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Co-development of early adolescent alcohol use and depressive feelings: The role of the mu-opioid receptor A118G polymorphism

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Abstract

Alcohol use and depressive feelings are often related among early adolescents. However, the nature and underlying mechanisms of this association are not yet clear. The aim of this study was to investigate the co-development of alcohol use and depressive feelings over time and to examine the effects of the mu-opioid receptor (*OPRM1*) A118G genotype on such co-development. Data from a five-wave longitudinal, genetically informed survey study, with intervals of 4 months among a group of 739 normative early adolescents (12–13 years of age at baseline), were analyzed using a dual latent growth curve approach. *OPRM1* status was evaluated from saliva-derived DNA samples. The results indicated a positive association between alcohol use and depressive feelings both at the initial levels and over time, indicating co-development in early adolescence. Compared to *OPRM1* 118G carriers, homozygous 118A carriers showed a greater increase in frequency of alcohol use and higher levels of depressive feelings over time. Evidence for co-development was only found within the group of homozygous 118A carriers, whereas in *OPRM1* 118G carriers the development of alcohol use and depressive feelings over time were not significantly associated. These results highlight the potential of *OPRM1* as a common etiological factor for the development of alcohol use and depressive feelings in early adolescence.

Adolescence represents the time during which the majority of individuals initiate alcohol use (Johnston, O'Malley, & Bachman, 2001). Two-thirds of Dutch adolescents have had their first drink by the age of 12 (Verdurmen, Monshouwer, van Dorsselaer, ter Bogt, & Vollebergh, 2005), and adolescents' alcohol use increases especially between 12 and 15 years of age (Poelen, Scholte, Engels, Boomsma, & Willemsen, 2005). Next to alcohol use, depressive feelings are common during adolescence (Hankin et al., 1998; Skitch & Abela, 2008), and the prevalence rate of depressive symptoms increases from early adolescence (McGee, Feehan, Williams, & Anderson, 1992), especially among girls (Costello, Mustillo, Erkanli, Keeler, & Angold, 2003). Thus, both alcohol use and depressive feelings are likely to develop during early adolescence and can have detrimental consequences for physical and mental health in adulthood.

Increasing interest in the developmental relation between alcohol use and depressive mood in adolescents has emerged recently (Saraceno, Munafó, Heron, Craddock, & van den Bree, 2009). It has been found that alcohol use and depressive feelings often co-occur among adolescents (Clark & Bukstein, 1998; Verdurmen et al., 2005). There have been some studies that focused on identifying psychosocial and health risk factors of developing a combination of substance use and mood disorders. Shared risk factors were found on both the individual and the environmental levels and included among others low academic achievement, family dysfunction, externalizing traits, and poor health status (Diaz, Simantov, & Rickert, 2002; Gau et al., 2007; Lewinsohn et al., 1994; Miller-Johnson, Lochman, Coie, Terry, & Hyman, 1998; Pardini, White, & Stouthamer-Loeber, 2007). Several twin studies have indicated that both adolescent and adult alcohol use as well as depressive mood are influenced by genetic factors (Pagan et al., 2006; Sullivan, Neale, & Kendler, 2000) and that there is overlap in the genetic influences on both traits (Edwards et al., 2011; Tambs, Harris, & Magnus, 1997). We examined the co-development of adolescents' alcohol use and depressive feelings by conducting a prospective study among early adolescents, because alcohol use and depressive feelings start to develop during that period. In addition, we aimed to investigate possible shared genetic effects in the development of both alcohol use and depressive feelings.

A gene that has been associated with both alcohol use and depression is the mu-opioid receptor gene (*OPRM1*, located on chromosome 6q24–q25). The *OPRM1* gene influences the affinity of mu-opioid receptors in the brain to bind β-en-

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dorphins and enkephalins. These opioid peptides are released after intake of alcohol (Town et al., 1999) and lead to a release of dopamine in particular brain reward areas (e.g., the nucleus accumbens and ventral tegmental area), known to result in feelings of reward and reinforcement. Functional genetic variants that change *OPRM1* gene regulation or function might affect the vulnerability of the brain reward system to bind opioids, and as a consequence, the reward experience might weaken or strengthen. This implies that the experience of reward is dependent on the *OPRM1* genotype. Thus far, the opioid system has been quite comprehensively studied in addiction, though less so in adolescent samples, and to an even lesser extent in depression.

A well-studied variant within the *OPRM1* gene is a single nucleotide polymorphism (SNP; *rs1799971*) in exon 1 (Lerman et al., 2004). A transition in this particular exon from A to G on nucleotide 118 (A118G) results in an amino acid change from asparagine to aspartic acid in the receptor protein. This amino acid change might affect gene function. With regard to addiction, the idea is that the more active allelic variant would have a stronger affinity to bind β-endorphins, which would lead to greater release of dopamine and, hence, more feelings of reward. However, studies focusing on the *OPRM1* gene in relation to alcohol use specifically report contrasting results. Gelernter, Kranzler, and Cubells (1999) found no difference in frequencies for the *OPRM1* A118G genotype among Caucasian controls and alcohol-dependent samples. Sander et al. (1998) also concluded that the *OPRM1* gene does not satisfactorily explain alcohol dependence. However, Town et al. (1999) and Schinka et al. (2002) found that the *OPRM1* A allele was significantly associated with increased risk for alcohol dependency, whereas other studies have indicated that individuals with the *OPRM1* G allele reported higher subjective feelings of intoxication, stimulation, sedation, and positive mood across rising levels of blood alcohol concentration, as compared to those with the A allele (e.g., Ray & Hutchison, 2004; Ray et al., 2010). Five studies so far have examined the *OPRM1* gene in relation to alcohol use among adolescents (Kleinjan, Poelen, Engels, & Verhagen, 2012; Miranda et al., 2010; Pieters et al., 2011, 2012; Van der Zwaluw, Otten, Kleinjan, & Engels, 2013). Miranda et al. found that adolescents with a G allele reported more alcohol-related problems, endorsed drinking to enhance positive effects more strongly, and were more likely to have a diagnosed alcohol abuse disorder than those that were homozygous for the A allele. Pieters et al. (2011) showed that compared to AA homozygotes, G carriers showed a significant positive relation between having an attention bias for environmental alcohol-related cues as measured by an implicit association task and the frequency and quantity of alcohol consumed. Pieters et al. (2012) and Van der Zwaluw et al. (2013) found that compared to *OPRM1* AA carriers, in *OPRM1* G carriers alcohol-specific parenting strategies are more robustly associated with alcohol consumption. Finally, Kleinjan et al. (2012) tested the increase in alcohol use in 428 adolescents aged 13 to 15 years over a 4-year time period with annual measurements. They did not find an effect of the *OPRM1* gene on the development of alcohol use. In sum, the role of the *OPRM1* gene in the development of problematic alcohol use is not clear, which is partly due to the differences in populations tested and the alcohol outcomes (phenotypes) utilized in these studies. In addition, the expressions of genes in relation to alcohol use may differ across the life course. Because previous prospective studies indicated that early initiation of alcohol use (<14 years of age) is associated with heavier alcohol use throughout adolescence and emerging adulthood (King & Chassin, 2007) and recent twin research indicated that the variance in early initiation of alcohol use (<15 years) is mainly explained by genetic factors (83% explained variance in males and 70% in females; Poelen et al., 2008), we adopted a developmentally appropriate and age-specific longitudinal model that focuses on exactly this phase in early adolescence. By means of five measurements with intervals of 4 months, we investigated whether the *OPRM1* gene is associated with levels of alcohol use and with concurrent change at the onset of alcohol use.

A link between the opioid system and depression has also been established. Kennedy, Koeppe, Young, and Zubieta (2006) concluded that depressed patients have altered mu-opioid receptor availability compared to controls and show antidepressant effects of opioid peptides. Next to this, it has been shown that the mu-opioid system is involved in emotion regulation and hypothalamic–pituitary–adrenocortical (HPA) axis activity and stress responses (Kalin, Shelton, & Barksdale, 1988; Zubieta et al., 2003), both of which are involved in depression symptomatology. It has, for example, been found that cortisol function, which is a reliable indicator of the HPA axis, was elevated in 40%–60% of adults diagnosed with major depressive disorder (Parker, Schatzberg, & Lyons, 2003).

Alterations in HPA axis functioning have also been consistently described in depressed adolescents compared to their control counterparts (see review and meta-analysis by Guerry & Hastings, 2011; Lopez-Duran, Kovacs, & George, 2009). It was found that at-risk youth with dysphoria displayed hyperreactivity to psychosocial challenges, whereas controls revealed an appropriate stress response on these tasks (Hankin, Badanes, Abela, & Watamura, 2010).

The *OPRM1* A118G variant was previously found to be related to HPA axis activity (Chong et al., 2006), and Kertes et al. (2011) found that the A118G variant and three other markers within the *OPRM1* gene reached nominal significance with regard to lifetime depressive symptom scores in alcohol-dependent adults. It is therefore concluded that genetic variation within the *OPRM1* A118G genotype could play a role at the interface of disturbed HPA axis activity, depression, and addiction. However, no studies have investigated the *OPRM1* gene in relation to depressive symptoms among adolescents.

Alcohol use and depressive feelings both develop during early adolescence and seem to share a genetic liability, possibly in the form of *OPRM1*. Even though single gene effects are often modest, there is evidence that the *OPRM1* polymorphism is associated with both internalizing and alcohol phenotypes. In

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most studies examining the *OPRM1* gene, either alcohol use or depressive feelings have been investigated, and primarily in adult samples. The first aim of this study is to investigate the baseline levels (intercept) and the co-development of alcohol use and depressive feelings over time (slope), using a longitudinal five-wave design covering 2 years. It is hypothesized that alcohol use in this age group will be associated with the development of depressive feelings over time. Furthermore, *OPRM1* is hypothesized to be part of the underlying mechanisms of the joint development of alcohol use and depressive feelings. Despite inconsistent findings in previous literature, we expected that the link between alcohol use and depressive feelings is partly conditional on the *OPRM1* gene. Finally, because previous studies found differential associations between depression and alcohol use for boys and girls (Crum, Storr, Ialongo, & Anthony, 2008; Fleming, Mason, Mazza, Abbott, & Catalano, 2008; Marmorstein, 2009; Needham, 2007), interactions between sex and the *OPRM1* genotype in relation to alcohol use and depression will be examined as well.

Method

Procedure and participants

A total of 804 adolescents (51.50% female) were recruited from 14 schools in the Netherlands, with an average age of 13.09 years (range = 11.59–15.60, *SD* = 0.48) at Time 1 (T1). Across the five waves (T1–T5), 783 (97.4), 736 (91.7%), 696 (86.6%), 684 (85.1%), and 636 (79.1%) adolescents participated, respectively. Because the current study focuses on a specific developmental period (i.e., 12–13 years old), adolescents younger than 12 and older than 14 were omitted from the analyses, leaving a sample of 739 adolescents (mean age = 13.03, *SD* = 0.39). Most of the adolescents were of Dutch origin (97.3%). The participants were in the first grade of secondary school at T1, and 11.6% of the participating adolescents were in university preparatory training, 30.2% in senior general secondary education, and 57.9% in preparatory vocational training and junior general secondary training at T1. At T1, saliva samples were collected for DNA extraction (Oragene, DNA Genotek Inc.). Active, informed consent for gene analysis was obtained from the adolescents as well as their parents. During each wave, the participants filled out an online or paper-and-pencil questionnaire during school hours. A total of 12.9% of the sample completed a paper questionnaire because their school did not have the necessary facilities to allow for the online completion of questionnaires. No differences were found between completers of online or paper questionnaires on demographic variables or on alcohol use or depressive feelings on any of the five waves. Students were explicitly instructed that all questions were about their regular patterns and not exceptional situations such as holidays, unless otherwise stated. The time between each of the five waves was approximately 4 months. The research design for this study was evaluated and ethically approved by an independent medical ethical committee (METiGG, Utrecht, The Netherlands).

We conducted power analyses using the software Quanto (Gauderman & Morrison, 2006). For the power calculation we applied the gene-only design option for continuous outcomes with independent individuals. To detect a small effect with an R^2 of .01 to .015, with 80% power ($\alpha = 0.05$), the sample size required is between 518 and 781. With our sample size of 739 adolescents, we should be able to detect a small effect size of *OPRM1*.

Materials

Genotyping. The *OPRM1* 118A>G polymorphism (*rs179 9971*) was genotyped using Taqman analysis (Taqman assay: C_8950074_1; reporter 1: VIC-A-allel, forward assay; Applied Biosystems, Nieuwekerk a/d IJssel, The Netherlands). The probe of the A allele was labeled with VIC and the probe of the G allele was labeled with Fam (see Oroszi et al., 2009). Genotyping was carried out in a volume of 10 μl containing 10 ng of genomic DNA, 5 μl of Taqman Mastermix (2X, Applied Biosystems), 0.125 μl of the Taqman assay, and 3.875 μl of water. Genotyping was performed on a 7500 Fast Real-Time PCR System, and genotypes were scored using the algorithm and software supplied by the manufacturer (Applied Biosystems). Generally, all genotyping assays have been validated earlier, and 5% duplicates and blanks were taken along as quality controls during genotyping. Of the 739 adolescents included in our analyses, 11 could not be genotyped with regard to the *OPRM1* genotype (1.5%).

Questionnaires.

Alcohol use. During each wave, adolescents' alcohol use was assessed with a single item asking about how often they had consumed alcohol during the past 4 weeks. They responded on a 6-point scale, ranging from 1 (*have not been drinking*) to 6 (*every day*; Engels & Knibbe, 2000). Because of the low frequencies in the last two categories (*5 or 6 days a week* and *every day*), these categories were summed into one.

Depressive feelings. Depressive feelings were assessed at each wave with a translated version of the Center for Epidemiologic Studies Depression Scale (Radloff, 1977). The scale consists of 20 items about how often adolescents felt a certain way or engaged in a certain behavior during the past week. Examples of items are "I felt depressed" and "I enjoyed life." The adolescents were asked to rate the items on a 4-point scale, ranging from 1 (*rarely or never*) to 4 (*often or always*). Cronbach αs for this scale were 0.79 (T1), 0.84 (T2), 0.84 (T3), 0.85 (T4), and 0.82 (T5). An average score for depressive feelings was computed at each wave.

Alcohol use of parents. Parental alcohol use at T1 was assessed with a single item per parent in which adolescents were asked how often their father or mother had consumed alcohol during the past 4 weeks. They responded on a 6-point

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scale, ranging from 1 (*have not been drinking*) to 6 (*every day*; Engels & Knibbe, 2000).

Alcohol use of friends. Alcohol use of friends was assessed by asking, "How many of your friends drink alcohol?" This item could be scored on a 5-point scale, ranging from 1 (*none of them*) to 5 (*all of them*).

Attrition analyses

Attrition analyses were conducted in order to examine whether adolescents who remained participants in the fifth wave of the study ($n = 636$; 79.1%) differed from adolescents who dropped out ($n = 168$; 20.9%). The t tests showed no significant differences ($p > .05$) in age, educational level, ethnicity, and *OPRM1* genotype at T1. Participants lost to follow-up were more likely to be boys, χ^2 (1, $N = 804$) = 6.34; $p < .05$, and to show a higher frequency of alcohol use, t (725) = –3.86, $p < .001$. No differences were found for depressive feelings, t (771) = –1.67, $p = .09$. All participants are included in the analyses regardless of missing data via the full information maximum likelihood estimation (see also the following section).

Strategy of analyses

The relation between the independent variables and the co-development of alcohol use and depressive feelings was examined with a latent growth curve model (cf. Kleinjan et al., 2012). First, we assessed the single growth curves of alcohol use and depressive feelings from T1 to T5 by estimating the initial level (intercept) and the rate of change over time (slope) for both alcohol use and depressive feelings. To correct for the skewed distribution of the alcohol frequency, we conducted our analyses using the maximum likelihood robust estimator. Second, we assessed a dual growth model in order to assess the simultaneous change in alcohol use and depressive feelings, using Mplus (Muthén & Muthén, 1998–2007). *OPRM1* was included as a predictor variable to assess whether it was predictive of initial values or growth over time of alcohol use and depression. In this approach, effects of the predictor variables on the intercepts and slopes of alcohol use are controlled for the development of depression and vice versa. In a final step, we examined whether the associations between initial values and growth effects were different for *OPRM1* A homozygotes compared to *OPRM1* G-allele carriers. These analyses are based on χ^2 difference testing between two identical models, where one model is subjected to constraints of one of the parameters, in this case *OPRM1*, whereas the other model is not. This was done by constraining all paths of interest (i.e., the six associations between the intercepts and the slopes) to be equal and testing whether the model fit ($\triangle\chi^2$) was significantly better for the model in which all paths were allowed to differ between *OPRM1* A homozygotes and *OPRM1* G-allele carriers, compared to the model in which all paths were constrained to be equal. To examine which specific paths between the intercepts and slopes of alcohol use and depressive feelings differ for A homozygotes and G-allele carriers, we constrained each path separately while all other paths were unconstrained and compared this model to the model in which the path of interest, as well as all other paths, were unconstrained. Because the χ^2 value cannot be used for standard χ^2 difference testing when using the maximum likelihood robust estimator, the Satorra–Bentler scaled χ^2 difference test was used (Satorra & Bentler, 2001). All models were controlled for the variables sex, age, educational level, ethnicity, and alcohol use of parents and friends. Possible interactions with sex and *OPRM1* were additionally examined. Full information maximum likelihood estimation was applied to make use of all available data. The model fit was investigated by the following global fit indices: χ^2, the comparative fit index (CFI; good fit > 0.90), and the root mean square error of approximation (RMSEA; good fit < 0.08; Hu & Bentler, 1999).

Results

Descriptives

The means and standard deviations for the four measures of alcohol use and depressive feelings are presented in Table 1.

Table 1. *Means (standard deviations) of model variables for the total sample and separate for OPRM1 AA carriers and AG/GG carriers*

	T1 ($N = 804$)	T2 ($N = 783$)	T3 ($N = 695$)	T4 ($N = 681$)	T5 ($N = 636$)
Alcohol use					
Total sample	1.21 (0.52)	1.20 (0.56)	1.22 (0.55)	1.35 (0.73)	1.33 (0.70)
OPRM1 AA	1.19 (0.50)	1.17 (0.51)	1.23 (0.56)	1.34 (0.71)	1.34 (0.70)
OPRM1 AG/GG	1.24 (0.59)	1.29 (0.72)	1.20 (0.51)	1.39 (0.80)	1.26 (0.70)
Depressive feelings					
Total sample	1.50 (0.35)	1.48 (0.38)	1.47 (0.38)	1.46 (0.40)	1.45 (0.37)
OPRM1 AA	1.50 (0.33)	1.46 (0.35)	1.47 (0.56)	1.45 (0.40)	1.47 (0.38)
OPRM1 AG/GG	1.51 (0.33)	1.50 (0.37)	1.45 (0.34)	1.46 (0.38)	1.37 (0.31)

Note: Alcohol use: min = 1, max = 5. Depressive feelings: min = 1, max = 4.

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At T1 56.6% of adolescents indicated that they had tried alcohol at least once, this was 53.4% at T2, 57.8% at T3, 61.2% at T4, and 57.2% at T5. Alcohol use in the past 4 weeks was reported by 14.3% at T1, 14.2% at T2, 17.7% at T3, 27.0% at T4, and 24.1% at T5. Descriptive findings on the *OPRM1* SNP revealed that 79.5% of the adolescents had the AA genotype, 19.1% the AG genotype, and 0.8% the GG genotype. No deviations from Hardy–Weinberg equilibrium were detected ($p = .18$). To maximize the power of the analyses, *OPRM1* genotype was dummy coded into 1 (AA) and 2 (AG and GG).

Correlations between model variables

Correlations between the model variables are presented in Table 2. These findings show some significant positive correlations between the measures of alcohol use and depressive feelings. There was a positive correlation between *OPRM1* and alcohol use at T2 and a negative correlation between *OPRM1* and depression at T5.

Model findings

First, we tested the latent growth model for alcohol use and depressive feelings separately and without predictors. The model for alcohol use showed a good fit to the data, χ^2 ($df = 9$, $p < .001$) = 35.63, CFI = 0.90, RMSEA = 0.06. The means of the intercept and slope were both significant (respectively, 2.96, $p < .001$; variance = 0.16, $p < .001$; and 0.38, $p < .001$; variance = 0.01, $p < .01$), suggesting that the participants scored greater than zero on alcohol use at baseline, that alcohol generally increased over time, and that participants differed around the means. The association between the intercept and the slope was significant ($\beta = -0.41$, $p < .001$). This suggests that higher initial levels of alcohol use are related to less growth in alcohol use over time. Quadratic trends were also examined, but they were not significant.

The model for depressive feelings also showed a good fit to the data, χ^2 ($df = 10, p < .001$) = 29.78, CFI = 0.97, RMSEA = 0.05. The means of both intercept and slope were significant (respectively, 5.26, $p < .001$; variance = 0.08, $p < .001$ and –0.17, $p < .001$; variance = 0.004, $p < .001$), suggesting that the participants scored greater than zero on depressive feelings at baseline, that depressive feelings generally decreased over time, and that participants differed around the means. The association between the intercept and the slope was significant ($\beta = -0.28$, $p < .01$). This suggests that higher initial levels of depressive feelings are associated with less growth in depressive feelings over time. It is important to note here that the negative slope does not mean that there is no individual growth in depression. In the latent growth curve approach, it is not assumed that all participants start at the same level of depression at baseline and have the same rate of change over time; instead, individual growth is examined for each participant. Finally, the possibility of a quadratic trend was examined, but this was not significant.

Table 2. *Pearson correlations between the model variables*

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
1. Sex	—																
2. Age	−.05	—															
3. Education	−.03	**−.18**	—														
4. Ethnicity	.04	*.07*	−.01	—													
5. *OPRM1*	.02	.03	.00	−.01	—												
6. Alcohol T1	**−.09**	*.03*	−.06	−.01	.04	—											
7. Alcohol T2	**−.10**	*.08*	*−.10*	.01	*.09*	**.48**	—										
8. Alcohol T3	−.05	**.11**	**−.14**	−.03	−.03	**.47**	**.53**	—									
9. Alcohol T4	**−.09**	*.10*	−.06	.03	.02	**.30**	**.38**	**.42**	—								
10. Alcohol T5	−.03	.08	**−.12**	.02	−.05	**.21**	**.18**	**.32**	**.42**	—							
11. Depression T1	**.13**	.05	**−.12**	−.04	.01	**.12**	.04	**.11**	*.10*	.07	—						
12. Depression T2	**.16**	.02	**−.19**	−.03	.05	**.10**	.07	.07	.02	.06	**.59**	—					
13. Depression T3	**.15**	.05	**−.14**	−.04	−.01	*.09*	*.10*	**.12**	*.08*	**.14**	**.54**	**.63**	—				
14. Depression T4	**.20**	.06	**−.13**	−.03	.00	.07	.05	**.12**	**.13**	**.18**	**.50**	**.54**	**.64**	—			
15. Depression T5	**.19**	*.10*	**−.15**	.02	*−.10*	.06	.05	.06	**.14**	**.12**	**.43**	**.47**	**.55**	**.64**	—		
16. Alcohol father	−.04	−.02	.03	−.07	−.01	**.17**	*.09*	**.14**	**.17**	**.14**	.04	−.02	−.00	.04	−.01	—	
17. Alcohol mother	−.01	.01	**.15**	−.01	−.01	**.14**	.06	**.09**	*.09*	.09	.05	−.02	−.02	.00	−.07	**.49**	—
18. Alcohol friends	−.05	**.13**	**−.16**	**.13**	.02	**.43**	**.36**	**.43**	**.30**	**.27**	**.12**	**.15**	**.13**	*.10*	**.15**	**.12**	*.08*

Note: Correlations with $p < .05$ are in italic; correlations with $p < .01$ are in bold.

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Second, we tested the dual growth model of alcohol use and depressive feelings. This model fits the data well, χ^2 ($df = 40$, $p < .001$) = 97.62, CFI = 0.95, RMSEA = 0.04. The association between the initial values of alcohol use and depressive feelings was significant ($\beta = 0.17$, $p < .01$). This means that higher baseline levels of alcohol use were associated with higher baseline levels of depressive feelings. The association between the initial values of alcohol use and the change in depressive feelings over time was not significant ($\beta = -0.12$, $p = .14$). In addition, the relationship between the initial values of depressive feelings and change in alcohol use over time was not significant ($\beta = -0.06$, $p = .48$). The slopes of alcohol use and depressive feelings were positively related ($\beta = 0.30$, $p < .05$), indicating that increases of depression co-occur with increases in alcohol use. Table 3 provides a further clarification of this association. For this purpose, individual scores on the intercepts and slopes of alcohol and depression were transferred from Mplus to SPSS. For depressive feelings, the sample was divided into a group containing individuals for whom the slope was negative (decliners: 60%) and a group for whom the slope was positive (increasers: 40%). For alcohol use, we used a median split to distinguish between those who showed no or moderate increases (55.6%) and those who showed a high increase (44.4%). A median split was chosen because only 12% of our sample showed a decrease in alcohol use over time. Table 3 shows that for the total sample, 77.6% of all individuals who increased in depression also showed a high increase in alcohol over time. In contrast, 77.5% of all individuals who declined in depression over time showed no or a moderate increase in alcohol use over time.

Third, the predictors were added to the dual growth model of alcohol use and depressive feelings. The model including the genetic and control variables fits the data well, χ^2 (88) = 154.28, $p < .001$, CFI = 0.96, RMSEA = 0.03. The control variables sex and perceived alcohol use of friends predicted initial levels of alcohol use (see Table 4). Initial values were higher for males and for participants whose friends drink more frequently. Higher initial levels of depressive feelings were predicted by being female, having a lower educational level, being of Dutch descent, and having more drinking friends. Girls also showed a higher increase in depression over time than boys. When controlled for sex, age, education level, ethnicity, and perceived drinking behavior of father, mother, and friends, the *OPRM1* genotype showed a main effect on both the slopes of alcohol use (R^2 change = .020) and depressive feelings (R^2 change = .022). The *OPRM1* G allele was associated with less increase in both alcohol use and depressive feelings over time. No effect of *OPRM1* on the initial values was found. Finally, no interaction effect of sex with *OPRM1* was found on the intercepts or slopes (not shown in Table 4). Figure 1 shows the growth curves for alcohol use and depressive feelings separately for *OPRM1* AA carriers and G carriers.

Fourth and finally, we conducted a multigroup analysis to test whether the effects that we found in the total sample differed for homozygous A-allele carriers compared to G-allele carriers. The Satorra–Bentler χ^2 difference test indicated that the model differed for *OPRM1* A homozygotes and *OPRM1* G carriers, χ^2 (6) = 10.52, $p < .01$ (Satorra & Bentler, 2001). The fit of the model, where the paths were allowed to differ for the *OPRM1* genotypes, was good, χ^2 (165) = 154.28, $p < .001$, CFI = 0.96, RMSEA = 0.04. Figure 2 depicts the standardized estimates of the dual growth model, separately for homozygous A carriers and G-allele carriers. The most important finding is reflected in the link between the slopes of alcohol use and depressive feelings. As depicted, the slopes were positively associated, but only in the AA carriers ($\beta = 0.41$, $p < .05$) and not in the G carriers ($\beta = 0.09$, $p = .65$). In the G carriers, the initial values of alcohol use were negatively related to the slopes, and the same pattern was found for depressive feelings. In AA carriers the intercept of alcohol use was not related to the slope, and the intercept and slope of depression were also not related. The Satorra–Bentler χ^2 difference test established support for this path difference, χ^2 (1) = 10.52, $p < .001$. Finally, no interaction effects of sex with *OPRM1* were found on the relations between the intercepts or slopes.

Table 3. *Increase in alcohol use for negative and positive depression slopes*

	Slope Depression								
	Total Sample ($N = 739$)			AA Carriers ($N = 582$)			AG/GG Carriers ($N = 146$)		
Slope Alcohol Use	Negative ($N = 445$)	Positive ($N = 294$)	Total	Negative ($N = 352$)	Positive ($N = 230$)	Total	Negative ($N = 85$)	Positive ($N = 61$)	Total
No or low increase									
N	345	66	411	273	45	318	65	21	86
% within depression	77.5	22.4		77.6	19.6		76.5	34.4	
High increase									
N	100	228	328	79	185	264	20	40	60
% within depression	22.5	77.6		22.4	80.4		23.5	65.6	

Note: For depressive feelings the sample was divided into a group containing individuals for whom the slope was negative and a group for whom the slope was positive. For alcohol use a median split was used to distinguish between low and high increase in use over time.

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Table 4. *Standardized estimates for control variables and OPRM1 on the intercepts and slopes of alcohol use and depressive feelings in the dual growth model*

	Intercept Alcohol Use	Linear Slope Alcohol Use	Intercept Depressive Feelings	Linear Slope Depressive Feelings
Sex	−.09*	.06	.17***	.13*
Age	−.01	.11	.02	.02
Education	−.02	−.07	−.17***	.03
Ethnicity	−.06	−.03	.08*	.06
Alcohol use				
Father	.08	.12	−.02	.06
Mother	.07	−.06	.07	−.14
Friends	.52***	−.10	.15**	.04
OPRM1	.08	−.14*	.04	−.15*
Explained variance (R^2)	32.0%	5.9%	9.0%	5.6%

Note: Sex: 0 = male and 1 = female; ethnicity: 0 = Dutch and 1 = not Dutch.
*$p < .05$. **$p < .01$. ***$p < .001$.

To more closely examine the association between alcohol use and depressive symptoms in AA carriers over time, we conducted a post hoc piecewise growth model. In a piecewise growth model, different phases of development are captured by more than one slope growth factor. We divided the five measurements into two developmental phases. Phase 1 includes the first three measurements (T1–T3), Phase 2 includes in the last three measures (T3–T5). The piecewise growth model showed a good fit, χ^2 (112) = 145.48, $p < .05$, CFI = 0.98, RMSEA = 0.03. We found that in AA carriers, the slope of depressive feelings in developmental Phase 1 was marginally positively associated with the slope of alcohol use in Phase 2 ($\beta = 0.21$, $p = .09$). The slope of alcohol use in Phase 1 was not associated with the slope of depressive feelings in Phase 1 or Phase 2 ($\beta = 0.16$, $p = .32$ and $\beta = 0.07$, $p = .63$). During Phase 2, the slopes of depressive feelings and alcohol use are marginally positively related ($\beta = 0.22$, $p = .07$). Within GG carriers, none of the slopes in the different phases were associated.

Discussion

The present study aimed at examining how the development of alcohol use and depressive feelings is related among a sample of early adolescents in a developmentally sensitive period, and how the *OPRM1* genetic variant affects this co-development. We found that higher levels of alcohol use at baseline were associated with higher levels of depressive feelings at baseline and that a greater increase in alcohol use was associated with a greater increase in depressive feelings. This is in accord with previous studies that showed alcohol use and depressive feelings to co-occur (Clark & Bukstein, 1998; Verdurmen et al., 2005).

Homozygous *OPRM1* 118A carriers showed the strongest increases in alcohol use and the least decrease in depressive feelings over time, and moreover, the increase in alcohol use and depressive feelings was associated only in this group. In AG and GG carriers no associations were found between early alcohol use and depressive feelings. It has been suggested that the molecular mechanism for the 118A allele in association with alcoholism involves hyposensitivity of the endogenous mu-opioid receptor system and that this leads to increased consumption of alcohol in order to compensate for this intrinsic opioid response deficit (Town et al., 1999). This is in accord with Bond et al. (1998), who demonstrated that the 118G receptor isoform binds endogenous β-endorphin approximately three times more tightly than 118A, giving rise to heightened feelings of reward. In the present study, we did not study alcohol dependency but frequency of alcohol use in early adolescence (early onset). It seems that at ages 12–14, adolescents who are homozygous for the 118A allele increase more in frequent alcohol use in a 2-year time window than adolescents with the 118G allele. A possible explanation for this finding may be that the lack of an intrinsic opioid response to alcohol in young AA

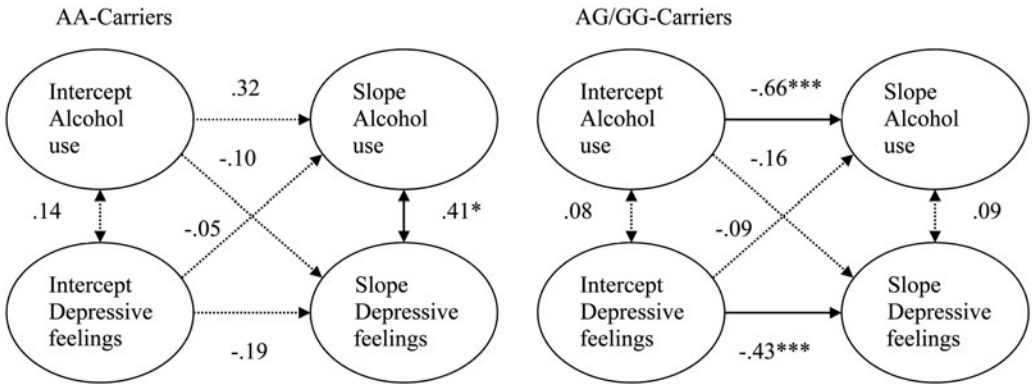

Figure 1. Dual growth models of alcohol use and depressive feelings separated for adolescents who are AA carriers and AG/GG carriers (standardized estimates). *$p < .05$, **$p < .01$, ***$p < .001$.

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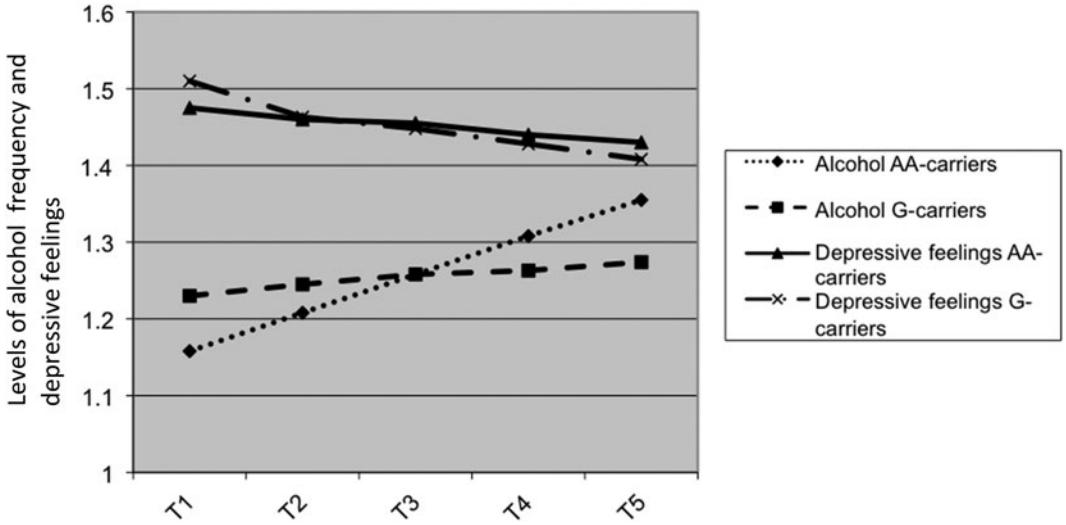

Figure 2. Plotted dual growth curves of alcohol use and depressive feelings separated for adolescents who are AA carriers and AG/GG carriers, controlled for sex, age, education level, and parental and peer alcohol use.

carriers may give them less reason to hold back on drinking once started because physiological reactions might be less prominent (e.g., unusual body sensations and the feeling of losing control). In G carriers alcohol use seemed to be relatively stable over time, and the development of alcohol use and depressive feelings seemed to be largely independent of each other. In this group, the initial scores on both phenotypes were reversely correlated with the slope, meaning that higher levels at baseline were associated with less increase of the respective phenotypes over time. Adolescent G carriers, who might experience a stronger response to alcohol use because of the stronger mu-opioid binding potential, seem to start out at somewhat higher levels of alcohol use, but these levels change relatively little over time and possible changes seem independent of depressive feelings.

Further, because young adolescents are novice drinkers, the effect of the activity and function of the *OPRM1* A118G SNP may be different compared to later stages of adolescence in which drinking patterns become more entrenched. When adolescents get older, drinking patterns become more established and drinking motives may change. Young adolescents who have little alcohol experience will probably drink because of social reasons. When more alcohol has been consumed, other drinking motives such as coping and enhancement motives will play a larger role (Kuntsche Knibbe, Gmel, & Engels, 2006). Coping motives were found to be particularly associated with problematic alcohol use, such as heavy episodic drinking and alcohol-related problems (e.g., Kuntsche, Knibbe, Gmel, & Engels, 2005). Therefore, because of the stronger binding potential of the receptors in G-allele carriers, adolescents with the 118G allele might be more at risk for excessive alcohol use and alcohol-related problems later in adolescence because the G allele generates more enhancement effects of alcohol. This is in line with Miranda et al. (2010), who found in a sample of older adolescents that those with a G allele reported more drinking to enhance positive affect and were more likely to report alcohol-related problems than those who were homozygous for the A allele. In this later stage of adolescence, sex differences in the relations between alcohol use and depression might also become more pronounced, seeing that boys tend to drink more excessively and girls tend to increase more in depressive feeling during adolescence (e.g., Costello et al., 2003).

The activity and function of the *OPRM1* A118G SNP in depression in humans has yet to be largely established (Garroick et al., 2010). Up until now, the *OPRM1* A118G has not been investigated in relation to depressive symptoms in normative adult or adolescent populations, though a few pharmacogenetic studies on the *OPRM1* gene in relation to antidepressant response have been conducted (Garroick et al., 2010; Perlis, Fijal, Dharia, Heinloth, & Houston, 2010). However, these studies did not yield significant associations for the A118G variant and treatment response. Therefore, assumptions on gene-based processes in relation to depression are highly speculative. Despite this, the mu-opioid system is likely to be involved in depression because previous studies have found that the binding potential of the mu-opioid receptor was significantly lower in women with major depressive disorder relative to nondepressed women (Kennedy et al., 2006). Further, it was shown that depressed women who did not respond to antidepressant treatment exhibited lower binding potential for the mu-opioid receptor than depressed women who responded positively to psychopharmacology. The link between being a homozygous *OPRM1* A-allele carrier and increases in depressive symptoms may thus be partly explained by the lower binding potential that characterizes the *OPRM1* +118A genotype.

Our results form an addition to the literature on the co-occurrence of alcohol use and depressive feelings in several

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ways. Most studies that focused on the link between alcohol use and depressive symptoms concentrated on more severe forms of psychopathology, such as clinical depression, mostly in individuals who present excessive alcohol use patterns. Our findings provide evidence that in a normative group of early adolescents, increases in depressive feelings, even at relatively low levels, are associated with increases in alcohol use over time but only in a subgroup with a specific genotype, namely, AA carriers of the *OPRM1* +118 gene. When probing the association between alcohol use and depressive feelings in AA carriers by looking at the associations between the slopes in two different developmental phases, we found a marginally significant positive association between the slope of depressive feelings for the first three measures and the slope of alcohol use for the last three measures. This finding tentatively indicates that the early increase in depressive feelings might influence later increases in alcohol use in AA carriers. It is possible that this association reflects the vulnerability to a subtle process that eventually leads to and accelerates a reinforcing interplay between depressive symptoms and alcohol use. Because adolescents who had their first drink between the ages of 11 to 14 years are more likely to develop an alcohol disorder later in life than adolescents who started drinking at a later age (King & Chassin, 2007), it may be that comorbidity of alcohol dependence and depression develops at an accelerated pace in AA carriers. Neurobiological studies have shown that "liking" processes are associated with opioid neurotransmission in the brain (Berridge, 2003). Stimulation of opioid receptors due to alcohol consumption results in dopaminergic firing in "reward areas." Whereas dopaminergic effects are thought to be especially important in the later stages of alcohol use, after sensitization has taken place, opioid neurotransmission may be more associated with the early stages of alcohol use. Particularly in AA carriers, who are thought to have less strong binding potential and therefore a more hyposensitive endogenous mu-opioid receptor system, low levels of alcohol use may already produce some form of compensation for the intrinsic opioid response deficit, adding to the risk of developing early signs of withdrawal. These early signs of withdrawal may trigger the experience of unpleasant feelings, which may ultimately be reflected in both increased alcohol use and depressive symptoms over time. In addition, the risk of unpleasant feelings might already be higher in AA carriers, seeing the previous established links between depression and lower binding potential of the mu-opioid receptor (Kennedy et al., 2006). To avoid these perceived unpleasant consequences, AA carriers may become increasingly motivated to use alcohol more regularly, leading to more severe levels of depressive feelings over time (Robinson & Berridge, 2000).

When interpreting the findings of this study, some caveats should be kept in mind. First, we tested one SNP, whereas multiple loci are likely to be involved in the path from initial alcohol use to more problematic patterns of use (Van der Zwaluw & Engels, 2009). Even though we found an effect of a single locus, that does not answer the question of whether this particular SNP is the functional variant responsible for the effect. Because of nonrandom association between alleles (i.e., linkage disequilibrium), genotyping several SNPs within the gene and adjacent genes can provide important insights into other variants that are associated with alcohol use and depression. In addition, it should be noted that our results should be interpreted in a broader framework. Previous studies already identified multiple shared underlying factors for the co-occurrence of alcohol use and depressive symptoms besides genetic factors (i.e., low academic achievement, family dysfunction, externalizing traits, and poor health status; Diaz et al., 2002; Gau et al., 2007; Lewinsohn et al., 1994; Miller-Johnson et al., 1998; Pardini et al., 2007). A growing body of evidence suggests a common neurobiological basis underlying both addiction and certain psychiatric disorders (Brady & Sinha, 2005). It is very well possible that multilevel mechanisms might be in play that link increases in alcohol use with depressive feelings for the AA carriers. Future research is needed to discern more comprehensive risk profiles for the co-occurrence of alcohol use and depressive feelings by taking to account a combination of genetic, (neuro)biological, and psychosocial features known to be associated with both phenotypes.

Second, we only used self-reports of alcohol use and depressive feelings of adolescents, and adolescents also reported on the alcohol use of their parents and friends themselves. However, it has been shown that adolescents can validly report their alcohol use (Brener, Billy, & Grady, 2003) and that of parents (Engels, Van der Vorst, Deković, & Meeus, 2007) and friends (Belendiuk, Molina, & Donovan, 2010) as well as depressive feelings (Kazdin, 1994). It should be kept in mind, though, that self-reports of one's own and other's drinking patterns may be susceptible to over- or underreporting.

Third, we chose to focus on the frequency of alcohol use in the past month and did not include measures on the quantity of alcohol. We did assess quantity of alcohol use in the past week, but seeing that in early adolescents alcohol use is incidental, our 1-week time frame to measure the quantity of alcohol use did not show much variance, and the use of this measure might have resulted in an underestimation of alcohol use.

Fourth, no information was available on depressive feelings of parents and friends, so we could not control for these variables in our analyses. However, previous studies indicated that the relation between parental and child depression in adolescence seems to be moderate (e.g., Van Roekel, Engels, Verhagen, Goossens, & Scholte, 2011).

Fifth, we used a community sample with adolescents not previously diagnosed with alcohol (mis)use or (sub)clinical depression. It is possible that findings would be different for adolescents who had already initiated alcohol use or had strongly elevated levels of alcohol use and depressive feelings, or for clinical samples.

Our results may also provide some implications for practice. The finding of co-development of alcohol with depressive symptoms can be used to inform and further specify

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prevention efforts. Recent studies investigated the effects of tailor-made interventions for the at-risk personality populations (Conrod, Castellanos, & Mackie, 2008; Conrod, Castellanos-Ryan, & Strang, 2010; Conrod, Stewart, Comeau, & Maclean, 2006). In these studies, tailor-made interventions were provided for the diverse risk groups based on prescreening with the Substance Use Risk-Profile Scale. Depression-prone adolescents, for instance, were provided an intervention program aimed at their specific personality traits or skill deficits (e.g., Conrod et al., 2006). This program targets at-risk groups by selecting adolescents who already had their first drink of alcohol and scored one standard deviation above the school mean on depressive feelings, anxiety sensitivity, sensation seeking, or impulsivity. Studies showed that participants in the intervention conditions show less substance use behaviors compared to a control group (Conrod et al., 2006, 2008, 2010). Knowledge about the *OPRM1* genetic marker could eventually lead to an even more personalized approach of such an intervention, by selecting those adolescents who are known to be at risk for the co-development of depressive feelings and alcohol use.

To conclude, the results of our longitudinal and age-specific study provide evidence for the notion that the development of alcohol use and depressive mood are already interrelated in early adolescence. In addition, our results suggest that the *OPRM1* genotype seems to be a shared underlying factor in the development of both alcohol use and depressive symptoms during this period.

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