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Developmental Trajectories of Alcohol Use and Alcohol Use Disorder

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Developmental Trajectories of Alcohol Use and Alcohol Use Disorder

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by

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*Indicates manuscripts that have already been accepted for publication. These manuscripts have been modified to be included in this dissertation.

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List of Abbreviations

A: Additive genetic factors

ADH7: Alcohol dehydrogenase 7

ADH1B: Alcohol dehydrogenase 1B

ADH1C: Alcohol dehydrogenase 1C

ALDH2: Alcohol dehydrogenase 2

ALSPAC: Avon Longitudinal Study of Parents and Children

ANKK1: Ankyrin repeat and kinase domain containing 1

ARM: Autoregressive model

AU: Alcohol use

AUD: Alcohol use disorder

AUDIT: Alcohol Use Disorder Identification Test

C: Shared environmental factors

CIDI: Composite International Diagnostic Interview

DCS: Dual change score model

DDC: Dopa decarboxylase

DNA: Deoxyribonucleic acid

DRD2: Dopamine receptor D_2

DRD4: Dopamine receptor-4 gene

DSM: Diagnostic and Statistical Manual of Mental Disorders

DZ: Dizygotic twins

E: Unique environmental factors

GABA: Gamma-aminobutyric acid

GABRA2: Gamma-aminobutyric acid type A receptor alpha2 subunit

GI: Gene-by-intervention interaction

GWAS: Genome-wide association studies

GxE: Gene-by-environment interaction

HWE: Hardy-Weinberg equilibrium

ICD: International Classification of Diseases

IRB: Institutional Review Board

LD: Linkage disequilibrium

LGM: Latent growth model

MAF: Minor allele frequency

MZ: Monozygotic twins

NIPH: Norwegian Institute of Public Health

PM: Parental monitoring

PGD: Peer group deviance

PD: Personality disorders

PRS: Polygenic risk scores

SIDP: Structured Interview for DSM-IV Personality

SNP: Single nucleotide polymorphism

TPH2: Tryptophan Hydroxylase 2

VATSPSUD: Virginia Adult Twin Study of Psychiatric and Substance Use Disorders

Abstract

DEVELOPMENTAL TRAJECTORIES OF ALCOHOL USE AND ALCOHOL USE DISORDER

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A dissertation submitted in partial fulfillment of the requirements for the degree Doctor of Philosophy at Virginia Commonwealth University.

Virginia Commonwealth University, 2017.

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Alcohol use (AU) and alcohol use disorder (AUD) are leading causes of morbidity, premature death, and economic burden. They are also associated with high levels of disability and many other negative outcomes. Twin and family studies have consistently shown that AU and AUD are complex traits influenced by both genetic and environmental factors. Although much has been learned about the genetic and environmental etiology of AU and AUD, significant gaps remain. These include the need for a more comprehensive understanding of the roles of risk and protective factors, and the nature of developmental trajectories underpinning the progression from AU to AUD. The aims of this dissertation are: (1) to examine the roles of resilience and personality disorders in the etiology of AU and AUD; (2) to investigate the nature of longitudinal

changes in genetic and environmental risk factors responsible for individual differences in AU; and (3) to determine the moderating roles of key environmental risk factors on the impact of aggregate molecular, or polygenic, risk for AU during adolescence. Using both biometrical behavioral genetic and molecular genetic methodologies, five key findings were observed: (1) Resilience is strongly associated with a reduction in risk for AUD, and this relationship appears to be the result of overlapping genetic and shared environmental influences; (2) Borderline and antisocial personality disorders are the strongest and most stable personality pathology predictors of the phenotypic and genotypic liability to AU and AUD across time; (3) Genetic influences on the development of AUD from early adulthood to mid-adulthood are dynamic, whereby two sets of genetic risk factors contribute to AUD risk; (4) The specific genetic influences on AU follow an unfolding pattern of growth over time, whereas unique environmental risk factors are consistent with an accumulation of environmental impacts and risks across time; and (5) High peer group deviance and low parental monitoring are associated with increased AU, while early parental monitoring moderates the polygenic risk for AU at age 20. The implications of these results with regard to prevention and intervention efforts are discussed.

Chapter 1: Global Introduction

Introduction

Alcohol use (AU) and alcohol use disorder (AUD) are leading causes of morbidity and premature death[1,2]. Excessive or chronic AU and AUD are a significant economic burden, costing the United States as much as $250 billion annually[3,4], and are associated with high levels of disability[5]. They are personally costly and associated with a plethora of negative consequences, such as greater interpersonal conflict[6-8], higher risk of injury[6-8], motor vehicle accidents[6-8], domestic violence[9], and neurocognitive impairment[10].

As defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5[11]), AUD is characterized by "a problematic pattern of alcohol use leading to clinically significant impairment or distress." In a previous edition, the DSM-IV-TR[12], AUD was classified into alcohol abuse (failing to fulfill role obligations, using in dangerous situations, legal problems, social/interpersonal problems) and alcohol dependence (a physical dependence, hallmarked by tolerance and withdrawal). However, the DSM-5 no longer maintains this distinction, and instead classifies AUD into levels of severity from mild, to moderate, to severe. Irrespective of these changes in classification, AUD is very common in the US. The lifetime prevalences of DSM-IV-TR alcohol abuse and dependence were estimated to be 17.8% and 12.5% respectively. Estimates based on the DSM-5 AUD reveal a lifetime prevalence of 29.1%[13] in the U.S.

AU is prevalent among U.S. adolescents with initiation typically occurring by age 18[14]. Over 70% of high school students in the US report having consumed at least one alcoholic beverage[15], 52.7% of high school seniors report using alcohol in the past 30 days, and 34% report drinking to intoxication[16]. Very early initiation (i.e., before age 14) is associated with significant alcohol-related problems[17-22]. For every year that alcohol initiation is delayed, there is

a 5-9% decrease in the risk of alcohol misuse[23]. Therefore, a comprehensive understanding of the etiology of AU within a developmental framework is critical, along with the need to explore and identify the behaviors and environmental risk factor that mitigate the risk of progression from AU to AUD.

Among the putative protective factors against AU and AUD is the behavioral trait of resilience. Resilience is defined as an "individual's ability to thrive despite adversity"[24-27], and has been shown to attenuate risk for AU problems among adult populations[25,28,29]. To our knowledge, resilience has not been examined as a protective trait against AU/AUD among adolescent populations or samples. This is somewhat surprising, given the large body of literature on resilience in general[30-32].

In terms of the risk factors linked to increased AU and risk for progression to AUD, personality disorders (PDs) are known to be significantly associated with AU/AUD among adults. In particular, antisocial[33-35] and borderline[35-38] PDs have been consistently and strongly associated with AU/AUD. In fact, antisocial has been shown to increase risk by as much as eight-fold[33]. Antisocial PD describes individuals with "a pervasive pattern of disregard for and violation of the rights of others," while borderline PD describes individuals with "a pervasive pattern of instability of interpersonal relationships, self-image, and affect[11]." A defining feature of both PDs is impulsivity.

AU and AUD are complex traits influenced by both genetic and environmental factors[39-41]. Genetic risk factors have consistently been shown to account for 50% - 60% of the variance, leaving 50 to 40% of the remaining variance accounted for in terms of random, non-shared aspects of the environment[41] including measurement error. The most salient and well-replicated environmental risk factors include parental monitoring (PM) (or lack of) and peer group

deviance (PGD)[20,21,42-46]. PM refers to parents' knowledge of their children's whereabouts, friends, and activities, including sources of parents' knowledge, such as child disclosure, parental solicitation, and parental control[47]. PGD describes the extent to which one's peer group engages in deviant behaviors, such as substance use and antisocial behavior. Both of these environmental risk factors have been shown to moderate the genetic risks in adolescent AU and AUD, whereby genetic influences for AU are stronger under conditions of low PM and high PGD[48-51]. These findings are consistent with genetic control of the sensitivity to the environment, whereby the risk for AU and progression to AUD is highest when permissive environments (e.g., low PM) provide the opportunity for individual differences to be increasingly explained by variance attributable to genetic risk factors[52,53]. Further, results of genetically informative, developmental studies suggest that genetic influences increase over time whereas the influence due to shared environmental factors decreases. Again, this pattern may be attributable to a relaxing or reduction in environmental constraints[51,54-56], as individuals mature and move away from environments with levels of high cultural constraint and conformity (e.g., the parental home) to environments with greater independence and freedom.

Historically, molecular genetic studies of AU and AUD focused on detecting single loci (either single nucleotide polymorphism (SNP) or single gene contributions such as in candidate gene studies)[57]. Apart from inadequate coverage, the limitations associated with candidate gene studies include insufficient power to detect true effects, lack of replication, biases resulting from specifying a specific gene a priori (which arises from reliance on prior knowledge about plausible genes that may not be sufficient, given our limited knowledge about the genes involved in complex traits)[57,58], and the consensus that behaviors such as AU and AUD are highly polygenic. Whereas candidate gene studies examine the association between one gene or one

SNP with a disorder, more recent genome-wide association studies (GWAS) examine the association between commonly tagged SNPs genome-wide with a particular disorder or disorders. Because GWAS is essentially hypothesis-free, conservative p-value corrections are required to adjust for multiple testing. However, despite the recognized need for extremely large and costly sample sizes, GWAS have already identified variants associated with increased risk of AU and AUD[58-63]. The most consistently replicated genes related to AU and AUD phenotypes involve alcohol metabolism, such as *ADH1B*[60], *ADH1C*[59,60], *ADH7*[61], and *ALDH2*[61,62]. These variants are found in genes coding for alcohol dehydrogenase (ADH cluster) and aldehyde dehydrogenase (ALDH cluster), which are enzymes that help to metabolize alcohol[58]. Some of these variants make it difficult for certain individuals to properly metabolize alcohol, resulting in unpleasant side effects, such as facial flushing and nausea, leading to decreased AU[64]. Other variants associated with AU and AUD reside within neurotransmitter systems[63,65-67]. Although evidence for these findings is mixed[68], these additional systems include serotonin synthesis (*TPH2*, *DDC*)[63,65], dopamine (*ANKK1*, *DRD2*)[66], and gamma-aminobutyric acid, or GABA (*GABRA2*)[67].

Despite these advances, the success of AU and AUD GWAS remains limited, with variants explaining only a small amount of the total phenotypic variance[58,69] (<2%[70]). Indeed, across complex psychiatric and behavioral genetics, attempts to isolate DNA polymorphisms associated with substance use disorders in general have had limited success. The primary cause is due to the large effect sizes required to overcome the statistical burden of GWAS. Although few genetic variants reach genome-wide significance in a typical GWAS, the upper tail of the distribution of GWA tests nevertheless likely contain meaningful information[58,71]. Consequently, approaches to predicting AU and AUD based on composite indices of genetic risk across many

loci (i.e., polygenic risk scores), especially when based on very large meta-analyses of all extant GWAS, are likely to have much greater success. Although this method at present typically explains between 1-3% of the variance[72,73], the approach has been successful in showing that polygenic risk scores do indeed predict AUD in independent samples[59,72-75].

Although polygenic risk scores have rarely been used in gene-by-environment (GxE) analyses to predict AU/AUD, there is at least one study that used this method and showed that polygenic risk predicted alcohol problems under conditions of low parental knowledge and high peer group deviance[76]. Classic GxE studies have historically used candidate genes in these analyses. However, this approach suffers from the same limitations posed by candidate gene studies, such as insufficient power to detect true effects and lack of consistent replication[57,58,77]. Thus, moving forward, it is likely that GxE studies will increasingly rely on polygenic risk, rather than single genes.

The broad aims of this dissertation will address significant gaps in the AU/AUD literature by: (1) examining the roles resilience and personality disorders play in the etiology of AU and AUD; (2) investigating the nature of longitudinal changes in the contributions of genetic and environmental risk factors in AU; and (3) determining the moderating roles of key environmental risk factors on the impact of polygenic risk for AU across adolescence. These three aims and the approaches required are summarized below.

The roles of resilience and personality disorders in the etiology of AU and AUD

To date, the few studies examining the extent to which resilience attenuates AUD have relied on older veteran adult samples[25,28] or samples of adults exposed to childhood abuse[29]. Importantly, only one study has examined the genetic and environmental sources of covariation[78] between resilience and AUD. Thus, the magnitude of the phenotypic relationship between AUD

and resilience, and the etiology of the covariance or overlap remain unclear, particularly among population-based samples.

Accordingly, the aim of Chapter 2 is to examine the strength of the relationship between resilience and AUD, and investigate the etiology of any covariance, using a large, population-based sample. The most commonly used multivariate technique to investigate etiological covariance is the Cholesky decomposition[79]. As shown in Figure 1.1, the Cholesky is a method of triangular decomposition where the first variable (y1) is assumed to be caused by a latent factor that can explain the variance in the remaining variables (y2…yn). The second variable (y2) is assumed to be caused by a second latent factor that can explain variance in the second as well as remaining variables. In this way, the second latent variable is restrained from explaining variance in the first observed variable. A Cholesky decomposition is specified for each latent source of variance (A, C, or E). One of the most common uses of this method is to determine the extent to which genetic and environmental influences are shared between two or more traits versus influences that are trait specific[79]. This method will be used throughout several chapters in this dissertation.

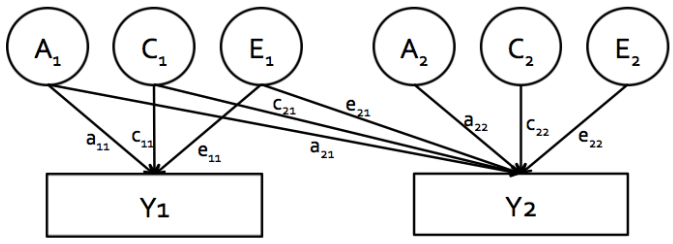

Figure 1.1. Cholesky decomposition

Regarding the second part of the first aim, most previous studies examining the links between personality disorders (PDs) and AU/AUD have invariably focused on a single PD[80-82]. Accordingly, it remains unclear which PD or PDs, when jointly analyzed, offer the best

phenotypic and genotypic prediction of AU or AUD. Chapter 3 will address this gap by examining the relationships between PDs and AU/AUD. Specifically, the aims of Chapter 3 are to: (1) identify which personality disorders provide the strongest phenotypic prediction of the liabilities to AU and AUD within a multivariate framework, (2) investigate the degree to which the significant relationships are due to common genetic or common environmental influences using Cholesky decomposition, and (3) determine if these associations are stable over time.

Importantly, Chapters 2 and 3, which address Aim 1, both utilized large, population-based samples. Thus, these chapters will identify significant protective and risk factors with a high level of precision, and increase our understanding of the genetic and environmental etiology shared between these behaviors and outcomes. This knowledge can collectively help to inform prevention and intervention efforts by focusing them towards fostering resilience and decreasing or avoiding early risk factors linked to personality disorders that are found to be significantly associated with increased AU.

Longitudinal changes in the contributions of genetic and environmental risk factors in AU and AUD

There is limited, conflicting research examining the question of whether genetic and environmental risk factors contributing to AUD are stable or dynamic over time[56,83]. Critically, many previous studies investigating the longitudinal changes in AU have not tested competing models with different developmental hypotheses[51,55,56,84]. Therefore, the precise nature of how these underlying mechanisms change over time remains unclear. Chapters 4 and 5 address these gaps as part of Aim 2, which is to investigate the nature of longitudinal changes in the contributions of genetic and environmental risk factors in AU/AUD.

Chapter 4 will investigate whether genetic influences are attributable to a single genetic factor or multiple factors that are qualitatively distinct. Chapter 5 will extend these analyses to investigate specifically how the genetic and environmental mechanisms influencing AU from adolescence through young adulthood change over time by testing competing developmental hypotheses. Taken together, these two chapters will improve our understanding of how genetic and environmental risk factors change over time to influence AU and AUD. This understanding can narrow the time frames where genetic influences are most important, leading to a more defined period of time during which prevention and intervention efforts may be most beneficial.

The moderating role of key environmental risk factors on the impact of polygenic risk across adolescence

To date, previous studies investigating the moderating effect of key environmental risk factors (PM and PGD) on genetic risk have mostly been limited to studies relying on latent genetic risk factors[48-51] inferred from twin and family data, instead of actual measured genotypes. There has only been one study to date that has relied on aggregate estimates of polygenic risk and analyzed their interaction with PM and PGD to predict AU/AUD [76]. Chapter 6 addresses this gap and the final aim of this dissertation by examining whether PM and PGD can moderate the impact of polygenic risk for AU through adolescence.

More specifically, the analyses outlined in Chapter 6 involve the creation of polygenic risk scores using data from a large sample of Australian twins, and testing genes-by-environment interactions between these polygenic risk scores and the environmental factors. Therefore, Chapter 6 will improve our understanding how polygenic risk and environmental factors interact to influence risk for adolescent AU across time, which can help determine whether focusing

efforts on increasing parental monitoring and decreasing peer group deviance during vulnerable adolescent time periods will be beneficial, or if the polygenic risk during this time is stronger.

Overall, this dissertation will examine risk/protective factors for the development of AU/AUD and the developmental trajectories of AU/AUD using both biometrical genetic and molecular genetic methodologies. The results will fill critical gaps in the AU/AUD literature, and will inform prevention and intervention efforts. This knowledge will be particularly useful to clinicians and scientists working within the prevention field, and will also provide a catalyst for future behavioral genetic research within the AU/AUD field.

Chapter 2: Resilience and risk for alcohol use disorders: A Swedish twin study[1]

Introduction

This chapter addresses the first aim of this dissertation by examining the strength of the relationship between resilience and AUD and investigating the degree to which this relationship is due to common genetic or common environmental influences. Because there is very little currently understood about these sources of covariation, this chapter will help to fill an important gap in the literature.

Resilience is defined as an "individual's ability to thrive despite adversity"[1-4]. It has been shown to attenuate risk for AU problems among veterans[2,5,6] and adults with a history of child abuse[6]. Twin and family studies have revealed that resilience and AUD are each influenced by genetic and environmental factors. For instance, the heritability of AUD has been consistently estimated to be approximately 50%[7,8]. Among the three studies that have investigated the heritability of resilience, each has operationalized resilience differently (e.g., difference between predicted and actual internalizing symptom score, positive affect despite chronic exposure to stress, and difference between actual score and score predicted by level of socioeconomic deprivation) and outcomes (stressful life events, cognitive and behavioral functioning). Consequently, the range of heritability is broad, spanning 31% to 71% (with *N*'s ranging from 527 to 7,500 twins)[9-11]. We are aware of only one study to date that has examined the genetic and environmental sources of covariation between resilience and AUD. Amstadter et al. showed that 20% of the covariation was attributable to genetic factors, while a negligible amount was due to environmental sources[12]. Given the potentially protective role that resilience may play in risk for

[1] This paper was modified from a manuscript that was previously published as: Long, E.C., Lönn, S.L., Ji, J., Lichtenstein, P., Sundquist, J., Sundquist, K., Kendler, K.S. (2017). Resilience and risk for alcohol use disorders: A Swedish twin study. *Alcoholism: Clinical and Experimental Research, 41*(1), 149-155.

AUD, it is important to validate these results with replication and variation using an independent sample.

In the present study based on Swedish military conscripts, resilience was operationalized by ratings of individuals' functioning across certain predefined areas of functioning, including experiences at school, work, home environment, and leisure time, as well as emotional stability. Higher values indicate better functioning. Previous reports have referred to this scale as "stress susceptibility"[13], "psychological functioning"[14], and "psychological strength"[15,16]. Here, we refer to it as resilience. This scale was designed for the Swedish military with the purpose of predicting individual differences in coping in response to stressful situations such as combat. This scale was designed to "reflect the level of adaptation in everyday life, including psychological and physical endurance under stress"[16, pg. 3-4]. This definition is consistent with other commonly used resilience measures such as the Connor-Davidson Resilience Scale[1].

The aims of the present chapter are to: (1) examine the magnitude of the relationship between AUD and the five traits that were components of the resilience assessment (social maturity, interest, psychological energy, home environment, and emotional control), as well as the total resilience score and (2) explore the extent to which the association between AUD and resilience is the result of common genetic or common environmental factors.

Methods

Sample

Using the unique 10-digit identification number that all Swedish residents are given at birth or immigration, nationwide Swedish registers were merged. To protect anonymity, this number was replaced by a serial number. We used the following eight registries to create our dataset: (1) the Total Population Register for year of birth, sex, and annual data on place of

residences; (2) the Twin Register for known zygosity; (3) the Swedish Hospital Discharge Register for hospitalizations of Swedish residents from 1964 to 2010; (4) the Swedish Prescribed Drug Register for prescriptions in Sweden obtained by patients from 2005 to 2010; (5) the Outpatient Care Register for information regarding outpatient clinics from 2001 to 2010; (6) the Swedish Crime Register for data on all convictions in lower court from 1973-2011; (7) the Swedish Suspicion Register for national data on individuals strongly suspected of crime from 1998-2011; and (8) the Swedish Conscription Register for information regarding the resilience assessment used for military service from 1969 to 2008.

Based on known zygosity, twin pairs were selected from the Swedish Twin Registry with birth years from 1950 to 1990 (ages 26-66). A larger age range was allowed to identify male twins with AUD.

To assign zygosity in the same-sex twin pairs, standard self-report items from mailed questionnaires were used, which were 95-99% accurate when compared with biological markers (for more details, see Lichtenstein et al. 2002[17]). This is an indirect screening for level of cooperation because at least one of the pair had to return a questionnaire to the twin registry and cooperation was lower in subjects with AUD. Thus, the prevalence is lower in this group, compared to twin pairs not returning the questionnaires.

Measures

AUD. AUD was coded as a binary variable (present/absent). Individuals with AUD were identified from Swedish medical, legal, and pharmacy records. From the Swedish hospital discharge and outpatient registers, we used the following codes from International Classification of Diseases, 9th revision (ICD9[18]; note the Swedish notation uses letters instead of the numbers, as in the U.S.), which are reflective of alcohol abuse and dependence, as well as health-related

consequences of heavy drinking, such as liver and heart diseases: V79B, 305A, 357F, 571A-D, 425F, 535D, 291, 303, 980, and from the ICD10[19]: E244, G312, G621, G721, I426, K292, K700, K701, K702, K703, K704, K709, K852, K860, O354, T510, T512, T511, T513, T518, T519, F101-109. Individuals were coded as present if they had any of these diagnoses. The hospital discharge and outpatient registries identified 242,949 individuals with AUD. Additionally, we identified 199,663 individuals with at least two convictions or suspicions (that did not lead to conviction) of drunk driving or drunk in charge of maritime vessel by law 1951:649, paragraph 4, and 4A, and law 1994:1009, paragraph 4 and 5 and the suspicion codes 3005 and 3201. We also identified AUD among 63,169 individuals who had retrieved disulfiram (Anatomical Therapeutic Chemical (ATC) Classification System, N07BB01), acamprosate (N07BB03), and naltrexone (N07BB04) from the Prescription Registry. From these three sources of information, we identified a total of 420,489 individuals with AUD, for a lifetime prevalence of 3.8%.

Resilience. The resilience scale was designed to measure the ability to cope with psychologically stressful situations that might occur in military service. It is assessed with a 1 to 9 graded scale corresponding to a categorized normal distribution centered at 5. Specially trained psychologists assigned the resilience score by administering a semi-structured interview that took on average 20–25 minutes to complete. Their training is conducted nationally and therefore their performance was unlikely to differ from region to region. During this free form interview, the conscript was asked to describe his everyday life. There are five predefined sections (experiences from school, work experiences, leisure time, home environment, and emotional stability), although the order in which the sections are administered can vary. The interviewer was provided with background information such as school grades, job experiences, and other test results in advance. Other specific details about the assessment methods, such test-retest or

validation data, exist only in Sweden and are classified by the military. Thus, this information is unfortunately not available[13]. Data were available for all males in the conscription register with an assessment of resilience between ages 17 and 25 (N = 1,653,721).

As part of the complete resilience assessment procedure, five single items from the assessment were made available to us during the years of 1969-1970 only (n = 49,393; the Swedish military restricted these items for the other years). These individual items assessed social maturity, interest, psychological energy, home environment, and emotional control. Each category corresponded to a categorized normal distribution.

We are not able to provide example questions from these five individual items because the Swedish military has classified these items. However, we consider it likely that they map onto some of the questions included in the Connor-Davidson Resilience Scale[1], as follows: "know where to turn for help" for social maturity; "likes challenges/strong sense of purpose" for interest; "bounce back after hardship/think of self as a strong person" for psychological energy; "close and secure relationships" for home environment; and "can handle unpleasant feelings/can deal with whatever comes" onto emotional control.

The Swedish army has demonstrated the predictive power of the resilience scale[20]. Carlstedt (1999) reported that the quality of military performance in both enlisted men and officers in the Air Force, under battle conditions, and for support troops was strongly predicted by the scale. As an example, for enlisted men serving in the Air Force assigned a resilience score of 3, a rating of a good performance was only awarded 30% of the time, compared to 75% who were assigned a score of 8 (scores of 3 and 8 were the lowest and highest scores for which adequate data were available[20]). There was also a strong link between resilience scores and the

probability of acceptance into the military: 1 – 2.0%, 2 – 14.3%, 3- 38.7%, 4 - 58.1%, 5 – 66.6%, 6 – 70.5%, 7 – 73.6%, 8 – 75.1%, and 9 – 76.1%.

Statistical methods

Logistic Regressions. First, we assessed the unique associations between the five single resilience constructs and AUD by conducting five separate logistic regressions using a subset of the full sample of Swedish male individuals for the two years this data was available (n = 49,393). We then assessed the association between the total resilience score and AUD with logistic regression, using the full sample of Swedish male individuals who had completed a resilience assessment (N = 1,653,721). Linear and quadratic terms were included in all regressions (given the nature of the data, shown below in Figure 2.1), and birth year was included as a covariate to adjust for age, as older males are more likely to be an AUD case than younger males. These analyses were performed in SAS 9.3[21].

Ordinal data methods. Because all analyses relied on ordinalized data, the twin modeling is based on the threshold liability model. By assuming a normal distribution for resilience, ordered thresholds can be estimated. These thresholds can then be conceptualized as "cut points" along the unobserved distribution. The probability of being in a respective category corresponds to the threshold for the lowest category and then increases for each successive category.

Polychoric correlations. The polychoric correlation estimates the correlation between two theorized normally distributed continuous latent variables. The likelihood function was set so that the parameter estimates are the values giving it its maximum value.

Twin modeling. Classical bivariate twin modeling was used to examine the sources of covariation between AUD and resilience using Swedish male twins. The bivariate twin model

included 5,765 twin pairs (2,750 monozygotic; 3,015 dizygotic). Bivariate twin modeling is an extension of the univariate twin model, which assumes three sources of liability to a phenotype: additive genetic (A), shared environment (C), and unique environment (E). The model assumes that monozygotic (MZ) twins share 100% of their genes, while dizygotic (DZ) twins share, on average, 50% of their genes. Therefore, the expected twin pair correlations for the additive genetic effects are 1.0 and 0.5, respectively. The model also assumes that the shared environment factors, which reflect family and community experiences, contribute equally to the similarity between MZ and DZ twins. Finally, the unique environment reflects experiences not shared by twins, random developmental effects, and random measurement error.

Bivariate twin modeling uses the additional information in the cross-correlations between twins for different traits and permits estimating the extent to which genetic and environmental influences are shared by the two traits or are trait specific[22]. The model specifies that the first and second observed variables have paths coming from the first latent component whereas a second orthogonal latent component has a path to only the second variable. In this model, the first latent component estimates the biometric portion of the covariation that is shared between the two observed variables with the second latent component identifying the portion unique to the second variable. This same factor structure is specified for each of the etiological sources (A, C, and E). The path estimates can then be used to estimate the latent genetic and environmental factor correlations.

We built the bivariate model with the first factor loading on both resilience and AUD, while the second loads only on the latter. This method can handle missing items and includes both individuals and pairs without a resilience assessment who still contribute to the AUD estimates.

Sullivan and Eaves[23] recommend presenting parameter estimates from the full model because they are usually more accurate than those from sub-models even if the sub-models provide a better model fit. Although they acknowledge that this may not be the case for large sample sizes that can increase precision, such as ours, they also argue that "it may not be sensible to search for parsimony," since large sample sizes can also detect smaller effects of A, C, and E. Thus, we chose to present estimates from the full bivariate ACE model with 95% CIs. The OpenMx software[24] was used to fit the models.

Results

Descriptive Statistics

The sample sizes and prevalences of individuals with AUD by level of the resilience score ($M = 5.1$; $S.D. = 1.9$[13]) are shown in Table 2.1. The prevalence of AUD dramatically increased as the resilience score decreased (also see Figure 2.1). At the highest level of resilience, the prevalence of AUD was 2.9%, whereas at the lowest level, the prevalence was 23.2%.

Table 2.1. Sample sizes and prevalence of AUD by resilience score

Resilience score	Number of Individuals	Number of Individuals with AUD (%)
1	37,864	8,799 (23.2%)
2	118,669	15,254 (12.9%)
3	186,940	16,240 (8.7%)
4	276,479	16,547 (6.0%)
5	372,889	16316 (4.4%)
6	306,998	10,392 (3.4%)
7	229,016	6,743 (2.9%)
8	98,335	2734 (2.8%)
9	26,531	766 (2.9%)

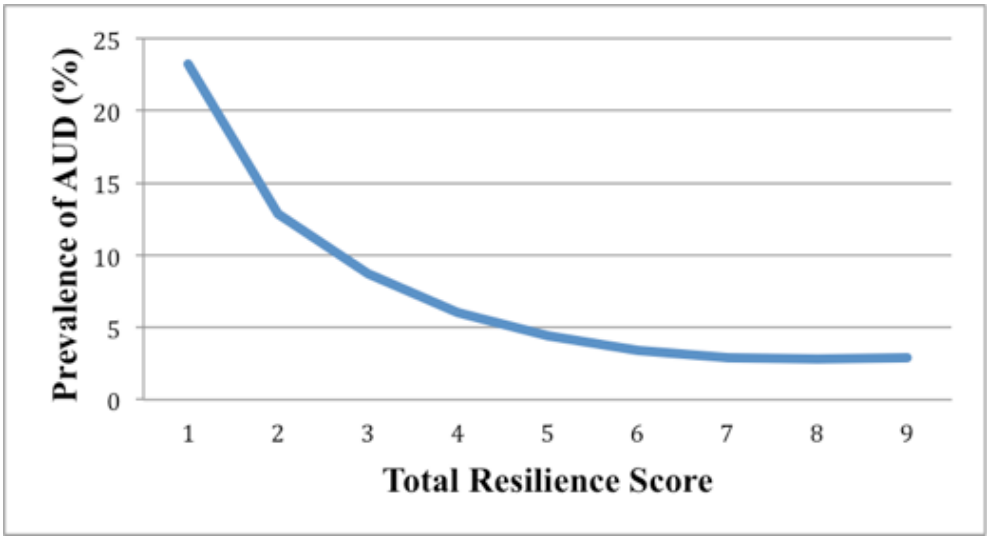

Figure 2.1. Prevalence of AUD as a function of total resilience score

The twin-pair correlations for the total resilience score and AUD are displayed in Table 2.2. The within-pair, cross trait MZ twin correlations, shown on the off diagonals, were modest (-0.23 and -0.26). The within-pair, cross trait DZ twin correlations were lower than the MZ correlation, but also modest (-0.14 and -0.18), suggesting genetic factors are important in the relationship between resilience and AUD. However, the DZ correlations were slightly greater than half of the MZ correlations, which suggest that shared environmental influences are also important, but may have a minor impact on the sources of familial aggregation underpinning the covariance between resilience and AUD.

Table 2.2. Twin correlations (SE) for resilience and AUD

Monozygotic Twins		
	T2 Resilience	T2 AUD
T1 Resilience	0.68 (0.01)	-0.26 (0.04)
T1 AUD	-0.23 (0.04)	0.66 (0.05)
Dizygotic Twins		
	T2 Resilience	T2 AUD
T1 Resilience	0.42 (0.02)	-0.14 (0.04)
T1 AUD	-0.18 (0.04)	0.43 (0.05)

Logistic Regression Analyses

The results of the associations between AUD and the five single items from the subsample of the conscript registry are shown in Table 2.3. Across all five items, Model 4 was always the best fitting model as per the AIC, which included birth year and the quadratic term. The odds ratios (ORs) from the linear effects clearly indicate that all five items reduced risk of AUD. Social maturity had the strongest effect, while interest was the weakest. However, because the quadratic term was also significant across all five items, these effects were not solely linear. Rather, the magnitude of the protective effect decreased after a certain point.

Table 2.3. Unique associations between AUD and five single items included in the resilience assessment during the years 1969-1970 (n = 49,393)

Item	Predictors	Model 1	Model 2	Model 3	Model 4
Social Maturity	Resilience (Linear)	0.64 (0.62-0.67)	0.32 (0.27-0.37)	0.65 (0.62-0.67)	0.31 (0.27-0.36)
	Resilience (Quadratic)		1.13 (1.11-1.16)		1.14 (1.11-1.17)
	Birth year			1.07 (1.01-1.13)	1.09 (1.03-1.15)
	AIC	29,276.781	29,193.283	29,273.748	29,186.793
Interest	Resilience (Linear)	0.78 (0.76-0.81)	0.68 (0.59-0.80)	0.78 (0.76-0.81)	0.68 (0.58-0.79)
	Resilience (Quadratic)		1.02 (1.00-1.05)		1.03 (1.00-1.05)
	Birth year			1.12 (1.06-1.19)	1.13 (1.06-1.19)
	AIC	29,661.123	29,659.987	29,646.075	29,644.537
Psychological Energy	Resilience (Linear)	0.68 (0.66-0.71)	0.48 (0.41-0.57)	0.68 (0.66-0.71)	0.48 (0.40-0.56)
	Resilience (Quadratic)		1.06 (1.03-1.09)		1.07 (1.04-1.10)
	Birth year			1.09 (1.03-1.16)	1.10 (1.04-1.16)
	AIC	29,470.288	29,455.017	29,462.775	29,446.368
Home Environment	Resilience (Linear)	0.65 (0.62-0.67)	0.45 (0.39-0.53)	0.65 (0.62-0.67)	0.45 (0.38-0.52)
	Resilience (Quadratic)		1.07 (1.04-1.10)		1.07 (1.04-1.10)
	Birth year			1.13 (1.07-1.20)	1.14 (1.08-1.21)
	AIC	29,320.754	29,302.896	29,303.414	29,283.548
Emotional Control	Resilience (Linear)	0.68 (0.66-0.70)	0.51 (0.44-0.58)	0.68 (0.66-0.70)	0.49 (0.43-0.57)
	Resilience (Quadratic)		1.06 (1.03-1.08)		1.06 (1.03-1.09)
	Birth year			1.13 (1.07-1.20)	1.15 (1.08-1.21)
	AIC	29,321.546	29,307.097	29,304.130	29,286.774

The results of the association between AUD and the total resilience score are presented in Table 2.4 and depicted graphically in Figure 2.1. Focusing first on the linear effect (Model 1), the OR is 0.71, indicating that each increasing point on the resilience scale is associated with a 29% reduction in the odds of AUD. In Model 3, birth year was included as a covariate, and a quadratic effect for resilience was added. All three parameters were significant. The quadratic effect is clearly shown in Figure 2.1, as the association between resilience and AUD was stronger at lower levels of resilience than at higher levels, where the reduction in risk of AUD stabilized.

Table 2.4. Association between AUD and the total resilience score during years 1969-2008 (entire sample; *N* = 1,653,721)

Item	Predictors	Model 1	Model 2	Model 3
Total score	Resilience (Linear)	0.71 (0.71-0.71)	0.70 (0.69-0.70)	0.49 (0.48-0.50)
	Resilience (Quadratic)		0.96 (0.96-0.96)	1.04 (1.04-1.04)
	Birth year			0.96 (0.96-0.96)
	AIC	687,928.05	670,222.35	667,955.52

Bivariate twin analyses of resilience and AUD

A bivariate Cholesky decomposition model was then fit to the total resilience score and AUD. The within-individual phenotypic correlation for these traits was -0.25. The heritability of resilience was 55%. As seen in Figure 2.2, the cross-path from the genetic effects (A) in resilience to AUD (-0.18) was of similar strength to the shared environmental (C) cross-path (-0.23). The 95% CIs for the A and C paths were overlapping, whereas the individual-specific environmental (E) pathway was not. However, both the A and C cross-paths were stronger than the E cross-path (−0.03). The genetic and shared environmental covariation-paths were both significant.

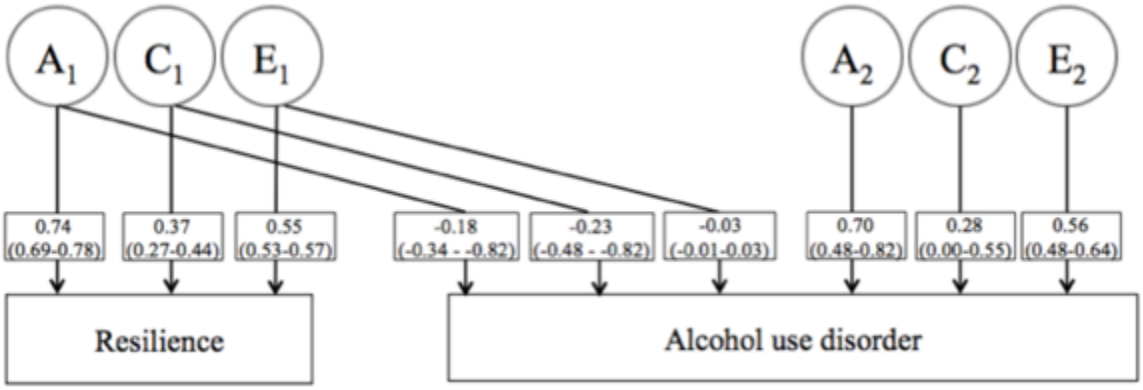

Figure 2.2. Parameter estimates and 95% confidence intervals from the bivariate Cholesky decomposition for the total resilience score and AUD

These results are presented in two other informative ways in Table 2.5, with genetic and environmental correlations shown in the left panel and proportions of the phenotypic correlation shown in the right panel. These are calculated from the parameter estimates shown in Figure 2.2. First, the genetic and environmental correlations show negative associations between resilience and AUD. The shared environmental correlation between resilience and AUD was quite high (−0.63), while the genetic correlation was more moderate (-0.25). The individual-specific environmental correlation was small (−0.06). Second, we used the parameter estimates from model fitting to decompose the total phenotypic correlation between resilience and AUD (-0.25). The proportion of the phenotypic correlation resulting from common individual-specific environmental risk factors was very modest (7%), while the proportion of the phenotypic correlation resulting from shared environmental factors was higher (36%), and was highest from genetic risk factors (57%). Therefore, although the phenotypic correlation between resilience and AUD was modest, shared environmental and additive genetic risk factors explained approximately one-third and one-half of the association, respectively.

Table 2.5. Correlations from bivariate twin model for total resilience score and AUD

Correlation (95% CI)			
	Genetic	Shared environmental	Individual specific environmental
	-0.25 (-0.48, 0.04)	-0.63 (-1.0, 0.05)	-0.06 (-0.18, 0.05)
Phenotypic correlation (95% CI)			
Total	% Genetic	% Shared environmental	% Individual specific environmental
-0.25 (-0.28, -0.20)	56.7 (10.1, 100)	36.2 (-2.1, 73.7)	7.1 (-7.3, 23.0)

Discussion

The aims of this chapter were to examine the magnitude of the relationship between AUD and resilience, and then to explore the degree to which the relationship results from common genetic or common environmental factors. First, using logistic regression, the association between AUD and the five single items that were used as part of the Swedish resilience assessment (social maturity, interest, psychological energy, home environment, and emotional control; available on a subsample) was examined. All five of these items themselves relatively strongly reduced the risk of AUD, although they were of different strengths. The rank order of the strength of association is similar to a recent report investigating the association between resilience (referred to as "psychological strength") and criminal behavior. The authors also found that social maturity showed the strongest association while interest showed the weakest[15]. This study also reported results of a factor analysis that revealed a one-factor solution with significant loadings from all five items[15], which supports the validity of the resilience measure.

The association between the total resilience score and AUD was also investigated. Consistent with previous studies[2,5,6], we showed that overall resilience substantially reduced the risk of AUD. The linear effect indicated that a one-point increase on the resilience scale was

associated with a 29% decrease in odds for AUD. The change in risk for AUD for a given change in resilience was much greater at lower resilience levels than at higher levels. At resilience levels of 6 or higher, the reduction of risk for AUD did not continue to decrease linearly as resilience levels increased, but instead showed a negligible impact. In other words, there is a diminishing return of increased resilience beyond a resilience score of 6.

Second, using a Cholesky decomposition model fit to MZ and DZ twin pairs, the resilience-AUD association was decomposed into its genetic and environmental components. The individual-specific environmental factors contributed very little to the covariance between resilience and AUD. The majority of the covariance could instead be attributed to overlapping genetic and shared environmental factors. In other words, part of the same genes and shared environments that contribute to increased resilience also contributed to reduced risk for AUD. These results support a 'liability index' model in which resilience reflects genetic and shared environmental influences that also impact risk for AUD, rather than a direct causal link.

We are aware of only one previous study that also examined these sources of covariation between resilience and AUD. Based on a smaller sample of 3,084 complete twin pairs from the U.S., Amstadter and colleagues[12] showed that most of the covariation was due to genetic influences with the negligible remainder due to overlapping unique environmental influences (E). There was no evidence for overlapping shared environmental influences (C). We also found that genetic influences were an important source of covariation between resilience and AUD, but to a higher degree (57% vs. 20%), and that unique environmental factors (E) were not. Conversely, we showed that 36% of the covariation was attributable to the shared environment (C). Potential explanations for this inconsistency may be due to differences in sample size (5,765 complete twin pairs vs. 3,084 complete twin pairs with 1,325 singletons), different populations

(Sweden vs. United States), and different measures of resilience (ability to cope with psychologically stressful situations vs. the difference between twins' total score of internalizing symptoms and their predicted score based on their cumulative exposure to stressful life events).

Limitations

These results should be considered within the context of two potential limitations. First, our analyses were limited to a Swedish male sample. It is therefore uncertain if our results generalize to other populations. However, it is likely that the results are generalizable to other industrialized countries.

Second, our measure of AUD was based on medical, legal, and pharmacy records. Although this method is not subject to recall or reporting biases, it can produce false negatives and false positives. The extent to which this occurred cannot be estimated. However, a recent report using the same sample found the prevalence of AUD to be lower than estimates from most epidemiologic surveys[25], including the nearby country of Norway[26,27]. Accordingly, it may be that registries only detect more severe cases of AUD compared to population-based interview studies. Despite this, there is support of our measure of AUD from high concordance rates for registration across the different methods[25]. In addition, those cases that require hospital care are more clinically relevant than those who are based on population-based interviews.

Conclusions

Using a nationwide Swedish male sample, we showed that higher scores on the five single items that comprised the resilience assessment (social maturity, interest, psychological energy, home environment, and emotional control), as well as a higher total resilience score, were all associated with a reduced risk of AUD. This effect was linear and quadratic, such that the risk for AUD was most strongly predicted by resilience at resilience levels of 6 or lower. We

also showed that the relationship between resilience and AUD was largely attributable to overlapping genetic and shared environmental factors. Future research should aim to identify the specific genetic and shared environmental factors common to resilience and AUD. Identification of shared genes can inform gene-finding efforts by providing plausible networks to locate specific genes involved in both phenotypes. Additionally, identification of shared environments common to resilience and AUD can inform prevention efforts by focusing prevention and intervention efforts on these environments.

Chapter 3: The Association Between Personality Disorders with Alcohol Use and Misuse: A Population-Based Twin Study[2]

Introduction

This chapter continues the examination of the associations between personality, AU, and AUD, and addresses the second part of Aim 1. Specifically, it examines the association personality disorders (PDs) and AU and AUD. Previous research examining these associations has nearly always focused on single PDs[1-6]. Thus, which PDs offer the best prediction of AU and AUD when all 10 PDs are simultaneously analyzed, and the nature of the etiologic overlap, remains unclear. Gaining a better understanding of these associations will inform prevention and intervention efforts, as early detection of the PD or AUD, depending on the direction of causality) may help prevent the other disorder.

The DSM-IV[7] and DSM-5[8] classify PDs into three clusters: Cluster A is characterized by odd and eccentric behavior and includes paranoid, schizoid, and schizotypal PDs; Cluster B is characterized by dramatic, overly emotional, and impulsive behavior and includes antisocial, borderline, histrionic, and narcissistic PDs; and Cluster C is characterized by anxious and fearful behavior and includes avoidant, dependent, and obsessive-compulsive PDs. The two PDs most consistently associated with AUD criteria are from Cluster B and include antisocial[1-3] and borderline[3-6]. This is perhaps unsurprising, given the links between impulsivity and AUD[9-14]. However, as mentioned, previous studies have focused on these PDs alone without accounting for the other PDs.

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[2] This paper was modified from a manuscript that was previously published as: **Long, E.C.,** Aggen, S.H., Neale, M.C., Knudsen, G.P., Krueger, R.F., South, S.C., Czajkowski, N., Nesvåg, R., Ystrom, E., Torvik, F.A., Kendler, K.S., Gillespie, N.A., & Reichborn-Kjennerud, T. (2017). The association between personality disorders with alcohol use and misuse: A population-based twin study. *Drug and Alcohol Dependence, 174,* 171-180.

As described in the methods section of Chapter 2, twin studies are the most commonly used method to estimate the relative proportions or contributions of latent genetic and environmental risk factors to individual differences in human behaviors, phenotypes, or disease/disorder outcomes. A number of twin studies provide compelling evidence that AU and AUD[15-17], and PDs[18,19] are all complex, heritable phenotypes. Bivariate Cholesky decompositions go beyond the basic univariate twin model and allow us to determine the extent to which genetic and environmental influences are shared by two traits or are trait specific[20]. Regarding these putative sources of covariation between AU and AUD with PDs, evidence based on bivariate modeling suggests that genetic risk factors are shared between borderline PD, alcohol, nicotine, and cannabis misuse[21], as well as between antisocial behavior and AU[22]. These shared genetic risks account for up to 50% of the total genetic variance in risk in AUD[23]. One limitation is that most previous studies have relied on the analysis of single or at most two PDs[21-23]. Only very recently have fully integrative and genetically informative data on all 10 PDs become available to elucidate the genetic and environmental pathways linking PDs to AU and AUD.

We are not aware of any published studies that have investigated the association between all 10 DSM-IV PDs, AU, and AUD. To address this gap, we examined the following three aims: (1) identify which of the 10 PDs provide the strongest phenotypic prediction of the liabilities to AU and AUD; (2) estimate the degree to which the associations between PDs and AU and AUD are due to shared genetic or shared environmental risks; and (3) determine if the patterns of associations between PDs and AU and AUD are stable across time.

Method

Sample

Twins were recruited by the Norwegian Institute of Public Health (NIPH) Twin Panel from the National Medical Birth Registry of Norway, which was established in 1967[24,25]. By mandate, the registry receives notification of all births in Norway. The NIPH Twin Panel initially ascertained twins born from 1967 through 1974 who were at least 18 years of age. They were first contacted for a study of health via a mail-out questionnaire (Q1) in 1992. These twins were re-contacted for a longitudinal follow-up using a second health questionnaire (Q2) in 1998. At that time, a younger cohort born 1975 to 1979 was also recruited and administered the same Q2. Altogether, 8,045 twins (63%) including 3,334 pairs (53%) responded to Q2.

All complete pairs from the Q2 study in which both twins were willing to be contacted again for new studies (N = 3,153 twin pairs) were invited by mail to participate in the Wave 1 interviews of mental health used in the present analyses. Due to technical problems, an additional 68 pairs were accidentally drawn from twin pairs that had not completed the Q2. The Wave 1 structured and semi-structured diagnostic interviews were carried out between 1999-2004 and assessed DSM-IV lifetime Axis I and Axis II disorders. Wave 1 interviews were mostly conducted face-to-face, with a small amount conducted by telephone (8.3%).

Data for Wave 2 came from a follow-up telephone interview administered between 2010-2011[26]. Of the 3,221 twin pairs eligible for Wave 1, there were 1,391 complete pairs (43.2%) and 19 single twins (0.6% pairwise), totaling 2,801 twins who participated (43.4%) and comprising 63% females (M_{age} = 28 years, range = 19-36). Of the 2,801 twins eligible for Wave 2, there were 2,393 twins who participated (85.43%), comprising 1,063 complete twin pairs and 267 single twins, including 64% females (M_{age} = 38 years, range = 30-44). For more detailed

information about the sampling process and twin sample, please see Tambs et al.[25] and Nilsen et al.[26].

Monozygotic (MZ) males and females as well as dizygotic (DZ) males, females, and opposite sex twins were included in all analyses. The sample sizes for each group by sex are as follows: MZ males = 225; MZ females = 453; DZ males = 120; DZ females = 267; DZ opposite sex = 345.

Different interviewers assessed each twin pair member. Interviewers at Wave 1 were mostly advanced psychology students, or experienced psychiatric nurses, who received standardized training and supervision during data collection. Interviewers at Wave 2 included senior clinical psychology graduate students, psychiatric nurses, and experienced clinical psychologists who were interviewers at Wave 1. Written informed consent was obtained from all participants who received stipends of $35 and $70 at Waves 1 and 2, respectively. Ethical approval for both assessments came from the Regional Ethical Committee.

Measures

Predictors: Personality Disorder Criteria. Lifetime DSM-IV PDs were assessed using a Norwegian version of the Structured Interview for DSM-IV Personality (SIDP-IV)[27]. The SIDP-IV is a comprehensive, semi-structured diagnostic interview that includes non-pejorative questions organized into topical sections rather than by individual PD thereby improving the flow of the interview. The number of criteria for each of the DSM-IV PDs used in the analyses were as follows: Cluster A: schizotypal (9 criteria), schizoid (8 criteria), and paranoid (7 criteria); Cluster B: histrionic (8 criteria), borderline (9 criteria), narcissistic (9 criteria), and antisocial (7 criteria); Cluster C: avoidant (7 criteria), dependent (8 criteria), obsessive-compulsive (8 criteria). The SIDP-IV considers the behaviors, cognitions, and feelings that are

reported to be predominately present over the past five years of a participant's life to be representative of the individual's personality. Importantly, the SIDP-IV interview was conducted after the Composite International Diagnostic Interview (CIDI)[28,29], which assesses Axis 1 disorders. This order of assessment allowed us to conclude that the symptoms of PDs were due to the PD, and not a temporary effect of an Axis I disorder. All 10 PDs were assessed face-to-face at Wave 1.

At Wave 2, six of the 10 PDs were assessed by telephone interview: paranoid, schizotypal, borderline, obsessive-compulsive, avoidant, and antisocial. Each criterion was scored on a 4-point scale (absent, sub-threshold, present, or strongly present), dichotomized (0 = absent, 1 ≥ sub-threshold), and summed into a PD trait score. However, because very few participants endorsed most PD criteria, the PD scores had strong positive skewness with a predominance of zero values. Therefore, for analytic purposes, each PD score was recoded onto a 3-point ordinal scale (0 criteria, 1-2 criteria, ≥3 criteria). This was also done to establish a common frame of reference to facilitate interpreting comparisons between odds ratios. Complete PD data were available from 2,793 twins for Wave 1 and 2,282 for Wave 2.

Outcome variables: Alcohol Use and Alcohol Use Disorder Criteria. Lifetime AU and AUD based on the number of DSM-IV criteria for alcohol abuse and dependence were assessed using a Norwegian version of the Composite International Diagnostic Interview[28]. The CIDI has good test-retest reliability for dependence[29-31] (kappas = 0.70 - 0.95), and the Norwegian version has been used previously[32]. Lifetime AU was assessed for the 12-month period where consumption was highest using a 3-point ordinal scale (0 = never tried; 1 = less than 1 time per month, and 1-3 times per month; 2 = 1-2 times per week, 3-4 times per week, and almost every day). This was followed by questions covering the 11 DSM-IV criteria and one craving item.

Criteria sum scores were then recoded onto a 3-point ordinal alcohol use disorder (AUD) scale (0 = 0 criteria, 1 = 1-3 criteria, and 2 = 4 or more criteria) and used for all subsequent analyses. Complete AU and AUD data were available from 2,482 twins for Wave 1. At Wave 2, data were available from 2,238 twins for AU and 2,239 twins for AUD. See Table 1 for the prevalences of AU and AUD at both waves.

Prevalences of AU and AUD and Reliability. The sample size and prevalences of AU and AUD are shown in Table 3.1. To obtain reliability estimates between the two waves of data, we estimated weighted kappa coefficients and polychoric correlations. The weighted kappas for AU and AUD between Wave 1 and Wave 2 were 0.31 and 0.40, respectively. The polychoric correlations were 0.49 for AU and 0.58 for AUD. Typical values of weighted kappa for psychiatric diagnoses range from .40 to .60[33-35], and although the weighted kappa for AU was low, the polychoric correlations suggest that agreement between the two waves is adequate.

Table 3.1. Sample size and prevalence of alcohol use (AU) and DSM-IV alcohol use disorder (AUD) criteria at Wave 1 and Wave 2

AU	**Number of Twins**	**Never tried (0)**	**Less than 1x/month; 1-3 times/month (1)**	**1-2x/week; 3-4x/week; Almost every day (2)**
Wave 1	2,482	58.2% (1,445)	39.8% (987)	0.02% (50)
Wave 2	2,238	77.1% (1,726)	20.7% (464)	0.02% (48)
AUD		**0 criteria (0)**	**1-3 criteria (1)**	**More than 4 criteria (2)**
Wave 1	2,482	74.2% (1,842)	18.8% (467)	0.07% (173)
Wave 2	2,239	84.1% (1,884)	10.6% (238)	0.05% (117)

Statistical Analyses

Logistic Regressions. Given the number of predictors, we implemented an empirical approach to identify a subset of PD criteria sum scores for inclusion in the bivariate twin analyses to explore the genetic and environmental associations between PDs with AU and AUD. First, univariate ordinal logistic regressions using the polr() function in $R_{3.1.1}$[36] were fitted for each PD as a predictor at Wave 1 and Wave 2 in order to examine the effects of PD criteria

scores independently. Second, four separate multiple regressions were run using the polr() function with a stepwise algorithm: (i) the regression of Wave 1 AU onto all 10 Wave 1 PDs; (ii) the regression of Wave 1 AUD onto all 10 Wave 1 PDs; (iii) the regression of Wave 2 AU onto all 6 Wave 2 PDs; and (iv) the regression of Wave 2 AUD onto all 6 Wave 2 PDs. All regressions included sex and age as covariates. PDs that significantly predicted AU and AUD in the multiple regressions were then brought forward into the bivariate twin analyses.

Twin Methods. Data were analyzed using the Full Information Maximum Likelihood (FIML) raw ordinal data method in the $R_{3.1.1}$ $OpenMx_{2.0}$ package[37]. This approach makes use of all available data from both complete and incomplete twin pairs, thereby increasing the precision of threshold estimates and improving estimation of the correlations between predictors and outcomes. Our approach assumes a multivariate normative liability threshold model in order to estimate thresholds, which are conceptualized as "cut points" along an unobserved continuous distribution of liability on which individuals can be ordered based on the observed frequencies of the ordinal categories.

Standard biometrical genetic methods[20,38] were used to exploit the expected genetic and environmental correlations of monozygotic (MZ) and dizygotic (DZ) twin pairs to estimate the size and significance of the genetic and environmental risk pathways between each selected predictor and the ordinalized AU and AUD criteria variables. The biometrical genetic model assumes that the covariance between MZ and DZ twin pairs can be decomposed into additive (A) genetic, shared environmental (C), and non-shared or unique (E) environmental variance components. Because MZ twin pairs are genetically identical while DZ twin pairs share, on average, half of their genes, the expected twin pair correlations for the genetic (A) effects are fixed at 1.0 and 0.5, respectively. An important assumption in the model is that C is equal in MZ

and DZ twin pairs since the model fixes this correlation to 1 for twin 1 and twin 2 in both MZ and DZ twin pairs. E is by definition uncorrelated and also includes random measurement error.

Our approach assumes that regardless of twin order and zygosity, subjects have the same threshold distribution for the AU and AUD outcomes. We were able to equate the thresholds across twin order ($p = 0.36$) and zygosity ($p = 0.33$) without any significant deterioration in model fit for Wave 1 AU. Threshold distributions for Wave 1 AUD could also be constrained equal across twin order and zygosity ($p = 0.77$ for twin order, $p = 0.78$ for zygosity).

Bivariate Cholesky decompositions use the additional information in the cross-correlations between twins for different traits and permit estimating the extent to which genetic and environmental influences are shared by the two traits or are trait specific[20]. The bivariate Cholesky decomposition specifies that the first and second observed variables have paths coming from the first latent component whereas a second orthogonal latent component has a path to only the second variable. In this decomposition, the first latent component estimates the biometric portion of the covariation that is shared between the two observed variables with the second latent component identifying the portion unique to the second variable. This same factor structure is specified for each of the etiological sources A, C, and E.

The antisocial and borderline criteria included items that made reference to substance use, or substance use related problems. Therefore, in order to determine if any degree of genetic or environmental associations with AU and AUD arise from overlapping content, the analyses were repeated after dropping the items '*Impulsivity in at least two areas that are potentially self-damaging (e.g., spending, sex, substance abuse, reckless driving, binge eating)*' and '*Failure to conform to social norms with respect to lawful behavior as indicated by repeatedly performing*

acts that are grounds for arrest' from the borderline and antisocial aggregate criteria sum scores, respectively. These variables are referred to as the "trimmed" PDs.

All models were run with age and sex as covariates, since the prevalence of AUD is greater among males and younger individuals[39]. To determine the best fitting model, the fully saturated 'ACE' model served as a baseline reference to compare models with the shared environmental (i.e., the additive genetic model; A+E model) and genetic (i.e., the shared environmental model; C+E model) parameters dropped by fixing these component pathways to zero. Model comparisons were evaluated using the Akaike Information Criterion (AIC)[40]. A stronger emphasis for model selection is placed on this parsimony index because model fit, measured as the Maximum Likelihood (-2LL, -2 times the log likelihood) values, will decrease with the addition of more parameters, which can lead to 'over-fitting' (i.e., including too many parameters relative to the number of observations). Indices of parsimony penalize models with increasing numbers of parameters, thereby providing a balance between model complexity and model or data misfit.

Results

Univariate and multiple logistic regressions

Wave 1 Alcohol Use. In the univariate regressions, five of the PDs significantly predicted AU at Wave 1 (see Table 3.2). In the stepwise multiple regression, only paranoid, borderline, and antisocial PDs remained significant and showed a positive association (see Table 3.3). Obsessive compulsive and dependent PDs also emerged as statistically significant, such that higher sum scores were associated with reduced AU.

Wave 1 Alcohol Use Disorder. In the univariate regression models predicting Wave 1 AUD criteria, eight out of the 10 PDs were significant positive predictors. In the multiple regression, borderline and antisocial PDs were significant predictors of AUD symptoms, with both showing positive associations. Schizoid and schizotypal PDs also emerged as significant, showing negative associations with AUD criteria.

Wave 2 Alcohol Use. In the univariate regressions predicting Wave 2 AU, four of the six PDs that were assessed at Wave 2 predicted increased AU. In the multiple regression that included the six PDs, only borderline and antisocial remained significant, positive predictors of AU.

Wave 2 Alcohol Use Disorder. In the univariate regression models predicting Wave 2 AUD criteria, all six PDs predicted increased AUD criteria. However, in the multiple regression, borderline and antisocial were again the only PDs that remained significant and positive predictors of AUD symptoms.

Table 3.2. Univariate logistic regression results of personality disorders predicting **WAVE 1 AND 2 ALCOHOL USE** and the symptoms of **WAVE 1 AND WAVE 2 ALCOHOL USE DISORDER**

	ALCOHOL USE				Symptoms of ALCOHOL USE DISORDER			
	Wave 1		Wave 2		Wave 1		Wave 2	
	OR	(95%CIs)	OR	(95%CIs)	OR	(95%CIs)	OR	(95%CIs)
Schizoid PD	1.03	(0.85 - 1.24)			1.04	(0.83 - 1.29)		
Paranoid PD	**1.33**	**(1.15 - 1.52)**	**1.45**	**(1.19 - 1.75)**	**1.50**	**(1.28 - 1.75)**	**1.70**	**(1.38 - 2.09)**
Schizotypal PD	1.16	(0.96 - 1.39)	1.24	(0.98 - 1.57)	1.22	(0.99 - 1.51)	**1.58**	**(1.21 - 2.04)**
Histrionic PD	**1.28**	**(1.12 - 1.46)**			**1.39**	**(1.20 - 1.61)**		
Borderline PD	**1.59**	**(1.39 - 1.81)**	**1.62**	**(1.38 - 1.90)**	**2.12**	**(1.83 - 2.46)**	**2.04**	**(1.71 - 2.44)**
Obsessive Compulsive PD	0.99	(0.87 - 1.12)	**1.23**	**(1.06 - 1.42)**	**1.17**	**(1.01 - 1.35)**	**1.31**	**(1.10 - 1.55)**
Dependent PD	1.03	(0.89 - 1.20)			**1.32**	**(1.12 - 1.55)**		
Avoidant PD	1.04	(0.91 - 1.18)	1.03	(0.86 - 1.22)	**1.27**	**(1.09 - 1.47)**	**1.24**	**(1.02 - 1.50)**
Narcissistic PD	**1.29**	**(1.12 - 1.48)**			**1.53**	**(1.31 - 1.78)**		
Antisocial PD	**2.10**	**(1.70 - 2.60)**	**2.11**	**(1.62 - 2.74)**	**3.08**	**(2.49 - 3.80)**	**2.67**	**(2.03 - 3.51)**

Table 3.3. Multiple logistic regression results using forward selection with personality disorders predicting **WAVE 1 AND WAVE 2 ALCOHOL USE** and the symptoms of **WAVE 1 AND WAVE 2 ALCOHOL USE DISORDER**

	ALCOHOL USE				Symptoms of ALCOHOL USE DISORDER			
	Wave 1		Wave 2		Wave 1		Wave 2	
	OR	(95%CIs)	OR	(95%CIs)	OR	(95%CIs)	OR	(95%CIs)
Sex	**2.08**	**(1.70 - 2.56)**	**2.46**	**(1.96 - 3.08)**	**2.65**	**(2.11 - 3.35)**	**3.35**	**(2.59 - 4.35)**
Age at interview	**0.94**	**(0.92 - 0.96)**	**0.95**	**(0.93 - 0.98)**	**0.93**	**(0.90 - 0.95)**	**0.94**	**(0.91 - 0.97)**
Schizoid PD					**0.77**	**(0.60 - 0.98)**		
Paranoid PD	**1.18**	**(1.01 - 1.39)**						
Schizotypal PD					**0.75**	**(0.58 - 0.97)**		
Histrionic PD								
Borderline PD	**1.50**	**(1.28 - 1.75)**	**1.45**	**(1.20 - 1.75)**	**1.75**	**(1.47 - 2.09)**	**1.79**	**(1.48 - 2.16)**
Obsessive Compulsive PD	**0.83**	**(0.72 - 0.95)**						
Dependent PD	**0.82**	**(0.70 - 0.96)**						
Avoidant PD								
Narcissistic PD								
Antisocial PD	**1.74**	**(1.39 - 2.19)**	**1.69**	**(1.28 - 2.23)**	**2.29**	**(1.82 - 2.89)**	**2.02**	**(1.51 - 2.69)**

Bivariate Twin Analyses (Cholesky decompositions)

All significant predictors of AU and AUD based on the multiple regressions for Waves 1 and 2 were then brought forward into the bivariate twin analyses: paranoid, obsessive compulsive, dependent, schizoid, schizotypal, borderline, and antisocial PDs. Results showed very little phenotypic (r_P), genetic (r_A), or environmental (r_E) correlations between Wave 1 AU with paranoid, obsessive-compulsive, and dependent PDs, as well as between Wave 1 AUD with schizoid and schizotypal PDs. Thus, full results of models with all correlations less than 0.2 are shown in Supplementary Table 3.8.

Predictors of Wave 1 Alcohol Use. For all of the Wave 1 AU bivariate models, the additive genetic (A+E) model in which the shared environmental components were removed provided the "best" parsimonious fit. As shown in Table 3.4, there were moderate correlations between AU with borderline and antisocial PDs. The proportions of total variance in AU explained by the genetic and environmental risks in the PDs were obtained by squaring the corresponding path coefficients. Despite the moderate genetic correlations between AU and

borderline or antisocial PDs, the additive genetic factors in each of the PDs explained relatively little total variance in AU. Additive genetic factors in borderline PD explained 4% of the total variance in AU, a small but statistically significant amount. Additive genetic factors in antisocial PD explained 3% of the total variance in AU, a statistically non-significant amount. Likewise, unique environmental risk factors in each of the PDs explained very little of the total variance in AU (2% and 6%, respectively). Although the environmental risks in antisocial PD explained a modest amount of the variance, it was a statistically significant amount.

Bivariate modeling results for the trimmed PD sum scores are shown at the bottom of Table 3.4. For borderline PD, note the reduction in the estimated genetic correlation from 0.32 to 0.21, as well as a corresponding drop from 4% to 1% of the total variance in AU attributable to genetic risk factors. For antisocial PD, the changes in the estimates for the trimmed vs. original PD were in the opposite direction, as the genetic correlation with AU increased from 0.33 to 0.39, which was consistent with the corresponding increase from 3% to 4% in terms of the total AU variance explained by antisocial PD genetic risk factors. All proportions of variance for the trimmed variables were statistically non-significant.

Table 3.4. Bivariate Cholesky A, C, and E decomposition comparisons and summaries for each personality disorder with **WAVE 1 ALCOHOL USE**

Bivariate model fit comparisons					Correlations (95% CI)			Proportion of total variance in **ALCOHOL USE** shared (with each predictor) versus unshared (95% CI)			
Predictor	Model	-2LL	df	AIC	r_P	r_A	r_E	A_{shared}	$A_{unshared}$	E_{shared}	$E_{unshared}$
Borderline PD (total)	ACE	9065.33	5266	-1466.67							
	AE	**9066.74**	**5269**	**-1471.27**	0.22	0.32	0.17	4%	30%	2%	65%
	CE	9073.87	5269	-1464.13	(0.16 - 0.28)	(0.26 - 0.52)	(0.06 - 0.19)	(1 - 9%)	(20 - 40%)	(0 - 5%)	(55 - 75%)
	E	9173.62	5272	-1370.38							
Antisocial PD (total)	ACE	6589.46	5266	-3942.54							
	AE	**6589.66**	**5269**	**-3948.34**	0.30	0.33	0.29	3%	27%	6%	64%
	CE	6602.51	5269	-3935.50	(0.23 - 0.36)	(0.07 - 0.58)	(0.15 - 0.42)	(0 - 10%)	(16 - 37%)	(2 - 12%)	(53 - 75%)
	E	6648.52	5272	-3895.48							
Borderline PD (trimmed)	ACE	8746.26	5266	-1785.74							
	AE	**8746.29**	**5269**	**-1791.71**	0.14	0.21	0.11	1%	32%	1%	65%
	CE	8756.47	5269	-1781.53	(0.09 - 0.20)	(0.00 - 0.42)	(-0.01 - 0.22)	(0 - 6%)	(22 - 42%)	(0 - 3%)	(55 - 75%)
	E	8843.32	5272	-1700.68							

Antisocial PD (trimmed)	ACE	6166.89	5266	-4365.11							
	AE	**6167.68**	**5269**	**-4370.32**	0.26	0.39	0.21	4%	26%	3%	67%
	CE	6178.42	5269	-4359.58	(0.19 - 0.33)	(0.10 - 0.69)	(0.06 - 0.35)	(0 - 14%)	(16 - 37%)	(0 - 8%)	(56 - 78%)
	E	6219.48	5272	-4324.52							

CI = confidence interval; -2LL = -2 X Log Likelihood; AIC = Akaike Information Criteria; ACE = additive genetic + shared environment + unique environmental risks; Trimmed = Borderline PD excluded 'Impulsivity in at least two areas that are potentially self-damaging (e.g., spending, sex, substance abuse, reckless driving binge eating)'; Antisocial PD excluded 'Failure to conform to social norms with respect to lawful behavior as indicated by repeatedly performing acts that are grounds for arrest.'

Predictors of Wave 1 Alcohol Use Disorder. For all of the Wave 1 AUD models, the additive genetic (A+E) model again showed the best fit. As shown in Table 3.5, the phenotypic correlations between AUD symptoms and borderline or antisocial PDs were higher (0.33 and 0.43, respectively). The genetic correlations were also higher (0.41 and 0.60), as were the unique environmental correlations (0.29 and 0.35). However, as with AU, the proportions of genetic and unique environmental variance that each PD explained in AUD were modest, but statistically significant (5-10%).

After removing the potentially confounding substance use criteria from the antisocial and borderline PDs, the phenotypic correlations were lower. For the trimmed borderline PD, the phenotypic correlation declined from 0.33 to 0.25 with the corresponding genetic correlation declining from 0.41 to 0.33. Therefore, the proportion of total variance in AUD symptoms attributable to the genetic risks in this PD also dropped from 5% to 3%, a non-significant amount. However, for the trimmed antisocial PD, the genetic correlation showed less of a decline (from 0.60 to 0.57). The proportion of total variance explained by the genetic risks correspondingly only dropped from 10% to 9% and remained statistically significant.

Table 3.5. Bivariate Cholesky A, C, and E decomposition comparisons and summaries for each personality disorder with **WAVE 1 DSM-IV ALCOHOL USE DISORDER** ordinal symptom criteria composite

Bivariate model fit comparisons					Correlations (95% CI)			Proportion of total variance in symptoms of **ALCOHOL USE DISORDER** shared (with each predictor) versus unshared (95% CI)			
Predictor	Model	-2LL	df	AIC	r_P	r_A	r_E	A_{shared}	$A_{unshared}$	E_{shared}	$E_{unshared}$
Borderline PD (total)	ACE	8806.52	5266	-1725.48							
	AE	**8809.00**	**5269**	**-1729.00**	0.33	0.41	0.29	5%	26%	6%	63%
	CE	8817.40	5269	-1720.61	(0.28 - 0.39)	(0.20 - 0.62)	(0.18 - 0.40)	(1 - 12%)	(14 - 37%)	(2 - 12%)	(52 - 75%)
	E	8900.76	5272	-1643.241							

Antisocial PD (total)	ACE	6296.44	5266	-4235.56							
	AE	**6296.47**	**5269**	**-4241.53**	0.43	0.60	0.35	10%	18%	9%	63%
	CE	6311.77	5269	-4226.23	(0.37 - 0.49)	(0.34 - 0.88)	(0.22 - 0.47)	(3-21%)	(5-30%)	(3-17%)	(51 - 76%)
	E	6343.73	5272	-4200.268							
Borderline PD (trimmed)	ACE	8515.76	5266	-2016.24							
	AE	**8515.87**	**5269**	**-2022.13**	0.25	0.33	0.21	3%	29%	3%	65%
	CE	8528.44	5269	-2009.57	(0.19 - 0.31)	(0.10 - 0.56)	(0.08 - 0.33)	(0 - 10%)	(16 - 40%)	(0 - 7%)	(53 - 77%)
	E	8598.42	5272	-1945.58							
Antisocial PD (trimmed)	ACE	5903.17	5266	-4628.84							
	AE	**5903.17**	**5269**	**-4634.84**	0.38	0.57	0.29	9%	18%	6%	67%
	CE	5914.90	5269	-4623.10	(0.31 - 0.44)	(0.27 - 0.90)	(0.14 - 0.42)	(2 - 21%)	(4 - 31%)	(1 - 14%)	(55 - 80%)
	E	5942.26	5272	-4601.74							

CI = confidence interval; -2LL = -2 X Log Likelihood; AIC = Akaike Information Criteria; ACE = additive genetic + shared environment + unique environmental risks; Trimmed = Borderline PD excluded 'Impulsivity in at least two areas that are potentially self-damaging (e.g., spending, sex, substance abuse, reckless driving, binge eating)'; Antisocial PD excluded 'Failure to conform to social norms with respect to lawful behavior as indicated by repeatedly performing acts that are grounds for arrest.'

Predictors of Wave 2 Alcohol Use. Similar to the models from Wave 1 AU and AUD, the additive genetic (A+E) model also provided the best fit for all Wave 2 AU models (see Table 3.6). The phenotypic correlations between borderline and antisocial PDs with AU were similar to those for Wave 1 AU. However, the genetic correlations showed a substantial increase from Wave 1 (0.44 and 0.77 from 0.32 and 0.33, respectively), while the unique environmental correlations decreased dramatically (0.06 and 0.04 from 0.17 and 0.29, respectively). Despite the higher genetic correlations, the genetic factors in each of the PDs similarly explained a relatively small, but statistically significant, amount of the total variance in AU (8% and 23%, respectively), although this was still an increase from Wave 1. The unique environmental risk factors in each of the PDs explained none of the total variance in Wave 2 AU.

For the trimmed borderline PD, the estimated genetic correlation dropped from 0.44 to 0.25. The total variance in AU attributable to genetic risk factors correspondingly dropped from 8% to 3% and was no longer statistically significant. This reduction was similar to the decrease shown in Wave 1. For the trimmed antisocial PD, the changes in the estimates from the original

PD were in the opposite direction, similar to Wave 1 AU. The genetic correlation increased from 0.77 to 1.00 for the trimmed PD. The total AU variance explained by the trimmed antisocial PD genetic risk factors increased from 23% to 38% and remained significant.

Table 3.6. Bivariate Cholesky A, C, and E decomposition comparisons and summaries for each personality disorder with **WAVE 2 ALCOHOL USE**

Bivariate model fit comparisons					Correlations (95% CI)			Proportion of total variance in **ALCOHOL USE** shared (with each predictor) versus unique (95% CI)			
Predictor	Model	-2LL	df	AIC	r_P	r_A	r_E	A_{shared}	$A_{unshared}$	E_{shared}	$E_{unshared}$
Borderline PD (total)	ACE	6470.03	4511	-2551.97							
	AE	**6472.89**	**4514**	**-2555.11**	0.20	0.44	0.06	8%	34%	0%	58%
	CE	6475.83	4514	-2552.18	(0.13 - 0.26)	(0.20 - 0.70)	(-0.09 - 0.21)	(2-20%)	(18-47%)	(0-3%)	(46-72%)
	E	6475.83	4514	-2552.18							
Antisocial PD (total)	ACE	4133.74	4510	-4886.26							
	AE	**4133.79**	**4513**	**-4892.22**	0.28	0.77	0.04	23%	16%	0%	61%
	CE	4139.39	4513	-4886.61	(0.20 - 0.37)	(0.39 - 0.99)	(-0.15 - 0.24)	(6-49%)	(0-37%)	(0-4%)	(49-75%)
	E	4139.39	4513	-4886.61							
Borderline PD (trimmed)	ACE	6277.30	4511	-2744.70							
	AE	**6278.74**	**4514**	**-2749.26**	0.10	0.25	0.02	3%	40%	0%	58%
	CE	6282.48	4514	-2745.52	(0.03 - 0.17)	(-0.01 - 0.52)	(-0.14 - 0.17)	(0-11%)	(25-53%)	(0-2%)	(45-71%)
	E	6282.48	4514	-2745.52							
Antisocial PD* (trimmed)	ACE	3453.59	4512	-5570.41							
	AE	**3453.64**	**4515**	**-5576.36**	0.23	1.00**	0.00	38%	0%	0%	62%
	CE	3456.92	4515	-5573.08	(0.13 - 0.32)	(1.00 - 1.00)	(-0.19 - 0.20)	(7-51%)	(0-35%)	(0-2%)	(49-76%)
	E	3487.41	4518	-5548.59							

CI = confidence interval; -2LL = -2 X Log Likelihood; AIC = Akaike Information Criteria; ACE = additive genetic + shared environment + unique environmental risks; Trimmed = Borderline PD excluded 'Impulsivity in at least two areas that are potentially self-damaging (e.g., spending, sex, substance abuse, reckless driving, binge eating)'; Antisocial PD excluded 'Failure to conform to social norms with respect to lawful behavior as indicated by repeatedly performing acts that are grounds for arrest.' *The Antisocial PD and alcohol use variables were recoded into binary variables for this model only due to empty cells. **Model estimation of the upper and/or lower 95% CIs failed.

Predictors of Wave 2 Alcohol Use Disorder. In contrast to all of the other models thus far, the additive genetic (A+E) model was not the best fitting model for all of the predictors of Wave 2 AUD symptoms (see Table 3.7). For both the borderline PD and the trimmed borderline PD, the ACE model was the best fitting model, indicating that the shared environmental (C) components could not be dropped to zero. Therefore, Table 3.7 shows the phenotypic, additive genetic, and unique environmental correlations between the PDs and Wave 2 AUD criteria, as well as the shared environmental correlations for the borderline and trimmed borderline PDs. The phenotypic and unique environmental correlations between borderline PD and AUD

symptoms were moderate, with a reduction in the correlation for the trimmed phenotype. The genetic correlation dropped from 0.75 to -0.01 for the trimmed PD, while the shared environmental correlation showed an increase from 0.33 to 0.50. Borderline PD explained a small and statistically non-significant amount of the genetic risk in AUD symptoms (17%), while the trimmed borderline PD explained none of the risk. The proportions of shared environmental and unique environmental variance that borderline PD and the trimmed borderline PD explained in AUD were negligible and statistically non-significant (1-4%).

The pattern of results for the antisocial and trimmed antisocial PDs was similar to those for Wave 1 AU and Wave 2 AU. The additive genetic (A+E) model provided the best fit for both models. The phenotypic correlations were similar to those for Wave 1 AUD (0.37 and 0.31, respectively). As with Wave 2 AU, the genetic correlations increased from 0.85 to 1.00 for the trimmed PD, while the unique environmental correlations decreased from 0.11 to 0.05. The genetic factors in the antisocial and trimmed antisocial PD correspondingly explained a more moderate and statistically significant portion of the total variance in AUD (33% and 44%, respectively). The unique environmental risk factors explained virtually none of the total variance in AUD.

Table 3.7. Bivariate Cholesky A, C, and E decomposition comparisons and summaries for each personality disorder with **WAVE 2 DSM-IV ALCOHOL USE DISORDER** ordinal symptom criteria composite

Bivariate model fit comparisons					Correlations (95% CI)				Proportion of total variance in symptoms of **ALCOHOL USE DISORDER** shared (with each predictor) versus unshared (95% CI)					
redictor	Model	-2LL	df	AIC	r_P	r_A	r_C	r_E	A_{shared}	$A_{unshared}$	C_{shared}	$C_{unshared}$	E_{shared}	E_{unshar}
orderline PD otal)	**ACE**	**6127.23**	**4512**	**-2896.77**	0.27	0.75**	0.33**	0.18	17%	14%	2%	13%	2%	53%
	AE	6130.44	4515	-2899.56	(0.20 - 0.34)	(-0.99 - 0.99)	(-1.00 - 0.99)	(0.01 - 0.36)	(0-59%)	(0-53%)	(0-38%)	(0-40%)	(0-7%)	(38-69%
	CE	6129.11	4515	-2900.89										
	E	6197.97	4518	-2838.03										
ntisocial PD otal)	ACE	3777.41	4511	-5244.59										
	AE	**3777.96**	**4514**	**-5250.04**	0.37	0.85	-	0.11	33%	12%	-	-	1%	55%
	CE	3781.50	4514	-5246.50	(0.28 - 0.45)	(0.49 - 0.99)		(-0.09 - 0.31)	(10-57%)	(0-37%)			(0-6%)	(41-70%
	E	3818.39	4517	-5215.61										

orderline PD rimmed)	**ACE**	**5948.43**	**4512**	**-3075.57**	0.15 (0.07 - 0.22)	-0.01** (-1.00 - 1.00)	0.50** (-0.99 - 0.99)	0.10 (-0.09 - 0.29)	0% (0-60%)	30% (0-59%)	4% (0-44%)	13% (0-44%)	1% (0-4%)	53% (38-70%
	AE	5950.88	4515	-3079.12										
	CE	5950.38	4515	-3079.62										
	E	6017.44	4518	-3018.56										
ntisocial PD* rimmed)	ACE	2979.70	4513	-6046.30										
	AE	**2980.02**	**4516**	**-6051.98**	0.31 (0.21 - 0.41)	1.00** (0.99 - 1.00)	-	0.05 (-0.15 - 0.25)	44% (13-58%)	0% (0-33%)	-	-	0% (0-4%)	56% (42-72%
	CE	2981.67	4516	-6050.33										
	E	3014.49	4519	-6023.51										

CI = confidence interval; -2LL = -2 X Log Likelihood; AIC = Akaike Information Criteria; ACE = additive genetic + shared environment + unique environmental isks; Trimmed = Borderline PD excluded 'Impulsivity in at least two areas that are potentially self-damaging (e.g., spending, sex, substance abuse, reckless lriving, binge eating)'; Antisocial PD excluded 'Failure to conform to social norms with respect to lawful behavior as indicated by repeatedly performing acts hat are grounds for arrest.' *The Antisocial PD and alcohol use disorder variables were recoded into binary variables for this model only due to empty cells. '*Model estimation of the upper and/or lower 95% CIs failed.

Discussion

This is the first study to examine jointly all 10 PDs with AU and AUD and to analyze the genetic and environmental etiology between PDs and AU/AUD. Although there were a number of PDs that significantly predicted AU and AUD, borderline and antisocial PDs emerged as the strongest phenotypic correlates of AU and AUD. Twin analyses also revealed that individual differences in borderline and antisocial PD criteria were the strongest phenotypic and genotypic correlates of AU and AUD at Waves 1 and 2. However, neither the genetic nor unique environmental risk factors in these PDs explained much of the total liability to AU or AUD at Wave 1. Instead, the genetic associations between borderline and antisocial PDs with AU and AUD increased with age. These results are consistent with previous research showing that genetic influences on AU and progression to AUD become more important over time[41-44].

Our estimates of the total genetic variance in AU and AUD attributable to antisocial PD criteria were lower than those reported by Fu et al.[23]. However, our confidence intervals span their estimated 50% of total genetic variance explained by antisocial PD in Wave 2 AUD. The moderate genetic correlation we found between borderline PD and Wave 1 AU is commensurate with a recent report finding the genetic correlation with alcohol abuse-dependence to be 0.33[45].

This correlation was slightly higher for Wave 1 AUD and Wave 2 AU (0.41-0.44), and highest for Wave 2 AUD (0.75). In terms of sources of covariation, Few et al.[45] found that the association between borderline and alcohol abuse-dependence was attributable to genetic risk factors only in the absence of neuroticism. In contrast, Distel et al.[46] found the association between heavy AU and borderline PD to be attributable largely to unique environmental risks. Distel et al.'s[46] results are somewhat inconsistent with our findings since most of the individual differences in borderline PD, AU, and AUD across both Waves were explained by unique environmental risks, which were unshared.

We also found a number of novel findings. For instance, our multiple regression analyses showed that increased obsessive compulsive and dependent PD criteria were associated with lower risk of Wave 1 AU, while increased paranoid PD criteria predicted increased risk of Wave 1 AU. In addition, schizoid PD predicted a decreased risk of Wave 1 AUD. Although our effect sizes were modest, we are unaware of any previous similar findings. Hasin et al.'s[47] analysis of National Epidemiologic Survey on Alcohol and Related Conditions data found no associations between these PDs and persistent alcohol abuse-dependence. One potential explanation for our results is that alcohol consumption may differ across samples and country of origin. Another explanation is that the analyses conducted by Hasin et al.[47] had lower power than ours. Although they had a larger sample size, they used only dichotomous diagnoses, which resulted in fewer cases and larger confidence intervals. Consequently, in the absence of a suitable replication sample, it should be emphasized that obsessive compulsive, dependent, paranoid, and schizoid PD criteria each explained very little of the total phenotypic and genetic variance in both AU and AUD. Accordingly, these other PDs remain less informative.

In terms of inconsistent findings, our Wave 1 findings are in sharp contrast to the pattern of results that we have recently observed with cannabis use and misuse (Gillespie et al., manuscript submitted for publication). Based on a similar design using PDs to predict cannabis use and misuse with personality as covariates, it was found that genetic risks in borderline and antisocial PDs shared 29-30% with the genetic risks in cannabis use, and 31-45% of the genetic risks in cannabis use disorder. Despite the fact that alcohol and cannabis use and misuse are frequently comorbid[48,49], one explanation for this discrepancy, apart from cannabis use being more deviant, could be related to AU and AUD being partially genetically distinct from cannabis use and misuse[50]. However, we note that our Wave 2 findings are more consistent with the cannabis use and cannabis use disorder estimates.

Our findings are also inconsistent with those of Hasin et al.[47], who found that in addition to antisocial and borderline, schizotypal PD also predicted three-year persistence of cannabis, alcohol, and nicotine use disorders. In our results, schizotypal PD had a significant negative association with Wave 1 AUD, rather than a positive association.

In a broader context, our results are consistent with role of PDs in the spectrum of externalizing disorders, which is highly heritable[51] and characterized by conduct and substance use disorders, including AUD[52], antisocial PD[52], and borderline PD[53] (Eaton et al., 2011). Elsewhere, we have shown that correlations across time between these two PDs can be attributed to common, longitudinally stable genetic risk factors[54]. Overall, our findings suggest that among the DSM-IV PDs, borderline and antisocial PD criteria are the key phenotypic and genotypic correlates of AU and AUD, and that these patterns of association are stable across time.

Limitations

Our results should be interpreted in the context of five potential limitations. First, all regression models assume independent observations. Failure to account for non-independence or clustered samples, such as twin data, typically does not impact parameter estimates, but may lead to slightly narrower estimates of confidence interval ranges. However, non-independence is in general much less problematic when group or cluster sizes are uniform and small, which is the case for twin pairs.

Second, although our twin analyses identified significant shared genetic pathways between PD criteria to alcohol use and misuse, the set of possible models examined was not exhaustive. In particular, we did not test competing causal hypotheses, which were beyond the scope of this report. Bornovalova et al.[21] have recently shown that associations between borderline PD and the frequency of past 12-month tobacco, alcohol, and cannabis use could be best explained by a correlated liabilities model, as opposed to any causal mechanism based model. Additionally, it is possible that a high genetic correlation with a high environmental correlation cancelled out any phenotypic association for some of the AU/AUD – PD pairings. A multivariate genetic analysis would be required to determine this.

Third, a natural limitation of twin models is that they cannot identify genetic processes underlying the observed covariation between the PDs and AU and AUD. There is, however, substantial evidence showing that AU and AUD[15-17] and PDs[18,19] are highly polygenic. In other words, the genetic variances and covariance are unlikely to be attributable to a single or pair of discrete genetic structures that influence the development of PDs, AU, or AUD, but rather to many genes of very small effect contributing to these phenotypes. Therefore, we can speculate

that the observed genetic covariation between AU and AUD and the PDs are also highly polygenic.

Fourth, while the sample is broadly representative of the Norwegian population, some attrition occurred from when the NIPH began recruiting twins through to Wave 1 (see Tambs et al.[25]. This may have introduced some bias if attrition was non-random with respect to the dependent variables[55]. We have shown that only demographic, and not mental health, or AU indicators predicted participation at Wave 1[25]. Participation in Wave 2 was predicted by high education ($p < 0.001$ adjusted for sex and age), female sex ($p = 0.003$), and monozygosity ($p = 0.001$). Non-participants in Wave 2 had on average 0.82 more sub-threshold PD criteria than participants ($p < 0.001$). Of the 10 PDs assessed at Wave 1, criteria were significantly higher in non-participants in Wave 2 only for antisocial PD (0.09 criteria difference, $p < 0.001$) and narcissistic PD (0.09 criteria difference, $p = 0.002$). Borderline PD did not predict participation (0.05 criteria difference, $p = 0.06$). Neither the total number of axis I disorders nor any specific disorder were significantly higher in the non-participation group[54].

Finally, the sample was underpowered to detect sex differences[20]. A power analysis would be required to determine the sample size needed, but this not done in the present study. Because endorsement of the PD symptoms were so low, the bivariate models had a difficult time converging themselves, and it was clear the sample was underpowered to detect sex differences. However, previous research has suggested that the magnitude of genetic influences among males and females were equally high, and that these sources of liability were partially overlapping between the two sexes[56].

Conclusion

Using a large Norwegian twin sample, we have shown that borderline and antisocial PDs were the strongest correlates of the phenotypic and genotypic liability to AU and AUD. These patterns of associations remained consistent across time. Our findings suggest that effective prediction of AU and misuse can rely more heavily on criteria for these two PDs in preference to other PD diagnoses. By contributing to our understanding of the etiologic overlap between PDs and AU/AUD, our findings may ultimately help to improve the treatment of individuals with these disorders.

Supplementary

Supplementary. Bivariate Cholesky A, C, and E decomposition comparisons and summaries for each personality disorder with WAVE 1 ALCOHOL USE and ALCOHOL USE DISORDER (correlations less than 0.2)

Bivariate model fit comparisons					Correlations (95% CI)			Proportion of total variance in **WAVE 1 ALCOHOL USE** shared (with each predictor) versus unshared (95% CI)			
Predictor	Model	-2LL	df	AIC	r_P	r_A	r_E	A_{shared}	$A_{unshared}$	E_{shared}	$E_{unshared}$
Paranoid PD	ACE	8776.15	5266	-1755.86							
	AE	**8777.90**	**5269**	**-1760.10**	0.14	0.12	0.15	1%	33%	2%	65%
	CE	8783.38	5269	-1754.62	(0.11 - 0.20)	(-0.17 - 0.41)	(0.05 - 0.26)	(0 - 6%)	(23 - 43%)	(0 - 4%)	(63-75%)
	E	8833.65	5272	-1710.56							
Obsessive Compulsive PD	ACE	9589.75	5266	-942.25							
	AE	**9589.75**	**5269**	**-948.25**	0.01	0.10	-0.03	0%	32%	0%	67%
	CE	9604.16	5269	-933.84	(-0.05 - 0.03)	(-0.13 - 0.35)	(-0.14 - 0.07)	(0-4%)	(22-42%)	(0-0%)	(57-78%)
	E	9695.57	5272	-848.43							
Dependent PD	ACE	8679.74	5266	-1852.27							
	AE	**8679.73**	**5269**	**-1858.27**	0.01	-0.04	0.03	0%	33%	0%	67%
	CE	8690.50	5269	-1847.50	(-0.05 - 0.07)	(-0.27 - 0.20)	(-0.08, 0.14)	(0-1%)	(23-43%)	(0-1%)	(57-77%)
	E	8777.74	5272	-1766.26							
								Proportion of total variance in symptoms of **WAVE 1 ALCOHOL USE DISORDER** shared (with each predictor) versus unshared			
								A_{shared}	$A_{unshared}$	E_{shared}	$E_{unshared}$
Schizoid PD	ACE	7156.67	5266	-3375.33							
	AE	**7156.82**	**5269**	**-3381.18**	-0.01	0.13	-0.07	1%	29%	0%	70%
	CE	7167.00	5269	-3371.00	(-0.08 - 0.06)	(-0.18 - 0.47)	(-0.20 - 0.07)	(0-6%)	(16-42%)	(0-0%)	(58-83%)
	E	7221.01	5272	-3323.00							
Schizotypal PD	ACE	7322.14	5266	-3209.86							
	AE	**7324.69**	**5269**	**-3213.31**	0.06	0.07	0.06	0%	32%	0%	68%
	CE	7331.12	5269	-3206.88	(-0.01 - 0.13)	(-0.24 - 0.39)	(-0.08, 0.19)	(0-5%)	(19-44%)	(0-3%)	(56-80%)
	E	7378.31	5272	-3165.69							

Chapter 4. A National Swedish Longitudinal Twin-Sibling Study of Alcohol Use Disorders[3]

Introduction

The second aim of this dissertation is to investigate the nature of longitudinal changes in the contributions of genetic and environmental risk factors in AU and AUD. This chapter will determine the number of genetic factors needed to account for genetic variance over time and whether these genetic factors are qualitatively distinct. This knowledge will contribute to our understanding of the ways in which these etiologic mechanisms contribute to AUD over time and will fill important gaps in the literature.

AUD is very common in both the United States and Sweden (the population used in the current analyses), affecting 12.5% of the U.S. population[1] and 6-11% of the Swedish population[2,3]. AUD is also a significant public health burden and a leading cause of premature death in both countries[3-7]. As previously mentioned, it has been well established that the development of AUDs are influenced by both genetic and environmental contributions, with consistent heritability estimates of 50% - 60%[8,9]. The majority of research to date has suggested that genetic influences on alcohol consumption become stronger with age, while shared environmental influences attenuate during adulthood[10-13]. However, these studies relied on AU, and thus, it is unclear whether the genetic contributions to the development of AUD are the same or qualitatively different across different age periods.

The findings of the limited studies to date are conflicting. One study showed that risks for AUD in male and female Dutch twins between the ages of 15 to 32 are attributable to a single, stable set of risk genes of increasing magnitude across time[14]. Conversely, another study showed

[3] This paper was modified from a manuscript that was previously published as: **Long, E.C.,** Lönn, S.L., Sundquist, J., Sundquist, K., Kendler, K.S. (2017). A national Swedish longitudinal twin-sibling study of alcohol use disorders. *Addiction, 112,* 1378-1385.

that two genetic factors accounted for the variance in alcohol consumption among male twins in the United States ages 12 to 33[13]. One factor was most influential during adolescence through age 21, when the influence of the other factor became pronounced. This discrepancy may be explained by different phenotypes – van Beek et al.[14] used symptoms of alcohol abuse and dependence while Edwards and Kendler[13] used alcohol consumption. However, high levels of consumption are often a significant predictor of AUD symptoms[15,16] and thus, may serve as a rough proxy for AUD.

Due to the limited, conflicting extant literature, more research is needed to clarify the underlying mechanisms of genetic influences on AUD across time. Examining these influences within a developmental framework can narrow the time frames where genetic influences are most important, leading to a better understanding of the etiologic mechanisms contributing to AUDs over time. Therefore, the aim of the present chapter is to examine whether genetic influences on the development of AUD from emerging adulthood through mid-adulthood are attributable to a single factor or multiple, qualitatively distinct factors.

Methods

Sample

We linked nationwide Swedish registers via the unique 10-digit identification number assigned at birth or immigration to all Swedish residents. The identification number was replaced by a serial number to ensure anonymity.

The following sources were used to create an analysis dataset: the Total Population Register, containing data such as year of birth, sex, and annual data on place of residences; the Swedish National Census; the Swedish Mortality Register, containing dates of death; the Multi-generation register, linking children born after 1932 to their parents; The Swedish Twin Register,

containing information about know zygosity; the Swedish Inpatient Register, containing hospitalizations from 1964 to 2010; and the Swedish Crime Register, which include national data an all convictions in lower court from 1973 to 2011.

We included male-male twin and full sibling pairs born between 1955 and 1971 with both individuals alive at least until age 20. Twins with known zygosity were identified from the Twin Register and full siblings were identified from the Multigenerational Register. We require that the siblings are born within two years of each other and reared together, defined as living together for at least 80% of the possible years until age 18. Females were not included in this analysis because the prevalence of AUD was too low (0.4% - 0.8% across the three age groups).

We previously noted that the prevalence of externalizing behavior, including AUD, is lower in same-sex monozygotic (MZ) and dizygotic (DZ) twin pairs than in opposite sex twin pairs[17,18]. This is almost surely because the former but not the latter were screened for level of cooperation because at least one of the pair had to return a questionnaire to the twin registry and cooperation was lower in subjects with AUD.

As detailed elsewhere[19], zygosity in the same-sex pairs from the twin registry was assigned using standard self-report items from mailed questionnaires. When validated against biological markers, these questionnaires were 95-99% accurate.

Measures

Our longitudinal measure of AUD requires sources covering the whole follow-up period. These sources include the Inpatient Register and the Crime Register. AUD was identified from the Inpatient Register by the following medical diagnoses: ICD-8 codes: 571.0, 291, 303, 980, ICD-9 codes: V79B, 305A, 357F, 571A, 571B, 571C, 571D, 425F, 535D, 291, 303, 980 and ICD-10 codes: E244, G312, G621, G721, I426, K292, K700, K701, K702, K703 ,K704, K709,

K852, K860, O354, T510, T511, T512, T513, T518, T519, F101, F102, F103, F104, F105, F106, F107, F108, and F109. AUD was identified from the Crime Register if individuals were convicted for at least two records of drunk driving (suspicion code: 3005 and law 1951:649 and Paragraph 4 and 4A) or drunk in charge of maritime vessel (suspicion code: 3201 and law 1994:1009 and Paragraph 4 and 5 and Chapter 20). The date of the second crime was chosen as the timing of the first AUD event while each following crime was counted as an event. The data were measured during three age ranges meant to correspond to meaningful developmental periods: 18-25 (emerging adulthood); 26-33 (early adulthood); and 33-41 (mid-adulthood). Individuals were defined to have an AUD during an age period if they had at least one hospitalization or conviction during that period.

Statistical analyses

We utilized an extended sib-pair design to decompose the sources of variation in AUD into additive genetic (A), shared environment (C), and unique environment (E). The need for an extended sib-pair design arose because the number of DZ twin pairs concordant for AUD in these age periods was insufficient to produce stable estimates. Therefore, we added full sibling pairs born within two years of each other and reared together with their siblings to the DZ pairs. The model assumes that MZ twins share all their genes while DZ twins and siblings share half of their genes identical by descent, and that the shared environment, reflecting family and community experiences, contributes equally to the similarity between each twin or sibling pair. Unique environment includes stochastic developmental effects, environmental experiences not shared by siblings, and random error.

We assumed the same thresholds for AUD for MZ and DZ twins – given they both were weakly screened for cooperation by returning zygosity questionnaires – and permitted a separate

threshold for full siblings who did not undergo a parallel screening. As illustrated in Figure 4.1, developmental changes in the genetic and environmental influences on AUD over the three age periods (18-25, 26-33, and 33-41) were modeled as a Cholesky decomposition. This developmentally informative approach divides genetic and environmental risk into three factors, the first of which begins during the first period (ages 18-25) and is continually active over the entire developmental period. The strength of its effect at each age is reflected in the path coefficients from this factor to AUD at ages 18-25, 26-33, and 33-41. The second factor begins in the second period (ages 26-33) and impacts on AUD at ages 26-33 and 33-41. The third and final factor begins at ages 33-41 and acts only during this period. To account for possible cohort effects, we allow each threshold to linearly depend on birth year by including the corresponding regression parameters (referred to as age regression).

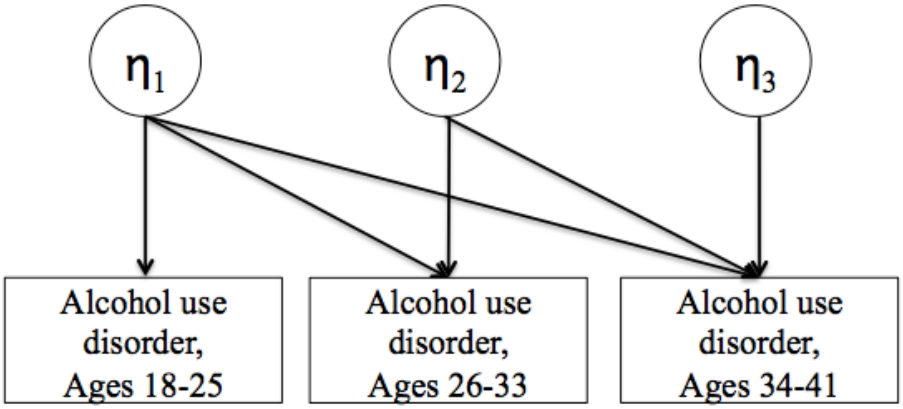

Figure 4.1. Cholesky decomposition for AUD across three age periods

The objective is to quantify the nature and magnitude of developmental changes in genetic and environmental risk factors for AUD. A full ACE model with no age regression was first run (Model 1). We then tested whether including the age regression would result in improved model fit (Model 2). Finally, we tested if removal of two C factors (one common C across the ages; Model 3) would result in deterioration of fit and if complete removal of the C factor would deteriorate fit (Model 4). Because the twin correlations suggested that genetic

factors are likely playing a more important role than shared environmental factors, we did not test sub-models removing any A factors. Sub-models were compared with the larger baseline model utilizing Akaike's Information Criterion (AIC)[20]. All models were fit with the OpenMx software[21].

Results

Descriptive Statistics

The total prevalences of AUD and prevalences by registration type for MZ twins, DZ twins, and full siblings born less than two years apart across the three age periods are shown in Table 4.1. The patterns of results across the years show a slight increase in prevalence from age 18 through age 41. Rates of AUD are similar in MZ and DZ twins, but are slightly higher in the full siblings.

Table 4.1. Sample size and prevalence of AUD

		Prevalence of AUD		
Relationship	Number of Pairs	Ages 18-25	Ages 26-33	Ages 34-41
MZ twins	1,532	37 (1.2%)	39 (1.3%)	56 (1.8%)
Registration type				
Hospitalization		20 (0.7%)	23 (0.8%)	35 (1.1%)
Crime		21 (0.7%)	25 (0.8%)	29 (0.9%)
DZ twins	1,940	55 (1.4%)	53 (1.4%)	77 (2.0%)
Registration type				
Hospitalization		31 (0.8%)	33 (0.9%)	54 (1.4%)
Crime		27 (0.7%)	28 (0.7%)	33 (0.9%)
Full siblings, born 0-2 years apart	66,033	3,001 (2.3%)	3,176 (2.4%)	3,451 (2.6%)
Registration type				
Hospitalization		1,290 (1.0%)	1,671 (1.3%)	2,119 (1.6%)
Crime		2,086 (1.6%)	1,986 (1.5%)	1,835 (1.4%)

The tetrachoric twin and sibling correlations for AUD by age period are displayed in Table 4.2. The within-pair twin/sibling correlations are shown along the diagonal for each age period. The within-pair MZ twin correlations are greater than both the within-pair DZ twin and within-pair sibling correlations, suggesting that genetic influences are playing an important role.

Of note is the increasing MZ correlation across the years, while the correlations for DZ twins and full siblings remain similar, suggesting that genetic factors increase in importance. Additionally, at ages 18-25 and 34-41, the within-pair within-trait DZ twin pair correlations are greater than half their MZ twin pair counterparts, suggesting that shared environmental effects also explain familial aggregation during these two later age periods, although these effects may be minimal. Both the within-DZ twin and within-sibling correlations were fairly stable across time. The DZ twin correlations are also quite similar to the full siblings, indicating that there is no evidence for the special twin environment. The cross-twin/sibling cross-time correlations are shown on the off-diagonals.

Table 4.2. Tetrachoric twin correlations (SE) for AUD by age period

	Twin 2		
Twin 1	Ages 18-25	Ages 26-33	Ages 34-41
Monozygotic Twins			
Ages 18-25	0.546 (0.138)	0.695 (0.103)	0.706 (0.089)
Ages 26-33	0.421 (0.164)	0.679 (0.105)	0.688 (0.091)
Ages 34-41	0.211 (0.202)	0.564 (0.123)	0.716 (0.080)
Dizygotic Twins			
Ages 18-25	0.317 (0.156)	0.419 (0.137)	0.284 (0.155)
Ages 26-33	0.181 (0.192)	0.333 (0.157)	0.150 (0.190)
Ages 34-41	0.399 (0.123)	0.399 (0.123)	0.477 (0.105)
Full siblings, born 0-2 years apart			
Ages 18-25	0.385 (0.019)	0.362 (0.019)	0.318 (0.020)
Ages 26-33	0.358 (0.019)	0.379 (0.019)	0.386 (0.018)
Ages 34-41	0.320 (0.020)	0.352 (0.019)	0.365 (0.018)

Multivariate Twin Modeling

Model fit statistics for the four models are shown in Table 4.3. The best-fitting model as per the AIC was Model 4, which included the age regression (i.e., age as a covariate on the item thresholds) and eliminated the C component (i.e., an AE model), indicating there is no evidence

for shared environmental influences on the development of AUD across the ages of 18-41. The parameter estimates and 95% confidence intervals for the genetic and individual-specific environmental risk factors from our AE Cholesky model are depicted in Figure 4.2. As illustrated in Figure 4.3, the first genetic factor (A_1) was robust and strongly impacted the liability to AUD at ages 18-25 (0.84; CI: 0.83, 0.88). The influence of this factor was sustained at ages 26-33 and 34-41, although its relative importance declined modestly. A second genetic factor (A_2) of much less impact contributed at ages 26-33 and increased modestly at ages 34-41 (0.31; CI: 0.05, 0.47). The third genetic factor (A_3) had virtually no influence on the liability to AUD at ages 34-41.

The first unique environmental factor (E_1) also has a strong influence on AUD at ages 18-25 but decreased substantially with time. A second unique environmental factor (E_2) contributed at ages 26-33 and also showed a declining influence over time. Finally, the third unique environmental factor (E_3) had the same effect at ages 34-41 as E_2 did at ages 26-33.

Table 4.3. Model fit statistics for AUD multivariate Cholesky decompositions

Model	-2LL	# Parameters	AIC	Compared to model	p -value
1. No age regression	79,483.22	21	-754,534.80		-
2. With age regression (ACE model)	79,303.11	27	-754,702.90	1	$3.6 \cdot 10^{-36}$
3. With age regression, common C (ACE model with 1 C factor)	79,303.14	24	-754,708.90	2	0.999
4. With age regression, no C (AE model)	79,304.08	21	**-754,713.90**	2	0.990

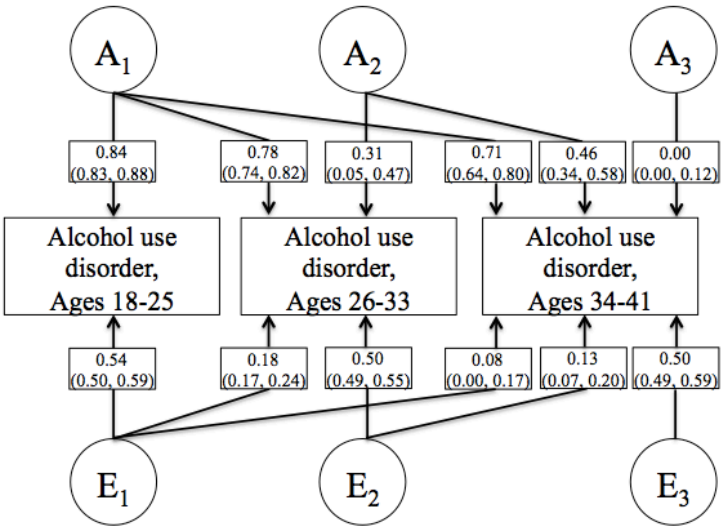

Figure 4.2. Parameter estimates (and SEs) for the genetic and unique environmental effects from the AE Cholesky Model. 'A' refers to additive genetic factors and 'E' refers to unique environmental factors. The subscripts 1, 2, and 3 indicate that the respective effects come online at ages 18–25, 26–33, and 34-41, respectively.

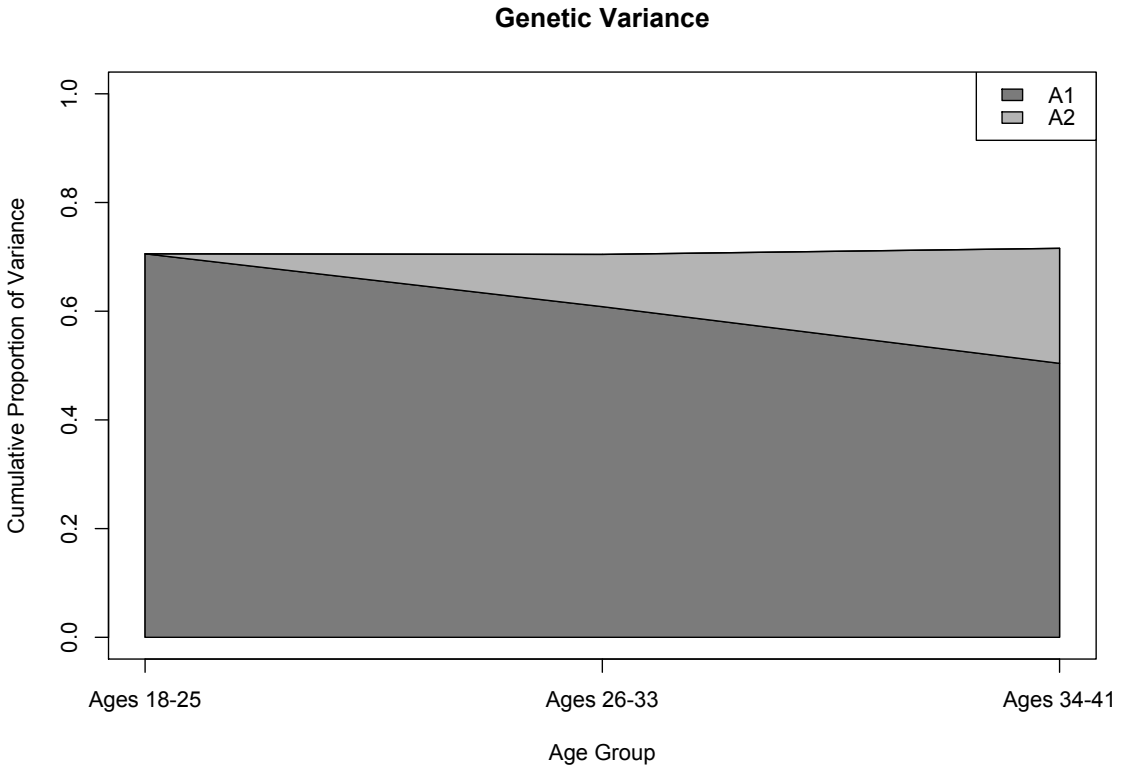

Figure 4.3. The proportion of total variance in alcohol use disorders accounted for by genetic factors from ages 18 to 41. The y-axis represents the cumulative proportion of variance. The first genetic factor, which starts at ages 18–25, is represented in dark grey. Light grey represents the second genetic factor, starting at ages 26–33.

The parameters from the full ACE model (Model 3) are shown in Supplementary Table 4.5. As shown, the C parameters are not statistically significant and could be dropped from the model without a significant deterioration of fit. Thus, the AE model was chosen on the basis of parsimony.

The standardized proportions of variance attributable to A and E (and their 95% confidence intervals) at each time period based on the best fitting multivariate models are displayed in Table 4.4. Both the heritability and unique environmental effects are stable across the three age periods.

Table 4.4. Estimates of additive genetic (a^2) and unique environmental (e^2) effects by age

	a^2 (95% CI)	e^2 (95% CI)
Ages 18-25	70.6% (68.9, 77.4)	29.2% (25.0, 34.8)
Ages 26-33	70.5% (55.0, 89.3)	28.2% (26.9, 36.0)
Ages 34-41	71.6% (52.5, 99.1)	27.3% (24.5, 41.7)

Note. Totals may not equal 100% due to rounding.

The cross-temporal genetic and unique environmental correlations are shown in Supplementary Table 4.6. The genetic correlations across the age groups are high, ranging from 0.84 to 0.98. The unique environmental correlations are low to moderate, ranging from -0.03 to 0.34.

Discussion

The aim of the present chapter was to determine the number of genetic factors needed to account for genetic variance over time and whether these genetic factors are qualitatively distinct. Our results showed significant changes in genetic variation over time that are consistent with both innovation and attenuation. Although the total heritability remained stable between ages 18 and 41, we showed evidence for two distinct but correlated genetic risks on AUD: one originating in emerging adulthood (ages 18-25) and another set with less impact coming online

during early adulthood (ages 26-33). By mid-adulthood (ages 34-41), there was no evidence for any additional genetic variation.

These results are inconsistent with those of van Beek et al.[14], who showed that risks for AUD are attributable to a single, stable set of risk genes. They are, however, broadly consistent with those of Edwards and Kendler[13], who showed that two genetic factors influenced risk for alcohol consumption, with one factor most influential during adolescence through age 21 and the second factor becoming more pronounced thereafter. This is somewhat surprising, given that our phenotype was similar to the phenotype used in the van Beek et al.[14] study. Similar age ranges were also used in all three studies, and, importantly, captured the important developmental period of emerging adulthood. However, one possible explanation for the inconsistency in results may be due to different prevalences of AUD in the three countries the samples were drawn from. Van Beek et al.[14] used a sample from the Netherlands, where the past 12-month prevalence of alcohol dependence is the lowest (0.7%) [22]. We used a Swedish sample and Edwards and Kendler[13] used a U.S. sample, where the past-12 month prevalences were more similar (6.3% and 3.8%, respectively)[1,3]. Thus, an important area for future research is to further examine how cultural influences may impact genetic influences across time.

Another possible explanation may be due to the different modeling approaches used. The present study and Edwards and Kendler[13] used Cholesky decompositions, whereas van Beek et al.[14] used both Cholesky decomposition and autoregressive "simplex" models. Future research should use more comprehensive modeling approaches that test competing developmental hypotheses for a deeper understanding of how genetic processes influence AUD risk over time.

Congruent with the findings of Grant et al. (2006)[23], we found no evidence for shared environmental influences in the development of AUD. However, because our first age group

started at age 18, we could not determine the role of these influences prior to this age. It is likely though that shared environmental risks impact alcohol consumption during adolescence but decline with age, due to relaxing social constraints during adulthood[10-12].

In terms of heritability estimates, our estimates are higher than those that are typically reported (50% - 60%)[8,9]. One possible explanation for this may be that we restricted our sample to ages 18 through 41, which further adds to the research showing that genetic factors become more important with increasing age. However, we are not able to make any conclusions regarding the role of genes after age 41. Another possible explanation is that our use of registries detected more severe cases where genes may play a more important role, thereby increasing our heritability estimates.

Our data also relied exclusively on males, and the degree to which our results can be generalized across sex or to Swedish females is unclear. One large recent study found a substantial sex difference where the heritability of AUD was estimated to be 22% for females, but 57% for males[18]. This study also showed that shared environmental influences and twin-specific environmental effects were more important in females than males.

Our finding that there are two major sets of genetic risk factors for AUD is broadly consistent with other developmental twin studies of externalizing behaviors and disorders. For example, genetic factors for antisocial behavior are more influential after the age of 15, and the heritability increases from childhood to adulthood[24,25]. There is also evidence that the genetic influences on childhood and adolescent conduct disorder (before age 18) overlap with those of adult antisocial behavior (after age 18)[26].

Likewise, the development of externalizing behavior is influenced by genetic continuity, but with some genetic innovation during early and late adolescence[27]. The genetic variation in

externalizing disorders has also been shown to increase from ages 17 to 24[28]. Relatedly, Kendler et al.[29] found evidence for two genetic factors influencing risk for criminal behavior. One began during the ages 15-19 and declined over time, while the other came online at ages 20-24 and showed stability over time. Taken together, these results suggest that genetic risk for AUD and the associated phenotypes (e.g., externalizing disorders) are developmentally dynamic from early adolescence through middle adulthood.

Our findings can help to inform gene-finding efforts. Recent genome-wide association studies have had limited success in identifying the genetic variants that increase the risk for developing AUD[30,31]. Our results suggest that this may be because these studies used a sample with too wide of an age range, thus increasing the amount of genetic heterogeneity. By restricting the sample to early adulthood (ages 18-25) or more likely, mature adults (age 26 or older), gene-finding efforts may be improved.

Limitations

These results should be considered within the context of three potential limitations. First, our analyses were limited to Swedish males between the ages of 18 and 41. It is therefore uncertain if our results generalize to women as well as other populations. However, it is likely that the results are generalizable to other industrialized countries. Additionally, although we had a large sample size, prevalence for AUD before age 18 and in females was too low to be able to obtain stable statistical results, and thus were not included in this analysis.

Second, we relied on medical and legal records for our measure of AUD. This method has the advantage of not being subject to recall or reporting biases, but it can produce false negatives and false positives. Although the extent to which this occurred could not be estimated, we suspect that registries detect more severe cases of AUD than population-based interview

studies, due to a recent report using the same sample that found the prevalence of AUD to be lower than estimates from most epidemiologic surveys[2,3], including the nearby country of Norway[32,33]. However, a previous study using the same registry data showed high concordance rates for registration across the different methods, providing support for our AUD measure[2]. In addition, those cases that require hospital care are more clinically relevant than those who are based on population-based interviews.

Third, individuals who were assigned a diagnosis based on inpatient registrations entered treatment for both voluntary and involuntary reasons. Accordingly, it is possible that including treatment-seeking individuals rather than using a population-based sample only may have resulted in different conclusions about the genetic and environmental influences on AUD risk across time[34,35]. For example, Prescott and Kendler[34] found evidence for shared environmental influences on AUD risk when using a treatment-seeking population, but not a population-based sample. However, it should be noted that we also diagnosed AUD cases from the criminal registry, which required no treatment seeking.

Conclusion

Using a nationwide sample of Swedish male twins and full siblings born less than two years apart, we showed stable heritability across time with two sets of genetic risk factors, one originating during the ages 18-25 and another coming online at ages 26-33. These results contribute to our understanding of the etiologic mechanisms contributing to AUDs by elucidating the nature of genetic influences across time.

Supplementary

Supplementary Table 4.5. Path coefficients from full ACE model (95% CI)

	A_1	A_2	A_3
Ages 18-25	0.68 (0.00, 0.88)		
Ages 26-33	0.64 (0.63, 0.88)	0.17 (0.00, 0.31)	
Ages 34-41	0.63 (-0.60, 0.89)	0.29 (-0.30, 0.57)	0.14 (0.00, 0.24)
	C_1	**C_2**	**C_3**
Ages 18-25	0.37 (0.00, 0.58)		
Ages 26-33	0.33 (-0.38, 0.57)	0.21 (0.00, 0.30)	
Ages 34-41	0.26 (-0.37, 0.60)	0.24 (-0.21, 0.37)	0.04 (0.00, 0.25)
	E_1	**E_2**	**E_3**
Ages 18-25	0.63 (0.47, 0.74)		
Ages 26-33	0.32 (0.30, 0.46)	0.55 (0.45, 0.59)	
Ages 34-41	0.20 (0.18, 0.42)	0.25 (0.08, 0.33)	0.53 (0.45, 0.57)

Supplementary Table 4.6. Genetic and environmental correlations

		Genetic	
Ages 18-25	1		
Ages 26-33	0.92 (0.86, 0.98)	1	
Ages 34-41	0.84 (0.77, 0.96)	0.98 (0.96, 1.00)	1
		Environmental	
Ages 18-25	1		
Ages 26-33	0.34 (0.23, 0.41)	1	
Ages 34-41	0.16 (-0.03, 0.19)	0.28 (0.16, 0.38)	1

Chapter 5. Contributions of Genes and Environment to Developmental Change in Alcohol Use[4]

Introduction

This chapter will address the second part of Aim 2 by investigating the precise mechanisms by which underlying genetic and environmental risk factors influence AU over time from adolescence through young adulthood. Understanding these etiologic mechanisms of change underlying the development of AU is important, given the high rates of AU initiation in early adolescence[1]. For example, over 70% of U.S. high school students report consumption of at least one alcoholic beverage[2], and 34% of high school seniors report drinking alcohol to intoxication[3]. Excessive AU among adolescents is associated with risky behaviors, such as physical fighting, automobile deaths, and homicides[4]. Understanding how the genetic and environmental risk factors emerge and change over time from adolescence through early adulthood will inform intervention and prevention efforts aimed at reducing AU-related risks and negative outcomes.

Developmental studies of AU have consistently shown that AU increases linearly throughout adolescence[5-9], with heavy drinking peaking among individuals in their early twenties, before decreasing[10]. Although these studies have been successful in identifying common trajectories of AU, they have not tested competing developmental models aimed at capturing the different processes that may be driving patterns of AU change over time.

As previously stated, twin and family studies have demonstrated that AU is influenced by genetic and environmental factors, with genetic risk factors explaining 50%-60% of AU variance[11-13]. Genetic influences have been shown to become relatively more prominent over

[4] This paper was modified from a manuscript that was previously published as: **Long, E.C.,** Verhulst, B., Aggen, S.H., Kendler, K.S., Gillespie, N.A. (in press). Contribution of genes and environment to developmental change in alcohol use. *Behavior Genetics.*

time, whereas shared environmental factors become less salient over time[14-17]. Previous longitudinal analyses of the data from the Virginia Adult Twin Study of Psychiatric and Substance Use Disorders (VATSPSUD) used in this present study also found that genetic variation increased over time[15,16]. Further, Van Beek and colleagues found evidence of single, stable set of genetic risk factors[17]. In contrast, Edwards and Kendler[18] found that while genetic variance increases over time, the genetic risks were attributable to two significant, dynamic and qualitatively different genetic risk factors[18], whereby one factor declines in young adulthood, while the other increases in variance.

The genetically informative reports to date, including the previous chapter, have been largely atheoretical insofar as they did not leverage the classical twin design within a defined, developmental framework, but instead relied on Cholesky decompositions. This approach makes no theoretical prediction with regard to the emerging and evolving genetic and environmental mechanisms underpinning changes in AU or AUD over time[15,16]. In other words, they did not specify and test competing models representing different developmental hypotheses[17,19].

It is plausible that genetic and environmental risk factors increase over time as predicted by latent growth models (LGMs)[20-24]. In LGMs, the rates of change (slope) from baseline levels (intercept) may be linear or non-linear. These processes have been referred to as an "unfolding" of risk factors or effects across time[25]. Alternatively, there may be an accumulation of random genetic or environmental effects as predicted by autoregressive models (ARMs)[26-28]. It is also possible that both processes may act jointly on the risk of AU as predicted by dual change score (DCS) models[29-31]. This hybrid approach is mathematically and statistically equivalent to a random coefficient, multilevel or hierarchical linear model[32-36]. Costanzo and colleagues[10] have used this approach to examine rates of change in AU (i.e., latent growth effects) and changes in

the probability of heavy drinking relative to the previous probability (i.e., autoregressive effects). Although based on genetically uninformative data, their results showed that heavy drinking was most common in the early 20's, but decreased thereafter, and that for a subset of individuals, heavy drinking persisted into later adulthood. The intent of the DCS modeling approach here was to simply identify age trajectories of heavy drinking for use in subsequent mixture modeling, rather than to compare the fits of the sub-models (i.e., latent growth vs. autoregressive effects).

The DCS model has been applied to other complex psychiatric behaviors. For example, Gillespie et al. have used this method to distinguish genetic and environmental mechanisms underlying adolescent depression[25]. They found that environmental risks were best explained with accumulating, autoregressive factors, whereas genetic risks were best explained in terms of latent growth factors that unfold or change at different rates across time. To our knowledge, this hybrid DCS method has not been used to examine the genetic and environmental influences underlying adolescent AU.

Given the importance of gaining a complete understanding of how genetic and environmental influences contribute to the etiology of adolescent AU, investigating these developmental features within a genetically informative, developmental framework is needed. This approach has the potential to identify critical time-dependent developmental periods for effective prevention and early intervention efforts.

Therefore, the aim of the present chapter is to examine within a broader developmental framework the nature of longitudinal changes in the contributions of genetic and environmental risk factors to AU from mid-adolescence through young adulthood. Because of the phenotypic and genetic correlations between internalizing disorders and AU[37-40], it is hypothesized that the developmental pattern of genetic and environmental risks in AU will be broadly similar and

follow the same patterns observed elsewhere[25]. Accordingly, consistent with the results of Gillespie et al. (2015)[25], we predict that (i) autoregressive effects will better characterize environmental influences on AU, and (ii) latent growth effects will describe genetic risk factors.

Method

Sample

Participants came from the Virginia Adult Twin Study of Psychiatric and Substance Use Disorders (VATSPSUD)[41]. VATSPSUD consists of Caucasian male, female, and opposite sex twin pairs from the Virginia Twin Registry (now the Mid-Atlantic Twin Registry) born between 1940 and 1974. Between 2000-2004, a subsample of the adult same sex male twin pairs were assessed as part of an interview to study the nature and pattern of risk and protective factors for psychoactive substance use and psychoactive substance use disorders across the lifespan. This study was completed by 1,794 males, aged 24-62 years (M = 40.3, SD = 9.0), and consisted of 752 complete twin pairs (467 monozygotic and 285 dizygotic) and 290 singletons. Zygosity was determined using a combination of self-report measures, photographs and DNA analysis[42].

Measures

The outcome variable used in the models was AU. AU was assessed using retrospective self-reports of the ages at which changes in AU occurred over the lifespan. A Life History Calendar method[43-45] was used to assess several variables related to AU. This method has shown that although human memory can be relatively poor when attempting to recall past behavior, self-report information may be improved significantly when probed with careful directed questioning involving specific time periods and events. Using this method, participants were asked how old they were when they first started drinking, at what age they drank the heaviest, how much they drank (quantity; drinks per day), and how often they drink (frequency; days

drank per month). Twins were asked to report on these consumption variables at the age when their alcohol intake changed. To reduce the number of missing values in the person year data, values were filled in for ages where no change in consumption was reported with the previous change amount. Interviews were administered via telephone or in-person interviews. The calendar alcohol response data was organized into a person year data set with person ages ranging from 0 to 61. The full interview included a number of retrospective assessments to coincide with the timing of major developmental milestones, such as alcohol initiation, leaving the parental home, finishing high school, and college entry and completion[46].

A person year change in average number of drinks per month variable was created using a 'standard' unit for a drink that equaled one and one half ounces of spirits, six ounces of wine, or twelve ounces of beer. All longitudinal modeling used this average number of drinks per month variable as the outcome for the selected range of person years 15-25. This age range was selected to correspond to the meaningful developmental milestones listed above. To adjust for wide ranges of the mean AU, we applied a log transformation to the data.

Statistical Analyses

Autoregressive (ARMs), latent growth (LGMs), and dual change score (DCS) developmental models were fitted to the AU data to test competing hypotheses regarding the nature of the genetic and environmental risk factors involved in changes in AU over time. ARMs predict an accumulation of time-specific random effects and formally capture the 'remembering' or the 'forgetting' of time-dependent risk factor influences. Genetic or environmental risks at each time point are a function of new time-specific random effects ("innovations") plus individual differences expressed from earlier times ("accumulation"). The "innovations" reflect novel, time-dependent genetic effects or environmental influences. Cross temporal correlations

within subjects arise because innovations may persist over time and accumulate during development, resulting in developmental increases in the genetic or environmental variances, and increasing correlations between adjacent measures.

LGMs predict that developmental change in a phenotype is a function of unfolding, random risks in baseline levels (intercept) and rates of change (slope) over time that can be decomposed into genetic and environmental sources of variance. Rates of change can be linear or non-linear. These models correspond with special cases of the latent factor model in which factor loadings for the baseline levels and change factors are functions of the coefficients of a priori contrasts on the ages at which the measures were taken.

DCS models are hybrid models specifying that change within the genetic or environmental risk factors is a function of both autoregressive and latent growth factors. The DCS model is a more complex developmental model, as it combines the LGM (linear and quadratic rates of changes) with first-order ARM effects for both genes and environment. The diagram in Figure 5.1 summarizes the principal features of this model and how these two types of developmental processes are integrated. For simplicity, the Figure only considers the elements of the model without distinction between genetic and environmental components, although our analysis evaluates the genetic and environmental components (A, C, and E) independently. This allows for the possibility that different processes underlie genetic and environmental components of developmental change.

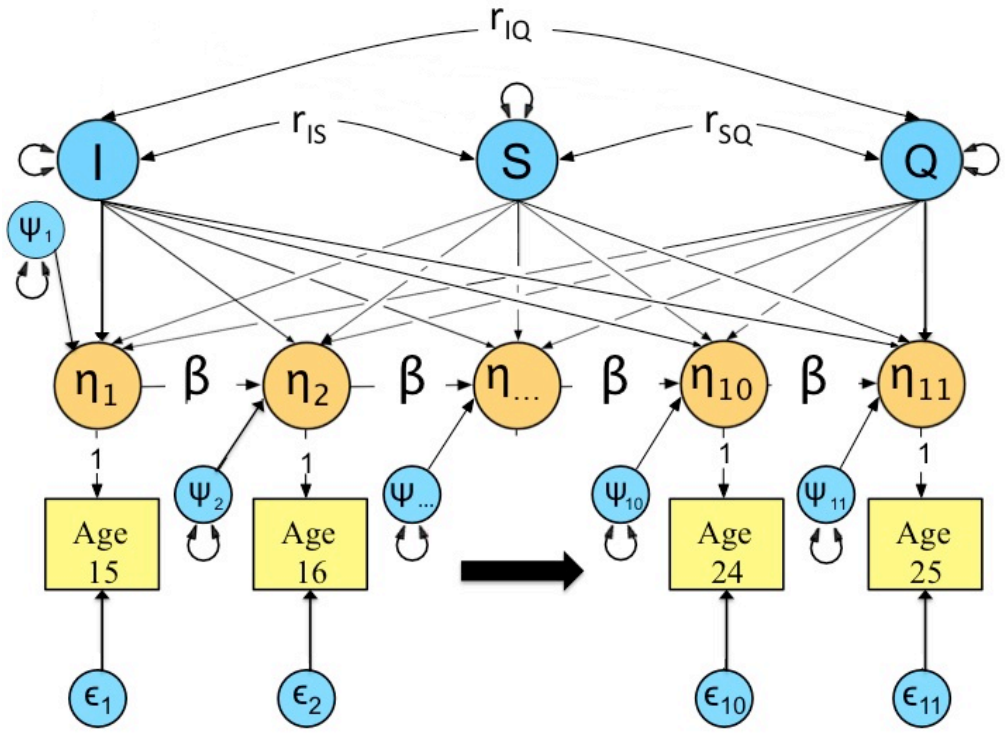

Figure 5.1. Path diagram of a structural model for the developmental changes in alcohol use for autoregressive and latent growth curve effects for ages 15 through 25. I = intercept (constant); S = slope (linear rate of change); Q = quadratic (nonlinear rate of change); β = first-order, autoregressive coefficients (the accumulation of risks due to the constant and change factors including latent residual error over time); Ψ = item-specific or residual variances; ϵ = error variances for the latent AU factors. This model can be applied to genetic or environmental developmental change, or both.

Normalized orthogonal contrasts were used for the latent growth factor loadings for the intercept (I), linear slope (S), and quadratic (Q) latent growth factors in the saturated DCS model are shown in Supplementary Table 5.3. In Figure 5.1, the first-order, autoregressive coefficients are denoted by β and reflect the accumulation of risks due to the constant and change factors including latent residual error over time. These were set to be equal across ages. The item-specific or residual variances in the observed AU frequencies are represented by Ψ, and finally, the error variances for the latent AU factors at each age (ages 15 - 25) not explained by the constant and change factors are represented by ϵ.

The variance components for the innovations in the autoregressive features, as well as the intercept and slope factors in the latent growth processes can be decomposed into additive (A) genetic, shared (C), and unique (E) environmental variance components using standard biometrical genetic methods[47,48]. Because monozygotic (MZ) twin pairs are genetically identical, while dizygotic (DZ) twin pairs share on average half of their segregating genes, the expected twin pair correlations for the genetic (A) effects are 1.0 and 0.5, respectively. An important assumption in twin modeling is that the common environments (C) contribute equally to the similarity in MZ and DZ twin pairs, and because non-shared environments (E) are by definition uncorrelated, E must also reflect measurement error. The developmental models were fitted and compared using structural equation modeling within the R-based OpenMx software package using Full Information Maximum Likelihood (FIML)[49-51].

The full DCS model (Model 1) can be modified by removing the LGM component to produce a pure ARM (Model 2), or by removing the ARM, resulting in a pure LGM (Model 3). Within the twin model, the structure can then be further simplified. Model 4 removed the effect of shared environmental influences for both the LGM and ARM components. Model 5 removed the genetic ARM component and the unique environmental LGM component. Thus, Model 5 predicted that LGM effects account for genetic risk factors, while ARM effects accounted for unique environmental influences on AU.

The best fitting model was identified by examining the lowest Akaike Information Criterion (AIC)[52], Bayesian Information Criterion (BIC), and sample-size adjusted BIC (sBIC)[53], which are information based parsimony indices. Selecting a best-fitting model based solely on log-likelihoods can be misleading due to 'over-fitting' since model-data misfit will decrease simply by adding more parameters to a model. Therefore, the advantage of parsimony indices is

that they penalize models with larger numbers of parameters, thereby providing an index of each model's efficiency to explain the patterning in observed data when balanced against model complexity. Our rationale for including BIC and sBIC is also based on simulations[54], which have shown that these indices outperform AICs[55]. Information based indices are appropriate when model comparisons are to be made for models that are not all nested, as is the case here. Under Model 5, the means for the unshared environmental (E) ARM component were necessarily modeled on the latent true scores for each observed phenotype, as opposed to the intercept, slope and quadratic in the full DCS model (Model 1).

Results

Descriptive Statistics

The full MZ and DZ twin correlation matrices by age are presented in Supplementary Tables 5.4 and 5.5, respectively. Generally, the MZ twin correlations showed an increase until peaking at age 21 ($r = 0.50$), after which the correlations stabilize or decline slightly, ranging between 0.46 and 0.48. Conversely, the DZ within-pair twin correlations are more modest, ranging between 0.17 and 0.37. Despite a slight increase from age 15 through age 18, the correlations subsequently decrease steadily. The size of the MZ correlations are greater than the DZ correlations at all time points, but the DZ correlations are also greater than twice the MZ correlations. This suggests that familial aggregation is likely attributable to a combination of additive genetic and shared environmental risk factors.

Developmental Models

Table 5.1 shows a summary of the fit indices for the different model comparisons. As hypothesized, the best-fitting developmental model as determined by the AIC, BIC, and sBIC was Model 5, which predicted that LGM effects account for genetic risk factors, whereas an

ARM better characterizes how unique environmental influences operate on AU. Figure 5.2a shows the expected means for AU change by age as predicted by Model 5. There is an approximately linear increase in changes in AU from age 15 through age 21, at which point changes in consumption stabilize. Figure 5.2b shows the patterns of change in the genetic, unique environmental, and total phenotypic unstandardized variances. The pattern of mean changes in AU roughly corresponds to the patterns of change in the variance of AU across the ages measured. There is a marked increase in the total phenotypic variance from age 15 to age 18, at which time the effect stabilizes followed by relatively small changes through age 25. The average contribution of the unique environment also shows a sharp increase from age 15 to age 18, but then shows a decline. The genetic variance, however, increases fairly linearly with age.

Table 5.1. Model fit statistics for developmental modeling

Model	EP	df	AIC	BIC	sBIC
1. Full DCS	55	19668	11826.45	-85508.46	51369.95
2. Autoregressive	45	19678	14735.04	-82649.36	54260.81
3. Latent Growth	24	19699	16317.53	-81170.79	55806.08
4. AE (No C)	38	19685	11826.00	-85593.05	51339.36
5. A growth + E autoregressive	**23**	**19700**	**11185.57**	**-86307.70**	**50672.35**

Note. EP = estimated parameters; df = degrees of freedom; AIC = Akaike Information Criteria; BIC = Bayesian Information Criterion; sBIC = sample-size adjusted Bayesian Information Criterion; DCS = dual change score; A = additive genetic risks; C = shared environmental risks; E = unique environmental risks.

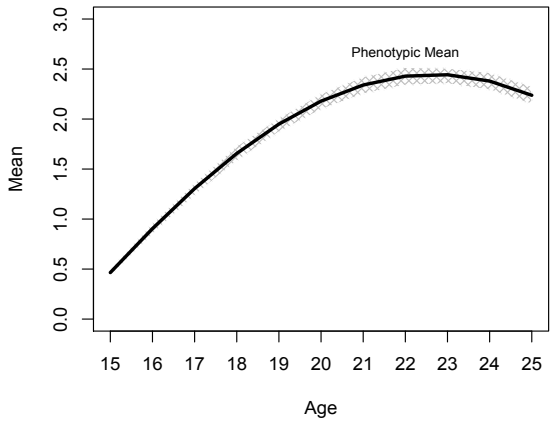

Figure 5.2a. Changes in the phenotypic means across age

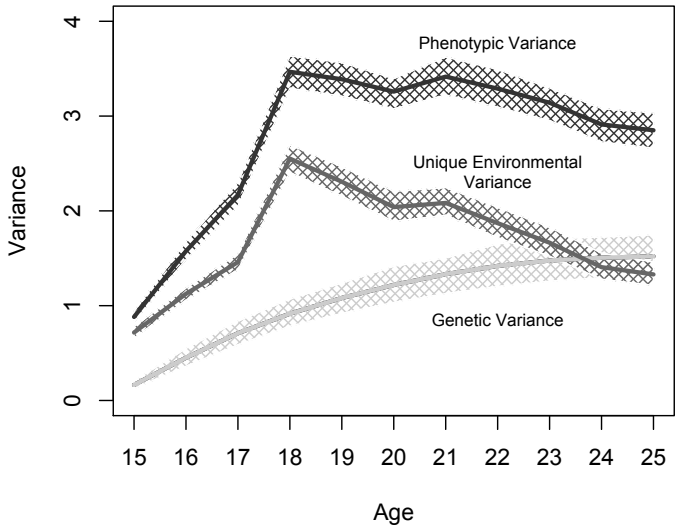

Figure 5.2b. Changes in the phenotypic, genetic, and unique environmental unstandardized variances across age

The key model parameter estimates from the best-fitting model are presented in Table 5.2. The top panel of the table presents the variances of the latent growth factors on the diagonal and their inter-correlations on the off diagonal. The middle panel presents the means of the latent growth parameters. The bottom panel presents the autoregressive parameter. As can be seen in the table, the mean of the latent intercept (1.95, 95% CI = 1.81 – 2.04) represents the average level of reported changes in AU across the age range. The relatively large variance in the intercept indicates that there is considerable heterogeneity in the level of AU. The small and statistically non-significant linear slope parameter suggests a lack of linear change in reported changes in AU across this time period in the aggregate. However, although relatively smaller, the presence of variance in the linear random slope effects implies that there were individual differences in the rate of linear change over time. The mean of the quadratic slope is larger, negative, and statistically significant, indicating a nonlinear curvature aspect to the expected trajectory of changes in AU. The smaller variance for the quadratic slope suggests there is less

heterogeneity in the nonlinear curvature. Finally, the autoregressive parameter, **β** (0.77, 95% CI = 0.75 - 0.79), represents the consistency of changes in AU over time.

Notably, the genetic correlations between the intercept and the linear slope and the intercept-quadratic slope correlations were relatively small and not statistically significant. However, the correlation between the linear and quadratic slopes is much larger and statistically significant, but caution should be used when interpreting this association because the magnitude of the variances of the two slopes (and hence the covariance) is quite small.

Table 5.2. Parameter estimates from best-fitting developmental model (95% CI)

	Intercept	Linear Slope	Quadratic Slope
Intercept	1.05 (0.85, 1.28)		
Linear Slope	-0.14 (-0.30, 0.02)	0.13 (0.08, 0.18)	
Quadratic Slope	-0.07 (-0.31, 0.16)	-0.48 (-0.95, -0.21)	0.06 (0.02, 0.10)
Means	1.95 (1.81, 2.04)	-0.05 (-0.12, 0.02)	-0.29 (-0.32, -0.24)
Autoregressive Parameter (**β**)	0.77 (0.75, 0.79)		

Note. The top panel presents the variances of the latent growth factors on the diagonal and the correlations between them on the off-diagonal.

Discussion

We investigated the nature of longitudinal contributions of genetic and environmental risk factors to changes in AU from mid-adolescence through young adulthood. While a cursory inspection of the twin correlations may suggest that familial aggregation in AU is potentially attributable to a combination of additive genetic and shared environmental risk factors, we were able to drop the shared environmental variance components with no statistically significant reduction in model fit. This type of global parameter testing is often performed first to determine if a more parsimonious model fits the data better. Therefore, on the basis of parsimony, we chose the best fitting model to be Model 5. Despite this, these patterns underscore the need for follow-up inspection of the shared environment as part of the developmental process.

With Model 5 as the best fitting model, the way genetic risk factors contribute to changes in AU over time between ages 15 and 25 were best described by expectations from a quadratic LGM (i.e., an unfolding). In other words, genes were found to affect baseline levels of AU and rates of change across time. The main implication of the LGM best describing how genes influence changes in AU is that the same genes may be expressed at different stages of development, although their effects, and potentially their expression, may increase with age. In contrast, unshared environmental influences were best described by expectations from the ARM (i.e., an accumulation), suggesting that the impact of idiosyncratic aspects of the environment is cumulative, or remembered. Thus, significant life events, adverse or protective, occurring at age 15, such as a break-up with a significant other, or becoming involved with a sport, can continue to influence AU at later ages, in addition to other life events.

Our results based on this more exhaustive, hybrid DCS model are broadly consistent with previous results based on the same data[16]. These results showed that genetic variation increased over time in AU, which we also found. However, as mentioned in the introduction, Kendler et al.[16] relied on Cholesky decomposition, which, while useful for describing the strength of genetic correlations over time, provides no information or posits no theory about the underlying mechanisms contributing to any changes in genetic and environmental variance components. The DCS model goes beyond the Cholesky decomposition to elucidate how these underlying mechanisms are changing over time.

Although DCS models have been applied to a variety of complex behaviors, to our knowledge, this is the first study to specify and compare a broader set of competing longitudinal developmental models within the context of a twin design to characterize the sources of genetic and environmental risks involved in changes in AU from mid-adolescence to young adulthood.

Previously, Gillespie and colleagues compared the fits of competing developmental models to investigate longitudinal change in adolescent depression[25]. Similar to our findings, environmental risks were best explained as an accumulating, autoregressive process, and genetic risks were best explained as an unfolding, latent growth process. One possible explanation for why both complex behaviors appear to follow similar genetic and environmental models for change is that they are modestly correlated[56,57]. It is possible that one pathway to problematic alcohol use is through internalizing disorders[58,59]. Thus, it may be that the genes and the environment that influence adolescent depression operate broadly in similar ways as do the processes influencing adolescent AU.

Another study that is relevant to the current findings is the report by Costanzo and colleagues[10]. Although they did not use genetically informative data, they used a similar modeling approach to examine rates of change in AU and changes in the probability of heavy drinking. They showed that heavy drinking is most common in the early 20's, but decreases thereafter, and that for a subset of individuals, heavy drinking persists into later adulthood. This is consistent with our findings that the mean changes in AU increased through age 21. Also of interest is that our MZ twin correlations and pattern of genetic variance increased steadily until age 21, when they peaked, and then stabilized thereafter. Accordingly, it is possible that genetic factors underlie the pattern of drinking behavior shown in the Costanzo et al.[10] study.

These results are also broadly consistent with the notion of there being two discernable genetic risk factors involved in changes in AU over time: an adolescent-limited genetic risk factor and an adult-onset genetic risk factor[18]. Because externalizing disorders and alcohol problems are genetically correlated during adolescence [60], it may be that the adolescent-limited genetic risk factor is broadly capturing liability to externalizing disorders, which includes AU,

while the adult-onset genetic risk factor is capturing liability specifically for alcohol use disorder[18].

Limitations

The findings of the present study should be considered in the context of three limitations. First, our sample only consisted of white male twins, and therefore, our results may not generalize beyond this population. However, white males were targeted because they have significantly higher rates of AU than other populations[61,62]. Previous analyses have shown that this sample is broadly representative of white U.S. males and do not differ from the general population in rates of psychopathology, drug use, and abuse[42].

Second, these analyses were carried out on retrospectively assessed data, which may be subject to various degrees of recall bias. A Life History Calendar (LHC) method[63] was used to improve recall accuracy when assessing the twins by providing multiple cues to improve recall. The reliability of retrospective recall of AU using the LHC method is good[64,65] and previous studies suggest that retrospective assessments might suffer less from underreporting than prospective assessments of AU[64,65]. The sampling time frame was also limited to age 25. It is unclear how genetic and environmental risks will continue to impact AU at later ages.

Third, because values were filled in for ages where no change in consumption was reported with the previous change amount, it is possible that participants' use was not constant in between the reported ages. To determine if this possibility would change the best-fitting model, we fitted the same sequence of models using only the actual reported change data. Because of the large amount of missing data, model solutions and parameters estimates were unable to reliably converge.

Conclusions

Using a large sample of male twins, we formally tested and compared hypothetical longitudinal developmental models to investigate the nature of genetic and environmental influences contributing to changes in AU over a developmentally relevant period from mid-adolescence through to young adulthood. Model fitting results showed that genetic influences were consistent with an unfolding, growing pattern of risks as predicted by a latent growth model, while unshared environmental factors were best described by an accumulating pattern of risk as predicted by autoregressive effects. These findings add to our understanding of how genetic and environmental risk factors may operate to influence changes in AU across time. The results of this study will inform gene identification efforts and ultimately help to identify critical developmental periods for effective prevention and early intervention efforts.

Supplementary

Supplementary Table 5.3. Normalized coefficients of contrasts (fixed factor loadings) for the constant, linear, and quadratic growth factors

Age	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**
Constant	0.3105	0.3105	0.3105	0.3105	0.3105	0.3105	0.3105	0.3105	0.3105	0.3105	0.3105
Linear	-0.4767	-0.3814	-0.2860	-0.1907	-0.0953	0.0000	0.0953	0.1907	0.2860	0.3814	0.4767
Quadratic	0.5121	0.2048	-0.0341	-0.2048	-0.3073	-0.3414	-0.3073	-0.2048	-0.0341	0.2048	0.5121

Supplementary Table 5.4. MZ twin correlations of log-transformed means for alcohol use across time

	Twin 1										
Twin 2	Age 15	Age 16	Age 17	Age 18	Age 19	Age 20	Age 21	Age 22	Age 23	Age 24	Age 25
Age 15	0.27	0.23	0.26	0.18	0.18	0.12	0.13	0.11	0.09	0.14	0.11
Age 16	0.31	0.35	0.35	0.29	0.26	0.21	0.24	0.24	0.22	0.23	0.19
Age 17	0.25	0.35	0.36	0.38	0.39	0.33	0.32	0.30	0.28	0.31	0.26
Age 18	0.16	0.27	0.37	0.44	0.42	0.38	0.38	0.36	0.33	0.35	0.28
Age 19	0.17	0.26	0.35	0.48	0.48	0.46	0.45	0.43	0.38	0.40	0.35
Age 20	0.19	0.25	0.33	0.44	0.46	0.44	0.44	0.41	0.38	0.40	0.37
Age 21	0.22	0.31	0.38	0.43	0.48	0.47	0.50	0.47	0.45	0.48	0.43
Age 22	0.16	0.24	0.34	0.40	0.45	0.44	0.50	0.47	0.45	0.47	0.44
Age 23	0.15	0.25	0.32	0.37	0.42	0.43	0.49	0.47	0.46	0.49	0.48
Age 24	0.13	0.22	0.29	0.37	0.42	0.41	0.45	0.44	0.48	0.48	0.49
Age 25	0.15	0.22	0.29	0.37	0.41	0.39	0.41	0.41	0.46	0.48	0.48

Supplementary Table 5.5. DZ twin correlations of log-transformed means for alcohol use across time

	Twin 1										
Twin 2	Age 15	Age 16	Age 17	Age 18	Age 19	Age 20	Age 21	Age 22	Age 23	Age 24	Age 25
Age 15	0.26	0.24	0.20	0.23	0.26	0.23	0.23	0.21	0.21	0.20	0.17
Age 16	0.26	0.26	0.24	0.30	0.31	0.27	0.29	0.25	0.24	0.23	0.21
Age 17	0.23	0.26	0.31	0.38	0.35	0.32	0.33	0.28	0.27	0.26	0.25
Age 18	0.19	0.24	0.28	0.37	0.37	0.33	0.32	0.26	0.24	0.21	0.22
Age 19	0.17	0.23	0.27	0.33	0.34	0.31	0.29	0.23	0.20	0.19	0.17
Age 20	0.14	0.19	0.26	0.32	0.34	0.32	0.30	0.24	0.22	0.22	0.19
Age 21	0.19	0.21	0.25	0.29	0.32	0.32	0.30	0.27	0.25	0.26	0.23
Age 22	0.19	0.19	0.26	0.31	0.32	0.34	0.32	0.31	0.29	0.29	0.27
Age 23	0.19	0.19	0.24	0.28	0.28	0.28	0.25	0.24	0.22	0.22	0.20
Age 24	0.17	0.18	0.21	0.27	0.27	0.28	0.25	0.23	0.21	0.21	0.21
Age 25	0.17	0.14	0.18	0.28	0.27	0.23	0.19	0.16	0.15	0.17	0.17

Chapter 6: The Moderating Role of Parental Monitoring and Peer Group Deviance on Polygenic Risk for Adolescent Alcohol Use Across Time

Introduction

This chapter addresses the final aim of this dissertation, which is to determine the moderating role of key environmental risk factors on the impact of polygenic risk for AU across adolescence. Given the substantial environmental influences on adolescent AU[1-4], testing specific measured genetic and environmental risk factors may inform interventions that focus on increasing adolescent skills when exposed to such environmental influences. Specifically, peer group deviance (PGD) and parental monitoring (PM) are among the most salient predictors of adolescent AU and AUD[5-17]. PGD is the extent to which one's peer group engages in deviant behaviors, such as substance use and antisocial behavior. PM measures parental knowledge of children's whereabouts, friends, and activities, including sources of parental knowledge, such as child disclosure, parental solicitation, and parental control[18]. Twin studies have shown that these risk factors moderate latent genetic variance in adolescent AU[2,19,20], such that genetic influences are stronger under conditions of low PM and high PGD[21,22]. Accordingly, genetic risk seems to become more pronounced when there is less social control and more social opportunity[23].

Despite twin heritability estimates for AU and AUD ranging 50 to 60%[24], genome-wide association studies (GWAS) have had limited success in identifying molecular genetic variants contributing to risk for AU/AUD, accounting for no more than 2% of the total variation in AU or AUD phenotypes[25]. Among the few variants identified include alcohol metabolizing genes, such as those coding for alcohol dehydrogenase (ADH cluster) and aldehyde dehydrogenase (ALDH cluster)[26-29]. However, these variants explain only a small fraction of the total phenotypic variance[30]. Thus, the polygenic approach[31] was developed to help remedy this issue. It is based on the expectation that the upper tail of the distribution of test statistics from large GWAS

studies are very likely to be enriched with true signals, and, in aggregate, can increase the amount of variance explained.

Measured gene-by-environment interactions are defined as genetic sensitivity to the environment[32]. In addition to problems arising from scale artifact[33], measured gene-by-environment moderation studies have been criticized for being underpowered, due to the inability of small sample sizes to detect the small effect sizes typically associated with genetic findings[32]. Thus, a more advantageous approach is to rely on the aggregate genome-wide genetic risk associated with AU and AUD. However, we are aware of only one study that has investigated the interaction between estimates of polygenic risk and environmental risk factors related to AU/AUD. In a sample of 14 year old Finnish twins[34] the authors found that individual differences in PGD and PM moderate the polygenic risk for alcohol related problems. Specifically, genetic risk for alcohol problems appear to be stronger under conditions of low PM and high PGD. Although the effect sizes were relatively small, these findings are consistent with results from twin studies[2,19,20], and support the hypothesis that environmental factors can moderate polygenic risk for behavioral outcomes.

However, these twin reports relied on estimates of imputed of latent genetic risk and not genetic risk based on molecular data. The one study that has investigated polygene by environmental interactions was cross-sectional[34]. Thus, the effects of PGD and PM on polygenic risk in terms of predicting adolescent AU within and across time remain unknown. Understanding how key environmental influences interact with polygenic risk over time has the potential to inform prevention and intervention efforts by targeting these environmental influences among adolescents with genetic predispositions. It can also provide insight as to what age these efforts may be most beneficial for preventing AU.

By applying a developmental framework to the study by Salvatore et al.[34], this chapter addresses three research questions: (1) Does polygenic risk predict AU across late adolescence? (2) Does peer deviance moderate the impact of polygenic risk on AU? (3) Does early parental monitoring moderate the impact of polygenic risk on AU?

Methods

Samples

The polygenic risk approach requires the use of a discovery and target sample to ensure that the samples are independent. Ensuring independence between the samples is important because non-independence will inflate the amount of variance accounted for by polygenic risk score. Thus, we relied on two large, independent population-based samples for these samples. Discovery GWAS results came from the Australian Adult Registry[35] and were used to create polygenic risk scores in the Avon Longitudinal Study of Parents and Children (ALSPAC[36]). These samples and the measures used are described below.

Australian Adult Registry. As described in detail elsewhere (Heath et al., 2011[35]), participants were drawn from a pool of approximately 11,700 Australian families identified through diagnostic interview surveys of two cohorts of same-sex and opposite-sex twin pairs from a volunteer Australian twin panel (Cohort 1: 5,995 twins born 1895–1964,[37] but for the purposes of this study twins were mostly born 1940–1964 (ages 53-77); and Cohort 2: 6,257 twins born 1964–1971 (ages 46-53[38]). Families were also identified through an interview survey of the spouses/partners of the former cohort (N = 3,846[39]). Index cases from these families, their full siblings, and parents were recruited for three coordinated studies: (1) the NAG (Nicotine Addiction Genetics) Study[40], which identified heavy smoking index cases; (2) the OZALC-EDAC study, which identified index cases with a history of alcohol dependence or scoring above

the 85th percentile for heaviness of drinking factor score[41]; and (3) the OZALC-BIGSIB study, which identified large sibships[37,41], regardless of sibling phenotypic values. Additional cases and controls were recruited from Cohorts 1 and 2, who did not complete the new interview protocol but had comparable alcohol use/dependence assessments. All projects underwent IRB review at the participating institutions. GWAS genotyping, using the Illumina 370K array, was performed on a total of 6,852 individuals selected from the BIGSIB and EDAC series (including 336 parents), on a subsample of the NAG families that had previously been selected for 10cM microsatellite scans[40], and on a smaller number of additional alcohol dependent cases and controls from Cohorts 1 and 2.

Australian Sample Genotyping and GWAS. All genotyping was conducted on Illumina platforms, with genotypes called using Illumina BeadStudio software. Standard quality control (QC) filters were applied, and are described in greater detail elsewhere (see Medland et al.[42]). The following single nucleotide polymorphisms (SNPs) were excluded for QC purposes[43]: SNPs with a mean Genotype Call score (GenCall; a confidence value for the reliability of SNP call rates) less than 70%; SNPs with call rates less than 95% to exclude SNPs of poor quality; SNPs with deviation from Hardy-Weinberg Equilibrium (HWE) significant at $p < 10^{-6}$, which can be reflective of genotyping error and population stratification; and SNPs with Minor Allele Frequency (MAF) less than 1% to exclude rare variants, which have extremely low power to detect an association. For the present study, Illumina CNV370-Quadv3 GWAS data were available on 4,241 individuals (including most alcohol dependent cases) genotyped at CIDR and an additional 2,611 individuals genotyped by deCODE for the OZALC project. Illumina 317K data were available for 53 individuals genotyped at the University of Helsinki Genome Center and Illumina 610 Quad data were available for the remaining individuals genotyped by deCODE.

Duplicate samples allowed comparison of genotyping across platforms/locations: a single SNP was identified, genotyped using the CNV370-Quadv3, that was called very differently at CIDR versus deCODE, and therefore deleted from the dataset. Checks were run on genetic relatedness, with incorrect relationships corrected prior to analysis to ensure that SNPs are independent. As discussed above, non-independence between SNPs will inflate the amount of variance accounted for, as well as Type I and II error rates. Polymorphisms with an R^2 imputation quality metric of <0.3 were excluded to ensure the imputation was of high quality (note these markers were filtered again before inclusion in the analysis using a more stringent threshold of 0.5 to match that of the target sample). After quality controls were applied, there were 7,681,669 markers remaining (from 39,210,718 markers available).

Genome-wide genotype data can be used to assess ethnic ancestry. This was accomplished via Eigenstrat analyses[44], which involves principal components (PCs) analysis to first infer genetic variation typically reflective of geographic regions. Then, the genotypes are continuously adjusted by amounts attributable to ancestry and association statistics are computed using ancestry-adjusted genotypes. Cohorts 1 and 2 were almost entirely of European ancestry, reflecting restrictive Australian immigration policies through to 1972, However, the Eigenstrat analyses[44], which included data from other Australian GWAS series, identified (operationalized by +/− 6 standard deviations) a small number of families from other ancestries as outliers. These included: mixed European and Asian ancestry (principally Chinese, Burmese, Indian or Malaysian); middle eastern (Lebanese) ancestry, with one or more grandparents of Aboriginal, Torres Strait Islander or Maori ancestry; and some African heritage (including individuals of self-report Maltese ancestry, consistent with the known population genetics of the Maltese population)[42]. A total of 153 individuals from 60 families were identified as outliers (i.e., as non-

European) and excluded from further analyses. This included 34 alcohol dependent and 119 unaffected individuals. In the present analyses, genotypes were imputed using the Michigan Imputation Server and the Haplotype Reference Consortium (HRC Release 1).

The GWAS was performed using RareMetalWorker[45]. Covariates included sex and ten PCs to adjust for ancestry. Age information was not available because some participants joined more than one project at different times that collected alcohol data. The phenotype was operationalized as the mean number of drinks consumed per week calculated across all projects (log-transformed; $N = 14,296$; assessed via the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA[46,47]).

Avon Longitudinal Study of Parents and Children (ALSPAC). ALSPAC is an ongoing, longitudinal birth-cohort study investigating the genetic and environmental risks affecting health and development in women and their children. It consists of 15,247 pregnancies from women living in Avon, UK, with delivery dates between April 1991 and December 1992, resulting in 15,458 children. Children have been followed-up annually from birth through to 18 years of age, and approximately every two years after age 18. Response rates were steady (~70%) from 33 months of age until 13 years of age, and declined slightly to 48% during adolescence. Approximately 82% of mothers have remained engaged throughout the study[36]. Data come from unrelated individuals who completed alcohol assessments and have genotypic data available ($N = 4,304$).

ALSPAC Genotyping. Genotyping was based on the Illumina HumanHap550 quad platform. Individuals were excluded on the basis of: excessive or minimal heterozygosity, which can reflect sample contamination or inbreeding); gender mismatch, which can reflect errors in external data or sample mix-up; individual missingness (0.3%) to remove low quality DNA;

cryptic relatedness as measured by genome-wide IBD (0.1%), which results in non-independence and can increase Type I and II error rates; and sample duplication to ensure sample independence. Population stratification was assessed using multi-dimensional scaling modeling seeded with HapMap Phase II release 22[48-50] reference populations to ensure that any associations with AU/AUD are due to predisposing loci, rather than ancestral differences. All individuals with non-European ancestry were excluded, with ancestry estimated using Eigenstrat analyses[44]. Single nucleotide polymorphisms (SNPs) were excluded based on final call rates <0.95%, MAF <1%, and significant departure from HWE (p < 5e-7). All individual genotypes were imputed based on the 1000 Genomes Phase 1 Version 3[51] reference panel by ALSPAC analysts using MACH for phasing[52] and Minimac for imputation[53]. Polymorphisms with an R^2 imputation quality metric of <0.5 were excluded to ensure high quality imputation. The association analysis was run using MACH2QTL[52] and included sex as a covariate. After quality controls were applied, genetic data were available for 4,304 individuals with phenotypic data (42.9% male), resulting in 423,140 markers available (from 8,232,035).

ALSPAC Measures

Alcohol use (AU). AU frequency was assessed using the Alcohol Use Disorder Identification Test (AUDIT[54]) at ages 16, 17, 18, and 20. Grams of ethanol per month were calculated using the raw frequency variable, the raw quantity variable, and multiplying by 8 (8 grams equals one alcoholic unit in the UK). The raw frequency item was a 5-level ordinal variable and asked the frequency with which the person has a drink. The raw responses included: never = 1; monthly or less = 2; 2-4 times per month = 3; 2-3 times per week = 4; 4 or more times per week = 5. These raw responses were recoded into the midpoints between the levels to obtain a proxy for frequency per week, as follows: never = 0 (and not asked the quantity question, so

are coded as missing); monthly or less = 0.5; 2-4 times per month = 3; 2-3 times per week = 10.7; 4 or more times per week = 23.54.

The raw quantity item was also a 5-level ordinal variable and asked the number of drinks containing alcohol on a typical day when drinking. The raw responses included: 1 or 2 = 1; 3 or 4 = 2; 5 or 6 = 3; 7-9 = 4; 10 or more = 5. These raw responses were also recoded into the midpoints between the levels, as follows: 1 or 2 = 1.5; 3 or 4 = 3.5; 5 or 6 = 5.5; 7-9 = 8; 10 or more = 15.5.

Peer group deviance (PGD). PGD was assessed at ages 10, 12 and 15 using 11, 13 and 17 items, respectively, that asked whether each participant's peers had engaged in deviant behaviors such as fighting, skipping school, theft, arson, property destruction, cruelty to animals, and cruelty to others. PGD sum scores were computed from the raw binary (yes/no) variables and were mean-centered to aid interpretation.

Parental monitoring (PM). PM was assessed via child report at ages 12 and 13 and via parent report at age 15 using a 24-item self-report version of the Parental Monitoring Questionnaire (PMQ)[55], designed to capture four domains: parental monitoring (9 items) measuring parents' knowledge of the child's location, activities, and associations; child disclosure (5 items) measuring whether the child provides information to the parent about school and activities; parental solicitation (5 items) measuring whether the parent initiates conversations with the child about their day, what happens during free time, and if the parent talks with the child's friends; and parental control (5 items) measuring whether the child is required to ask permission to explain plans, to be out late, and to explain why if they are past curfew. Internal consistencies (alpha) ranged from .68 to .81. The disclosure, solicitation, and control subscales load onto three factors, with loadings ranging from .56 to .82, demonstrating sufficient validity[18].

Each PMQ item was scored on 5-point scale levels of ordinal response (1 = never to 5 = always). Sum scores were computed from the raw responses and were mean-centered. The available measures and ages at which they are available are summarized in Table 6.1.

Table 6.1. Available ALSPAC measures and ages

	Age 10	Age 12	Age 13	Age 15	Age 16	Age 17	Age 18	Age 20
Alcohol use					X	X	X	X
Peer group deviance	X	X		X				
Parental monitoring		X	X	X				

Statistical Analyses

Polygenic Scoring. Standard methods for estimating polygenic risk scores (PRSs) were applied using PLINK[31]. The PRS approach assumes that the upper tail of the distribution of SNPs from a well-powered GWAS that do not meet the stringent genome-wide significance threshold should be enriched with true signals[31]. Thus, the PRS method makes use of as much GWAS data as possible by including influential SNPs that would otherwise be discarded, following a true Fisherian approach. A set of "independent" SNPs that are in linkage equilibrium were first selected from a discovery sample (Australian Twin Registry) to generate *p*-values and their associated weights for SNPs below an arbitrary threshold. These independent SNPs were then used to create polygenic sum scores in the independent sample (ALSPAC). A series of 9 polygenic scores based on *p*-value thresholds ranging from 0.0001 to 0.50 were used. Currently, there are no criteria for creating or determining a maximally informative PRS[56]. In other words, the number of *p*-value thresholds to include for a PRS that provides the greatest signal is unclear, and we accordingly used a range.

Standard data cleaning and quality control procedures were applied. The R^2 information score (a measure of imputation quality) was filtered using a threshold of 0.5, the minor allele frequency was filtered using a threshold of 1% to exclude rare variants, which have extremely

low power to detect an association, and ambiguous SNPs were removed (i.e., SNPs with strands that cannot be differentiated). Common SNPs were pruned out using the linkage disequilibrium (LD) clumping method. The LD clumping method prunes out markers that are in LD with one another (i.e., alleles that are non-randomly associated with another) and only extracts SNPs that represent LD-independent regions. Thus, the markers are not redundant and provide independent signals specific to their region. Finally, 264 SNPs with mismatched alleles were removed.

PRSxE moderation analyses. Using the lm function in R[57], the 9 PRSs were each regressed onto AU at each of the four time points (ages 16, 17, 18, and 20) to test if the PRS predicted AU in the independent target sample (ALSPAC). Sex and ethnic ancestry measured as the first ten principal components were included as covariates. Although the analyses were restricted to Europeans, it is possible there is still subtle background genetic variation (which can lead to spurious results if unaccounted for)[58] and that the self-reported ancestry does not match that of the PCs[59] (e.g., admixture from African ancestry). The PRS that accounted for the most variance at each age was used in subsequent moderation analyses.

Multiple linear regressions were run with PRSxE interactions to test the hypothesis that PM and PGD moderate the association between PRS and AU at each time point. The parameters of interest were the statistical interactions between the environmental factors (PM and PGD) and the polygenic risk scores. PM, PGD, and the PRSs were included as main effects. Since our analyses are exploratory, Bonferroni corrections were used to correct for multiple testing, as failure to do so will inflate the Type I error rate (i.e., increase the likelihood of false positives). After quality control and data cleaning procedures were applied, the final *N* for subjects with complete data was 1,670.

Results

Pearson correlations. Table 6.2 shows the correlations between the nine PRSs and AU at each of the four ages. The correlations between the PRSs were mostly significant and increased with more liberal p-value thresholds. The correlations between the PRSs and AU at age 16 were non-existent to very small, but increased slightly with more liberal thresholds. For ages 17 and 18, they were all less than 0.1 and none were statistically significantly (all standard errors were approximately 0.05, not shown). However, by age 20, the correlations were higher than at any other age (all above 0.13, starting at the threshold of p = 0.01). Although small, these correlations were mostly significant, and were in the expected direction (i.e., positive correlations, suggesting the PRS predicted increased AU).

Table 6.2. Pearson correlations between the PRSs and AU

	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.
PRSs													
1. PRS, p = 0.0001	1.000												
2. PRS, p = 0.001	**0.449**	1.000											
3. PRS, p = 0.01	**0.268**	**0.567**	1.000										
4. PRS, p = 0.05	**0.174**	**0.437**	**0.782**	1.000									
5. PRS, p = 0.1	**0.137**	**0.379**	**0.717**	**0.925**	1.000								
6. PRS, p = 0.2	**0.110**	**0.346**	**0.680**	**0.879**	**0.955**	1.000							
7. PRS, p = 0.3	0.096	**0.335**	**0.663**	**0.856**	**0.936**	**0.979**	1.000						
8. PRS, p = 0.4	0.090	**0.326**	**0.647**	**0.841**	**0.923**	**0.970**	**0.991**	1.000					
9. PRS, p = 0.5	0.087	**0.315**	**0.641**	**0.836**	**0.920**	**0.965**	**0.985**	**0.995**	1.000				
AU													
10. AU, age 16	-0.016	-0.002	0.028	**0.106**	**0.120**	**0.137**	**0.124**	**0.136**	**0.131**	1.000			
11. AU, age 17	-0.031	0.019	0.002	0.031	0.015	0.027	0.013	0.017	0.015	**0.544**	1.000		
12. AU, age 18	0.070	0.085	0.069	0.012	0.022	0.030	0.038	0.036	0.037	**0.376**	**0.522**	1.000	
13. AU, age 20	0.018	0.086	**0.141**	**0.139**	**0.162**	**0.162**	**0.166**	**0.164**	**0.165**	**0.274**	**0.359**	**0.425**	1.000

Table 6.3 shows the correlations between AU at the four ages, PGD, and PM. The correlations within the AU variables were moderate to high (ranging from 0.27 to 0.54) and followed a simplex pattern, whereby the size of the correlation decreases with increasing time points. Turning to the associations between PGD and AU, all correlations were < 0.10 at age 10.

At age 12, they showed a small but significant positive correlation (at $p = 0.05$) with AU at ages 16 ($r = 0.14$) and 17 ($r = 0.14$), but the effect diminished with time. The same pattern was seen for PGD at age 15. Finally, in terms of the relationship between PM at ages 12, 13 and 15 and AU there was a small but significant correlation between AU at age 16 and PM at age 12 ($r = -0.18$), but not at later ages. This pattern was very similar for PM at age 13. However, for age 15 PM, they all were less than 0.10.

Table 6.3. Pearson correlations between AU, PGD, and PM

	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.
AU										
1. AU, age 16	1.000									
2. AU, age 17	**0.544**	1.000								
3. AU, age 18	**0.376**	**0.522**	1.000							
4. AU, age 20	**0.274**	**0.359**	**0.425**	1.000						
Peer group deviance										
5. Peer group deviance, age 10	0.045	0.024	0.017	-0.070	1.000					
6. Peer group deviance, age 12	**0.142**	**0.140**	0.012	-0.020	0.313	1.000				
7. Peer group deviance, age 15	**0.198**	**0.168**	**0.120**	0.096	**0.134**	**0.356**	1.000			
Parental monitoring										
8. Parental monitoring, age 12	**-0.176**	-0.026	0.047	0.039	-0.081	**-0.203**	**-0.176**	1.000		
9. Parental monitoring, age 13	**-0.185**	-0.073	-0.055	0.043	-0.143	**-0.189**	**-0.224**	**0.422**	1.000	
10. Parental monitoring, age 15	-0.041	0.059	-0.017	0.042	-0.014	-0.019	-0.068	**0.232**	**0.120**	1.000

Age 16 Results. Table 6.4 shows the results of the linear regressions to test if PRSs predict age AU at 16. None of the scores remained significant after Bonferroni correction for nine tests was applied (adjusted $p = 0.005$) and all scores explained <1% of the total variance. However, because the first PRS accounted for the most variance on age 16 AU ($r^2 = 0.008$), we moved this score forward into the moderated multiple regressions.

Table 6.4. Univariate linear regressions of age 16 AU on PRSs at each threshold

	R-squared (Adjusted)	P-value	Beta (SE)
Score 1 (p = 0.0001)	**0.0080**	**0.0437**	**-0.1578 (0.0782)**
Score 2 (p = 0.001)	0.0063	0.1563	-0.0391 (0.0276)
Score 3 (p = 0.01)	0.0053	0.3884	-0.0087 (0.0101)
Score 4 (p = 0.05)	0.0048	0.6944	0.0021 (0.0053)
Score 5 (p = 0.1)	0.0054	0.3538	0.0038 (0.0041)

Score 6 (p = 0.2)	0.0058	0.2361	0.0039 (0.0032)
Score 7 (p = 0.3)	0.0057	0.2627	0.0033 (0.0029)
Score 8 (p = 0.4)	0.0064	0.1498	0.0040 (0.0028)
Score 9 (p = 0.5)	0.0061	0.1828	0.0036 (0.0027)

Table 6.5 shows the results of the regressions testing the moderating effect of PGD at ages 10, 12, and 15 and PM at ages 12, 13, and 15 on polygenic risk for AU at age 16. Prior to correction for multiple testing, there were no significant main effects of the PRS across all ages. There was a significant influence of PGD at ages 12 and 15 on AU. The main effects of PGD at these ages remained significant after correcting for multiple testing in six tests ($p = 0.008$). There was a significant influence of PM at all ages, with high levels of PM being associated with significantly reduced AU at all ages. The main effects of PM remained significant after correcting for multiple testing. Regarding the results the PRS x PGD and PRS x PM analyses, there were no significant moderating effects of PGD or PM at any age.

Table 6.5. Moderated multiple regressions of age 16 AU on sex, PRS, PGD (top), and PM (bottom)

Peer Group Deviance		
	Beta (SE)	P-value
AGE 1O		
Intercept	**1.786 (0.038)**	**<2e-16**
Sex	-0.072 (0.047)	0.126
PRS	-0.144 (0.082)	0.079
Peer group deviance, age 10	0.027 (0.018)	0.144
PRS x Peer group deviance, age 10	0.032 (0.067)	0.634
AGE 12		
Intercept	**1.788 (0.037)**	**<2e-16**
Sex	-0.080 (0.046)	0.086
PRS	-0.150 (0.082)	0.068
Peer group deviance, age 12	**0.053 (0.011)**	**2.22e-06**
PRS x Peer group deviance, age 12	0.001 (0.044)	0.9875
AGE 15		
Intercept	1.766 (0.037)	**<2e-16**
Sex	-0.064 (0.046)	0.1657
PRS	-0.137 (0.081)	0.090
Peer group deviance, age 15	**0.059 (0.007)**	**2.4e-16**
PRS x Peer group deviance, age 15	0.017 (0.025)	0.5036
Parental Monitoring		

	Beta (SE)	P-value
AGE 12		
Intercept	**1.801 (0.041)**	**<2e-16**
Sex	-0.112 (0.051)	0.027
PRS	-0.121 (0.090)	0.179
Parental monitoring, age 12	**-0.007 (0.002)**	**0.0004**
PRS x Parental monitoring, age 12	-0.016 (0.008)	0.036
AGE 13		
Intercept	**1.796 (0.037)**	**<2e-16**
Sex	-0.103 (0.046)	0.025
PRS	-0.136 (0.082)	0.097
Parental monitoring, age 13	**-0.015 (0.002)**	**6.17e-12**
PRS x Parental monitoring, age 13	0.001 (0.008)	0.931
AGE 15		
Intercept	**1.762 (0.039)**	**<2e-16**
Sex	-0.071 (0.048)	0.141
PRS	-0.116 (0.085)	0.173
Parental monitoring (parent-reported), age 15	**-0.008 (0.002)**	**0.0007**
PRS x Parental monitoring (parent-reported), age 15	0.001 (0.009)	0.908

Age 17 Results. Table 6.6 shows the results of the linear regressions testing if the PRSs predict age 17 AU. None of the PRSs were statistically significant. However, the score that accounted for the most variance was again the first score and was moved forward into the multiple regressions.

Table 6.6. Univariate linear regressions of age 17 AU on PRSs at each threshold

	R-squared (Adjusted)	P-value	Beta (SE)
Score 1 (p = 0.0001)	**0.0016**	**0.1581**	**-0.1019 (0.0721)**
Score 2 (p = 0.001)	-0.0002	0.7656	-0.0077 (0.0258)
Score 3 (p = 0.01)	0.0003	0.4315	0.0076 (0.0096)
Score 4 (p = 0.05)	-0.0003	0.7696	0.0015 (0.0051)
Score 5 (p = 0.1)	-0.0002	0.7042	-0.0014 (0.0038)
Score 6 (p = 0.2)	-0.0003	0.8741	-0.0004 (0.0031)
Score 7 (p = 0.3)	-0.0002	0.6885	-0.0011 (0.0028)
Score 8 (p = 0.4)	-0.0003	0.8238	-0.0006 (0.0027)
Score 9 (p = 0.5)	-0.0003	0.7796	-0.0007 (0.0026)

Table 6.7 shows the results of the regressions testing the moderating effect of PGD at ages 10, 12, and 15 and PM at ages 12, 13, and 15 on polygenic risk for AU at age 17. Using the

Bonferroni corrected *p*-value of 0.008, there was a significant influence of PGD at ages 12 and 15 on AU. However, there were no main effects of the PRS or PM at any age, and there were no significant moderating effects of the PRS x PGD or the PRS x PM at any age.

Table 6.7. Moderated multiple regressions of age 17 AU on sex, PRS, PGD (top), and PM (bottom)

Peer Group Deviance		
	Beta (SE)	P-value
AGE 1O		
Intercept	**1.9814 (0.0340)**	**<2e-16**
Sex	-0.1112 (0.0429)	0.0096
PRS	-0.1280 (0.0745)	0.0860
Peer group deviance, age 10	-0.0054 (0.0176)	0.7582
PRS x Peer group deviance, age 10	0.0286 (0.0601)	0.6348
AGE 12		
Intercept	**1.9810 (0.0334)**	**<2e-16**
Sex	-0.0965 (0.0420)	0.0217
PRS	-0.1484 (0.0749)	0.0480
Peer group deviance, age 12	**0.0464 (0.0105)**	**1.13e-05**
PRS x Peer group deviance, age 12	-0.0494 (0.0417)	0.2358
AGE 15		
Intercept	**1.9828 (0.0334)**	**<2e-16**
Sex	**-0.1188 (0.0419)**	**0.0047**
PRS	-0.1640 (0.0737)	0.0262
Peer group deviance, age 15	**0.0450 (0.0066)**	**1.96e-11**
PRS x Peer group deviance, age 15	0.0284 (0.0228)	0.2127
Parental Monitoring		
	Beta (SE)	P-value
AGE 12		
Intercept	**1.9817 (0.0377)**	**<2e-16**
Sex	-0.1149 (0.0471)	0.0149
PRS	-0.0687 (0.0833)	0.4096
Parental monitoring, age 12	-0.0006 (0.0018)	0.7570
PRS x Parental monitoring, age 12	-0.0009 (0.0067)	0.8916
AGE 13		
Intercept	**1.9802 (0.0336)**	**<2e-16**
Sex	**-0.1143 (0.0421)**	**0.0068**
PRS	-0.1075 (0.0751)	0.1522
Parental monitoring, age 13	-0.0045 (0.0020)	0.0239
PRS x Parental monitoring, age 13	0.0026 (0.0075)	0.7294
AGE 15		
Intercept	**1.9868 (0.0351)**	**<2e-16**
Sex	**-0.1330 (0.0440)**	**0.0026**
PRS	-0.1379 (0.0775)	0.0757
Parental monitoring (parent-reported), age 15	5.051e-07 (0.0020)	0.9998

PRS x Parental monitoring (parent-reported), age 15	0.0043 (0.0081)	0.5953

Age 18 Results. Table 6.8 shows the results of the linear regressions testing if the PRSs predict age 18 AU. The score that accounted for the most variance was the second score and was moved forward into the multiple regressions. However, none of the scores were significantly associative of AU.

Table 6.8. Univariate linear regressions of age 18 AU on PRSs at each threshold

	R-squared (Adjusted)	P-value	Beta (SE)
Score 1 (p = 0.0001)	0.00745	0.2593	-0.0907 (0.0804)
Score 2 (p = 0.001)	**0.00751**	**0.2493**	**-0.0332 (0.0288)**
Score 3 (p = 0.01)	0.00613	0.9698	0.0004 (0.0107)
Score 4 (p = 0.05)	0.00613	0.9988	-0.00001 (0.0057)
Score 5 (p = 0.1)	0.00613	0.9902	0.00005 (0.0043)
Score 6 (p = 0.2)	0.00616	0.8455	0.0006 (0.0034)
Score 7 (p = 0.3)	0.00634	0.6498	0.0014 (0.0031)
Score 8 (p = 0.4)	0.00624	0.7401	0.0010 (0.0029)
Score 9 (p = 0.5)	0.00622	0.7548	0.0008 (0.0028)

Table 6.9 shows the results of the regressions testing the moderating effect of PGD at ages 10, 12, and 15 and PM at ages 12, 13, and 15 on polygenic risk for AU at age 18. Using the Bonferroni corrected *p*-value of 0.008, there was a significant influence of PGD at age 15 on AU. There were no main effects of the PRS or PM at any age, and there were no significant moderating effects of the PRS x PGD or the PRS x PM at any age.

Table 6.9. Moderated multiple regressions of age 18 AU on sex, PRS, PGD (top), and PM (bottom)

Peer Group Deviance		
	Beta (SE)	P-value
AGE 1O		
Intercept	**2.2654 (0.0405)**	**<2e-16**
Sex	-0.1161 (0.0501)	0.0207
PRS	-0.0320 (0.0307)	0.2976
Peer group deviance, age 10	0.0008 (0.0190)	0.9681
PRS x Peer group deviance, age 10	-0.0002 (0.0252)	0.9941
AGE 12		
Intercept	**2.2595 (0.0404)**	**<2e-16**

Sex	-0.0913 (0.0498)	0.0670
PRS	-0.0160 (0.0311)	0.6079
Peer group deviance, age 12	0.0254 (0.0128)	0.0467
PRS x Peer group deviance, age 12	0.0097 (0.0172)	0.5727
AGE 15		
Intercept	**2.2673 (0.0404)**	**<2e-16**
Sex	-0.1219 (0.0500)	0.0150
PRS	-0.0215 (0.0309)	0.4865
Peer group deviance, age 15	**0.0383 (0.0082)**	**0.0000**
PRS x Peer group deviance, age 15	0.0212 (0.0103)	0.0403
Parental Monitoring		
	Beta (SE)	P-value
AGE 12		
Intercept	**2.2432 (0.0440)**	**<2e-16**
Sex	-0.1169 (0.0543)	0.0317
PRS	0.0195 (0.0339)	0.5641
Parental monitoring, age 12	0.0005 (0.0022)	0.8034
PRS x Parental monitoring, age 12	-0.0035 (0.0029)	0.2184
AGE 13		
Intercept	**2.2554 (0.0405)**	**<2e-16**
Sex	-0.1023 (0.0499)	0.0409
PRS	-0.0114 (0.0312)	0.7139
Parental monitoring, age 13	-0.0019 (0.0023)	0.4261
PRS x Parental monitoring, age 13	-0.0047 (0.0030)	0.1185
AGE 15		
Intercept	**2.2574 (0.0425)**	**<2e-16**
Sex	-0.1169 (0.0522)	0.0255
PRS	-0.0160 (0.0324)	0.6219
Parental monitoring (parent-reported), age 15	-0.0012 (0.0025)	0.6254
PRS x Parental monitoring (parent-reported), age 15	0.0016 (0.0032)	0.6216

Age 20 Results. Table 6.10 shows the results of the linear regressions testing if the PRSs predict age 20 AU. None of the PRSs were significantly associative of AU, but the score that accounted for the most variance was the seventh score and was moved forward into the multiple regressions.

Table 6.10. Univariate linear regressions of age 20 AU on PRSs at each threshold

	R-squared (Adjusted)	P-value	Beta (SE)
Score 1 (p = 0.0001)	0.0337	0.2648	-0.0683 (0.0613)
Score 2 (p = 0.001)	0.0332	0.5203	-0.0141 (0.0219)
Score 3 (p = 0.01)	0.0331	0.6067	0.0042 (0.0081)

Score 4 (p = 0.05)	0.0343	0.1344	0.0064 (0.0043)
Score 5 (p = 0.1)	0.0349	0.0693	0.0060 (0.0033)
Score 6 (p = 0.2)	0.0363	0.0162	0.0062 (0.0026)
Score 7 (p = 0.3)	**0.0367**	**0.0113**	**0.0060 (0.0024)**
Score 8 (p = 0.4)	0.0364	0.0155	0.0054 (0.0022)
Score 9 (p = 0.5)	0.0365	0.0131	0.0053 (0.0021)

Table 6.11 shows the results of the regressions testing the moderating effect of PGD at ages 10, 12, and 15 and PM at ages 12, 13, and 15 on polygenic risk for AU at age 20. Using the Bonferroni corrected *p*-value of 0.008, there was a significant influence of PGD at age 15 on AU. There was also a significant main effect of the PRS within the age 12 PM model and a significant moderating effect of the PRS x age 12 PM on AU.

Table 6.11. Moderated multiple regressions of age 20 AU on sex, PRS, PGD (top), and PM (bottom)

Peer Group Deviance		
	Beta (SE)	P-value
AGE 1O		
Intercept	**2.2919 (0.0295)**	**<2e-16**
Sex	**-0.2138 (0.0374)**	**0.0000**
PRS	0.0054 (0.0025)	0.0301
Peer group deviance, age 10	-0.0050 (0.0144)	0.7300
PRS x Peer group deviance, age 10	0.0008 (0.0019)	0.6700
AGE 12		
Intercept	**2.2914 (0.0295)**	**<2e-16**
Sex	**-0.2099 (0.0371)**	**0.0000**
PRS	0.0062 (0.0025)	0.0153
Peer group deviance, age 12	0.0077 (0.0090)	0.3956
PRS x Peer group deviance, age 12	0.0022 (0.0012)	0.0794
AGE 15		
Intercept	**2.2817 (0.0308)**	**<2e-16**
Sex	**-0.2227 (0.0388)**	**0.0000**
PRS	0.0058 (0.0026)	0.0274
Peer group deviance, age 15	**0.0110 (0.0059)**	**0.0008**
PRS x Peer group deviance, age 15	0.0005 (0.0008)	0.5012
Parental Monitoring		
	Beta (SE)	P-value
AGE 12		
Intercept	**2.2777 (0.0322)**	**<2e-16**
Sex	**-0.1936 (0.0403)**	**0.0000**
PRS	**0.0076 (0.0027)**	**0.0053**
Parental monitoring, age 12	0.0019 (0.0015)	0.2161

PRS x Parental monitoring, age 12	**-0.0006 (0.0002)**	**0.0070**
AGE 13		
Intercept	**2.2901 (0.0297)**	**<2e-16**
Sex	**-0.2278 (0.0373)**	**0.0000**
PRS	0.0062 (0.0026)	0.0163
Parental monitoring, age 13	-0.0027 (0.0017)	0.1191
PRS x Parental monitoring, age 13	-0.0002 (0.0002)	0.4354
AGE 15		
Intercept	**2.2859 (0.0313)**	**<2e-16**
Sex	**-0.2161 (0.0394)**	**0.0000**
PRS	0.0059 (0.0027)	0.0292
Parental monitoring (parent-reported), age 15	-0.0020 (0.0018)	0.2865
PRS x Parental monitoring (parent-reported), age 15	-0.0001 (0.0003)	0.8519

Discussion

Using a large, population-based sample of adolescents in the U.K., we examined whether polygenic risk is associated with AU across late adolescence, and whether PGD and PM moderated the impact of polygenic risk on AU. We found that higher polygenic risk at age 12 predicted increased AU at age 20, as well as a significant interaction of PRS by PM at age 12 for age 20 AU, such that under conditions of high PM at age 12, polygenic risk for AU at age 20 was lower. These findings build upon those of Salvatore et al[34] and extend them to a developmental framework. Additionally, although PRS-by-environment studies are in their infancy and future research based on large discovery and replication samples are needed, initial findings from the present study and those of Salvatore et al[34] suggest that prevention and intervention efforts focused on increasing PM may be effective in decreasing the impact of polygenic risk for AU.

Of note is that polygenic risk did not significantly predict AU until age 20. One likely explanation for this is the consistent finding that genetic influences become more important over time[1-4]. It is possible the aggregate genetic influences were not strong enough at the younger ages for us to be able to detect them. However, a post-hoc power analysis revealed that we had

enough power to be able to do so if they were present. The results of the power analysis suggested that we were able to detect 1% of the heritability with 80% power (with an *N* of 1,670).

With regard to the main effects of PGD and PM, we found main effects of PGD, such that PGD at age 12 increased AU at ages 16 and 17, and PGD at age 15 increased AU at ages 16, 17 18, and 20. We also found main effects of PM, such that PM at ages 12, 13, and 15 decreased AU at age 16 only. These findings are consistent with prior literature showing that PGD and PM are important predictors of adolescent AU[5-17].

Our results suggest that the influence of PGD on AU is enduring and stable across time. PGD at age 12 predicted increased AU until age 17. Following this, PGD at age 15 predicted increased AU until age 20. Given these results, future research should examine the temporal pattern into young adulthood since alcohol becomes more socially available during this developmental stage. The influences of PM were shorter lived, with the protective effect not extending beyond age 16. One possible explanation for this finding is that, as adolescents become older and more independent, parents have less control and ability to monitor their activities compared to peers and siblings.

Such findings have important implications for prevention and intervention programming. It appears that targeting deviant peer groups at all ages may be beneficial, since the effects appear to be stable. Additionally, educating parents on the means of increasing monitoring has the potential to delay AU initiation. This is important for the prevention of alcohol misuse, given the finding that for every year that alcohol initiation is delayed, there is a 5-9% decrease in the risk of alcohol misuse[60].

Limitations

These findings should be considered within the context of three limitations. First, participants in both our discovery and target samples were exclusively of European ancestry. Thus, it is unclear if our results will generalize to other populations with different ancestral backgrounds. Second, the effect size for our PRS that significantly predicted AU at age 20 was small, accounting for only about 3% of the variance (in the univariate regression). However, it should be noted that this effect size is larger than the results of similar polygenic studies that have accounted for approximately 1% of the variance in AU[34]. The effect size for the moderating effect of the PRS x age 12 PM on AU at age 20 was also very small, and accounted for <1% of the variance. Third, the polygenic approach by its nature does not provide any information regarding the specific genes involved in AU. Fine mapping approaches are required for this information, which is beyond the scope of this chapter. Finally, our discovery sample was based on adults, while our target (replication) sample was based on adolescents. Thus, age related genetic heterogeneity in AU might downwardly bias the predictive power of the PRS. We expect that as the target sample approaches the age of the discovery sample, predictive power will increase, as we saw with the analyses at age 20.

Conclusions

PGD at age 12 increased AU at ages 16 and 17, and PGD at age 15 increased AU at ages 16, 17, 18, and 20, while PM at ages 12, 13, and 15 decreased AU at age 16. Higher polygenic predispositions for AU (based on GWAS estimates from a population-based sample of adults) predicted increased AU at age 20 in an independent, population-based sample. Further, PM at age 12 moderated polygenic risk for AU at age 20. Polygenic risk for AU at age 20 was less influential under conditions of high PM at age 12. Given these findings, prevention and

intervention efforts that focus on decreasing exposure to deviant peers at all ages during adolescence, and focus on encouraging high levels of parental monitoring, particularly during early adolescence, may reduce risk for alcohol misuse.

Chapter 7: Global Discussion

The overarching aim of this dissertation was to fill critical gaps in the AU/AUD literature. These gaps include: (1) the magnitude and nature of the relationships between AU/AUD and resilience, and which personality disorder offers the best prediction of AU/AUD, as well as the nature of their etiologic overlap; (2) the ways in which longitudinal changes in genetic and environmental influence risk for AU over time; and (3) the moderating effects of key environmental risk factors on polygenic risks for AU within a developmental framework. Therefore, the specific aims of this dissertation were: (1) to examine the roles that resilience and personality disorders play in the etiology of AU and AUD; (2) to investigate the nature of longitudinal changes in the contributions of genetic and environmental risk factors in AU; and (3) to determine the moderating role of key environmental risk factors on the impact of polygenic risk for AU across adolescence.

Review of main findings

Chapter 2 examined the magnitude of the relationship between AUD and the five traits that were components of the resilience assessment (social maturity, interest, psychological energy, home environment, and emotional control), as well as the total resilience score. It was found that higher scores on the five single items that comprised the resilience assessment and a higher total resilience score were associated with a reduced risk of AUD (a 29% decrease in the odds of AUD). However, this effect was also non-linear, such that risk of AUD abruptly increased with resilience levels in the middle range. In other words, there is a diminishing return for increasing levels of resilience. The extent to which the resilience–AUD relationship is the result of common genetic or

common environmental factors was also explored using a bivariate Cholesky decomposition from which we showed that the relationship was largely attributable to overlapping genetic and shared environmental factors (57 and 36%, respectively).

Chapter 3 continued examining the associations between personality, AU, and AUD by specifically focusing on the role of personality disorders (PDs). This chapter investigated which of the 10 PDs provided the strongest phenotypic prediction of the liabilities to AU and AUD, the degree to which the associations between PDs and AU and AUD were due to shared genetic or shared environmental risks using Cholesky decomposition, and if the patterns of associations were stable across time. Borderline and antisocial PDs were the strongest correlates of the phenotypic and genotypic liability to AU and AUD. These patterns of associations remained consistent across time (at ages 28 and 38).

Chapter 4 tested the second aim of this dissertation and investigated whether the changes in genetic variation in AUD between early and mid adulthood were attributable to a single factor or multiple, qualitatively distinct factors. Developmental changes in the genetic and environmental influences on AUD over three age periods (18-25, 26-33, and 33-41) were investigated using Cholesky decomposition. We found evidence for two sets of qualitatively distinct genetic risk factors: one originated during the ages 18-25 and declined in magnitude, while the other came online or emerged at ages 26-33.

Chapter 5 went further by investigating the precise mechanisms of how underlying genetic and environmental risk factors influence AU from adolescence through young adulthood. The fits of five competing developmental hypotheses that each making different predictions about the nature of genetic and environmental influences in

AU over time were compared. The best-fitting model suggested that genetic influences were consistent with an unfolding, growing pattern of risks as predicted by a latent growth model, while unshared environmental factors were best described in terms of accumulating or remembering of environmental risk, as indicated by the significant autoregressive components.

Finally, Chapter 6 explored whether polygenic risk predicted AU across late adolescence. In addition, it tested whether peer group deviance (PGD) and parental monitoring (PM) moderated the impact of polygenic risk on AU. Polygenic risk scores were created based on GWAS results from the Australian adult sample and were first regressed onto AU at four time points (ages 16, 17, 18, and 20) to test if the PRS predicted AU in an independent sample of adolescents in the U.K. Multiple linear regressions were then run with PRSxE interactions to test the hypothesis that PGD and PM moderate the association of the PRS for AU at each of the four time points. PGD at age 12 increased AU at ages 16 and 17, and PGD at age 15 increased AU at ages 16, 17, 18, and 20, while PM at ages 12, 13, and 15 decreased AU at age 16. Higher polygenic predispositions for AU predicted increased AU at age 20 in an independent, population-based sample. Further, PM at age 12 moderated polygenic risk for AU at age 20, with polygenic risk for AU at age 20 being less influential under conditions of high PM at age 12.

The bigger picture: Implications and future directions

Although many published behavioral genetic research papers mention that, "findings can inform prevention and intervention efforts," rarely are the mechanisms describing how results can be translated discussed or elucicated. In fact, there have been

relatively few efforts to translate behavioral genetics research findings directly into prevention efforts [1]. Although the field of behavioral genetics is a basic science, it exists on a translational pathway and the broader implications of results should be discussed. This will facilitate an understanding of mechanisms of behavior change and provide advancement toward the long-term goal of personalized prevention approaches[1].

The observed finding that nearly all complex psychiatric disorders are not Mendelian, are highly polygenic, and report heritability < 100% implies that AU/AUD are influenced by the environment, and consequently can potentially be modified through prevention and intervention efforts[2]. Behavioral genetics research within a developmental framework provides invaluable insights for understanding how critical environmental factors are during adolescence[3-6], suggesting that adolescent AU will be heavily influenced by family, peer, and school prevention and intervention efforts[2]. However, this pattern evolves as individuals age, such that genetic factors become more important than environmental influences. This suggests that the protective effects of environmental efforts or attempts to delay AU or reduce the symptoms of AUD become less salient over time at least with respective to population-based samples that have not received any form of clinical intervention. Importantly, although environmental efforts may be less impactful during adulthood, we speculate that they would not be futile. However, this is critical for informing the importance of prevention efforts during early adolescence, when these efforts are likely to show the greatest benefit. Taken together, we can speculate that the large-scale implication from this research is that for environmental interventions to be successful they ought to be implemented during periods when environmental influences reach their peak during mid-adolescence.

More specific to this dissertation, the associations between resilience and AU found in Chapter 2 suggest that interventions aimed at encouraging and teaching greater resilience may result in delayed AU and reduced AUD symptomatology, as we showed resilience reduced the risk of developing AUD by as much 29%. Further, the protective effect or benefit of resilience began to asymptote beyond resilience scores of 6 or more. Accordingly, moderate levels of resilience may be sufficient in order to reduce risk of AUD. These results build upon previous studies showing that resilience can attenuate risk for AU problems[7-9]. Collectively, it is clear that focusing prevention and intervention efforts on increasing resilience may be an effective means of reducing risk of AUD.

The results of the bivariate Cholesky decomposition showed that much of the resilience-AUD relationship was attributable to overlapping genetic (57%) and shared environmental factors (36%). Accordingly, these shared genes inform gene-finding efforts by providing plausible networks to locate specific genes involved, and the shared environments can be targeted for prevention efforts. Although the results of this chapter do not directly inform when these efforts would be of greatest benefit, we can infer based on previous findings that the optimal timing would be when environmental influences have the greatest impact (i.e., before mid-adolescence)[3-6].

Chapter 3 showed that among all of the DSM-IV PDS, borderline and antisocial PDs are the strongest correlates of increased risk for AU and AUD, and that this effect remains constant over lengthy time periods (i.e., 10 years apart). These findings are consistent with a large body of literature that has implicated these two personality disorders in the development of AUD[10-15]. Thus, individuals with borderline and antisocial PDs appear to be at higher risk for developing AUD, which is informative for

clinicians treating them. However, the question of whether the PDs are a pre-cursor for AU/AUD, or whether AU/AUD causally increases the risk of PDs has not been resolved. If the direction of causation suggests that the PDs are a causal pre-cursor for AU/AUD, the implication for prevention would be that individuals displaying characteristics of borderline and antisocial PD would be likely to benefit from efforts targeted towards teaching healthy coping mechanisms targeted for the PD, with downstream reduction of risk for AU/AUD. However, if the opposite is true (that AU/AUD increases risk of PDs), then the focus of the prevention should directly target risk reduction for AU/AUD.

Although we have not formally modeled competing causal hypotheses between PDs and AU/AUD, the bivariate results are consistent with the hypothesis that risk of antisocial PD, borderline PD, and AUD can be attributable to correlated genetic factors and to a much lesser extent shared environmental risk factors. In other words, the genes that influence the development of AUD are shared with those that influence levels of borderline and antisocial PD. As described above, these shared genes can inform gene-finding efforts.

The findings from Chapter 4 helped to clarify the question of whether genetic variation can be accounted for by a single factor or multiple factors across time. Because the extant literature is conflicting[6,16], this remains an important research area. While the present results, which are based on a very large population-based sample, shows evidence for two qualitatively distinct genetic risk factors, further research with an independent sample are required to validate our findings. If our results replicate, they can inform gene-finding efforts by identifying the age ranges at which genetic variance is greatest. Alternatively, if replication efforts provide more support for a single set of genes, the

implication for gene-finding efforts would be that the ages of the sample used should not impact the success of such efforts.

The results from Chapter 5 extended the findings from Chapter 4 by showing that two distinct developmental processes influence adolescent and young adult AU between the ages of 15 to 25. Genetic effects not only influence baseline levels of AU but the rate of change in AU across time, whereas unique environmental effects appear to be 'remembered' and accumulate over time. Our hypothesis that the same genetic influences on AU 'unfold' or are increasingly expressed over time is broadly consistent with reports showing that genetic variation increases over time[3-6]. As previously mentioned, the primary implication here is that prevention efforts are likely to be most optimal when targeted or implemented during early adolescence, before genetic influences become prominent. Further, the finding that unique environmental influences were consistent with an accumulating pattern of risk suggests that prevention efforts should focus on ways to reduce the number of unique risk factors that adolescents are exposed to, such as associations with deviant peers.

A significant innovation of this chapter is that it is the first study to apply and test dual change score (DCS) or dynamic developmental models to adolescent AU. Our results were consistent with those of the report by Gillespie et al.[17] who applied the DCS approach to examine adolescent depression, which is consistent with the literature supporting the links between AU and internalizing disorders[18-21]. Future research should formally test whether the same developmental patterns in genetic and environmental risk can be observed in all forms of adolescent psychopathology. To what extent the development of normative or non-psychiatric phenotypes (e.g., height, weight, stature)

follow the same developmental patterns is unclear. If there were support for this notion, the implications for prevention efforts discussed above would be similar, but would be generalizable to other forms of psychopathology.

Finally, the findings from Chapter 6 have clear implications for prevention programming focused on reducing associations with deviant peer groups and increasing parental monitoring. Further, because the analyses were conducted at multiple time points across adolescence, an interesting temporal patterning was revealed, such that prevention programs targeting deviant peer groups are likely to be beneficial at all ages during adolescence, since the protective effects appeared to last for several years. In contrast, the protective effects of parental monitoring appear to be of shorter duration, and not extending beyond age 16. Despite this, efforts that focus on increasing parental monitoring may still delay AU, which can prevent the development of downstream alcohol problems[22].

Regarding the results of the polygenic risk and moderation analyses, the finding that polygenic risk did not significantly predict AU until age 20 is consistent with the twin literature showing that the impact of genetic variation increases over time[3-6]. It is also consistent with the need for significantly larger discovery samples with more precise phenotyping in order to improve the beta weights used to derive and estimate PRS in independent samples, as well as the fact that the weights were based on an older discovery GWAS sample. There was, however, one interaction that passed the Bonferroni corrected p-value threshold of 0.008, which revealed that under conditions of high parental monitoring at age 12, the polygenic risk for AU at age 20 is lower. To date, there has only been one study showing genetic risk for alcohol problems was stronger under

conditions of low parental knowledge or high peer deviance[23]. Clearly, more research examining polygenic risk by environment effects is needed, and with the release of the U.K. Biobank data[24] and the forthcoming Psychiatric Genetics Consortium-AUD GWAS meta- and mega-analyses, we anticipate that the sensitivity and specificity of PRS scores will be significantly enhanced.

Also of note here is the line of research examining gene by intervention (GI) effects. Before the development of polygenic methods, GI studies examined how individuals with a specific gene might respond to a given prevention or intervention (see Brody et al.[25] for a review). For example, one such study found that toddlers who carried the 7-repeat version of the dopamine receptor-4 gene (DRD4) showed a greater decrease in disruptive behavior following a parenting skill intervention than toddlers who did not carry this allele [26]. Although compelling, this candidate gene literature suffers from the critical limitations described in Chapters 1 and 6, such as lack of power to detect true effects[27,28]. In the current genomic era, it is now understood that many genes of small effect influence the development of psychiatric disorders[27]. Thus, an important area for future research is to increase power by using post-GWAS candidate selection, polygenic scoring, or pathway analysis to conduct these types of GI trials[29]. A recent article by Latendresse and colleagues[29] presents guidelines for these approaches, including genotype quality control and correction for population stratification.

Taken together, within the context of the three aims of this dissertation, four key implications for prevention and intervention efforts emerge: (1) Programs targeting environments that foster resilience, and decrease risk for borderline and antisocial PDs by treating the early psychiatric symptoms of these PDs *may* also reduce AU; (2) Programs

are likely to be more beneficial during early adolescence, before genetic influences for AU increasingly explain a greater proportion of the total phenotypic variation in AU and AUD; (3) Because of the accumulative nature of unique environmental risk factors on AU, efforts should focus on decreasing the number of these risk factors adolescents are exposed to; and (4) Peer group deviance and parental monitoring are critical areas and opportunities for focus on prevention efforts, with initial findings showing support for the ability of parental monitoring to decrease the polygenic impact of AU.

Conclusions

This dissertation examined risk/protective factors for the development of AU/AUD and the developmental trajectories of AU/AUD using both biometrical behavioral genetic and molecular genetic methodologies. We showed five main findings: (1) Resilience was strongly associated with a reduction in risk for AUD, and this relationship appeared to be the result of overlapping genetic and shared environmental influences; (2) Borderline and antisocial personality disorders were the strongest predictors of the phenotypic and genotypic liability to AU and AUD, and this effect remained consistent across time; (3) Genetic influences on the development of AUD observed during early adulthood through mid-adulthood were dynamic, with two sets of genetic risk factors contributing to AUD risk: one set of risks originating during ages 18-25 and a second set of risk emerging during ages 26-33; (4) Genetic influences in AU appear to follow a pattern of unfolding and growth over time, whereas unique environmental risk factors were consistent with an accumulation of environmental impacts across time; and (5) High peer group deviance and low parental monitoring were associated with increased AU, and early parental monitoring moderated polygenic risk

for AU at age 20. These findings have important prevention and intervention implications for reducing AU and risk for AUD.

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Vita

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