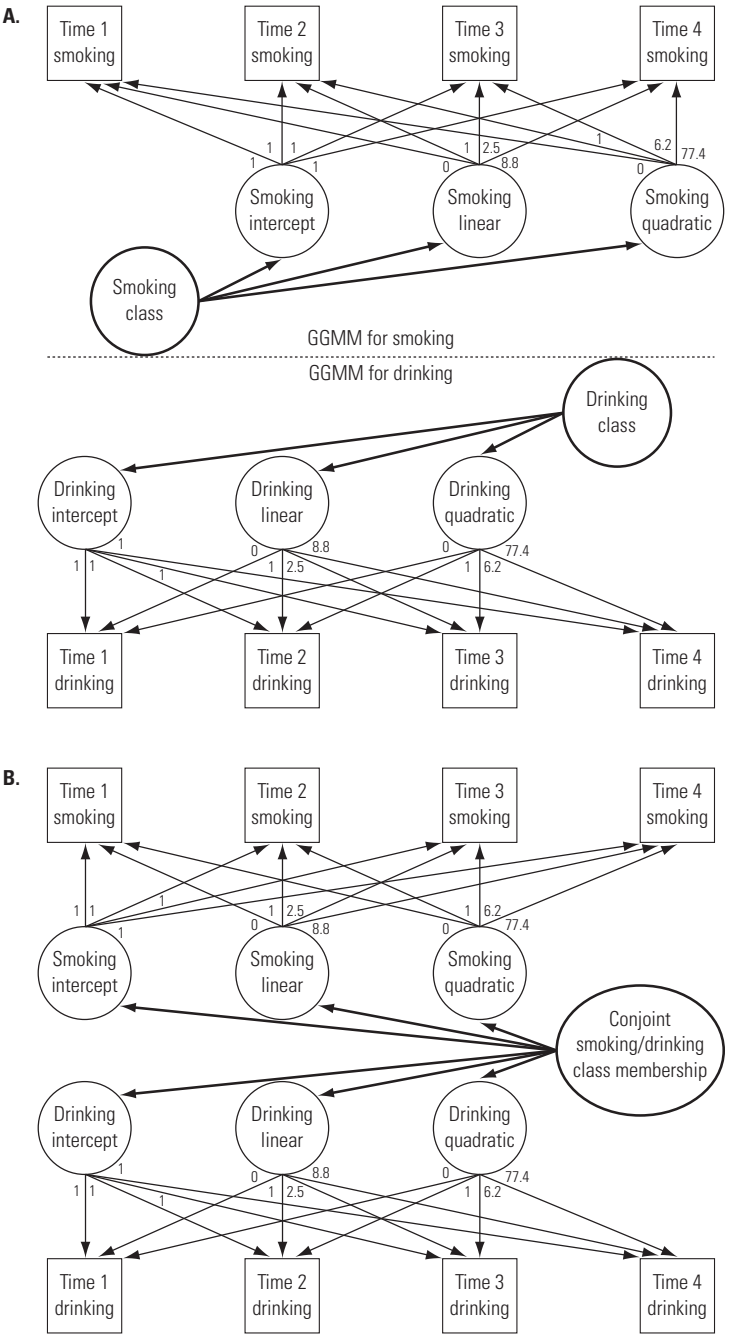
First, associations between drinking and smoking at each of the assessments were examined. As table 7.2 indicates, smoking and drinking are highly intercorrelated, particularly during the adolescent years. In addition, smoking and drinking are highly associated across twins, with twin 1 smoking moderately associated with twin 2 drinking at the ages of 16, 17, and 18 years (r = .37, .33, and .27, respectively) but less so at 25 years of age (r = .06; note that correlations for twin 1 drinking and twin 2 smoking were comparable). Not unexpectedly, the associations were stronger for monozygotic twins (r = .42, .41, .36, and .17 at ages 16, 17, 18, and 25 years, respectively) than for dizygotic twins (r = .34, .26, .20, and –.04, respectively).

Identification of Trajectories

As recommended by Muthén,[174] model fit was evaluated using a likelihood ratio test for relative improvement in fit—namely, the Vuong-Lo-Mendell-Rubin likelihood ratio (VLMR LR) test.[175,176] An information criteria fit index was also considered (Bayesian

*Although it would have been preferable to estimate within-class variability, model convergence was greatly facilitated by constraining within-class variances to zero.

Figure 7.2 Underlying General Growth Mixture Model for Characterizing Trajectories of Smoking and Trajectories of Drinking (A) and for Characterizing Conjoint Trajectories of Smoking and Drinking (B)



Note. GGMM = general growth mixture model/modeling. Factor loadings, set according to the interval between assessments, are shown for each growth factor. Correlations between intercept and slope factors were estimated but are not presented in the figure. For the dual-trajectory model, correlations were estimated between corresponding slope factors across substance.

Table 7.2 Correlations across Smoking and Drinking at Each of the Four Waves for the Full Sample

	Smoking				Drinking			
Behavior/age	Age 16	Age 17	Age 18	Age 25	Age 16	Age 17	Age 18	Age 25
Smoking–age 16	—							
Smoking–age 17	.80	—						
Smoking–age 18	.76	.82	—					
Smoking–age 25	.59	.64	.70	—				
Drinking–age 16	.46	.41	.38	.30	—			
Drinking–age 17	.39	.44	.39	.34	.69	—		
Drinking–age 18	.31	.34	.34	.32	.54	.66	—	
Drinking–age 25	.13	.15	.13	.20	.41	.46	.55	—

Information Criterion [BIC])[177] as well as class interpretability (the extent to which an additional class provided unique information) when determining number of classes.

Extracting Courses for Alcohol Use and for Tobacco Use

The first approach was to characterize course of smoking and course of drinking in two separate analyses. For each substance, one- through six-class models were tested (see table 7.3 for fit indices). For smoking, the VLMR LR test suggested that four classes were sufficient, although the Akaike Information Criterion (AIC) and the BIC supported a six-class model. The four-class solution was selected for its interpretability and parsimony; the fifth class divided the moderate class into two moderate classes that primarily differed on intercept; and the sixth class was characterized by a very sharp escalation, but only contained 1% of the sample. For drinking, the six-class model showed the best fit in terms of the AIC, BIC, and VLMR LR. However, the sixth class did not offer much additional information, essentially splitting the early-onset, chronic heavy-drinking group and the moderate adolescent/heavy adult group into three groups that primarily differed on intercept. As a result, the five-class model was selected.

For courses of smoking, group membership for each was characterized by the following trajectories: (1) nonsmokers and low-frequency smokers (50%); (2) stable moderate smokers (23%); (3) delayed-onset smokers (7%); and (4) early-onset, chronic heavy smokers (20%). Figure 7.3 (top) shows frequency of smoking as a function of class membership. For courses of drinking, group membership for each was characterized by the following trajectories: (1) nondrinkers and low-frequency drinkers (6%); (2) stable moderate drinkers (8%); (3) delayed-onset drinkers (10%); (4) moderate adolescent/heavy adult drinkers (47%), and (5) early-onset, chronic heavy drinkers (29%). Figure 7.3 (bottom) shows frequency of drinking as a function of class membership.

To evaluate concordance between courses of tobacco and alcohol use, a cross-tabulation of group membership for smoking and drinking was created (i.e., a 4×5 table) and measures of association were calculated. Given the lack of independence with twin pairs, the p-value is reported for the design-based χ^2.[178] For this analysis, group membership was assigned using posterior probabilities—that is, assigning an individual to the class to which he or she was most likely to belong. As shown in table 7.4, smoking and drinking were associated: $\chi^2(12, N = 970) = 221.85$, $p < .001$; $\Phi = .48$; Cramer's V = .28.

Table 7.3 Fit Indices and Likelihood Ratio Tests for Relative Improvement in Fit for Smoking, Drinking, and Dual Smoking and Drinking

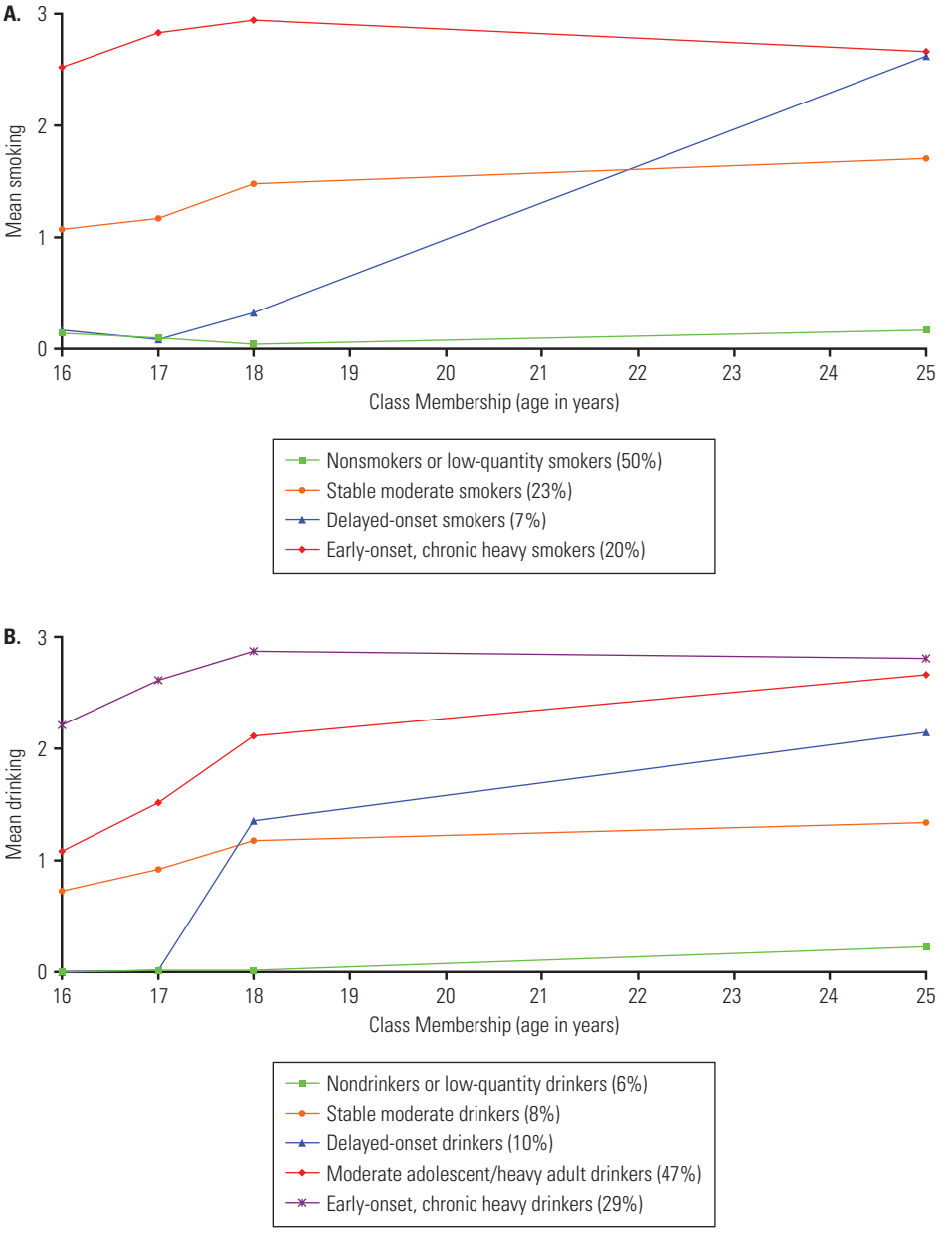
Number of classes	Test of model fit	Smoking	Drinking	Smoking and drinking
1	AIC	8973.74	9607.94	18581.69
	BIC	8998.13	9632.33	18630.46
	VLMR LR	N/A	N/A	N/A
	Entropy	N/A	N/A	N/A
2	AIC	7068.13	8661.23	16091.76
	BIC	7112.02	8705.13	16174.68
	VLMR LR	$p < .0001$	$p < .0001$	$p < .0001$
	Entropy	.92	.82	.91
3	AIC	6645.32	8251.50	15541.20
	BIC	6708.72	8314.91	15658.26
	VLMR LR	$p < .0001$	$p < .0001$	$p = .2986$
	Entropy	.88	.80	.90
4	AIC	6563.85	8141.28	15137.59
	BIC	6646.77	8224.19	15288.78
	VLMR LR	$p < .0001$	$p = .0062$	$p = .0008$
	Entropy	.87	.74	.88
5	AIC	6522.93	8095.42	14837.60
	BIC	6625.36	8197.84	15022.94
	VLMR LR	$p = .1355$	$p = .0089$	$p = .0003$
	Entropy	.82	.76	.88
6	AIC	6503.06	8054.69	14696.31
	BIC	6624.99	8176.62	14915.79
	VLMR LR	$p = .2774$	$p = .0011$	$p = .3274$
	Entropy	.84	.74	.85
7	AIC	—	—	14583.52
	BIC			14837.15
	VLMR LR			—[a]
	Entropy			.84
8	AIC	—	—	14505.21
	BIC			14792.97
	VLMR LR			—[a]
	Entropy			.83

Note. $N = 970$. AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; VLMR LR = Vuong-Lo-Mendell-Rubin likelihood ratio test for k versus $k+1$ classes; N/A = not applicable; — = model could not be estimated.

[a]Likelihood ratio test would not converge properly.

To identify specific patterns of comorbidity that accounted for the concordance between courses of tobacco and alcohol use, a first-order configural frequency analysis technique was used.[179] Although there were 20 (4×5) different potential trajectories of smoking and drinking, some of these particular combinations of smoking and drinking were more likely to occur than chance ("types") and some were less likely to occur than chance ("antitypes"). This was done by testing observed versus expected cell frequencies in the smoking-drinking contingency table shown in table 7.4. Using Lehmacher's approximation to the binomial probability (with Küchenhoff's correction for continuity),[179] significant types and antitypes were identified on the basis of a cell χ^2 value 6.64, which indicates significance at $p < .01$ for a single degree of freedom. From these types and antitypes (denoted in table 7.4 by up and down arrows, respectively), several

Figure 7.3 Trajectories of Smoking (A) and Drinking (B)



Note. In the top graph (A), the y-axis indicates (0) I have never smoked, (1) I smoke less than once a week or am trying to quit, (2) I smoke once or more a week but not daily, and (3) I smoke once or more daily. In the bottom graph (B), the y-axis indicates (0) I do not use alcohol at all, (1) I drink less than once a month, (2) I drink at least once a month but less than weekly, and (3) I drink at least once a week. Data for analyses were collected between 1991–2003.

Table 7.4 Cross-Tabulations of Frequency and Cell Proportions of Group Membership for Smoking and Drinking for the Full Sample

	Smoking									
	Nonsmokers and low freq.		Stable moderate		Delayed onset		Early onset, chronic heavy		Marginals	
Drinking	Freq.	%	Freq.	%	Freq.	%	Freq.	%	Freq.	%
Nondrinkers and low frequency	40	4.1	11	1.1	3	0.3	8	0.8	62	6.4
Stable moderate	64↑	6.6	8	0.8	3	0.3	5↓	0.5	80	8.2
Delayed onset	73↑	7.5	7↓	0.7	14↑	1.4	1↓	0.1	95	9.8
Moderate adolescent/ heavy adult	248	25.6	105	10.8	34	3.5	65↓	6.7	452	46.6
Early onset, chronic high	58↓	6.0	95↑	9.8	12	1.2	116↑	12.0	281	29.0
Marginals	483	49.8	226	23.3	66	6.8	195	20.1	970	

Note. Freq. = frequency. $\chi^2(12, N = 970) = 221.85$, $p < .001$; $\Phi = .48$; Cramer's V = .28. Numbers with up arrows (↑) indicate values that are significantly greater ($p < .01$, based on a cell χ^2 value of 6.64 with 1 degree of freedom) than would be expected by chance ("types"). Numbers with down arrows (↓) indicate values that are significantly less ($p < .01$) than would be expected by chance ("antitypes").

conclusions can be drawn. Early-onset, chronic heavy smokers were most likely to be early-onset, chronic heavy drinkers and least likely to be moderate- or delayed-onset drinkers. Stable moderate smokers were also likely to be early-onset, chronic heavy drinkers. Those with a delayed onset in smoking also showed a delayed onset for drinking, suggesting that these patterns of use track one another. Finally, non/low smokers were most likely to be stable moderate drinkers or to show delayed onset of drinking.

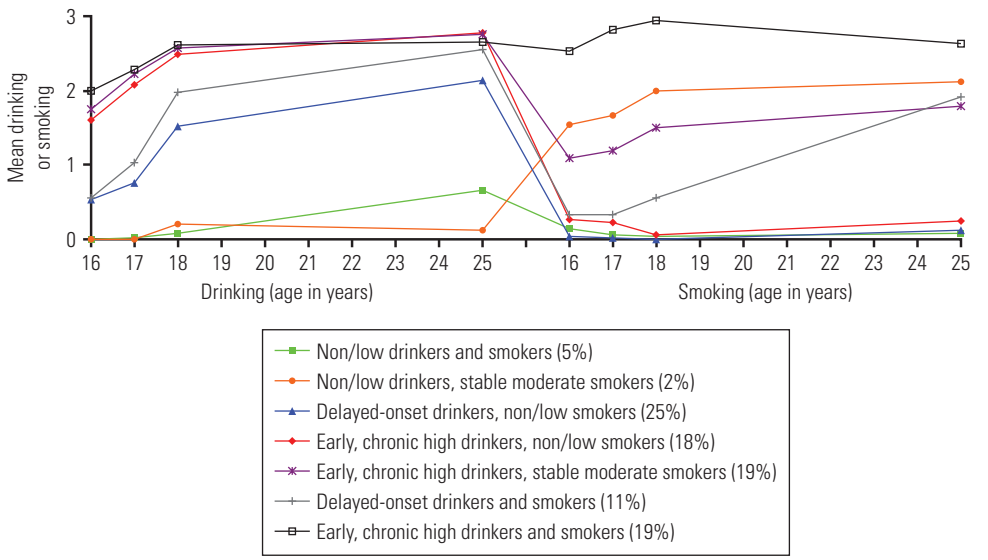
Extracting Conjoint Courses of Tobacco and Alcohol Use

Next, courses of smoking and drinking were identified in a single multivariate analysis. One- through eight-class models were tested (see table 7.3 for fit indices). The eight-class model demonstrated the best fit on the basis of the AIC and BIC, but the eighth class was not substantively meaningful (partitioning a single group into two groups that differed only in level of frequency). As such, the seven-class model was selected; figure 7.4 presents the developmental courses for the conjoint trajectories of smoking and drinking. Group membership for each was characterized by the following trajectories: (1) non/low drinkers and smokers (5%); (2) non/low drinkers, stable moderate smokers (2%); (3) delayed-onset drinkers, non/low smokers (25%); (4) early, chronic high drinkers, non/low smokers (18%); (5) early, chronic high drinkers, stable moderate smokers (19%); (6) delayed-onset drinkers and smokers (11%); and (7) early, chronic high drinkers and smokers (19%).

Comparison of Approaches to Studying Conjoint Use

Two methods are presented to examine concurrent smoking and drinking: (1) modeling course of each substance separately and examining concordance between the substances, and (2) extracting a single factor of latent group membership from both smoking and drinking measurements. For the most part, similar conclusions could be reached from these two analyses. The three most prevalent

Figure 7.4 Trajectories of Conjoint Drinking (left side) and Smoking (right side)



Note. The y-axis for drinking indicates (0) I do not use alcohol at all, (1) I drink less than once a month, (2) I drink at least once a month but less than weekly, and (3) I drink at least once a week. The y-axis for smoking indicates (0) I have never smoked, (1) I smoke less than once a week or am trying to quit, (2) I smoke once or more a week but not daily, and (3) I smoke once or more daily. Data for analyses were collected between 1991–2003.

groups in the dual-trajectory model (delayed-onset drinkers, non/low smokers; early, chronic high drinkers, stable moderate smokers; and early, chronic high drinkers and smokers) were identified as types according to the contingency table (table 7.4). In addition, the delayed-onset drinker and smoker class, which was somewhat prevalent (11%), was identified as a type. The two smallest classes in the dual-trajectory model—the non/low drinkers and smokers and the non/low drinkers and stable moderate smokers—were not identified as types in the contingency table. The only discrepant finding was that of the early, chronic high drinker and non/low smoker group. Although this group was rather prevalent in the dual-trajectory model, it was actually an antitype in the contingency table. However, there was a significant type for the stable moderate drinking group and non/low smoking group. Given that the levels of drinking frequency of the early, chronic high drinkers and the stable moderate drinkers had converged by 25 years of age, this finding is not so anomalous.

In sum, the two approaches showed consistency in identifying distinct phenotypes of smokers and drinkers that may be valuable for genetic study. However, clear differences exist in methodological approach, and it is faulty to assume that classes that "exist" in one approach will be mirrored in the other.

Trajectories as Informative Phenotypes

To establish the value of these trajectories as informative phenotypes for genetic study, the extent to which membership in the trajectories was concordant for twin 1 and twin 2 was considered, followed by an examination of agreement as a function of zygosity. Table 7.5 shows the concordance between twin 1 and twin 2 for the four smoking courses (top) and for

the five drinking courses (bottom) for the full sample (collapsed across zygosity). Concordance was high for smoking class membership: $\chi^2(9, N = 485) = 280.12$, $p < .001$; $\Phi = .76$; Cramer's V = .44; $\kappa = .45$ (95% confidence interval [CI], .39–.51). Concordance was equally high for drinking class membership: $\chi^2(16, N = 485) = 490.31$, $p < .001$; $\Phi = 1.01$; Cramer's V = .50; $\kappa = .46$ (95% CI, .40–.53). Not unexpectedly, twin pairs showed overlap for corresponding classes (i.e., significant types represented by the cells along the diagonal of table 7.5; several significant antitypes along the off-diagonal).

Next, cross-substance twin concordance was explored; that is, the associations between twin 1 smoking and twin 2 drinking and vice versa were examined (table 7.6). Developmental course of smoking in one twin and course of drinking in the other twin showed a moderate association: $\chi^2(12, N = 485) = 71.45$, $p < .001$; $\Phi = .38$; Cramer's V = .22 (for twin 1 smoking and twin 2 drinking; the converse association was nearly identical). Given the strength of the cross-twin agreement (table 7.5) for smoking ($\Phi = .76$; Cramer's V = .44) and for drinking ($\Phi = 1.01$; Cramer's V = .50), these cross-substance associations are notable.

Finally, the extent to which twin 1 membership in the conjoint smoking-drinking course was concordant with twin 2 membership was examined. Concordance for the dual trajectories was very good: $\chi^2(36, N = 485) = 719.81$, $p < .001$; $\Phi = 1.22$; Cramer's V = .50; $\kappa = .41$ (95% CI, .36–.47). Interestingly, when considering the likelihood-based parameters (Φ and Cramer's V), cross-twin agreement for the conjoint trajectories was higher than concordance for each substance modeled individually; the magnitude for the kappas was nearly identical.

Next, concordance within and between substances as a function of zygosity was examined. For smoking, monozygotic twins showed stronger class membership agreement, $\chi^2(9, N = 213) = 190.36$, $p < .001$; $\Phi = .95$; Cramer's V = .55; $\kappa = .57$ (95% CI, .48–.66), than did dizygotic twins, $\chi^2(9, N = 272) = 109.49$, $p < .001$; $\Phi = .63$; Cramer's V = .37; $\kappa = .36$ (95% CI, .27–.44). The nonoverlapping confidence intervals on the kappa coefficients suggest that the stronger concordance for monozygotic twins was significant.

A similar pattern was observed for drinking: monozygotic twins showed higher concordance, $\chi^2(16, N = 213) = 341.81$, $p < .001$; $\Phi = 1.27$; Cramer's V = .63; $\kappa = .58$ (95% CI, .49–.67), than did dizygotic twins, $\chi^2(16, N = 272) = 185.83$, $p < .001$; $\Phi = 0.83$; Cramer's V = .41; $\kappa = .36$ (95% CI, .28–.45). Again, nonoverlapping confidence intervals on the kappa coefficients suggest significant differences in concordance for monozygotic versus dizygotic twins.

Finally, using the conjoint trajectories, cross-twin concordance was higher for monozygotic twins, $\chi^2(36, N = 213) = 463.73$, $p < .001$; $\Phi = 1.48$; Cramer's V = .60; $\kappa = .55$ (95% CI, .47–.63), than for dizygotic twins, $\chi^2(36, N = 272) = 298.29$, $p < .001$; $\Phi = 1.05$; Cramer's V = .43; $\kappa = .31$ (95% CI, .24–.38), again with evidence that the concordance was significantly higher among monozygotic twin pairs.

Summary of Empirical Example

In the example from Finn Twin16-25, the general techniques involved in characterizing developmental course of the use of two co-occurring substances is illustrated and preliminary evidence of genetic influences underlying conjoint substance use is presented. Four trajectories of smoking during adolescence and young adulthood are identified, including nonsmokers, stable moderate smokers (perhaps "chippers"),[180] and two groups that exhibited high smoking by 25 years of

Table 7.5 Cross-Tabulations of Frequency (Cell Proportion) of Group Membership for Twin 1 Versus Twin 2 (across Zygosity) for Smoking (top) and for Drinking (bottom)

	Twin 2 smoking									
	Nonsmokers and low frequency		Stable moderate		Delayed onset		Early onset, chronic heavy		Marginals	
Twin 1 smoking	Frequency	%	Frequency	%	Frequency	%	Frequency	%	Frequency	%
Nonsmokers or low frequency	181↑	37.3	32↓	6.6	11	2.3	10↓	2.1	234	48.2
Stable moderate	32↓	6.6	57↑	11.8	4	0.8	20	4.1	113	23.3
Delayed onset	21	4.3	3	0.6	11↑	2.3	4	0.8	39	8.0
Early onset, chronic heavy	15↓	3.1	21	4.3	1	0.2	62↑	12.8	99	20.4
Marginals	249	51.3	113	23.3	27	5.6	96	19.8	485	

	Twin 2 drinking											
	Nondrinkers and low frequency		Stable moderate		Delayed onset		Moderate adolescent/ heavy adult		Early onset, chronic high		Marginals	
Twin 1 drinking	Frequency	%	Frequency	%	Frequency	%	Frequency	%	Frequency	%	Frequency	%
Nondrinkers or low frequency	20↑	4.1	4	0.8	3	0.6	3↓	0.6	0↓	0	30	6.2
Stable moderate	3	0.6	14↑	2.9	4	0.8	14	2.9	3	0.6	38	7.8
Delayed onset	4	0.8	5	1.0	26↑	5.4	14	2.9	1↓	0.2	50	10.3
Moderate adolescent, heavy adult	4↓	0.8	17	3.5	11	2.3	153↑	31.6	43↓	8.9	228	47.0
Early onset, chronic high	1↓	0.2	2↓	0.4	1↓	0.2	40↓	8.2	95↑	19.6	139	28.7
Marginals	32	6.6	42	8.7	45	9.3	224	46.2	142	29.3	485	

Note. For top: $\chi^2(9, N = 485) = 280.12$, $p < .001$; $\Phi = .76$; Cramer's V = .44; $\kappa = .45$ (95% confidence interval [CI], .39–.51) (across zygosity). For monozygotic twins (cross-tabulations not shown), $\chi^2(9, N = 213) = 190.36$, $p < .001$; $\Phi = .95$; Cramer's V = .55; $\kappa = .57$ (95% CI, .48–.66). For dizygotic twins (cross-tabulations not shown), $\chi^2(9, N = 272) = 109.49$, $p < .001$; $\Phi = .63$; Cramer's V = .37; $\kappa = .36$ (95% CI, .27–.44). For bottom: $\chi^2(16, N = 485) = 490.31$, $p < .001$; $\Phi = 1.01$; Cramer's V = .50; $\kappa = .46$ (95% CI, .40–.53) (across zygosity). For monozygotic twins (cross-tabulations not shown), $\chi^2(16, N = 213) = 341.81$, $p < .001$; $\Phi = 1.27$; Cramer's V = .63; $\kappa = .58$ (95% CI, .49–.67). For dizygotic twins (cross-tabulations not shown), $\chi^2(16, N = 272) = 185.83$, $p < .001$; $\Phi = 0.83$; Cramer's V = .41; $\kappa = .36$ (95% CI, .28–.45).

Numbers with up arrows (↑) indicate values that are significantly greater ($p < .01$, based on a cell χ^2 value of 6.64 with one degree of freedom) than would be expected by chance ("types"). Numbers with down arrows (↓) indicate values that are significantly less ($p < .01$) than would be expected by chance ("antitypes"). Not all numbers add to 100% because of rounding.

Table 7.6 Cross-Tabulations of Frequency (Cell Proportion) of Group Membership for Twin 1 Smoking by Twin 2 Drinking (top) and Twin 2 Smoking by Twin 1 Drinking (bottom)

	Twin 1 smoking									
	Nonsmokers and low frequency		Stable moderate		Delayed onset		Early onset, chronic heavy		Marginals	
Twin 2 drinking	Frequency	%	Frequency	%	Frequency	%	Frequency	%	Frequency	%
Nondrinkers and low frequency	16	3.3	8	1.6	2	0.4	6	1.2	32	6.6
Stable moderate	26	5.4	8	1.6	2	0.4	6	1.2	42	8.7
Delayed onset	34↑	7.0	5	1.0	6	1.2	0↓	0	45	9.3
Moderate adolescent/heavy adult	118	24.3	56	11.6	21	4.3	29	6.0	224	46.2
Early onset, chronic high	40↓	8.2	36	7.4	8	1.6	58↑	12.0	142	29.3
Marginals	234	48.2	113	23.3	39	8.0	99	20.4	485	

	Twin 2 smoking									
	Nonsmokers and low frequency		Stable moderate		Delayed onset		Early onset, chronic heavy		Marginals	
Twin 1 drinking	Frequency	%	Frequency	%	Frequency	%	Frequency	%	Frequency	%
Nondrinkers and low frequency	14	2.9	10	2.1	3	0.6	3	0.6	30	6.2
Stable moderate	27	5.6	5	1.0	2	0.4	4	0.8	38	7.8
Delayed onset	39↑	8.0	4	0.8	3	0.6	4	0.8	50	10.3
Moderate adolescent/heavy adult	130	26.8	51	10.5	14	2.9	33	6.8	228	47.0
Early onset, chronic high	39↓	8.0	43	8.9	5	1.0	52↑	10.7	139	28.7

Note. $\chi^2(12, N = 485) = 74.08$, $p < .001$; $\Phi = .39$; Cramer's V = .23 (top) and $\chi^2(12, N = 485) = 71.45$, $p < .001$; $\Phi = .38$; Cramer's V = .22 (bottom). For top (twin 1 smoking by twin 2 drinking): for monozygotic twins (tables not shown), $\chi^2(12, N = 213) = 34.63$, $p < .001$; $\Phi = .40$; Cramer's V = .23; for dizygotic twins, $\chi^2(12, N = 272) = 57.47$, $p < .001$; $\Phi = .46$; Cramer's V = .27. For bottom (twin 1 drinking by twin 2 smoking): for monozygotic twins (tables not shown), $\chi^2(12, N = 213) = 36.71$, $p < .001$; $\Phi = .42$; Cramer's V = .24; for dizygotic twins, $\chi^2(12, N = 272) = 49.58$, $p < .001$; $\Phi = .43$; Cramer's V = .25.

Numbers with up arrows (↑) indicate values that are significantly greater ($p < .01$, based on a cell χ^2 value of 6.64 with one degree of freedom) than would be expected by chance ("types"). Numbers with down arrows (↓) indicate values that are significantly less ($p < .01$) than would be expected by chance ("antitypes"). Not all numbers add to 100% because of rounding.

age but whose smoking was distinguished during adolescence, with one group initiating use at a much earlier age than the other group. Five trajectories of drinking were characterized, including the same patterns of use as those identified for smoking as well as an additional one that reflected high use by 25 years of age but moderate use at study initiation. It was demonstrated that longitudinal phenotypes of smoking and drinking showed similar patterns of change, particularly for those with onset at an early age and those who exhibited delayed onset but still heavy use by young adulthood. In addition, smokers who began at an early age were also likely to initiate heavy drinking at some later point; this could be evidence for a directional relation between smoking and drinking, or perhaps it might be due to contextual variables that permitted the younger adolescent access or opportunity to smoke but not drink. Non/low smokers generally exhibited some drinking, consistent with norms in Finland for high-density drinking, often to intoxication.[181,182]

In addition to examining the relation between developmental courses of two substances, conjoint courses were characterized represented by both smoking and drinking behaviors. Some groups were identified that might be expected on the basis of the results from the single-substance trajectories (i.e., early-onset, chronic high users of both substances; delayed-onset users of both substances; non/low smokers who drank with low frequency), as well as some additional groups that were discriminated on the basis of smoking and drinking (i.e., non/low drinking with stable moderate smoking; early-onset, chronic high drinkers who were non/low smokers or moderate smokers; delayed-onset drinkers who were non/low smokers).

For both approaches, the question was asked as to whether there was preliminary evidence for genetic influences underlying course of substance use, as well as common influences underlying the courses of conjoint substance use. Concordance between twin pairs differed as a function of zygosity, with monozygotic twins showing greater concordance for smoking and for drinking than did dizygotic twins. Of importance, the conjoint trajectories revealed even greater concordance than the single-substance trajectories, underscoring the value of utilizing substance-use phenotypes that capture as much information as possible.

That greater concordance for trajectories of substance use among monozygotic twin brothers was found suggests genetic influences, but it must be emphasized that genetic effects suggested by these analyses may reflect gene-environment correlations, arising from genetically conditioned differences in susceptibility to environmental exposure rather than from independent genetic effects. It should also be emphasized that these analyses necessarily make the usual assumptions underlying twin comparisons, including the assumption that outcome-relevant environmental experience does not differ between monozygotic and dizygotic twin brothers. Substance use is influenced by siblings' shared experiences and their reciprocal interactions,[183] and greater similarities in smoking and drinking trajectories of monozygotic twin brothers may, in part, reflect their greater frequency of social contact and greater overlap in peer networks.[184] Social contact among adult Finnish twin brothers accounts for significant variance in their patterns of alcohol consumption, but modeling the effect of social contact does not markedly reduce estimates of genetic variance; instead, it reduces the variance otherwise attributed to unmeasured (and unshared) residual environmental sources.[183] Accordingly, the inference made here that genetic influences contribute to different trajectories of substance use appears to be an appropriate one.

This is the first study to consider the extent to which courses of substance use might be heritable and to offer evidence that pathways of substance use may be genetically influenced. Given that there is value in using longitudinal phenotypes such as these, it is important to consider how genetic research might use these phenotypes. Membership in a given developmental trajectory, captured by a single categorical latent variable, reflects age of onset and severity as well as change (slope) in use of a substance; moreover, membership in a trajectory characterized by concurrent use of two (or more) substances simultaneously provides information for multiple substances. Previously, research that sought to examine these constructs had to model four separate pieces of information. Although latent growth models do provide information regarding onset, severity, and course, they reflect "average" change and fail to capture homogeneous groups or subtypes. To explore the heritability of class membership, the variance components of the underlying variability can be modeled (e.g., with Cholesky decomposition models) by using a series of dummy codes that represent the nominal classes (or polychoric correlations if the classes lie on an underlying continuum). These analyses might build on work by Eaves and colleagues,[185,186] which examined the extent to which patterns of pairwise concordance and discordance in latent class membership differed between monozygotic and dizygotic twin pairs. A quantifiable estimate of the genetic contribution to the risk of taking different pathways in development is an area for further development. In addition, certain groups might be selected as "extreme" groups that can be genotyped in a more efficient manner than genetic analyses that must consider the entire sample.

This study has demonstrated the utility of using a latent variable reflecting course characterizing use of multiple substances. However, researchers must use theory to guide analyses with the goal of comparing subtypes that are of theoretical interest. For example, a researcher might select two courses of smoking that are characterized by similar age of onset but different slope or level of severity (or vice versa) and conduct comparisons between these courses. For concurrent use of substances, a researcher may wish to compare courses represented by a single substance with courses represented by multiple substances (e.g., a course characterized by high smoking and low drinking versus a course characterized by high smoking and high drinking). If the genetic influence underlying the latter is no stronger than the former, one might infer presence of a common underlying genetic influence.

The methodological issues that arise when characterizing course of multiple substances should be noted. First, the investigator should decide what analytic approach to take—that is, whether to simultaneously model multiple latent growth factors (e.g., one for each substance) in a single multivariate analysis or whether to derive courses for each substance separately and then model conjoint use by estimating concordance between each substance-based trajectory.[187] Each approach has advantages.

The first approach (i.e., the multivariate approach) explicitly models comorbidity and its change over time. It is also more parsimonious than the second approach. For example, if one considers four courses of smoking and five courses of drinking (as suggested in the preceding univariate analyses), there are 20 possible combinations of smoking and drinking. However, the analyses presented here suggest no more than seven dual trajectories. That is, using multiple univariate (one substance at a time) approaches to model comorbidity, the investigator can be modeling forms of comorbidity that are unlikely to exist in nature but are implied by bringing together univariate solutions.

However, the virtue of the univariate approach is that it provides estimates of trajectories that are specific to a target outcome (e.g., smoking only) and thus are not influenced by aspects of the comorbid behavior not directly relevant to the substances under consideration. For example, one might expect differing determinants of a comorbid course than of a single-substance course (e.g., availability of both substances; social norming of both smoking and drinking behavior). In addition, a common genetic influence is likely for multiple problem behaviors other than substance use.[48,49] As a result, adequately specifying the phenotype underlying use of both substances becomes increasingly complex. Finally, this essentially univariate approach provides estimates of comorbidity (e.g., concordance) that are similar to more traditional cross-sectional approaches (e.g., a likelihood-based measure or a measure of agreement such as Cohen's kappa). It is noted that both approaches become more challenging when three or more substances are considered both illustratively and, especially in the multivariate case, computationally. It is reassuring, however, that the two approaches yielded similar findings in the empirical example.

In addition, the empirical example fails to resolve other aspects of substance involvement such as average and maximum quantity consumed and substance-use disorders and problems. In prior work,[117] it was shown that classes based on different facets of drinking behavior can show similar course shapes (i.e., corresponding intercepts and slopes) but different course prevalences and low-to-moderate cross-class memberships (i.e., assignment to "similar-looking" classes on the basis of different input variables). As such, the present example is a simplification, and distinctions may be observed between different aspects of smoking behavior in terms of developmental course.

In a related way, trajectory shape and prevalence may differ as a function of the developmental period under consideration. In chapter 5, the authors characterize trajectories over a broader age span (ages 10–32 years) than in the present example (ages 16–25 years); the authors were able to extract five latent classes as well as identify three a priori groups. Many of the trajectories observed in that chapter correspond to this one, including an early-onset, persistent group; a moderate/experimenter group; and a group of abstainers making up roughly one-half the sample. However, in contrast to the findings presented here, chapter 5 identifies two distinct delayed-onset groups. It is likely that the present delayed-onset group—those who began smoking at about 17 years of age—maps onto the two delayed-onset groups in chapter 5, with onset at ages 14 and 18 years, respectively. In addition, whereas smoking by 25 years of age was equally high for the early- and delayed-onset groups in the present example, in chapter 5 the delayed-onset groups failed to "catch up" to the early-onset, persistent group by 32 years of age. Finally, the present chapter did not identify a group of smokers who had quit; it is not unlikely that had the participants been followed for an additional decade or so, a corresponding quitter group would have been observed.

Another methodological consideration concerns modeling age of onset for simultaneous processes. There is an exciting class of models in which trajectory classes can be derived on the basis of growth mixtures, but initiation serves as the intercept (i.e., course is modeled separately from age).[188] However, there appear to be conceptual and estimation challenges extending such "initiation-based intercept models" to multiple substances; courses of multiple substances may show comparable trajectory structure but mismatched onsets.

In addition, when considering the association between two substances, it is important to consider the extent to which an association is due to a group of constant nonusers or abstainers. Prescott and Kendler[81] raised the question of whether much of the genetic covariation between tobacco and alcohol use may be due to the large group of abstainers; they found that shared (genetic) variation between tobacco and alcohol use was much reduced when abstainers were removed. Tucker and colleagues[156] noted that the greatest overlap across substances was among abstainers. Interestingly, when excluding abstainers from the present analyses, virtually no reduction was observed in cross-twin association for the conjoint trajectories: $\chi^2(25, N = 485) = 618.88$, $p < .001$; $\Phi = 1.18$; Cramer's V = .53; $\kappa = .42$ (95% CI, .37–.48); this was true within zygosity as well.

An alternative approach to examining genetic influences on variability on course involves two-stage genetic models that distinguish between initiation and progression of use;[189,190] integration of these models with the developmental approach might yield the most informative phenotypes. It seems likely that the two approaches (i.e., two-stage genetic models that independently estimate effects on initiation and effects on progression, conditional on initiation, and genetic models of growth mixtures or other types of trajectories) will yield different types of insights or phenomena. For example, the two-stage genetic models seem especially useful for identifying risk factors that are specific to various phases of substance-use careers.[191] The growth mixture approach offers an opportunity to derive empirically based complex phenotypes that capture associated clinical features, course, and developmental references.

It is important to note that although course is an essential dimension for characterizing behavior or disorder, it is not necessarily a "genetic" one. Although some degree of chronicity is almost certainly related to the degree of genetic risk, genetically identical individuals who are afflicted with the same largely genetic condition can show marked variation in course.[192] As is true in all forms of genetic modeling, inclusion of more explicit measures of the environment—both fixed (e.g., early toxic exposure) or time varying (e.g., environments supportive or suppressive of substance use, various role occupancies)—can only serve to sharpen an assessment of the environment and better understand key characteristics such as course.

Finally, these analyses were based on a Finnish sample of twin brothers; generalizability to nontwins and other cultures with different genetic backgrounds, cultural influences surrounding tobacco and other drug use, and formal alcohol and tobacco prevention and control policies may not be straightforward. However, prior work[160,193,194] shows that overall patterns of trajectories are quite similar in Finland to those studied elsewhere.

Summary

The goal of this chapter is to explore the extent to which developmental courses of substance use are nonspecific or whether there are developmental phenotypes that are unique to tobacco use. The review of the extant literature and the empirical example suggest that there is evidence for both of these notions. The identification of comparable overlapping developmental pathways for smoking and drinking supports the idea of an underlying general factor indicating common liability (perhaps genetic) to the use of multiple substances. Yet, identification of groups with divergent trajectories of multiple substances (e.g., moderate or chronic high drinking by nonsmokers; both abstention and early-onset, chronic drinking by

moderate smokers) suggests substance-specific pathways. As the example in this chapter clearly shows, both common and specific developmental pathways can coexist. A worthwhile goal for future genetic research would be to examine the extent to which different combinations of course are genetically influenced. For example, one might expect, based on Prescott and Kendler[81] and Tucker and colleagues[156] (although perhaps not from the example in the present chapter), that membership in the low-using/abstaining course for both groups would be highly genetically influenced and that membership in a course marked by low smoking and delayed-onset drinking might be more environmentally influenced. Clearly, the opportunities for identifying highly genetically influenced substance-use behaviors are considerable.

As summarized earlier, a body of research demonstrates evidence of shared genetic risk for use of different substances. However, much of this work relies on lifetime substance use or dependence. If one wishes to distinguish among syndromes that are chronic, episodic, developmentally limited, or reactive and transient, it is critical to prospectively characterize the course of substance use and problems. Although much work has described the developmental course of single substances over the period from adolescence to adulthood, researchers have now begun to simultaneously consider multiple substances. Studies that jointly consider comorbidity and course will permit researchers to determine the extent to which trajectories unique to a single substance versus those reflecting substance use more generally best identify longitudinal phenotypes for genetic study. If it can be shown that phenotypes represented by broader substance-use trajectories are equally or more heritable than single-substance trajectories, both phenotypic and genetic work can proceed more efficiently. Findings would also have implications for whether researchers should take a more generic approach in the prevention and treatment of substance-use disorders. It is hoped that this chapter will inspire researchers to conduct work that reveals the optimal longitudinal phenotype for understanding genetic effects on substance use and substance-use disorders.

Conclusions

1. Studies examining the developmental course of multiple substances have shown relatively high concordance between identified trajectories despite diverse course shapes and different course prevalences.
2. Membership in a given developmental trajectory, which can be captured by a single categorical latent variable, represents age of onset and severity as well as change (slope) in use of a substance; moreover, membership in a trajectory characterized by concurrent use of two (or more) substances simultaneously provides information for multiple substances.
3. Developmental course might serve as a valuable phenotype for biometric models, and determining the degree to which a phenotype of developmental course is substance specific is valuable for the genetic study of addictive behavior.
4. Evidence using twin data indicates that courses of substance use are genetically influenced, with monozygotic twins showing greater concordance for smoking and for drinking than do dizygotic twins. The genetic contribution to the risk of taking different pathways in development represents an area for further study.
5. Conjoint trajectories of drinking and smoking reveal even greater concordance than do single-substance trajectories, suggesting greater heritability for courses extracted from several substances. This underscores the value of considering

substance use across multiple domains when constructing phenotypes for research and perhaps even for clinical use. However, extending the concept of the components of developmental substance-use phenotypes raises new questions such as, Which substances? What aspects of substance use or its consequences? Which periods of development? Thus, the findings show the value of extending the concept of substance-use phenotypes but not necessarily optimal phenotypes that "carve nature at its joints."

6. If resources are limited for genetic analyses, focusing on those with the most "extreme" phenotypes marked by both high initial level and chronic continued use may represent an efficient strategy for identifying genes associated with more problematic forms of substance use.

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