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## Early onset alcohol use and self-harm: A discordant twin analysis

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### Abstract

**Background**—Self-harm has considerable societal and economic costs and has been extensively studied in relation to alcohol involvement. Whereas early onset alcohol use (EAU) has been causally linked to maladaptive clinical outcomes, its association with self-harm is less well characterized. The current study aimed to further examine the link between EAU and both non-suicidal self-injury (NSSI) and suicide attempt (SA), and elucidate shared familial and causal/individual-specific pathways that explain this co-occurrence.

**Methods**—Using data from 6,082 Australian same-sex twin pairs (1,732 MZ and 1,309 DZ), ages 23–40, we examined prevalence rates of NSSI and SA among twin pairs concordant and discordant for EAU. Conditional logistic regression, controlling for early clinical covariates and the influence of zygosity on EAU, was used to examine the odds ratio (OR) of self-harm within twin pairs discordant for EAU.

**Results**—Prevalence rates of both NSSI and SA were highest among twin pairs concordant for EAU and for twins who reported EAU within discordant twin pairs. Results from discordant twin analyses revealed nearly four-fold increased odds of SA for the twin who endorsed EAU, and this OR was equal across monozygotic (MZ) and dizygotic (DZ) twins. EAU also was associated with

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elevated odds of NSSI (OR=7.62), although this was only the case for DZ twins in discordant pairs.

**Conclusions**—The equivalent increase in odds of SA for both MZ and DZ twins suggests that causal or individual-specific influences explain the link between EAU and SA. For NSSI, elevated odds for DZ twins and nonsignificant findings for MZ twins implicate correlated genetic factors in the association between EAU and NSSI. Future studies should test mechanisms through which EAU may causally influence SA, as well as examine whether genetic risk for third variables (e.g., negative urgency, stress reactivity) may explain the genetic overlap between EAU and NSSI.

Self-harm can be broadly categorized into two main forms: suicide attempt (SA) and non-suicidal self-injury (NSSI), the latter of which is defined as deliberate destruction or alteration of body tissue in the absence of suicidal intent (Nock and Favazza 2009). Self-harm is the 18<sup>th</sup> leading contributor to the global disease burden and 13<sup>th</sup> highest contributor to years of life lost globally (GBD 2010 Country Collaboration 2013). Strikingly, SA is the second most common cause of death among individuals ages 10–24 (Patton et al. 2009). The cross-national lifetime prevalence of SA among adults is estimated at 3.1% (Nock et al. 2008), and meta-analysis has estimated that 5.5% of adults have engaged in lifetime NSSI, although due to the considerable heterogeneity in the methodology used to study NSSI (Swannell et al. 2014), estimates vary from study to study. In adolescent samples, prevalence rates are higher with 4.1% reporting SA (Nock et al. 2013) and approximately 17.2% of adolescents endorsing NSSI (Swannell et al. 2014). Although NSSI and SA are distinct phenotypically, they frequently co-occur, which is evident in both clinical and community samples (Bebbington et al. 2010; e.g., Nock et al. 2006). Furthermore, NSSI has been shown to be a risk factor for SA (see Hamza et al. 2012, for a review). More importantly, they both share similar clinical correlates, which further supports the notion that there may be common mechanisms underlying their co-occurrence.

Alcohol involvement has been strongly implicated in the epidemiology and clinical course of self-harm. Several cross-sectional studies have demonstrated a significant relationship between both adolescent and adult alcohol involvement (e.g., frequency of use; alcohol use disorder) and self-harm (Bagge and Sher 2008; Conner et al. 2014; Glowinski et al. 2001; Moller et al. 2013). Another prominent area of research has focused on acute use of alcohol prior to suicide, finding substantially increased risk for intoxication prior to suicide completion relative to non-suicidal controls (Kaplan et al. 2014). A few prospective studies have further demonstrated that distal adolescent alcohol use predicts both SA (Stewart et al. 2001) and NSSI (Tuisku et al. 2014). These findings are consistent with adult studies demonstrating that alcohol abuse and dependence predict prospective repetition of self-harm (Larkin et al. 2014).

Despite elevated rates of self-harm in adolescence, a particular aspect of alcohol involvement that has received somewhat less attention in relation to self-harm is early alcohol use (EAU). In general, EAU has been associated with a host of maladaptive outcomes, including alcohol problems and sexual risk-taking (Stueve and O'Donnell 2005), as well as lower education attainment (Grant et al. 2012). It has also been linked more specifically to increased risk for SA (Bossarte and Swahn 2011; Swahn et al. 2010; Swahn

and Bossarte 2007) and comorbid reports of SA and physical fighting among high school students (Swahn et al. 2013). Far fewer studies have examined EAU and NSSI. Among them is Giletta and colleagues' multinational study (2012), which found no association between frequency of binge drinking and NSSI among adolescents in three countries. However, this study did not differentiate between early vs. late adolescent initiators of alcohol use.

There are several potential theoretical explanations for the association between EAU and self-harm. One possibility is that these two phenotypes reflect shared genetic liability. There is inconsistent evidence for genetic influences on EAU (Agrawal et al. 2009; Prescott and Kendler 1999; Richmond-Rakerd et al. 2014; Sartor et al. 2009a) and evidence that genetic factors influence NSSI (Maciejewski et al. 2014) as well as SA (Glowinski et al. 2001). It is also possible that the overlap between EAU and self-harm reflects an underlying personality disposition, such as negative urgency (Dir et al. 2013) or that these behaviors may be a consequence of other known risk factors, such as childhood sexual abuse (Moller et al. 2013; Sartor et al. 2013). An alternative hypothesis that has not been explored is that the link between EAU and self-harm is causal, such that initiating drinking at a young age independently and directly increases the likelihood of subsequent self-harm. A median onset of SA in the mid-20s has been retrospectively reported in adult samples (Kessler et al. 1999), which is typically after initiation of alcohol use. In adolescent samples, the median age of onset of SA (Nock et al. 2013) and NSSI (Klonsky 2011) is 14, which is within the same age range as has been reported for EAU (Hingson and White 2014; Sartor et al. 2009b), suggesting that a causal relationship is plausible. The existing work linking these phenotypes, however, is cross-sectional, thus minimizing the ability to disentangle causality. In addition, it has focused solely on SA compared to NSSI. Lastly, these studies are unable to control for genetic risk factors in order to study causality.

Even in the absence of longitudinal data, cross-sectional twin samples offer a unique opportunity to elucidate potential mechanisms underlying the association between EAU and self-harm. Specifically, the relative role of shared genes and individual-specific environmental factors, which can exert putative causal influence, can be disentangled by selecting pairs of twins discordant for EAU. Monozygotic (MZ) twins share 100% of their genes and their shared familial environment, while dizygotic (DZ) twin pairs share 50% of their genes (and 100% of their shared familial environment). Therefore, an attenuation of the association between EAU and self-harm with increasing levels of genetic identity-by-descent (e.g. Unrelated pairs > discordant DZ pairs > discordant MZ pairs) reflects the role of shared genetic influences. Evidence for potentially causal effects can be gleaned by examining the extent to which the likelihood of self-harm is elevated in the early alcohol using twin in discordant MZ pairs. If the association is significant, then factors other than those shared by a pair of MZ twins contribute to the relationship. These factors could be causal (i.e. EAU directly causes self-harm) or related to a mediating individual-specific environmental factor. For example, EAU has been shown to result in maladaptive brain development and deficits in executive functioning (see Guerri and Pascual 2010, for a review), which may contribute to subsequent self-harming behaviors. Thus, even though the presence of longitudinal data is critical to establishing temporality and causation, the discordant twin approach can offer a window into possible non-genetic pathways for further study.

In the current study, we use data from a large population-representative sample of adult Australian twins (N=9591, ages 23–40 years) to examine whether (a) EAU is associated with SA and NSSI and further (b) whether this association persists in 698 discordant twins pairs (363 MZ and 335 DZ) after accounting for other early confounders (e.g., marijuana use, childhood sexual abuse, conduct disorder, etc.).

## METHOD

### Participants

The sample consisted of 9,591 adult twins from the Australian Twin Registry assessed in two separate cohorts. The first cohort of twins was born between 1964 and 1971 and interviewed between 1996 and 2000. The second cohort was born between 1972 and 1979 and interviewed between 2005 and 2009. More information on interview procedures and participant demographics is documented elsewhere (Lynskey et al. 2003, for more information on interview procedures and participant demographics; Lynskey et al. 2012). In the current study, we used data only from the 7,334 same-sex monozygotic (MZ) and dizygotic (DZ) twins. Lifetime non-drinkers (N=125) and singletons (N=1,127) were removed for the discordant twin analyses leaving 6,082 twin individuals (3,464 MZ and 2,618 DZ), ages 23–40 (mean age=30.47), 59% of whom were female. For the bivariate twin modeling, singletons were included in the analyses (MZ: 1,080 pairs + 287 unpaired; MSM: 652 pairs + 295 unpaired; MZF: 800 pairs + 254 unpaired; DZF: 504 pairs + 292 unpaired)

### Measures

All variables were assessed via interview using the Australian version of the Semi-Structured Assessment of the Genetics of Alcoholism (SSAGA-OZ).

**Early Onset Alcohol Use**—To assess EAU, participants who reported ever drinking in their lifetime were asked, “How old were you the first time you had a full drink of beer, wine or spirits?” Participants were previously told that a full drink is defined as “a standard can or stubbie of beer, a glass of wine, a nip of spirits, or any other kind of drink with alcohol in it.” The age threshold for determining EAU was based on examination of previous research reporting poor clinical outcomes associated with initiation of alcohol use before age 15 (see Hingson and White 2014, for a review; Sartor et al. 2009b) and the frequency distribution for initiation of alcohol use in the current study. Therefore, EAU was operationalized as drinking prior to age 15 which was associated with a prevalence of 20.42% ( 13: 12.14%; 15: 36.77%; 16: 60.28%). Therefore, participants received a 1 if they reported their first drink prior to age 15 (i.e., 14 years old or earlier), and a 0 if their first drink was at age 15 or older.

**Self-Harm**—The two self-harm variables were also dichotomously coded as 0 (“No”) or 1 (“Yes”). For SA, participants responded to the question, “Have you ever tried to take your own life?” This question was asked of all participants, not just those who reported depressed mood or suicidal thoughts. Following a positive endorsement of SA, age of onset for the first occurrence was also assessed. In order to maximize the ability to make causal inferences

regarding the association between EAU and self-harm, participants were excluded if they reported an age of SA onset prior to the age of onset of alcohol use. This resulted in 49 individuals being excluded for SA analyses. For NSSI, participants were asked, “(Other than when you tried to take your own life), have you ever hurt yourself on purpose, for example, by cutting or burning yourself?” Age of onset was not assessed for NSSI. For participants endorsing SA or NSSI, additional questions were asked including the method used in the most serious SA (e.g., medication ingestion, hanging, etc.) as well as the individual’s emotional/behavioral state prior to the SA (i.e., feeling depressed, drinking heavily, feeling extremely good or high, using drugs, having strange thoughts or experiences or seeing visions). In a subset of individuals, methods of NSSI (e.g., cutting, burning, etc.) were also assessed.

**Clinical Covariates**—Several clinical covariates were included in the analyses. In order for a covariate to be considered present, the age of onset had to occur either prior to or within the same year as the age of onset of alcohol use, thereby ensuring that it also occurred in the same year or prior to the age of onset of SA (although for NSSI, this could not be determined because of the lack of age of onset assessment). Dichotomous covariates included (a) *Depressed mood* was assessed by asking participants if there has “ever been two weeks or more when you were depressed or down most of the day, nearly every day.” (b) *Anhedonia* was operationalized as a two week period of being “a lot less interested in most things or unable to enjoy the things you need to enjoy.” (c) *Childhood sexual abuse* was assessed by asking participants if they were ever forced into sexual intercourse or sexual activity before the age of 18. (d) *Family history of suicide* was determined by having participants report on whether one of their relatives had ever committed suicide. (e) *Family history of excessive alcohol use* was assessed by asking participants if they have ever felt that either their biological mother or father was an excessive drinker. Notably, family history of suicide and excessive drinking were not included in the discordant twin analyses, because twins are matched for family history. In addition, a (f) *Risky Behavior* count variable was created via summation of four endorsed risky behaviors including *marijuana use*, operationalized as using the drug, even once, during the lifetime; *early smoking*, defined as smoking a cigarette at least one day a week for a period of three weeks or more; *early sex*, assessed by asking participants the age of first voluntary sexual intercourse; and *conduct problems*, defined as the presence of one or more conduct disorder symptoms (e.g., physical fighting, hurting animals, shoplifting). From this count variable, four dummy coded variables were created (all 4; 3 only; 2 only; 1 only). Lastly, gender was also included as a covariate but not in the discordant twin analyses, because twins are matched for gender.

**Data Analysis**—All of the data preparation and descriptive analyses were conducted using SAS. STATA was used for logistic regression analyses examining the association between EAU and self-harm variables. First, self-harm was characterized by examining the overlap between SA and NSSI, its association with EAU (adjusting for family structure), as well as methods of SA and NSSI among those with and without a history of EAU. Correlations between self-harm and EAU and other clinical covariates were then examined to identify variables to include in subsequent analyses. The prevalence of EAU and clinical covariates was also reported in individuals who endorsed self-harm versus those individuals who

denied a lifetime history of self-harm. We then examined the prevalence of self-harm across four groups: 1) twins concordant for early onset alcohol use (i.e., prior to age 15), 2) twins concordant for not using alcohol before the age of 15, 3) individuals from discordant twin pairs who reported early onset alcohol use, and 4) individuals from discordant twin pairs who did not drink before age 15. Prevalence of clinical covariates across these groups was also examined, and logistic regression was used to test whether the association between EAU and self-harm was significant after controlling for these covariates. Gender was also included as a covariate in this model.

The discordant MZ and DZ twin pairs were then utilized in conditional logistic regression analyses to examine the link between EAU and self-harm while accounting for shared predispositions. Importantly, to test whether associations were significantly different in discordant DZ and MZ pairs (the latter being critical for demonstration of causal/individual-specific environmental effects), an interaction term between zygosity (MZ or not) and EAU status was entered into the adjusted models. If the interaction was significant, then the unadjusted models were re-run in MZ and DZ twins separately to examine differences in ORs.

## Results

### Characterizing self-harm and its associations with EAU

The tetrachoric correlation between NSSI and SA was .53 ( $p < .01$ ). Of the 6,082 twins retained in the final sample, 247 (4.1%) reported a history of NSSI only, 144 (2.4%) reported SA only, and 59 (1.0%) participants endorsed a history of both NSSI and SA. The mean age of SA onset was 21.12 years (median=20.0). EAU was significantly associated with both NSSI and SA, with ORs of 2.41 (95% confidence interval [CI]: 1.89-3.07;  $p < .01$ ) and 2.35 (95% CI: 1.75-3.15,  $p < .01$ ), respectively (see Supplemental Table 1 for parameter estimates and test statistics).

There was no evidence for significant differences in features of SA or NSSI in those reporting EAU relative to the full sample. Across individuals reporting EAU and those with later onset, the most common methods of NSSI were cutting (67.88%) and burning (21.17%), while the most commonly reported methods for SA were ingestion of medication (56.10%) and bleeding, such as cutting wrists or stabbing self (20.70%). Further, for SA, 56% of individuals reporting EAU (versus 52.30% of later-onset users) reported intent to die and 45.33% (versus 53.91% of later-onset users) of individuals reported requiring treatment following the SA. Depressed mood, followed by being drunk, were the two most commonly reported emotional states prior to SA in the sample, regardless of EAU.

### Prevalence of early onset alcohol use, self-harm and clinical covariates

Table 1 provides the prevalence of EAU and clinical covariates among twin individuals with and without a history of self-harm. Among those reporting NSSI, the prevalence of EAU was 36.9% but only 19.6% for individuals without a history of NSSI. The prevalence of EAU was 37.0% and 20.0% for those with and without a history of SA, respectively.

All clinical covariates were significantly associated with self-harm variables (see Supplemental Table 2 for tetrachoric correlations and Chi-Square test results), with the exception of depressed mood and having endorsed only one risky behavior. Significant correlations ranged from .09 (two risky behaviors) to .38 (anhedonia, regardless of depressed mood) for NSSI, and from .13 (two risky behaviors) to .46 (childhood sexual abuse) for SA. Females reported significantly more SA relative to males,  $\chi^2(1, 6033)=7.23$ ,  $p<.01$ , but there were no significant gender differences for NSSI. For all clinical covariates except the dummy coded variable encompassing individuals reporting only risky behavior, prevalence rates were higher among those with a history of self-harm (i.e., 95% confidence limits did not overlap). Again, this was not the case for depressed mood, which was removed from subsequent analyses due to the lack of an association with the self-harm variables<sup>1</sup>. The ORs between EAU and self-harm remained significant when adjusting for these clinical covariates (NSSI: OR=2.71, 95% CI: 2.10-3.51; SA: OR=2.56, 95% CI: 1.89-3.54; see Supplemental Table 1 for parameter estimates and test statistics).

The prevalence of SA and NSSI in the full sample most closely approximated estimates from individuals (in concordant and discordant twin pairs) who did not endorse EAU (Table 2; columns 2 and 3). Chi-square tests revealed no significant differences between the prevalence rates of SA and NSSI by EAU status, nor were their differences in self-harm between twins in concordant and discordant pairs who endorsed EAU (columns 4 and 5). However, within the discordant pairs, EAU was associated with significantly higher rates of both SA,  $\chi^2(1, N=1396)=6.93$ ,  $p<.01$ , and NSSI,  $\chi^2(1, N=1396)=14.40$ ,  $p<.01$ , relative to prevalence rates of self-harm for the non-EAU co-twins (columns 3 and 4).

### Early onset alcohol use and risk for self-harm

The mean discordance within twin pairs for EAU was 3.61 years. Within the discordant pairs (Table 3), the twin reporting EAU was at nearly three-fold increased likelihood of also reporting NSSI (OR=2.75, 95% CI: 1.65-4.59,  $p<.01$ ) relative to their later onset co-twin. A significant elevation in odds for SA was also observed (OR=2.40, 95% CI: 1.31-4.38,  $p<.05$ ). When adjusting for covariates, EAU resulted in a nearly eight-fold increased likelihood of NSSI (OR=7.62, 95% CI: 2.58-22.54,  $p<.01$ ) and an almost four-fold increased likelihood of SA (OR=3.72, 95% CI: 1.19-11.64,  $p<.05$ ), although the confidence limits around these point estimates were wide. Only anhedonia emerged as a significant covariate for SA. All parameter estimates and test statistics are reported in Supplemental Table 1.

Finally, the zygosity interaction term, reflecting whether the strength of the association differed across discordant MZ and DZ pairs was not significant for SA ( $p=.96$ ) and was nominally significant for NSSI ( $p=.054$ ). Therefore, we examined the association between EAU and NSSI separately for MZ ( $n=363$ ) and DZ ( $n=335$ ) twin pairs (results presented in Table 3). The association was significant for the DZ pairs alone (OR=4.86, 95% CI: 2.15-10.96,  $p<.01$ ; see Supplemental Table 3 for parameter estimates and test statistics).

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<sup>1</sup>A dichotomous variable was also created by combining depressed mood and anhedonia (i.e., scored "1" if either were endorsed). Correlations were .09 and -.04 for NSSI and SA, respectively. Hence, only anhedonia, which was significantly correlated with self-harm was included in discordant twin models.



As the zygosity difference indicated the role of overlapping genetic but not individual-specific environmental influences on the covariance between EAU and NSSI, we fit a bivariate twin model in Mx (Neale, 2004) to all available same-sex twin data. EAU was moderately heritable (0.33, 95% C.I. 0.10 – 0.57) with the remainder of the variance attributable to shared (0.22, [95% C.I. 0.02-0.41]) and individual-specific environmental (0.45, [95% C.I. 0.35-0.60]) factors. Consistent with prior work, 54% (95% CI: 0.40 – 0.65) of the variance in NSSI could be attributed to broad sense heritability (A+D; see Maciejewski et al., 2014) with the remainder accounted for by individual-specific environmental factors (0.46 [95% CI: 0.35-0.60]). In line with the findings from the discordant twin modeling, a moderate genetic correlation emerged between EAU and NSSI ( $r_G=0.35$ , 95% CI: 0.14-0.70). The corresponding environmental correlation was modest ( $r_E=0.24$ , 95% CI: 0.05-0.42). Power to resolve whether genetic or individual-specific environmental influences exclusively influenced the covariation was limited as both  $r_G$  and  $r_E$  could be individually constrained to zero but not both.

We also conducted a number of sensitivity analyses. To examine whether our results were sensitive to the age threshold for EAU, we reran the discordant twin analyses using age cutoffs of 13 and 15 years. Due to power limitations, the SA model for 13 years could not be estimated, but for 15 years, the adjusted OR (3.45) was significant and highly comparable to the existing results. Adjusted ORs were significant for NSSI using both age cutoffs: 13 (OR=10.91) and 15 (OR=3.56), which is also consistent with the current findings. Notably, confidence limits around point estimates were extremely wide when 13 years was used for the EAU cutoff, suggesting that our choice of 14 years optimizes power while also capturing individuals with early onsets. Additional analyses examined whether results from the discordant twin models were sex or cohort specific. Neither the interaction of EAU with sex nor with cohort was significant indicating that the results generalize to both men and women and across both twin samples.

## Discussion

Self-harm is associated with considerable costs, individually, socially and economically, and therefore, understanding its etiology is critical in order to identify potential intervention targets. The current study was the first, to our knowledge, to examine mechanisms underlying the association between EAU and self-harm, while controlling for shared environmental and genetic influences. Broadly, prevalence rates of lifetime self-harm in the current study were comparable to those reported in meta-analytic work using adult samples (Nock et al. 2008;Swannell et al. 2014), but they were somewhat lower than those reported in adolescent samples (Nock et al. 2013;Swannell et al. 2014). This discrepancy between lifetime self-harm (and particularly NSSI) in adolescents relative to adults is perplexing, and potential explanations for this include recent increases in adolescent self-harm and/or retrospective reporting bias by adults, the latter of which is more consistent with existing literature (see Nock et al. 2008). The results of this study also confirm the established overlap between NSSI and SA (Hamza et al. 2012) (Hamza, Stewart, & Willoughby, 2012), as approximately 13% of those endorsing lifetime self-harm (i.e., 59 out of 450) reported a history of both SA and NSSI.

In terms of the link between EAU and self-harm, the prevalence of EAU was substantially higher among those with a reported history of SA or NSSI, and, even after controlling for other potential early risk factors (e.g., childhood sexual abuse, conduct disorder, anhedonia, early drug use, family history of suicide, etc.), EAU was significantly associated with increased risk for both NSSI (OR=2.71) and SA (OR=2.56). These results confirm previous findings linking EAU to SA (e.g., Bossarte and Swahn 2011; Swahn et al. 2010). Although there is less research examining EAU in relation to NSSI, the current findings are consistent with research in high-risk adolescent samples demonstrating that alcohol use predicts NSSI at a one-year follow-up (Tuisku et al. 2014).

The prevalence of self-harm was also examined in the full sample and across four groups, which differed in concordance and exposure to EAU. The prevalence of SA and NSSI was significantly higher in twin pairs concordant for EAU and in the EAU exposed twin in discordant pairs relative to twin pairs concordant for no EAU and unexposed twins in discordant twin pairs. However, there were no significant differences in the latter two groups, which would be expected if shared predispositions were strongly influencing the co-occurrence of EAU and self-harm. Importantly, the elevated rates of both SA and NSSI among EAU exposed twins from discordant pairs relative to their unexposed co-twin suggest that the link between these phenotypes is either causal or due to individual-specific factors. In other words, if there were shared familial factors strongly influencing EAU and self-harm, it would be expected that twin pairs - who share genes and the familial environment - would exhibit similar rates of self-harm regardless of exposure to EAU, which was not the case. Importantly, however, these analyses did not differentiate between MZ and DZ discordant pairs to examine whether the association between EAU and self-harm depends on the level of genetic similarity, nor did they take into account other clinical variables (e.g., conduct disorder) which may be influencing this relationship. Therefore, more rigorous tests of the link between EAU and both SA and NSSI were examined among discordant twin pairs when controlling for zygosity and other clinical covariates.

In these more stringent analyses within discordant twin pairs, the risk for SA among those reporting EAU was elevated nearly four-fold even after controlling for other potentially causal influences (e.g., childhood sexual abuse, other substance use). This elevated risk for SA among twins who reported drinking prior to age 15 could reflect individual specific factors that precede EAU, such as other traumatic childhood events or different peer groups that facilitate risky behavior. For example, Trucco and colleagues (2011) found that peer delinquency prospectively predicts peer approval of alcohol and peer use, which in turn predicted initiation of alcohol use among adolescents. Delinquency during adolescence has been linked to a number of maladaptive outcomes, including less positive parenting (Trucco et al. 2011), and furthermore, lack of perceived familial support has been associated with SA (Miller et al. 2015; Wolff et al. 2013). Therefore, these unshared individual-specific influences may be critical in understanding the link between EAU and SA. However, these findings also support the possibility of a causal pathway from EAU to SA. This is consistent with epidemiological research in multiple countries implicating EAU among boys and girls as a risk factor for SA (Kim and Kim 2010; Swahn et al. 2010; Swahn et al. 2012; Swahn and Bossarte 2007). All of these studies controlled for additional childhood risk factors, but

importantly, did not control for shared familial influences. Thus, the current study enables the assertion that the link between EAU and SA is potentially independent from genetic or shared environmental factors.

With this said, we did not examine intermediate variables, or individual-specific *consequences* of EAU, that may explain the causal link between EAU and SA. For example, it's possible that EAU may exert risk for SA via the development of more problematic alcohol use, such as an alcohol use disorder, which is elevated among those reporting early onset drinking (Grant and Dawson 1997; Sartor et al. 2007). Furthermore, the median age of onset of SA in the current study is identical to the median age of onset for both alcohol abuse and dependence in the Australian population (i.e., 20 years; Teesson et al. 2010), which indicates that alcohol use disorders may be an important phenotype to consider in this pathway. It is also possible that EAU contributes to alterations in brain regions that influence response inhibition, which in turn increases risk for later SA. Wetherill and colleagues (2013) found differences in activation of brain regions associated with inhibitory control (e.g., frontal regions) both before and after the onset of heavy drinking among adolescents relative to non-drinking controls. Alterations in frontal brain regions associated with decision-making/inhibition have also been identified among individuals with a history of SA (see van Heeringen et al. 2011, for a review). Therefore, future studies should examine these potential mediators explaining the linking between EAU and SA.

For NSSI, results from the discordant twin analysis demonstrated substantially increased risk for twins reporting EAU (OR=7.62). However, odds for NSSI were increased only for DZ twins who reported EAU, but not for MZ twins, thereby suggesting that correlated genes may explain the association between EAU and NSSI. These findings indicate that differences in prevalence rates of NSSI between EAU exposed and unexposed co-twins were likely driven by genes unshared by DZ twins. The nonsignificant association in MZ twins pairs is inconsistent with bivariate twin analyses demonstrating a significant environmental correlation between EAU and NSSI ( $r_E=0.24$ ), which could reflect limited power in the discordant twin analyses. In line with the discordant results, however, the bivariate twin analyses indicated that both EAU and NSSI were influenced by genetic factors, and furthermore, the significant genetic correlation showed that a portion of these genetic influences are shared ( $r_G=0.35$ ). Notably, previous work has found limited evidence for genetic influences on EAU and instead exclusively highlighted the role of unique and shared environmental factors (Richmond-Rakerd et al., 2014). Alternatively, results from the current study, which did not include opposite-sex pairs or unpaired twins, are consistent with research demonstrating that both EAU (heritability=.36; Young-Wolff et al. 2012) and NSSI (heritability=.59 for women and .37 for men; Maciejewski et al. 2014) are partially influenced by genetic factors. One plausible explanation for these results is that this shared genetic liability may reflect vulnerability to other forms of psychopathology, such as borderline personality disorder, or to dispositional risk factors not assessed in the current study, namely disinhibition or negative urgency, a facet of impulsivity that manifests as a tendency to engage in rash behavior when experiencing negative emotions (Whiteside and Lynam 2003). For example, Squeglia and colleagues (2014) have demonstrated that poor inhibitory control predicts early adolescent transition to alcohol use. Self-reported

impulsivity, and more specifically negative urgency, has also been linked to self-harm (Hamza et al. 2015), although these findings do not translate to laboratory-based measures of impulsivity. Therefore, future research should examine whether the association between EAU and self-harm remains when controlling for personality traits and other dispositional factors.

There are several limitations of the current study, namely the use of retrospective reporting of both self-harm and age at first drink, the latter of which may be susceptible to reporting bias (Sartor et al. 2011). Additionally, due to the lack of assessment of the age of onset of NSSI, the hypothesis that EAU exerts a causal influence on subsequent NSSI could not be fully tested (i.e., participants who engaged in NSSI prior to their first drink could be included in the analyses). Future studies would benefit from more detailed assessment of the time of initiation of these self-harm behaviors relative to initiation of alcohol use. Larger sample sizes could also confirm the differential odds of NSSI for MZ and DZ twins endorsing EAU, which would substantiate the lack of a causal pathway between these phenotypes observed in the current study. Additionally, due to lack of power, it was not possible to examine potential differences in the link between EAU and subgroups of individuals engaging in SA. Previous work has established that cannabis use is associated with increased odds for SA, but only for unplanned rather than planned attempts (Delforterie et al. 2015). Therefore, it may be the case that other substance use, such as EAU, may be related to certain types of SA. It is also possible that NSSI and SA were somewhat confounded in the current study, in that only about half of individuals endorsing SA reported intent to die. Therefore, future studies should examine the association between EAU and SA with intent relative to SA without intent. Finally, the current study was a homogenous Caucasian sample from Australia, so these findings may not generalize to other samples, particularly given research demonstrating differences in the association between NSSI and substance use across cultures (Giletta et al. 2012) and in the heritability of age at first drink for African-Americans and European Americans (Sartor et al. 2013).

In conclusion, the results of the current study confirm previous research demonstrating an association between EAU and self-harm. Specifically, the findings suggest that shared genes influence the link between EAU and NSSI, and that there may be a putatively causal link between EAU and SA. This highlights the need for further studies aimed at identifying genetic factors (e.g., predisposition to negative urgency) that contribute to the overlap between EAU and NSSI and through which EAU may causally influence SA (e.g., brain development). The results also suggest that interventions aimed at delaying initiation of alcohol use may be influential in minimizing risk for SA.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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**Table 1**

Prevalence (%) and 95% confidence limits of EAU and clinical covariates among twins with and without a history of self-harm

|                                      | NSSI                   |                        | SA                     |                        |
|--------------------------------------|------------------------|------------------------|------------------------|------------------------|
|                                      | Present                | Absent                 | Present                | Absent                 |
| Early alcohol use (EAU)              | 36.93<br>(31.52–42.34) | 19.55<br>(18.52–20.57) | 36.95<br>(30.31–43.59) | 19.97<br>(18.94–20.99) |
| Depressed mood                       | 26.47<br>(21.53–31.41) | 25.43<br>(24.31–26.56) | 19.70<br>(14.23–25.18) | 25.56<br>(24.44–26.68) |
| Anhedonia                            | 16.67<br>(12.49–20.84) | 3.95<br>(3.45–4.45)    | 15.76<br>(10.75–20.78) | 3.96<br>(3.46–4.46)    |
| Childhood sexual abuse               | 19.28<br>(14.86–23.70) | 6.58<br>(5.94–7.22)    | 30.54<br>(24.29–37.38) | 6.16<br>(5.54–6.77)    |
| Family history of SA                 | 19.93<br>(15.46–24.41) | 8.95<br>(8.21–9.69)    | 18.23<br>(12.92–23.54) | 9.11<br>(8.37–9.85)    |
| Family history of excessive drinking | 34.31<br>(28.99–39.63) | 24.74<br>(23.63–25.85) | 38.92<br>(32.21–45.62) | 24.67<br>(23.56–25.77) |
| Risky behavior                       |                        |                        |                        |                        |
| - 1                                  | 38.89<br>(33.43–44.35) | 37.00<br>(35.75–38.24) | 35.96<br>(29.36–42.56) | 37.26<br>(36.01–38.50) |
| - 2                                  | 22.22<br>(17.56–26.88) | 17.04<br>(16.07–18.03) | 25.12<br>(19.16–31.09) | 16.95<br>(15.98–17.91) |
| - 3                                  | 17.32<br>(13.08–21.56) | 7.70<br>(7.02–8.39)    | 17.24<br>(12.05–22.44) | 7.75<br>(7.07–8.44)    |
| - 4                                  | 4.58<br>(2.52–7.56)    | 2.30<br>(1.92–2.69)    | 4.93<br>(1.95–7.90)    | 2.23<br>(1.85–2.61)    |

*Note:* SA=suicide attempt; NSSI=non-suicidal self-injury; EAU=prior to age 15; covariates were only considered present if occurring prior to or within the same year as EAU; Risky behavior=the number of risky behaviors endorsed (i.e., ever use of marijuana, smoking a cigarette a day at least one day a week for 3+ weeks, early voluntary sexual intercourse, and 1+ conduct disorder symptoms)

Prevalence (%) and 95% confidence limits of self-harm among all twins, concordant +, concordant -, and discordant early alcohol users vs. discordant non-EAU co-twin

**Table 2**

|               | All twins           | Concordant for no EAU use (n=4142) | No EAU twin from disc pairs (n=698) | EAU twin from disc. pairs (n=698) | Concordant for EAU (n=544)        |
|---------------|---------------------|------------------------------------|-------------------------------------|-----------------------------------|-----------------------------------|
| SA (n=6033)   | 3.36<br>(2.91–3.82) | 2.58 <sup>a</sup><br>(2.10–3.07)   | 3.18 <sup>a</sup><br>(1.87–4.49)    | 6.17 <sup>b</sup><br>(4.38–7.96)  | 5.90 <sup>b</sup><br>(3.92–7.89)  |
| NSSI (n=6082) | 5.03<br>(4.50–5.61) | 3.98 <sup>a</sup><br>(3.39–4.58)   | 4.01 <sup>a</sup><br>(2.56–5.47)    | 9.03 <sup>b</sup><br>(6.90–11.15) | 9.19 <sup>b</sup><br>(6.76–11.62) |

Note:

<sup>a,b</sup> similar superscripts in rows indicate prevalence rates that could be statistically equated to each other based on Chi-Square tests.

**Table 3**

Odds of lifetime self-harm in the early alcohol using twin relative to the later using twin

| Outcome              | Unadjusted Conditional Odds Ratio | Adjusted Conditional Odds Ratio | Significant covariates |
|----------------------|-----------------------------------|---------------------------------|------------------------|
| SA<br>(n=1388)       | 2.40**<br>(1.31–4.38)             | 3.72*<br>(1.19–11.64)           | Anhedonia *            |
| NSSI<br>(n=1396)     | 2.75**<br>(1.65–4.59)             | 7.62**<br>(2.58–22.54)          | none                   |
| NSSI (MZ)<br>(n=726) | 1.62<br>(0.81–3.23)               | -                               | -                      |
| NSSI (DZ)<br>(n=670) | 4.86**<br>(2.15–10.96)            | -                               | -                      |

Note:

\*  
 $p < .05$ ;\*\*  
 $p < .01$ ;

SA=suicide attempt; NSSI=non-suicidal self-injury; MZ=monozygotic; DZ=dizygotic; Adjusted model covariates include: anhedonia, childhood sexual abuse, risky behavior (4 dummy coded variables representing the number of risky behaviors endorsed: marijuana use, early smoking, early sex, conduct problems)