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Jueun Kim
Syracuse University

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Abstract

Emerging evidence shows that the 5-HTTLPR genotype interacts with social environments and influences drinking behaviors. However, few studies have examined interaction effects between the 5-HTTLPR genotype and specific aspects of family environments on adolescent drinking. The present study investigated whether the effects of family conflict or parental monitoring on adolescent drinking differed as a function of the 5-HTTLPR genotype cross-sectionally and longitudinally. It was replicated in two independent samples consisting of 175 adolescents in the U.S. and 4,916 adolescents in the U.K. The results of path analyses and multi-group analyses showed that, in the two samples, the 5-HTTLPR low-activity allele carriers exposed to high levels of family conflict were more likely to engage in concurrent alcohol misuse at Time 1 than non-carriers. The results of analyses testing the interaction between the 5-HTTLPR genotype and parental monitoring were inconsistent in the two samples. Overall, our results suggest that the 5-HTTLPR low activity allele carriers are more susceptible to the effect of family conflict on concurrent alcohol misuse. This finding highlights the importance of identifying and reducing family conflict in alcohol prevention and intervention programs in adolescents with the 5-HTTLPR low-activity allele.

Interaction Effects between the 5-HTTLPR Genotype and Family Environments on
Adolescent Alcohol Use and Misuse

By

Jueun Kim

B.A. Handong Global University, 2008

M.A. Teachers College, Columbia University, 2010

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Interaction Effects between the 5-HTTLPR Genotype and Family Environments on Adolescent Alcohol Use and Misuse

Underage alcohol use and misuse is a pervasive and serious public health concern. In the United States, 39% of adolescents in grades 9 through 12 reported consuming alcohol in the past 30 days (U.S. Department of Health and Human Services, 2012) and 15% reported having been drunk in the U.S. (Johnson, O'Malley, Bachman, & Schulenberg, 2013). In the United Kingdom (U.K.), 65% of adolescents age 15 to 16 reported consuming alcohol in the past 30 days and 52% reported heavy episodic drinking (defined as having five or more drinks on one occasion; Hibell et al., 2011). Underage drinking brings harmful results; in 2008, approximately 190,000 adolescents visited an emergency room for alcohol-related injuries (U.S. Department of Health and Human Services, 2011) and 5,000 adolescents die from alcohol-related car accidents, suicide, homicide, and alcohol poisoning every year (U.S. Department of Health and Human Services, 2007). Underage drinking also brings long-term negative consequences such as damage to brain development (Monti et al., 2005), later alcoholism and drug problems (Grant et al., 2006), and dropping out of school, thus negatively affecting later education and occupation (Chatterji & DeSimone, 2005). The grave consequences of adolescent drinking highlight the need for a better understanding of the determinants of adolescent drinking to inform prevention and intervention strategies.

Drinking is a behavior driven by complicated interplay among biological, psychological, and social factors. An individual's genetic makeup is one significant factor among determinants of adolescent drinking. Behavioral genetic studies including adoption (Cloninger, Bohman, & Sigvardsson, 1981; Sigvardsson, Bohman, & Cloninger, 1996) and twin studies (Fowler et al., 2007; Maes et al., 1999; Rhee et al., 2003; Viken, Kaprio, Koskenvuo, & Rose, 1999) have consistently found substantial aggregate genetic effects (ranging from 21 to 55%) on adolescent alcohol use and misuse. Among specific genes

potentially associated with drinking, genes involved in the regulation of serotonin have been extensively studied due to serotonin's role in the brain's reward, mood regulation, and stress reaction systems related to drinking behavior (Oroszi & Goldman, 2004). The gene encodes the serotonin transporter which regulates serotonin reuptake in the synaptic cleft and thus plays a key role in serotonin signaling. The gene has a 44 base pair insertion/deletion polymorphism in its promoter region (i.e., the 5-Hydroxy Tryptamine Transporter-linked polymorphic region; 5-HTTLPR). (Kranzler & Anton, 1994; LeMarquand, Pihl, & Benkelfat, 1994). Initially, this polymorphism was thought to be a bi-allelic variable number of tandem repeats (VNTR) polymorphism: The short (S) allele was associated with reducing transcriptional activity of the serotonin transporter as compared to the long (L) allele (Heils et al., 1996). More recent research suggested the 5-HTTLPR to be tri-allelic (Hu et al., 2006): A single nucleotide polymorphism (A/G) in the first of two extra 22 base-pair repeats of the L allele yields L_G and L_A , and the L_G and S alleles show the same level of the reduced transcriptional activity of the serotonin transporter as compared to the L_A allele. Thus, tri-allelic 5-HTTLPR has two functional allele groups: the low-activity alleles (i.e., the S and L_G alleles) and the high-activity allele (i.e., the L_A allele). Although an animal experimental study manipulating serotonergic levels (LeMarquand et al., 1994) showed that decreasing serotonergic functioning increased alcohol intake, behavior studies have yielded inconsistent results concerning the association of the 5-HTTLPR genotype with adolescent alcohol use and misuse (Dawes et al., 2009; Gerra et al., 2005; Hinckers et al., 2006; Merenakk et al., 2011; van der Zwaluw et al., 2010).

Emerging evidence suggest that these inconsistent findings may reflect the fact that the association differs as a function of environmental factors that are closely related to drinking behaviors. For example, among carriers of the 5-HTTLPR risky genotype, negative life events, including family adversity (Covault et al., 2007; Kranzler et al., 2012), childhood

maltreatment (Kaufman et al., 2007), and low family support (Brody et al., 2009a), were found to be positively associated with early alcohol initiation, alcohol use and misuse, and substance use among adolescents. However, among non-carriers, these environments were not related to alcohol use. These findings are supported by animal research: Female rhesus macaque monkeys with the 5-HTTLPR risk genotype reared in mother-absent peer-only settings showed a greater increase in alcohol consumption over time than female monkeys without the 5-HTTLPR risk genotype reared in the same environment (Barr et al., 2004). These findings suggest that adverse family environments may modulate the effect of the 5-HTTLPR genotype on alcohol use behaviors among adolescents.

If this is the case, what specific adverse family environments may be interacting with the 5-HTTLPR genotype? Because most of the previous gene and environment interaction (GxE) studies examined overarching environmental factors such as negative life events or childhood maltreatment, it is difficult to determine the role that specific family stressors may play in shaping how the 5-HTTLPR genotype influences adolescent alcohol use and misuse. Although the external social influences on adolescent drinking increase during adolescence period (Windle et al., 2008), family has been studied to have independent influence as a dominant physical context for teenagers over and above other life events such as peer interactions (Hayes, Smart, Toumbourou, & Sanson, 2004). Thus, this study will address the question by focusing on two variables, family conflict and poor parental monitoring, which have been shown to be closely associated with adolescent drinking.

Family Conflict

Prior studies have shown that higher levels of family conflict are associated with earlier ages of alcohol initiation (Shortt, Hutchinson, Chapman, & Toumbourou, 2007) and heavier and more frequent alcohol use (Bray, Adams, Getz, & Baer, 2001; Mason, Hitchings, McMahon, & Spoth, 2007). Stress response dampening theory (Sher, 1987) maintains that

individuals in stressful situations drink alcohol to cope with stress, and over time their drinking behaviors are reinforced by stress-dampening effects of drinking. Given that, among adolescents, coping motives (e.g., drinking to forget worries) are one of the important motives for drinking, along with social motives (Kuntsche, Rehm, & Gmel, 2004), adolescents may consume more alcohol to cope with their family stress.

In a previous study, adolescents with the 5-HTTLPR risky genotype in poor family relationships have been found to have a higher risk of drinking than non-carriers (Nilsson et al., 2005). Specifically, among adolescents carrying the 5-HTTLPR risky genotype, poor family relationships were associated with a greater intoxication frequency than neutral or good family relationships. However, the intoxication frequency of adolescents not carrying the 5-HTTLPR risky genotype was lower than that of carriers regardless of family relationships. Poor family relationships in that study were measured based on the adolescents' evaluation about family relationship at the three levels of good / neutral / bad quality of family relationship. Whereas the quality of family relationships generally includes subjective perceptions, family conflict usually is generally measured with more explicit behavioral indices such as yelling, blaming, criticizing, or physical violence among family members (McKelvey et al., 2011; Sillars, Canary, & Tafoya, 2004). Examining explicit behaviors in family interaction (i.e., family conflict) is important, because it may lead us to develop specific behavioral strategies to improve family interactions among those at greater risk for the detrimental influences of adverse family interactions. However, family conflict has not been examined in the context of the 5-HTTLPR genotype on alcohol use and misuse.

Parental monitoring

Another aspect of the family environment that may modulate the relationship between the 5-HTTLPR genotype and adolescent drinking is parental monitoring. Parental monitoring is conceptually defined as a set of behaviors that parents do to supervise their children's

activities and whereabouts (Dishion & McMahon, 1998). Low levels of parental monitoring have been associated with the early initiation of alcohol use (Cohen, Richardson, & LaBree, 1994) and an increase in heavy drinking (Nash, McQueen, & Bray, 2005) in adolescence. Social control theory (Hirschi, 1969) suggests that appropriate parental control of children's misbehaviors through parental monitoring helps children to develop the self-control capabilities that let them regulate their own behaviors. However, in a family where parents do not monitor their children's activities and communicate standards of behavior, children may be more likely to engage in problematic drinking.

A recent randomized clinical trial of a prevention program targeting parenting behaviors in African American families found that adolescents carrying the 5-HTTLPR risky genotype were more influenced by good parenting, compared to those not carrying the allele (Brody, Beach, Philibert, Chen, & Murry, 2009b). When assigned to the control condition (in which parents did not participate in a parenting program), adolescents who carried the 5-HTTLPR risky genotype showed a higher rate of risky behavior initiation than adolescents without the allele. However, the rate of risk behavior initiation among non-carriers was low, regardless of their group assignments. The parenting program in this study, however, targeted very broad parenting skills including supportive parenting practices, communication about sex or alcohol use, dealing with racial discrimination, and parental monitoring. Thus, it is unclear whether parental monitoring by itself plays a significant role. It is important to examine the specific effects of parental monitoring among adolescents with risk genetic markers, because such research could reveal which particular aspects of the family environment should be addressed in family intervention/prevention for adolescents at risk. Despite its importance, no study has examined whether parental monitoring modulates the relationship between the 5-HTTLPR genotype and adolescent alcohol use and misuse.

The Current Study

In the present study, I examined interaction of the 5-HTTLPR genotype with two specific family environments (i.e., family conflict and parental monitoring) on alcohol use and misuse among adolescents. Specifically I tested the following four hypotheses. First, I hypothesized cross-sectionally adolescents carrying the 5-HTTLPR low-activity allele (i.e., the S or L_G alleles) would be more likely to be engaging in alcohol use and misuse than non-carriers when they were exposed to higher levels of family conflict. Second, I hypothesized when exposed to higher levels of family conflict, adolescents carrying the 5-HTTLPR low-activity allele would increase alcohol use and misuse over time more than non-carriers. Third, I hypothesized cross-sectionally adolescents carrying the 5-HTTLPR low-activity allele would be less likely to engage in alcohol use and misuse than non-carriers when exposed to higher levels of parental monitoring. Finally, I hypothesized when exposed to higher levels of parental monitoring, adolescents carrying the low-activity allele would decrease alcohol use and misuse to a greater degree than would non-carriers. Age, gender, race, and primary care giver's education level as a proxy of socioeconomic status were included as covariates in the analyses. Levels of alcohol consumption among adolescents have been shown to differ as a function of age (Downs & Robertson, 1982), gender (Kelly et al., 2011), race (Johnson, O'Malley, Bachman, & Schulenberg, 2010), and socioeconomic status (Droomers, Schrijvers, Casswell, & Mackenbach, 2003).

In addition to conducting analyses to test the four main hypotheses, four sets of ancillary analyses were conducted to examine whether the results remained the same when the analyses used (a) data from participants who do not have any missing data on any of the study variables (instead of data from all participants with missing data), (b) a three-level tri-allelic genotype categorization such as the number of the low-activity alleles (instead of a two-level tri-allelic genotype categorization of the presence of the low-activity allele), (c) other substance use as an outcome variable (instead of alcohol use and misuse), and (d) other

negative environments such as bullying victimization and neighborhood stress as predictor variables (instead of family environments).

The present research sought to advance the literature by the following three important methodologies. First, the study used measures of both alcohol use and alcohol misuse. The frequency of alcohol use was found to have high sensitivity and specificity in detecting risks for alcohol dependence among adolescents (Chung et al., 2012). The frequency of alcohol misuse (such as frequency of heavy drinking) has consistently been found to be positively associated with experiences of stressors (Dawson, Grant, & Ruan, 2005), such as family conflict. Second, I examined my hypotheses with adolescent samples from a community-based longitudinal study, Project inSight, conducted in the City of Syracuse, NY. Then, I examined whether the results from Project inSight are replicated in another samples available publically from a large population-based longitudinal study, the Avon Longitudinal Study of Parents and Children (ALSPAC), in the UK. In the current study, I applied direct replication in GxE studies (Duncan & Keller, 2011), which is defined as the use of the same statistical model on the same outcome and environmental constructs (as opposed to the use of the same measures) across two datasets. Given that the failure to replicate GxE findings has been an important concern (Hewitt, 2012), replication would help to address criticism concerning false positives and negatives in GxE studies (Duncan & Keller, 2011). Third, I investigated the 5-HTTLPR genotype and family environment interactions cross-sectionally and longitudinally, which can help to better elucidate the GxE effects on both concurrent and prospective alcohol behaviors among adolescents.

Method

Participants and Procedures

Sample 1 (Project inSight). The first set of data was derived from a longitudinal and community-based study of 250 adolescents who were entering or were in the ninth grade in

the City of Syracuse school district (13–17 years old at the first assessment [$M = 15.02$, $SD = 0.67$]; 57% Female; 47% African American). Adolescents were recruited from the community via information booths at school lunches and community events, and by means of information delivered through print media, street outreach efforts, and respondent-driven sampling. Participants completed two paper-and-pencil surveys with an approximately six-month inter-survey interval (mean interval = 188 days, $SD = 27$ days) between Time 1 (T1; August 3rd 2010 to May 31th 2011) and Time 2 (T2; January 24th to September 22nd 2011) assessments. As shown in the left panel of Figure 1, among the T1 participants, 202 were invited to the T2 assessment and 182 (90% of the invited T1 participants) also participated at T2. Consent was obtained from each participant's parents or legal guardian, and assent was obtained from each participant. Because saliva donation was one component of the overall study, participants were given an option that they can refuse to donate saliva. Participants received 30 dollars for each assessment and received 5 dollars (up to a maximum of 15 dollars) for referring a qualified youth to the study as part of respondent-driven sampling. All study measures and procedures were reviewed and approved by the human subjects institutional review board of Syracuse University.

For the current analyses, data from 175 participants who provided a saliva sample for DNA testing were used (70% of the T1 participants). To determine whether the sample size of 175 yields an appropriate level of power for detecting gene and environment interaction effects, a power analysis was performed using the Quanto program version 1.2.4. (Gauderman, & Morrison, 2009) under the conditions of dominant genetic model, and continuous environmental and alcohol outcome measures. Expected effect sizes (R^2) of the interaction between the 5-HTTLPR and negative environments on alcohol outcomes ($R^2 = .040$; Cavault et al., 2007), the main effect of the 5-HTTLPR on alcohol outcomes ($R^2 = .023$; Cavault et al., 2007), and the main effect of stressful environments on alcohol

outcomes ($R^2 = .069$; Park, Armeli, & Tennen, 2004) were based on prior studies. The result of power analysis showed that the necessary sample size that reaches power of 0.80 is 174, which indicated that our final sample size of 175 has enough power to detect gene and environment interaction effects.

This final sample was between ages 13 and 17 years old at T1 ($M = 15.04$, $SD = 0.69$) and 56% ($n = 97$) were female. Based on self-report, the final sample was racially diverse: 44% ($n = 77$) African American, 20% ($n = 35$) Caucasian, 5% ($n = 9$) Native American, 2% ($n = 3$) Asian, 23% ($n = 40$) multi-racial, and 6% ($n = 11$) not reporting the race. People who did not donate saliva ($n = 75$) were compared to the people who did donate saliva ($n = 175$) on the study variable, and there were no significant differences at p -value level of .05. Among these 175 participants who participated in the T1 survey, 123 (70%) participated in the T2 survey as well. The attrition group in the study ($n = 52$) did not show significant differences from respondents concerning race, maternal education, family conflict, and any drinking variables at p -value level of .05. However, a significant difference was found between the groups; attrition was associated with lower parental monitoring ($p = .02$), greater likelihood of being female gender ($p = .02$), and being older ($p < .001$). As described in Data Analytic Strategies, full-information maximum likelihood procedures were used as a missing data procedure; thus, the current analyses were based on all available data without excluding data from participants with missing data.

Sample 2 (ALSPAC). The second set of data was derived from the Avon Longitudinal Study of Parents and Children (ALSPAC), which is an ongoing, large, population-based longitudinal study conducted in the U.K. (Boyd et al., 2012). As shown in the right panel of Figure 1, ASLPAC comprised 15,247 mother-child dyads in the Avon area of Great Britain. A sample of 14,541 pregnant women who had an expected delivery date between April 1, 1991 and December 31, 1992 was recruited through posters, cards, media,

and brochures. Additional post-natal recruitment to clinical assessment and subsequent opportunistic contact added a further 706 mother-child dyads. Study offspring and their parents have been followed up with postal questionnaires and clinic visits.

For the current analyses, the data were collected when the offspring were at the mean age of 12 (T1) and again at the mean age of 15 (T2). At T1, the adolescents' mothers ($n = 7,099$) completed a postal questionnaire assessing family environments and the adolescents ($n = 6,832$; mean age = 12 [range = 11 to 13]) completed a computerized questionnaire assessing their family environments and alcohol use. At T2, adolescents ($n = 5,515$; mean age = 15 [range = 14 to 17]) followed up with a computerized questionnaire assessing their alcohol use. All study measures and procedures were reviewed and approved by the ALSPAC Law and Ethics Committee and local research ethics committees. Written consent was obtained from parents and written assent was obtained from the children.

For the current analyses, data obtained from 4,916 study adolescents and their parents were used, after excluding 10,529 participants (68%) on the basis of the following two criteria. First, to control for potential confounds due to population stratification (for details, see *Measures, Demographics*), I excluded 3,902 participants who were either non-White ($n = 623$) or missing the race variable ($n = 3,289$). Second, I excluded an additional 6,627 participants who did not provide biological samples for DNA testing. People who did not donate saliva ($n = 9,644$) showed no significant differences from people who did donate saliva ($n = 5,603$) concerning parental monitoring and any drinking variables at ages 12 and 15 at p -value level of .05. A significant difference was found between the groups; donors were more likely to be male gender ($p = .01$), show greater maternal education ($p < .001$) and lower family conflict ($p = .01$).

The resulting final sample ($n = 4,916$) included 47% women and 53% men. Among 4,916 participants who participated in the T1 survey and donated a biological sample, 2,857

(58%) also participated in the T2 survey. The attrition group in the study ($n = 1,317$) did not show significant differences from respondents concerning the frequency of the 5-HTTLPR low-activity allele and frequency of binge drinking at p -value level of .05. However, a significant difference was found between the groups; attrition was associated with being older ($p < .001$), being male gender ($p < .001$), lower maternal education ($p < .001$), greater family conflict ($p < .001$), lower parental monitoring ($p = .001$), greater frequency of drinking ($p = .01$), and greater largest number of drinks ($p = .01$). As described in *Data Analytic Strategies*, full-information maximum likelihood procedures were used as a missing data procedure; thus, the current analyses were based on all available data without excluding data from participants with missing data.

Measures

Demographics. In Project inSight, adolescents responded to questions pertaining to their age, gender, maternal education levels, and race at T1. For maternal education level, participants responded using a 4-point scale, from 1 (*some high school or less*), 2 (*completed high school*), 3 (*some college*), to 4 (*completed college*). For race, due to the highly mixed racial composition of the sample, instead of self-report, a White ancestry proportion score was estimated with genetic Ancestry Informative Markers (AIMs; Pritchard, Stephens, & Donnelly, 2000). The White ancestry proportion score, ranging from 0 to 1, was estimated using the STRUCTURE program (Pritchard et al., 2000), which has been widely used to control for the potential confounding effects of mixed race composition in molecular genetic studies (e.g., Kaufman et al., 2007; Luo et al., 2005; Yang et al., 2007). A higher score indicates a higher proportion of White ancestry in the person's genetic make-up.

In ALSPAC, adolescents responded to a question regarding their age at T1. Race was not controlled for because non-White participants were excluded from the final sample of ALSPAC. Mothers answered questions about their education levels in the third trimester of

their pregnancy and their child's gender. Regarding the question about education, mothers responded using a 5-point response scale, from 0 (*Certificate of Secondary Education*, which is a non-exam based and general high school certificate), 1 (*Vocational*, equivalent to an apprenticeship), 2 (*Ordinary level*, a subject-based certificate by examination in 10th/11th grades), 3 (*Advanced level*, an advanced subject-based certificate by examination in 11th/12th grades), to 4 (*University degree*).

Serotonin transporter gene polymorphism (5-HTTLPR). In Project inSight, genotyping the 5-HTTLPR genotype was conducted based on procedures described in a previous study (Wendland et al., 2008). Tri-allelic dichotomized categorization of the 5-HTTLPR genotype was used for the current analyses: carriers of at least one 5-HTTLPR low-activity allele ($n = 131$; 75%) versus non-carriers of the low-activity allele ($n = 44$; 25%). In addition, three-group tri-allelic categorization was used for ancillary analyses: carriers of two low-activity alleles ($n = 42$; 24%), carriers of one low-activity allele ($n = 89$; 51%), and non-carriers ($n = 44$; 25%).

In ALSPAC, the same tri-allelic dichotomized genotyping category and analyses were applied: carriers of at least one 5-HTTLPR low-activity allele ($n = 3,661$; 75%) versus non-carriers ($n = 1,255$; 25%). In addition, three-group tri-allelic categorization was used for ancillary analyses: carriers of two low-activity alleles ($n = 1,153$; 24%), carriers of one low-activity allele ($n = 2,508$; 51%), and non-carriers ($n = 1,255$; 25%).

Family conflict. In Project inSight, a 9-item family conflict subscale of the Family Environment Scale (Moos & Moos, 1994) was administered at T1 to assess experiences of family members' fighting, hitting, criticizing, or being angry. Adolescents responded to the questions using a scale of 0 (*No*) and 1 (*Yes*). The mean score of the subscale was used for current analyses.

In ALSPAC, at T1, adolescents' mothers responded to two measures assessing family

conflict: (1) two items asking whether the adolescent participant had arguments and fights with his/her siblings and (2) three items assessing whether mothers had arguments, hit, shouted, or broke things with their partners in the past three months. Mothers responded to the questions using a scale of 0 (*No*) and 1 (*Yes*). The mean score of the five items was used for current analyses.

Parental monitoring. In Project inSight, a 4-item abbreviated version of Silverberg's Parental Monitoring scale (Li, Stanton, & Feigelman, 2000) was used at T1. Adolescents were asked questions such as "Do your parents usually know where you are after school?" and "Are you expected to tell your parents where you go before going out?" Participants responded to each item using a 5-point scale, from 0 (*never*), 1 (*rarely*), 2 (*sometimes*), 3 (*most of the time*), to 4 (*always*). The mean score was used for current analyses.

In ALSPAC, a 24-item questionnaire that the ALSPAC research team developed (The ALSPAC team, 2011) was administered at T1. This measure was designed to measure four types of parental monitoring behaviors (i.e., child disclosure, parental solicitation, parental knowledge, parental control; Stattin & Kerr, 2000). Adolescents responded to each item using a 5-point scale, from 0 (*Never*), 1 (*Hardly ever*), 2 (*Sometimes*), 3 (*Most of the time*), to 4 (*Always*). The mean score was used for current analyses.

Alcohol use. In Project inSight, the past-month frequency of drinking (Bachman, Johnston, & O'Malley, 2009) was measured at T1 and T2. Adolescents responded to each of the questions using a 5-point scale, from 0 (*zero day*), 1 (*one to two days*), 2 (*three to five days*), 3 (*six to nine days*), to 4 (*ten or more days*).

In ALSPAC, the past six-month frequency of drinking was measured at T1 and T2. Adolescents responded to the questions using an 8-point scale, from 0 (*zero*), 1 (*one to two times*), 2 (*three to five times*), 3 (*six to nine times*), 4 (*ten to nineteen times*), 5 (*twenty to thirty-nine times*), 6 (*forty to ninety-nine times*), to 7 (*one hundred or more times*).

Alcohol misuse. In Project inSight, the past-month frequency of intoxication (Bachman et al., 2009) was measured at T1 and T2. Adolescents responded to each of the questions using a 5-point scale, from 0 (*zero day*), 1 (*one to two days*), 2 (*three to five days*), 3 (*six to nine days*), to 4 (*ten or more days*).

In ALSPAC, three items were used to assess alcohol misuse. First, the frequency of having three or more drinks in a single evening was measured at T1. Adolescents reported the number of times they have drunk three or more drinks in their life time. Second, the frequency of binge drinking (defined as having four drinks or more for girls and five drinks or more for boys in a single evening) in their life time was measured at T1; the frequency of binge drinking (defined as four drinks or more for girls and five drinks or more for boys in 24 hours) in the last two years was measured at T2. Adolescents responded to the questions using an 8-point scale, from 0 (*zero*), 1 (*one to two times*), 2 (*three to five times*), 3 (*six to nine times*), 4 (*ten to nineteen times*), 5 (*twenty to thirty-nine times*), 6 (*forty to ninety-nine times*), to 7 (*one hundred or more times*). Third, the largest number of drinks in a 24 hour period was measured at T1 and T2. Adolescents entered the largest number of drinks they consumed in their lifetime at T1 and in the last two years at T2.

Other substance use. In Project inSight, cigarette and marijuana use in the past month (Bachman et al., 2009) were measured at T1 and T2. Adolescents were asked whether they had smoked a cigarette or used marijuana in the past month at T1 and T2 and responded to the questions using a scale of 0 (*No*) and 1 (*Yes*). The sum scores of the two items of cigarette and marijuana use at T1 and T2 were used for ancillary analyses.

In ALSPAC, at T1, adolescents were asked whether they have smoked cigarettes or used marijuana in the past six months and responded to each question using a scale of 0 (*No*) and 1 (*Yes*). At T2, adolescents were asked whether they have smoked cigarettes in the past 30 days or used marijuana in the past 12 months and responded to each question using a scale

of 0 (*No*) and 1 (*Yes*). The sum scores of the two items of cigarette and marijuana use at T1 and T2 were used for ancillary analyses.

Other negative environments. In Project inSight, bullying victimization was assessed by a 9-item modified version of bullying victimization measure in School Crime Victimization Survey (U. S. Department of Justice Bureau of Justice Statistics, 2001) at T1. Adolescents responded to the questions using a scale of 0 (*No*) and 1 (*Yes*). In addition, in Project inSight, a 5-item abbreviated version of Neighborhood Stress Index (Ewart, & Suchday, 2002) was used at T1. Adolescents responded to the questions using a 4-point scale, from 0 (*never*), 1 (*once*), 2 (*a few times*), to 3 (*often*). The mean scores were used for current analyses. Bullying victimization and neighborhood stress were only included in Project inSight but not in ALSPAC.

Data Analytic Strategies

Descriptive analyses and attrition analyses were conducted using SPSS, Version 19.0 (IBM, 2010). Path analyses were conducted using Mplus, Version 5.21 (Muthén & Muthén, 1998–2009) for main analyses. Both path analysis and general linear modeling (e.g., multiple regression) test cause and effect relationships between variables. However, path analysis has advantages over general linear modeling in that it deals with non-normality of the dependent variables using Maximum Likelihood Estimation with Robust Standard Errors. A Full-information maximum likelihood (FIML) procedure was used to accommodate missing data. FIML has been shown to yield excellent estimates of a likelihood function of each individual based on the variables that are present, without imputing missing data (Graham, Cumsille, & Elek-Fisk, 2003).

Path diagrams of the estimated six path models to test interaction effects between the 5-HTTLPR genotype and family conflict on T1 alcohol outcomes (two alcohol outcome variables in Project inSight; four alcohol outcome variables in ALSPAC) are presented in

Figure 2. In each path model, two main effects and one interaction effect were included. Main effects of the 5-HTTLPR genotype variable and family conflict were included as manifest and exogenous variables. An interaction term was calculated by multiplying the 5-HTTLPR variable with the centered family conflict variable and was included as a manifest and exogenous variable. An alcohol outcome variable at T1 was included as a manifest and endogenous variable. When the path models showed a significant interaction effect, multi-group analysis was conducted as a post hoc test to estimate the simple effects of the family conflict on the alcohol outcome as a function of the 5-HTTLPR genotype. Effects of gender, age, race, and mother's education levels on the alcohol outcome were controlled for in Project inSight analyses; effects of gender, age, and mother's education levels on the alcohol outcome were controlled for in ALSPAC analyses.

Path diagrams of the estimated five path models to test interaction effects between the 5-HTTLPR genotype and family conflict on T2 alcohol outcomes (two alcohol outcome variables in Project inSight; three alcohol outcome variables in ALSPAC) are presented in Figure 4. These models were different from the models for T1 alcohol outcomes in that an alcohol outcome variable at T2 was included as a manifest and endogenous variable and a corresponding alcohol variable at T1 was included as a covariate as a manifest and exogenous variable. Thus, the outcome variable for these models represented changes in the alcohol outcome between T1 and T2 (i.e., T2 alcohol outcome after controlling for T1 alcohol outcome).

In addition, 11 path models were estimated to test interaction effects between the 5-HTTLPR genotype and parental monitoring on alcohol outcomes at T1 (shown in Figure 5) and alcohol outcomes at T2 after controlling for alcohol outcomes at T1 (shown in Figure 6) in the two samples.

Regarding criterion of successful replication, like most previous GxE studies that

attempted to replicate the result across two independent samples (Bradley et al., 2008 ; Polanczyk et al., 2009) , I used the p -value of .05 as a cut-off score. I also reported effect sizes (i.e., Cohen's d) of the gene and environment interaction effect of interest to complement significance testing which is heavily affected by sample sizes (Royall, 1986).

Results

Descriptive Statistics

Means (and standard deviations in parentheses) and zero-order Pearson correlations of Project inSight study variables are presented in Table 1 and those of ALSPAC study variables are presented in Table 2. In both samples, associations of the 5-HTTLPR genotype with the two family environment variables at T1 ($r = -.05$ to $.12$) were very small and not significant. The associations of the 5-HTTLPR genotype with alcohol use and misuse variables at T1 and T2 ($r = .03$ to $.07$) were also very small and not significant. Associations between the two family environment variables (i.e., family conflict and parental monitoring; $r = -.22$ to $-.08$) and association of the family environment variables with alcohol use and misuse variables ($r = -.30$ to $.17$) were small to moderate. Associations among alcohol use and misuse at two different time points were small to large ($r = .19$ to $.76$).

Interaction between Family Conflict and the 5-HTTLPR Genotype on T1 Alcohol

Outcomes

As shown in Figure 2, upper panels, results from Project inSight analyses showed no significant interaction effect between the 5-HTTLPR genotype and family conflict on alcohol use at T1 (standardized estimate $[\beta] = .44$, unstandardized estimate $[b] = 0.96$, $p = .16$) but a significant interaction effect on alcohol misuse at T1 ($\beta = .57$, $b = 0.79$, $p = .001$). As shown in Figure 2, middle and bottom panels, results from ALSPAC analyses also showed no significant interaction effect between the 5-HTTLPR genotype and family conflict on alcohol use at T1 ($\beta = .07$, $b = 0.31$, $p = .29$) but a significant interaction effect on the frequency of

three or more drinks at T1 ($\beta = .19, b = 0.78, p = .01$). However, there was no significant interaction on the frequency of binge drinking ($\beta = .08, b = 0.13, p = .43$), and the maximum number of drinks ($\beta = .09, b = 0.41, p = .19$).

Results from multi-group analyses of Project inSight as a function of the 5-HTTLPR genotype showed that, as adolescents were exposed to higher levels of family conflict, those carrying the 5-HTTLPR low activity-allele were more likely to be involved in alcohol misuse at T1 ($\beta = .26, b = 0.45, p = .001$). However, the opposite pattern of results was found among non-carriers; that is, as they were exposed to higher levels of family conflict, non-carriers were less likely to be involved in alcohol misuse at T1 ($\beta = -.31, b = -0.40, p = .02$). A similar pattern of results was shown in the left panel of Figure 3 which shows means of alcohol misuse as a function of the 5-HTTLPR genotype and family conflict. Results from multi-group analyses of ALSPAC showed the similar pattern with Project inSight which is in line with results in the right panel of Figure 3. That is, as adolescents were exposed to higher levels of family conflict, carriers were more likely to be involved in having three or more drinks at T1 ($\beta = .10, b = 0.43, p = .004$). However, among non-carriers, there was no significant association between family conflict and the frequency of having three or more drinks at T1 ($\beta = -.07, b = -0.37, p = .14$).

Interaction between Family Conflict and the 5-HTTLPR Genotype on Change in Alcohol Outcomes over Time

As shown in Figure 4, upper panels, results from Project inSight analyses showed no significant interaction effect between the 5-HTTLPR genotype and family conflict on a change in alcohol use between T1 and T2 ($\beta = .28, b = 0.77, p = .49$). However, it showed a significant interaction effect on a change in alcohol misuse over time ($\beta = .49, b = 0.82, p = .04$). As shown in Figure 4, bottom panels, results from ALSPAC analyses showed no significant interaction effects between the 5-HTTLPR genotype and family conflict on

changes in alcohol use ($\beta = .02$, $b = 0.14$, $p = .70$) and in all the three alcohol misuse variables (binge drinking, $\beta = .02$, $b = 0.15$, $p = .72$; maximum number of drinks, $\beta = .08$, $b = 0.14$, $p = .19$; three or more drinks was not measured at T2) over time.

Results from multi-group analyses of Project inSight as a function of the 5-HTTLPR genotype showed that, as adolescents were exposed to higher levels of family conflict, those carrying the 5-HTTLPR low-activity allele were more likely to increase alcohol misuse over time ($\beta = .13$, $b = 0.24$, $p = .07$). However, alcohol misuse among non-carriers did not significantly change over time as a function of family conflict ($\beta = -.13$, $b = -0.37$, $p = .19$).

Interaction Effects between Parental Monitoring and the 5-HTTLPR Genotype on T1 Alcohol Outcomes

As shown in Figure 5, upper panels, results from the Project inSight analyses showed no significant interaction effect between the 5-HTTLPR genotype and parental monitoring on alcohol use at T1 ($\beta = -.30$, $b = -0.17$, $p = .15$). However, there was a significant interaction effect on alcohol misuse at T1 ($\beta = -.67$, $b = -0.25$, $p < .001$). As shown in Figure 5, middle and bottom panels, results from ALSPAC analyses showed no significant interaction effect between the 5-HTTLPR genotype and parental monitoring on alcohol use at T1 ($\beta = .05$, $b = 0.06$, $p = .52$) and all the three alcohol misuse variables at T1 (three or more drinks, $\beta = .04$, $b = 0.04$, $p = .65$; binge drinking, $\beta = .03$, $b = 0.01$, $p = .71$; maximum number of drinks, $\beta = .01$, $b = 0.01$, $p = .89$).

Results from multi-group analyses of Project inSight as a function of the 5-HTTLPR genotype showed that, as adolescents were exposed to higher levels of parental monitoring, those carrying the 5-HTTLPR low-activity allele were less likely to be involved in alcohol misuse at T1 ($\beta = -.41$, $b = -0.24$, $p < .001$). However, concurrent alcohol misuse among non-carriers did not differ significantly as a function of parental monitoring ($\beta = .01$, $b = 0.01$, $p = .90$).

Interaction between Parental Monitoring and the 5-HTTLPR Genotype on Changes in Alcohol Outcomes over Time

As shown in Figure 6, upper panels, results from the Project inSight analyses showed no significant interaction effect between the 5-HTTLPR genotype and parental monitoring on changes in alcohol use ($\beta = .25$, $b = 0.18$, $p = .30$) and in alcohol misuse ($\beta = -.19$, $b = -0.08$, $p = .32$) between T 1 and T2. As shown in Figure 6, bottom panels, results from ALSPAC analyses showed no significant interaction effects between the 5-HTTLPR genotype and parental monitoring on changes in alcohol use ($\beta = .11$, $b = -0.47$, $p = .10$) and maximum number of drinks ($\beta = .03$, $b = 0.12$, $p = .71$) over time. However, there was a significant interaction effect on the change in the frequency of binge drinking over time ($\beta = .13$, $b = -0.66$, $p = .03$)

Results from multi-group analyses of ALSPAC as a function of the 5-HTTLPR genotype showed that, as adolescents were exposed to higher levels of parental monitoring, non-carriers were much less likely to increase the frequency of binge drinking over time ($\beta = -.26$, $b = -0.67$, $p < .001$), compared to those carrying the 5-HTTLPR low-activity allele ($\beta = -.18$, $b = -0.41$, $p < .001$).

Effect Sizes of Gene and Environment Interactions

Interaction effect sizes of the 5-HTTLPR genotype with family environments (i.e., family conflict or parental monitoring) were calculated by comparing effect sizes of family environments on alcohol outcomes between the 5-HTTLPR low-activity allele carriers and non-carriers, using Cohen's d (Cohen, 1988, pp. 18–22, 175–179). Specifically, alcohol mean differences between the two genotype groups were calculated separately among individuals in upper 50% of family conflict (or parental monitoring) and among those in the lower 50%. Then, the effect sizes of family environments between the 5-HTTLPR genotypes in the lower 50% were subtracted from the effect sizes in the upper 50% to obtain interaction effect sizes

between the 5-HTTLPR genotype and family environments.

Regarding family conflict, as shown in Table 3, results from Project inSight showed that the 5-HTTLPR genotype and family conflict interaction had small to medium effects on alcohol use at T1 and T2 ($ds = 0.41 - 0.53$) and medium to large effects on alcohol misuse at T1 and T2 ($ds = 0.52 - 1.18$). Results from ALSPAC showed that the 5-HTTLPR genotype and family conflict interaction had trivial effects on all alcohol outcomes ($ds = 0.00 - 0.19$), but among them, the interaction had the biggest effect on the frequency of three or more drinks at T1 ($d = 0.19$).

Regarding parental monitoring, as shown in Table 4, results from Project inSight showed that the 5-HTTLPR genotype and parental monitoring interaction had trivial to medium effects on alcohol use ($ds = 0.10 - 0.55$) and medium to large effects on alcohol misuse ($ds = 0.76 - 1.08$). Results from ALSPAC showed that the 5-HTTLPR and parental monitoring interaction had small effects on the frequency of binge drinking at T2 ($d = 0.26$), but had trivial effects on all other alcohol outcomes ($ds = 0.00 - 0.19$).

Ancillary Analyses

The first set of ancillary analyses was conducted to examine whether missing data affected the results. All analyses were conducted again with complete data obtained from participants who did not have any missing data on any of the study variables ($n = 105 - 154$ [60 – 88% of the final sample] for Project inSight; $n = 1,037 - 1,855$ [21– 38% of the final sample] for ALSPAC). The ancillary analyses of participants with complete data showed a patterns of results similar to that of participants with missing data presented earlier, including significant interaction effects between the 5-HTTLPR and family conflict on alcohol misuse at T1 both in Project inSight ($\beta = .31, b = 0.42, p = .01$) and in ALSPAC ($\beta = .17, b = 0.71, p = .01$).

The second set of ancillary analyses was conducted to examine whether using a

different 5-HTTLPR genotype categorization affected the results. A three-level categorization (carriers of two low-activity alleles, vs. carriers of one low-activity allele, vs. non-carriers) was used, instead of the two-level categorization (carriers of one or two low-activity allele vs. non-carriers). Regarding family conflict, results from the ancillary analyses using the three-level categorization were comparable to the results obtained when using the two-level categorization as presented earlier, including a significant interaction effect between the 5-HTTLPR genotype and family conflict on alcohol misuse both in Project inSight ($\beta = .40, b = 0.38, p = .04$) and in ALSPAC ($\beta = .22, b = 0.59, p = .003$). However, the ancillary analyses did not show a significant interaction between the 5-HTTLPR genotype and parental monitoring on change in binge drinking over time ($\beta = .09, b = 0.10, p = .14$) in ASLPAC, which was significant in the analyses using the two-level genotype categorization.

The third set of ancillary analyses was conducted to examine whether the 5-HTTLPR genotype and family environment interactions had significant effects on substance use (i.e., cigarette and marijuana use). Results showed inconsistent findings in the two samples. Regarding family conflict, results from Project inSight showed a significant interaction effect between the 5-HTTLPR genotype and family conflict on substance use at T1 ($\beta = .66, b = 0.76, p = .01$) but did not show a significant interaction effect on change in substance use over time ($\beta = .20, b = 0.34, p = .23$). However, results from ALSPAC did not show a significant interaction effect between the 5-HTTLPR genotype and family conflict on substance use at T1 ($\beta = -.01, b = -0.004, p = .93$) but showed a significant interaction effect on a change in substance use over time ($\beta = -.14, b = -0.29, p = .02$). Regarding parental monitoring, results from Project inSight showed a significant interaction effect between the 5-HTTLPR genotype and parental monitoring on substance use at T1 ($\beta = -.54, b = -0.16, p = .03$) but did not show a significant interaction effect on a change in substance use over time ($\beta = -.24, b = -0.07, p = .40$). However, in ALSPAC, there was no significant interaction

effect between the 5-HTTLPR genotype and parental monitoring on substance use at T1 ($\beta = .06$, $b = 0.01$, $p = .39$) and change in substance use over time ($\beta = .10$, $b = 0.06$, $p = .13$).

The fourth set of ancillary analyses was conducted to examine whether the 5-HTTLPR genotype interacts with other negative environment (e.g., bullying victimization and neighborhood stress) and influences adolescent drinking. Before examining interaction effects, correlation analysis among family conflict, bullying victimization, and neighborhood stress was conducted, and the results showed that the association was small and not significant ($r = .24-.29$). Results from Project inSight showed no interaction effects between the 5-HTTLPR and bullying victimization/neighborhood stress on any alcohol outcomes at any time ($\beta = -.26 -.11$, $b = -.03 -.03$, $p = .40 -.98$). Because ASLPAC does not have the environment variables, it could not be tested in the sample from ALSPAC.

Discussion

Family environments have been shown to affect adolescents' alcohol use behaviors. However, because family environments show more impact on some individuals compared to others, finding factors that exacerbate family environmental effects has been an important topic for understanding individual differences in susceptibility to family environmental effects on alcohol use behaviors. This study examined whether the impact of two family environmental variables (i.e., family conflict and parental monitoring) on adolescent alcohol use and misuse differed as a function of the 5-HTTLPR genotype. Results showed that impact of family conflict on concurrent alcohol misuse was larger among adolescents carrying the 5-HTTLPR low-activity allele than among non-carriers, which was replicated in two independent samples. This replication is noteworthy given that most efforts to replicate gene and environment findings have not been successful. In addition, the same patterns of results was found in analyses using a different 5-HTTLPR genotype categorization and analyses using complete data obtained from participants who did not have any missing data.

However, with respect to alcohol use, the effects of family conflict were not moderated by the 5-HTTLPR genotype in both samples. For interaction effects between the 5-HTTLPR genotype and parental monitoring on alcohol use and misuse, I did not find consistent support across the two samples. Overall, our results suggest that the impact of family conflict (but not parental monitoring) on adolescent alcohol misuse differs as a function of the 5-HTTLPR genotype.

Our finding of a significant interaction between the 5-HTTLPR genotype and family conflict may in part explain the mixed findings regarding the association of family conflict with adolescent drinking (Bray et al., 2001; Brody & Ge, 2001; Mason et al., 2007; Sieving, Maruyama, Williams, & Perry, 2000). Our results address bio-social etiology of adolescent drinking by showing that there is a subgroup of adolescents who are genetically more susceptible to family conflict, and more likely to engage in alcohol misuse in response to family conflict compared to others. Our finding indicated that, when exposed to higher levels of family conflict, carriers of the low-activity allele were more likely to misuse alcohol than non-carriers. This finding is in line with previous studies showing greater susceptibility of carriers of the 5-HTTLPR risky genotype to stressors, compared to non-carriers. Previous studies (Covault et al., 2007; Kranzler et al., 2012) found that, when college students experienced stressful life events, those carrying the 5-HTTLPR risky genotype were more likely to engage in alcohol use and misuse than non-carriers. Another study (Nilsson et al., 2005) found a similar result among mid- and late-adolescents (mean ages = 16 and 19): When the adolescents perceived that they did not have good family relationships, those carrying the 5-HTTLPR risky genotype consumed more alcohol and showed higher frequencies of alcohol intoxication than non-carriers. This study extends the existing literature by showing the interaction effects between the 5-HTTLPR genotype and a negative environment in early and mid- adolescence (mean ages = 12 and 15). This study is the first to find an interaction effect

of a specific family environment aspect, family conflict, with the 5-HTTLPR genotype. In our study, the interaction effects were only limited to family conflict but not to other negative environments such as bullying victimization and neighborhood stress.

I found a significant interaction effect between the 5-HTTLPR genotype and family conflict on alcohol misuse but not on alcohol use in both samples. Effect size analyses also showed a similar pattern of results: The interaction between the 5-HTTLPR genotype and family conflict had bigger effect sizes on alcohol misuse than alcohol use in both samples. This finding accords with previous studies in showing that drinking to cope with stress increases risk of alcohol misuse and alcohol related problems rather than risk of alcohol use (Read, Wood, Kahler, Maddock, & Palfai, 2003). Thus, it indicates that coping motives or tension reduction expectancies may be potential psychological mechanisms underlying the gene and environment interaction effects. Although social motivations for drinking became predominant in the late teens and early twenties, coping with the stress of parental conflict was found to be a main motivation for drinking in the early and middle teens (Aseltine & Gore, 2000). Also, the expectancies that alcohol will reduce tension has been shown to be associated with high risk-drinking among adolescents (Mann, Chassin, & Sher, 1987). However, in ALSPAC, the interaction between the 5-HTTLPR genotype and family conflict did not consistently show significant effects across all alcohol misuse measures. Considering that the ALSPAC samples were on average 12 years old and most of them had not engaged in extreme levels of alcohol misuse, measures of binge drinking and maximum number of drinks may not have been able to capture individual differences in alcohol misuse. In contrast, a measure of intoxication and a measure of consuming three or more drinks may have more sensitivity to assess the risk for alcohol misuse among young adolescents. In fact, a measure of consuming three or more drinks has been used in a number of previous studies to assess adolescent drinking (Barnett et al., 2002; Migneault, Pallonen, & Velicer, 1997).

Along with the potential psychological mechanisms, biological mechanisms involved in differential stress response as a function of the 5-HTTLPR genotype may in part explain the differences in sensitivity to the effects of family conflict on alcohol misuse. Individuals with the 5-HTTLPR risky genotype showed increased amygdala reactivity, which was associated with heightened anxiety and fear in response to stressful environmental stimuli (Hariri et al., 2002, 2005). It was also found that the 5-HTTLPR risky genotype carriers showed decreased volume of gray matter in the prefrontal cortex as well as in the amygdala, which was associated with dysfunctional emotion regulation (Pezawas et al., 2005). Thus, the susceptibility to adverse family environments of the 5-HTTLPR low activity carriers may be due to their heightened stress responses.

Belsky and his colleagues (2007) suggested the idea of a plasticity gene, indicating that individuals with certain genotypes are more vulnerable to adverse environments but also benefit more from positive environments than those without the genotypes. Our results provide mixed support regarding whether or not the 5-HTTLPR acts as a plasticity gene. That is, in ALSPAC, when exposed to lower levels of family conflict, the low-activity allele carriers were less likely to misuse alcohol than non-carriers. However, in Project inSight, there was no significant difference in alcohol misuse among carriers and non-carriers when they were exposed to lower levels of family conflict. Thus, our results suggest that adolescents with the 5-HTTLPR low-activity allele represent a subgroup that is more vulnerable to the negative effects of an adverse family environment.

Regarding the interaction between parental monitoring and the 5-HTTLPR genotype, I found inconsistent results in the two samples. Cross-sectional analyses in Project inSight showed that the 5-HTTLPR low-activity carriers who received high levels of parental monitoring were less likely to misuse alcohol than non-carriers. This result is in line with our hypothesis and previous studies that found a significant interaction effect between the 5-

HTTLPR genotype and good parenting on risky behavior initiation (Brody et al., 2009b). However, the opposite result was found in the longitudinal analysis in ALSPAC. That is, the 5-HTTLPR low-activity allele carriers who received high levels of parental monitoring were more likely to increase the frequency of binge drinking over time than non-carriers. Greater parental monitoring has been found to be associated with decreased levels of alcohol use in some studies (Barnes, Hoffman, Welte, Farrell, & Dintcheff, 2006; Curran & Chassin, 1996), but other studies also found that extremely strict parental control was linked to high levels of antisocial behaviors (e.g., Farrington, 1989). Thus, the effect of parental monitoring on alcohol use and misuse may be curvilinear, such that lowest and highest levels are associated with greater risk for alcohol use and misuse whereas middle levels are associated with lower risk. Alternatively, the effect of parental monitoring may differ as a function of specific types of monitoring. For example, parental solicitation, parental control, and child disclosure have been found to have different importance for children's delinquency (Stattin & Kerr, 2000). Future studies may consider more specific levels and types of parental monitoring that may interact with the 5-HTTLPR genotypes differently.

Our findings have clinical implications for prevention and intervention efforts to curtail alcohol misuse among adolescents and to prevent upward trajectories of alcohol misuse over time. The findings suggest that the 5-HTTLPR low-activity allele carriers are the "high-risk" group that is more susceptible to family conflict environments. A previous study demonstrated that a family prevention program targeting overall parenting competence and control was more effective for carriers of the 5-HTTLPR risky genotype to delay risk behavior initiation than non-carriers (Brody et al., 2009b). Our study suggests that intervention/prevention programs specifically designed to reduce family conflict and develop strategies to cope with family conflict without resorting to alcohol misuse may be helpful for adolescents with the 5-HTTLPR low-activity allele. This selective prevention/intervention

approach addressing family conflict for adolescents with the risky genotype may be more efficient and effective than a universal approach targeting all adolescents regardless of genetic and environmental risks.

Several limitations and future directions of the current study are worthy of mention. First, participants in Project inSight were recruited in the U.S. and those in ALSPAC were recruited in the U.K. Given that youth drinking and intoxication rates in the U.K. are considerably higher than those in the U.S. (Friese & Grube, 2005) and potential differences in correlates of alcohol use behaviors in the two countries (Kuntsche et al., 2004), the present failure to replicate some of the analyses may be due to the differences between the two countries. However, community characteristics associated with risky drinking (e.g., unemployment, marriage status, income, and education; Cooper, Russell, & Frone, 1990 ; Horwitz & White, 1991; Sampson & Laub, 1990) between Syracuse in the U.S. and Bristol in the U.K. were similar. Second, family conflict and parental monitoring were measured at age 12 in Project inSight but at age 15 in ALSPAC. Although family interactions in adolescence have been shown to remain consistent across ages compared to other social environments such as peer interactions at school (Loeber et al., 2000), it is unclear whether the time difference in the measurements of family environments confounded present replication results. Third, measures of alcohol misuse were not the same in the two datasets. That is, a frequency of intoxication was used in the Project inSight, whereas frequencies of three or more drinks and binge drinking, and maximum number of alcohol drinks consumed were used in ALSPAC. Thus, it remains unclear how different measures of alcohol misuse affected present replication results. Thus, future replication attempts with independent samples with a similar cultural background and the use of the same alcohol and family environmental measurements would help to corroborate the current analyses. Fourth, we could not test adolescents' drinking with and without parent's permission separately. While some studies

reported that drinking with parent's permission tends to encourage responsible drinking and to reduce negative drinking consequences (Reboussin, Song, & Wolfson, 2012), to our knowledge, no study has specifically examined how gene and environment interactions differently affect supervised and unsupervised alcohol use. Fifth, present ancillary results regarding the interaction effects between the 5-HTTLPR genotype and family environments on cigarette and marijuana use were inconsistent in the two samples. However, the results should be interpreted in the context of limited measures regarding substance use in our data. Thus, future studies will be needed to examine whether the interaction effects reported here are limited to alcohol use or generalized to overarching substance use with various substance use measures. Sixth, the multi-group analysis result from Project inSight indicated that non-carriers were less likely to misuse alcohol when they were exposed to higher levels of family conflict than the lower levels. However, because this finding was not consistent in a larger sample from ALSPAC, the results from Project inSight need to be interpreted in the context of a limitation of the small sample size. Seventh, we could not test potential gender differences because each gender group in Project inSight had a small size and thus afforded low statistical power which might increase Type II error rates (Streiner, 1990). Given some evidence for a gender difference in the effect of parental monitoring on alcohol outcomes (Barnes, Reifman, Farrell, & Dintcheff, 2000) and in the effect of the 5-HTTLPR genotype and negative life experiences interaction on drinking (Kranzler et al., 2012), investigating gender differences, specifically in the interactions of the 5-HTTLPR genotype with family environments, is an important question for future studies. Finally, many studies reported that the 5-HTTLPR interacts with negative life events and influences negative affect. In order to understand underlying mechanism, it is important to examine the mediating role of negative affect between the 5-HTTLPR x family conflict and adolescent drinking.

In sum, this study provides evidence that the 5-HTTLPR low-activity allele is

associated with heightened sensitivity to family conflict and, thereby, with increased levels of concurrent alcohol misuse in mid-adolescence. The present findings contribute to the understanding of complex and multi-faceted etiologies of alcohol misuse among early and middle teenagers. This study also represents a promising step forward in addressing concerns regarding a lack of replication of gene and environment interaction findings (Hewitt, 2012), and also yielded consistent results across two independent samples.

Table 1
Means (and Standard Deviations) of Study Variables and Their Pearson Correlations: Data obtained from Project inSight

	<i>M (SD) or %</i>	1	2	3	4	5	6	7	8	9	10
1. Male sex	44%	—									
2. White ancestry proportion (0–100)	41%	-.06	—								
3. Age at T1 (13–17)	15.05 (0.69)	.17*	-.13	—							
4. Mother's education (1–4)	2.39 (1.16)	.01	.12	-.10	—						
5. 5-HTTLPR low-activity allele carriers ^a	75 %	-.11	.12	-.11	.12	—					
6. Family conflict at T1	0.47 (0.25)	-.20**	-.08	.13	-.23**	-.05	—				
7. Parental monitoring at T1	2.12 (0.78)	-.17*	.10	-.08	.02	.12	-.22**	—			
8. Alcohol use frequency at T1	0.29 (0.67)	-.11	.004	.002	-.09	.01	.10	-.20**	—		
9. Frequency of intoxication at T1	0.14 (0.43)	-.07	-.02	.10	.002	.07	.17*	-.30***	.67***	—	
10. Alcohol use frequency at T2	0.45 (0.81)	-.06	-.19*	.07	.05	.02	.06	-.13	.24**	.37***	—
11. Frequency of intoxication at T2	0.19 (0.50)	-.15	-.11	.07	.00	-.03	.09	-.19*	.43***	.61***	.64***

Note. 5-HTTLPR = 5-Hydroxy Tryptamine Transporter-linked polymorphic region.

^a5-HTTLPR low activity allele carriers = carriers of two low-activity alleles and carriers of one low-activity allele

* $p < .05$. ** $p < .01$. *** $p < .001$.

Table 2

Means (and Standard Deviations) of Study Variables and Their Pearson Correlations: Data obtained from ALSPAC

	<i>M (SD) or %</i>	1	2	3	4	5	6	7	8	9	10	11	12
1. Male sex	53%	—											
2. Mother's education (1–4)	2.25 (1.21)	-.01	—										
3. Age at T1 (11–14)	12.80 (0.22)	.03*	-.01	—									
4. 5-HTTLPR low-activity allele carriers ^a	74%	.01	.02	-.02	—								
5. Family conflict at T1	0.47 (0.27)	.04*	-.05**	.04*	.01	—							
6. Parental monitoring at T1	2.00 (0.82)	-.12***	.04*	-.06**	.006	-.08***	—						
7. Alcohol use frequency at T1	0.86 (1.33)	-.03	-.02	.11***	.01	.002	-.22***	—					
8. Binge drinking at T1	0.11 (0.50)	-.03	-.02	.10***	-.02	.05*	-.15***	.44***	—				
9. Maximum drinks at T1	1.38 (2.03)	-.001	-.04	.10***	.01	.04	-.24***	.68***	.41***	—			
10. Three or more drinks at T1	0.36 (1.25)	-.01	-.04	.09***	-.02	.05	-.15***	.52***	.75***	.61***	—		
11. Alcohol use frequency at T2	2.61 (1.94)	.02	.002	.04*	-.02	.02	-.21***	.33***	.19***	.33***	.21***	—	
12. Binge drinking at T2	1.64 (1.97)	-.12	-.03	.04	-.03	.03	-.21***	.32***	.23***	.32***	.27***	.76***	—
13. Maximum drinks at T2	5.72 (5.00)	.01	-.01	.03	-.02	.03	-.21***	.29***	.19***	.31***	.23***	.72***	.72***

Note. 5-HTTLPR = 5-Hydroxy Tryptamine Transporter-linked polymorphic region.

^a5-HTTLPR low activity allele carriers = carriers of two low-activity alleles and carriers of one low-activity allele

* $p < .05$. ** $p < .01$. *** $p < .001$.

Table 3

Per-Cell Sample Sizes, Cell Means and Standard Deviations, and Effect Sizes of the interaction between the 5-HTTLPR and family conflict

Sample	Alcohol outcome	Family conflict	5-HTTLPR low-activity carriers		Non-carriers of the low-activity allele		Cohen's <i>d</i>	
			<i>n</i>	<i>M (SD)</i>	<i>n</i>	<i>M (SD)</i>	Effect of family conflict	Family conflict X 5-HTTLPR
Project inSight	Alcohol use at T1	Upper 50%	61	0.34 (0.63)	21	0.19 (0.40)	0.26	0.41
		Lower 50%	70	0.24 (0.69)	23	0.35 (0.89)	-0.15	
	Alcohol misuse at T1	Upper 50%	61	0.25 (0.57)	21	0.05 (0.22)	0.40	0.52
		Lower 50%	70	0.09 (0.33)	23	0.13 (0.34)	-0.12	
	Alcohol use T2	Upper 50%	47	0.53 (0.78)	14	0.29 (0.61)	0.32	0.53
		Lower 50%	47	0.38 (0.82)	14	0.57 (1.09)	-0.21	
	Alcohol misuse T2	Upper 50%	47	0.26 (0.53)	14	0.00 (0.00)	0.56	1.18
		Lower 50%	47	0.11 (0.38)	14	0.43 (0.85)	0.62	
ALSPAC	Alcohol use at T1	Upper 50%	463	0.83 (1.30)	148	0.90 (1.27)	-0.06	0.07
		Lower 50%	850	0.82 (1.32)	296	0.82 (1.32)	0.01	
	Binge drinking at T1	Upper 50%	498	0.12 (0.47)	156	0.12 (0.65)	-0.01	0.16
		Lower 50%	893	0.07 (0.36)	313	0.14 (0.61)	-0.15	
	Maximum number of drinks at T1	Upper 50%	474	1.09 (1.43)	147	1.09 (1.33)	0.00	0.00
		Lower 50%	868	0.95 (1.33)	297	0.96 (1.31)	0.00	
	Three or more drinks at T1	Upper 50%	503	0.15 (0.36)	158	0.15 (0.35)	0.02	0.19
		Lower 50%	898	0.10 (0.30)	319	0.16 (0.36)	-0.17	
	Alcohol use at T2	Upper 50%	643	2.64 (1.95)	211	2.63 (1.99)	0.01	0.09
		Lower 50%	1298	2.50 (1.93)	438	2.65 (1.92)	-0.08	
	Binge drinking at T2	Upper 50%	640	1.69 (1.94)	209	1.80 (2.09)	-0.06	0.12
		Lower 50%	1293	1.53 (1.92)	431	1.64 (1.97)	-0.06	
Maximum number of drinks at T2	Upper 50%	602	6.00 (5.10)	193	5.92 (5.13)	0.02	0.10	
	Lower 50%	1217	5.40 (4.84)	405	5.78 (5.03)	-0.08		

Table 4
Per-Cell Sample sizes, Cell Means and Standard Deviations, and Effect Sizes of the interaction between the 5-HTTLPR and parental monitoring

Sample	Alcohol outcome	Parental monitoring	5-HTTLPR low-activity carriers		Non-carriers of the low activity allele		Cohen's <i>d</i>	
			<i>n</i>	<i>M (SD)</i>	<i>n</i>	<i>M (SD)</i>	Effect of family conflict	Parental monitoring X 5-HTTLPR
Project inSight	Alcohol use at T1	Upper 50%	53	0.15 (0.60)	12	0.08 (0.29)	0.13	0.10
		Lower 50%	62	0.42 (0.74)	25	0.40 (0.87)	0.03	
	Alcohol misuse at T1	Upper 50%	53	0.02 (0.14)	12	0.08 (0.29)	-0.34	0.76
		Lower 50%	62	0.31 (0.62)	25	0.08 (0.28)	0.42	
	Alcohol use T2	Upper 50%	42	0.36 (0.76)	9	0.11 (0.33)	0.35	0.55
		Lower 50%	39	0.54 (0.85)	13	0.38 (0.65)	0.20	
	Alcohol misuse T2	Upper 50%	42	0.05 (0.22)	9	0.22 (0.67)	0.50	1.08
		Lower 50%	39	0.31 (0.61)	13	0.00 (0.00)	0.58	
ALSPAC	Alcohol use at T1	Upper 50%	529	0.68 (1.11)	164	0.67 (1.07)	0.01	0.06
		Lower 50%	692	1.24 (1.51)	268	1.14 (1.46)	0.07	
	Binge drinking at T1	Upper 50%	523	0.05 (0.25)	162	0.05 (0.29)	0.00	0.01
		Lower 50%	685	0.19 (0.63)	266	0.20 (0.77)	-0.01	
	Maximum number of drinks at T1	Upper 50%	514	0.82 (1.26)	158	0.81 (1.21)	0.01	0.11
		Lower 50%	634	1.46 (1.57)	239	1.28 (1.46)	0.12	
	Three or more drinks at T1	Upper 50%	503	0.25 (1.08)	152	0.27 (1.28)	-0.02	0.01
		Lower 50%	615	0.60 (1.54)	239	0.62 (1.58)	-0.01	
	Alcohol use at T2	Upper 50%	875	2.24 (1.83)	300	2.18 (1.81)	0.03	0.19
		Lower 50%	814	2.86 (2.01)	295	3.18 (1.97)	-0.16	
	Binge drinking at T2	Upper 50%	877	1.25 (1.76)	299	1.14 (1.71)	0.06	0.26
		Lower 50%	806	1.87 (2.09)	290	2.29 (2.10)	-0.20	
	Maximum number of drinks at T2	Upper 50%	842	4.69 (4.60)	289	4.76 (4.81)	-0.02	0.12
		Lower 50%	741	6.37 (5.18)	263	7.07 (5.05)	-0.14	

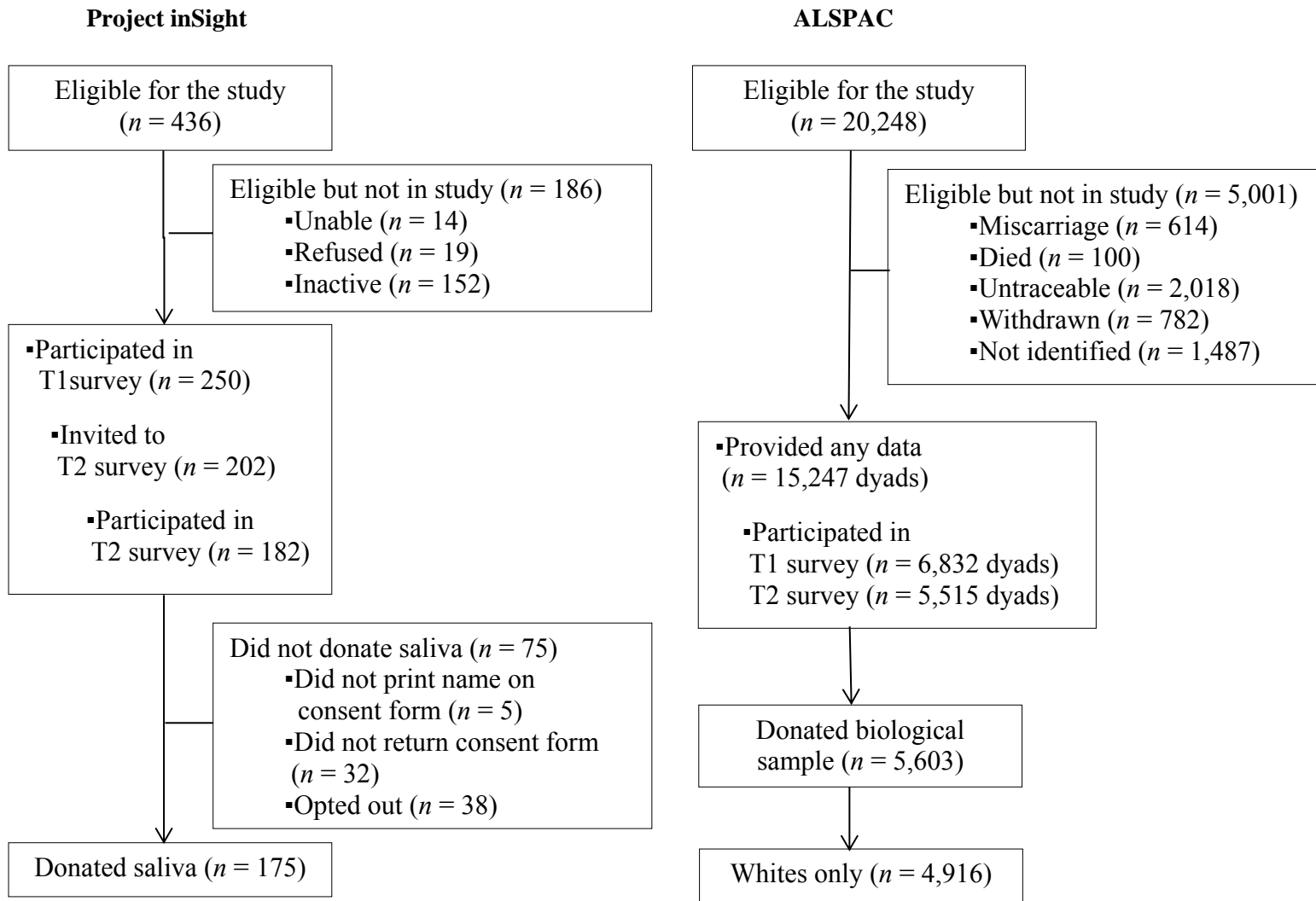


Figure 1. Participant flow charts of Project inSight and ALSPAC

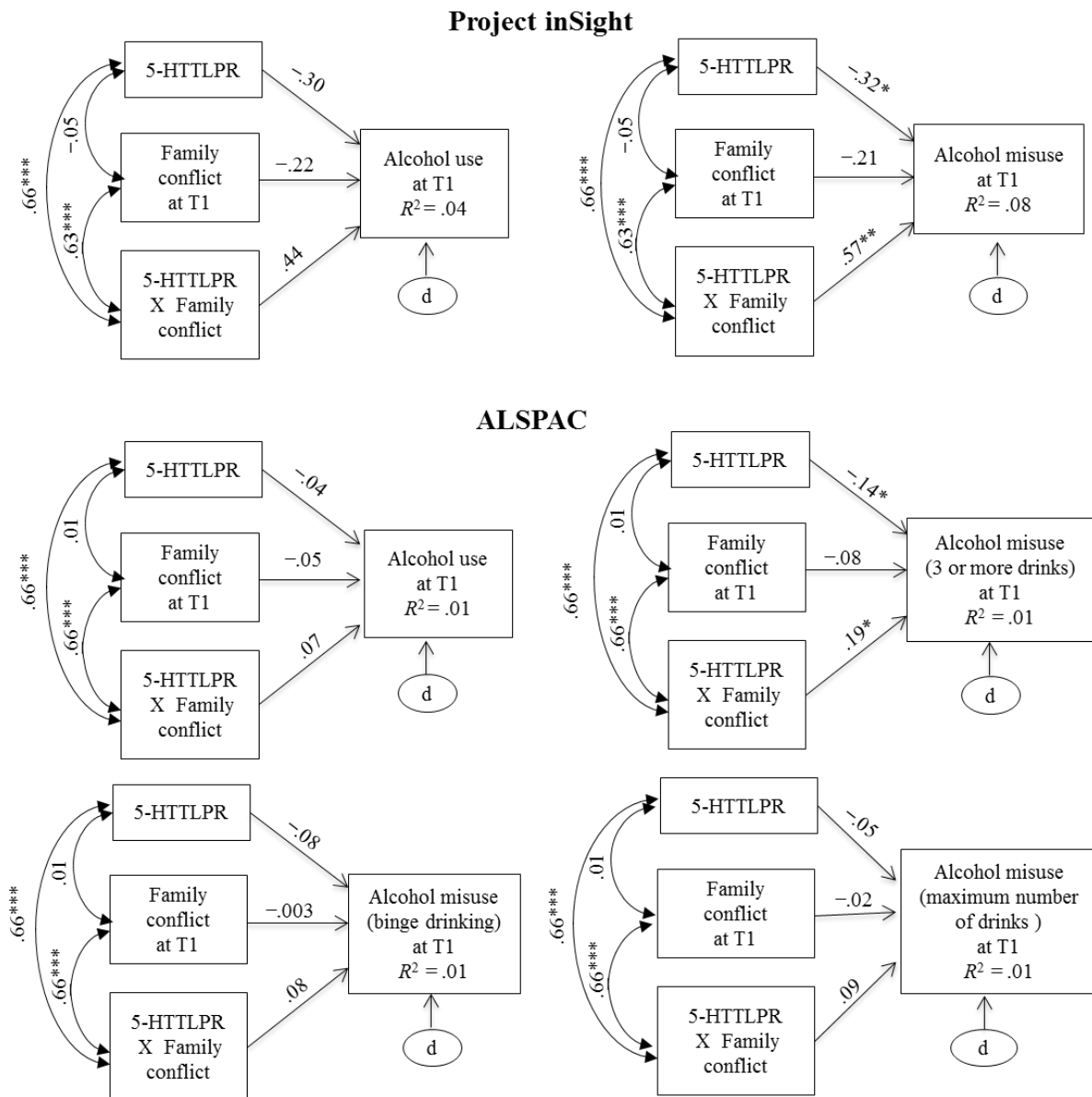


Figure 2. Path analyses testing the interaction effects between the 5-HTTLPR genotype and family conflict on alcohol use/misuse at T1. The upper left and right panels show the results from Project inSight and the rest of panels show the results from ALSPAC. Standardized estimates are shown; the effects of gender, age, and mother's education on all variables in the models were controlled for in all analyses (paths are not shown; in analyses of Project inSight, race was also controlled for). d = disturbance (residual variance).

* $p < .05$. ** $p < .01$. *** $p < .001$.

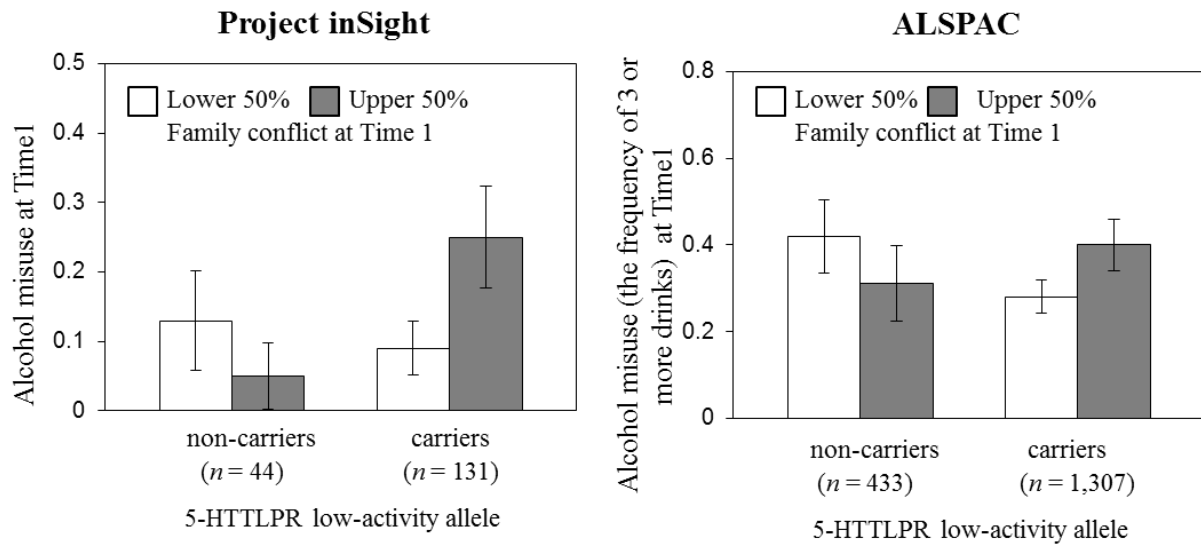


Figure 3. Means of alcohol misuse as a function of the 5-HTTLPR genotype (the low-activity allele carriers vs. non-carriers) and family conflict at T1 (the upper 50% vs. lower 50% of family conflict). The left figure is the result from the Project inSight and the right figure is the results from ALSPAC. Vertical bars represent the standard error below and above the mean scores.

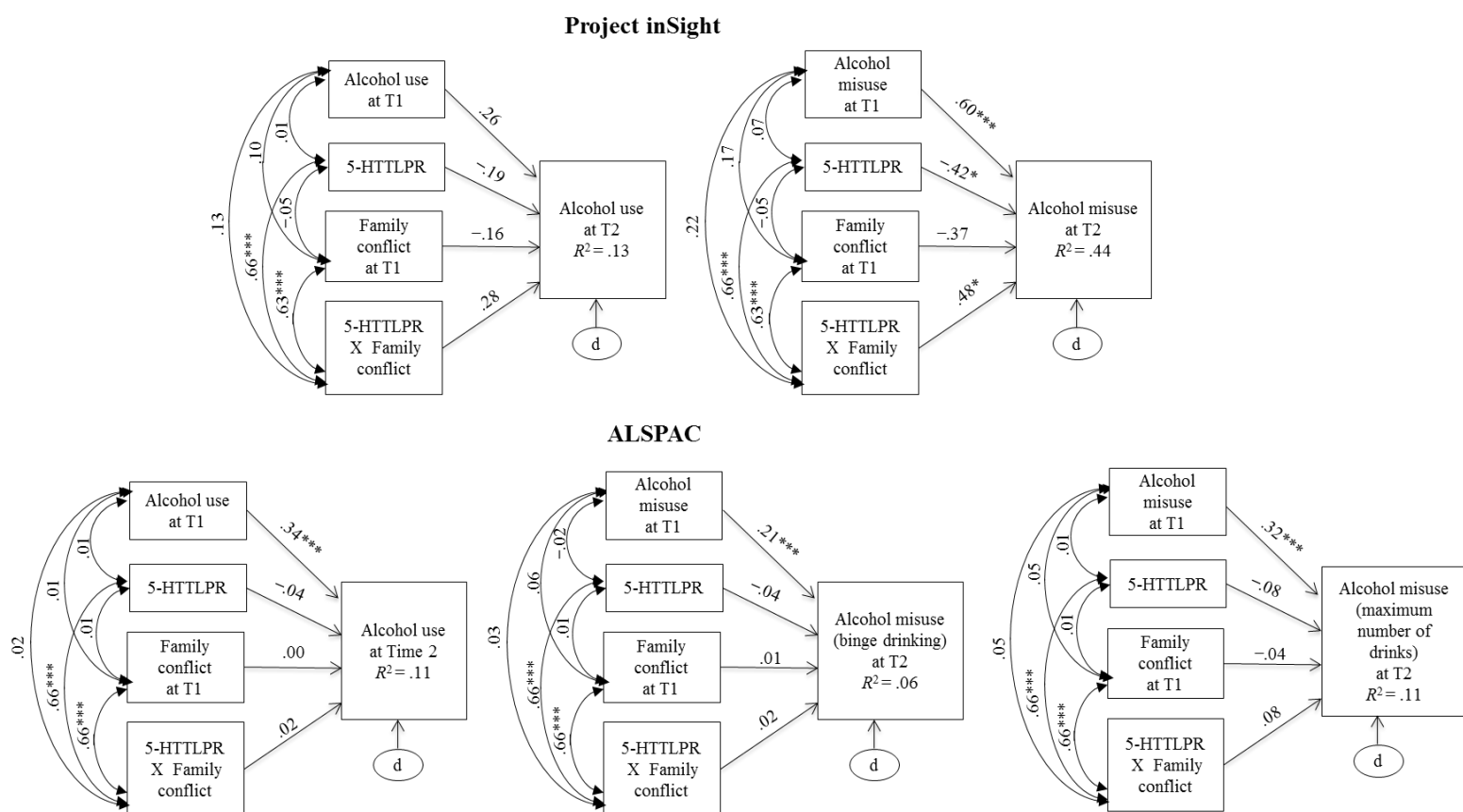


Figure 4. Path analyses testing the interaction effects between the 5-HTTLPR genotype and family conflict on changes in alcohol outcomes between T1 and T2 (i.e., T2 alcohol outcome after controlling for T1 alcohol outcome). The upper left and right panels show the results from Project inSight and the bottom three panels show the results from ALSPAC. Standardized estimates are shown; the effects of gender, age, and mother's education on all variables in the models were controlled for in all analyses (paths are not shown; in analyses of Project inSight, race was also controlled for). d = disturbance (residual variance).

* $p < .05$. *** $p < .001$.

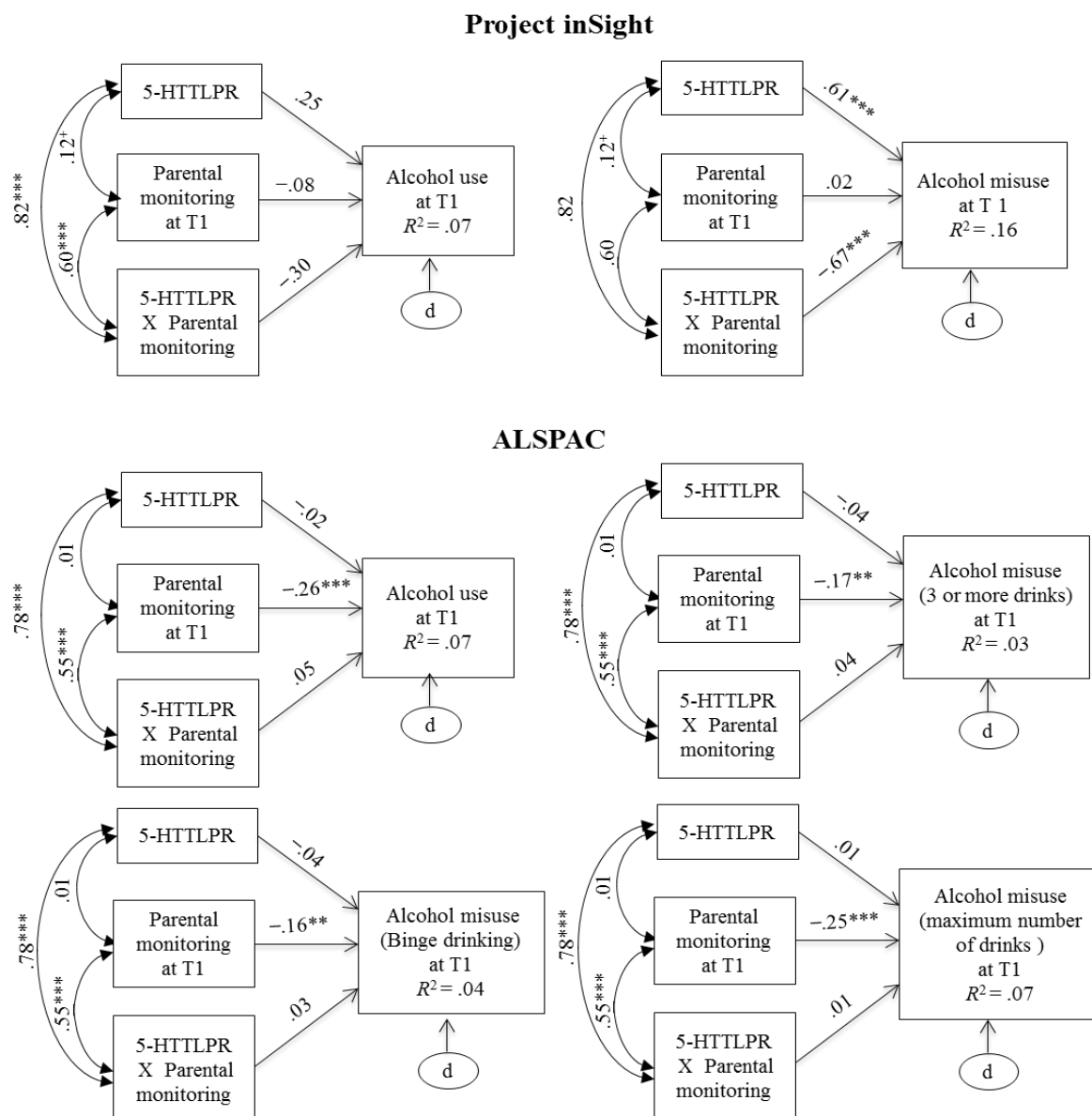


Figure 5. Path analyses testing the interaction effects between the 5-HTTLPR genotype and parental monitoring on alcohol use/misuse at T1. The upper left and right panels show the results from the Project inSight and the bottom left and the rest of panels show the results from ALSPAC. Standardized estimates are shown; the effects of gender, age, and mother's education on all variables in the models were controlled for in analyses (paths are not shown; in analyses of Project inSight, race was also controlled for). d = disturbance (residual variance).

** $p < .01$. *** $p < .001$.

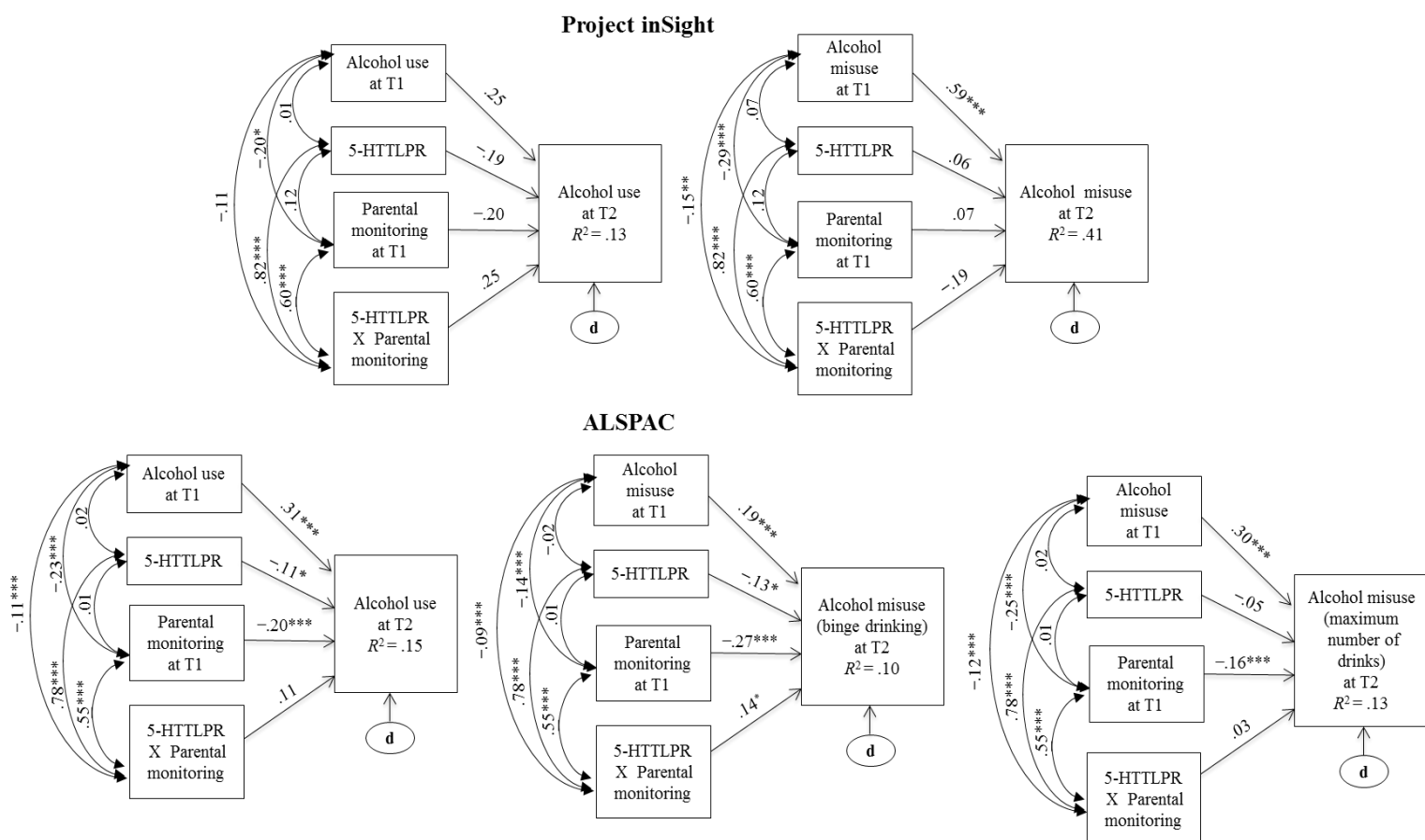


Figure 6. Path analyses testing the interaction effects between the 5-HTTLPR genotype and parental monitoring on changes in alcohol outcomes between T1 and T2 (i.e., T2 alcohol outcome after controlling for T1 alcohol outcome). The upper left and right panels show the results from Project inSight and the bottom three panels show the results from ALSPAC. Standardized estimates are shown; the effects of gender, age, and mother's education on all variables in the models were controlled for in all analyses (paths are not shown; in analyses of Project inSight, race was also controlled for). d = disturbance (residual variance).

* $p < .05$. ** $p < .01$. *** $p < .001$.

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VITA

NAME OF AUTHOR: Jueun Kim

GRADUATE AND UNDERGRADUATE SCHOOLS ATTENDED:

Handong Global University, Pohang, South Korea
Teachers College, Columbia University, New York
Syracuse University, Syracuse, New York

DEGREES AWARDED:

Bachelor of Arts in Counseling Psychology and English, 2008, Handong Global University
Master of Arts in Clinical Psychology, 2010, Teachers College, Columbia University

PUBLICATIONS:

- Park, A., **Kim, J.** Gellis, L. A., Zaso, M. J., & Maisto, S. A. (Submitted). Short-term prospective effects of impulsivity on heavy drinking: Mediation by positive and negative drinking consequences.
- Park, A., **Kim, J.** & Sori, M. E. (2013). Short-term prospective influences of positive drinking consequences on heavy drinking. *Psychology of Addictive Behaviors*, 27(3), 799-805.
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