

## Research paper

## Associations between major depressive symptoms and drinking onset: Do sex and age matter?

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## ABSTRACT

**Background:** There has been mixed evidence about whether major depression predicts drinking onset. Empirical evidence about whether the heterogeneity of major depressive symptoms differentially predicts drinking onset is scarce, and potential sex- and age-variations have not been fully studied. In this study, we estimate sex- and age-specific relationships linking (a) depressed mood and/or anhedonia with drinking onset among all ‘at-risk’ individuals and (b) three latent depressive constructs, manifested by 13 clinical features, with drinking onset among individuals with depressed mood and/or anhedonia.

**Methods:** Study population was non-institutionalized civilian residents 12 years of age and older living in the United States. Major depressive symptoms and drinking onset were assessed via audio-computer-assisted self-interviews. Logistic regressions and structural equation modeling were used for analysis.

**Results:** Among all ‘at risk’ individuals, depressed mood or anhedonia strongly predicted early-adolescent drinking onset, whereas they did not predict at-age drinking onset. Among individuals with depressed mood or anhedonia, a 3-factor model provided a good fit to the data for all sex- and age-subgroups. With the exception of early-adolescent boys, neurovegetative symptoms and suicide-related symptoms tended to positively predict underage drinking onset, whereas Low mood or energy tended to inversely predict underage drinking onset; limited evidence was found for at-age and post-21 drinking onset.

**Limitations:** The observational nature precludes causal inference. Few people initiated alcohol drinking later than 21 years of age, which resulted in less precise estimates.

**Conclusions:** Strengths and directions of major depressive symptoms predicting drinking onset vary across age, sex, and depressive symptoms.

## 1. Introduction

Alcohol consumption is common in the United States (US) (Center for Behavioral Health Statistics and Quality, 2018a; Cheng et al., 2016a; Johnston et al., 2019). Over 80% of the US population took their first full drink before the age of 21 years, the minimum legal drinking age (Cheng et al., 2016a). It has been a leading cause of premature death and disability, especially among adolescents and young adults (Murray et al., 2018). Underage drinking can induce irreversible changes to the developing brain and has been associated with a range of potential short-term and long-term negative consequences, including traffic accidents, violence, high-risk sex, and the development of alcohol dependence and other mental or behavioral disorders (Brown et al., 2009; Koob and Volkow, 2016; Miller et al., 2015; Zucker et al., 2008). Therefore, the identification of individuals

at high-risk for drinking onset, especially underage drinking onset, can help alleviate the substantial personal and societal burden associated with drinking-related problems.

Major depressive disorder (MDD) is a psychiatric condition characterized by persistent feelings of sadness (depressed mood) and loss of interest (anhedonia). It is manifested by a cluster of behaviors and experiences that often co-occur (American Psychiatric Association, 2013). Major depressive disorder is common among adolescents (Merikangas et al., 2010), and there has been a sizable increase in the prevalence of adolescent major depressive episode during the past decade in the US, from 8.7% in 2005 to 11.3% in 2014 and 13.3% in 2017 (Center for Behavioral Health Statistics and Quality, 2018a; Mojtabai et al., 2016). Major depressive disorder and alcohol drinking as well as drinking-related problems often co-occur (Blumenthal et al., 2019; Hasin et al., 2007; Kessler et al., 2005). A few studies have

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investigated whether MDD or MDD symptoms predicted drinking onset and found mixed evidence: some support a positive relationship linking antecedent MDD (King et al., 2004) or MDD symptoms (Johannessen et al., 2017; Kaplow et al., 2001; Wu et al., 2006) with drinking onset; however, null relationships (Hallfors et al., 2005 for MDD symptoms; McGue et al., 2001 for MDD) have also been documented. In addition, a study on internalizing symptoms among children found inverse relationships between a composite internalizing symptom score and drinking onset (Stice et al., 1998).

Sex differences have been observed in both MDD and alcohol drinking. At the population level, a female excess in MDD and a male excess in alcohol drinking and other drinking-related outcomes have been well documented (Anthony et al., 1994; Hasin et al., 2007, 2005; Kessler et al., 1997; Merikangas et al., 2010). With respect to the relationship between MDD or MDD symptoms and drinking, stronger associations have been shown for females compared to males (Johannessen et al., 2017; KUO et al., 2006; Saraceno et al., 2012).

Similarly, there is substantial age variation in the prevalence of MDD and alcohol drinking, both of which show incremental increases during adolescence (Breslau et al., 2017; Cheng et al., 2016a). Furthermore, sex differences vary across age for both MDD and alcohol drinking. For major depressive episode (i.e., a condition when diagnostic criteria for major depressive disorder are met without consideration of the diagnostic hierarchy), female excess emerges during early adolescence and persists into adulthood (Breslau et al., 2017). In contrast, for the onset of alcohol drinking, recent evidence suggests early-adolescent female excess, late-adolescent parity, and male excess in adulthood (Cheng et al., 2016b).

A few studies that investigated the association between MDD and drinking-related outcomes across age yielded mixed findings. For example, Kuo and colleagues found that the strength of the association between antecedent MDD and alcohol dependence tended to decrease with age (KUO et al., 2006). In contrast, results from a large cohort study suggest MDD may play a more important role for adult-onset (vs. adolescent-onset) alcohol dependence (Meier et al., 2013). As mentioned above, MDD is classified by a cluster of inter-correlated symptoms resulting from potentially heterogeneous underlying mechanisms. To our best knowledge, symptom-level prediction of drinking onset has not been investigated in the general US population.

Central to MDD is low mood and anhedonia; other manifestations include weight or sleep change, low energy, and suicidal thoughts and behaviors. These manifestations may differentially predict drinking onset across age and sex. Most previous studies have studied MDD or the occurrence of any MDD symptoms as a binary outcome (i.e., ‘yes’ or ‘no’) or the number of MDD symptoms as a count, assigning equal weights to each major depressive symptom assessed. The lack of evidence about symptom-level relationships is a major gap in knowledge when trying to predict the onset of drinking. Moreover, despite the aforementioned robust variations across age groups and between males and females in both MDD and drinking onset, there has been a lack of evidence about whether MDD symptoms predict drinking onset differentially across age- and sex-subgroups.

In this study, we hypothesize heterogeneity in the direction and extent of MDD symptoms predicting drinking onset (1) between males and females, (2) across age groups, and (3) across depressive symptoms. Our hypotheses are grounded in lines of evidence cited above as well as evidence from related fields. For example, a 4-year follow-up study found differential relationships linking various dimensions of anxiety symptoms - another manifestation of internalizing problems that frequently co-occur with depression - with drinking onset among 9-to-13-year-old children. Specifically, separation anxiety was inversely associated with drinking onset, whereas generalized anxiety was positively associated with drinking onset. As a result, the overall level of anxiety was not predictive of drinking onset due to opposite directionalities of these relationship (Kaplow et al., 2001). In the current study, we query the association between MDD symptoms and drinking onset from two

perspectives. First, we examine the relationship between depressed mood and/or anhedonia and drinking onset among all individuals who were at risk for drinking onset. In this study, the “at risk” population consisted of all individuals who had not had their first drink before the 12 months prior to the assessment. Second, we explore how constructs of MDD symptoms among individuals with depressed mood and/or anhedonia are related to drinking onset. Importantly, we examine these associations separately by sex and age subgroups. Prominent features of this study include (a) our sole focus on the risk of becoming a new drinker without any interference from the persistence of drinking (i.e., continued drinking after the first drink), as in prevalence-based measures (Kramer, 1957; Lapouse, 1967), (b) the use of a structural equation modeling approach to investigate potential variations across depression dimensions, and (c) enhanced external validity by using representative samples of US non-institutionalized civilian adolescent and adult population. In this study, the recall period for drinking onset is no longer than the prior 12 months, which helps minimize potential biases associated with memory errors and delineate temporal relationships between depressive symptoms and drinking onset.

## 2. Materials and methods

### 2.1 study population and design

The study population consisted of non-institutionalized civilian residents of the United States 12 years of age and older. Data were from the National Surveys on Drug Use and Health (NSDUH) 2004–2018. A multi-stage probability sampling scheme with over-sampling of 12–17 year olds was used to draw representative samples ( $n > 55,000$  for each year). The response levels were between 49% and 76% in 2004–2018 (Center for Behavioral Health Statistics and Quality, 2018b; <https://www.datafiles.samhsa.gov/study/national-survey-drug-use-and-health-nsduh-2018-nid18757>). Assessments were conducted after child assent and parental consent obtained by an IRB-approved protocol. The resulting sample consisted of 821,346 individuals, among whom 273,021 were ‘at risk’ for drinking onset (i.e., after excluding individuals who had their first drink more than 12 months ago). A total of 5353 individuals had missing values in all depressive symptoms. Therefore, the final analytic sample size was 267,668.

### 2.2. Assessment of drinking onset

Confidential audio computer assisted self-interviews (ACASI) were used to collect information about the month and year of the first full drink and the age of first full drink via a standard NSDUH multi-item alcohol module (United States Center for Behavioral Health Statistics and Quality, 2018b). New drinkers are defined as individuals who took their first full drink during the 12 months prior to the assessment. Incidence of drinking (i.e., the risk of becoming a new drinker) is defined as the number of new drinkers divided by the number of ‘at risk’ population comprised of new drinkers and never drinkers using an ‘age-of-onset’ approach, which is given by,

$$\text{Incidence} = \frac{\text{newdrinkerswhohad1stdrinkatparticularageduring12monthspriortoassessment}}{\text{neverdrinkersassessedatparticularage} + \text{newdrinkersinthenumerator}}$$

More details about this approach are provided elsewhere (Cheng et al., 2017).

### 2.3. Assessment of major depressive symptoms and other covariates

In this study, participants were asked to consider the time during which symptoms of major depression were at their worst prior to the assessment. Major depressive symptoms were assessed for adolescents and adults with two respective modules (namely ‘Adolescent Depression’ and ‘Adult Depression’). An identical list of symptoms was assessed in these two modules with slight differences in wording

adapted to youth or adult audience. The assessment of depressive symptoms followed the DSM-IV diagnostic hierarchy for major depressive episode. First, participants provided information about whether they had experienced either depressed mood or anhedonia (i.e., loss of interest/pleasure), and if so, whether these symptoms lasted “most of the day almost every day for two weeks or longer”. Next, participants who provided positive answers to the above questions were asked three questions about the duration, frequency, and intensity of their symptoms. Participants were asked questions about additional major depressive symptoms only when their depressed mood and/or anhedonia were rated as at least ‘moderate’ and lasting at least an hour per day, and they felt at least ‘sometimes’ cannot be cheered up. To ease discussion, we refer to this conditional skip as the ‘depressive mood/anhedonia threshold’ hereafter. Information about the following 13 additional depressive symptoms were obtained via standardized questions: (i) appetite change, (ii) weight change (weight loss or weight gain), (iii) sleep problems (insomnia or hypersomnia), (iv) fatigue or loss of energy, (v) slow thinking, (vi) physical or motor retardation, (vii) diminished ability to think or concentrate, (viii) indecisiveness, (ix) feelings of worthlessness or excessive or inappropriate guilt, (x) recurrent thoughts of death, (xi) suicidal ideation, (xii) suicidal plan, and (xiii) suicidal attempt. Actual survey questions can be found in NSDUH questionnaires (<https://www.datafiles.samhsa.gov/study-series/national-survey-drug-use-and-health-nsduh-nid13517>).

Sex was based on self-reported information about being male or female. Age was based on self-reported date of birth. We categorized age into the following six groups: 12–14 (early adolescence), 15–17 (late adolescence), 18–20 (early adulthood), 21 (legal minimum drinking age), 22–25 (post legal drinking age), and 26 and older (post-post legal drinking age). The categorization of age groups was guided by both general developmental and socioenvironmental changes a person typically experiences and a nonlinear curve for the risk of drinking onset documented in the literature (Cheng et al., 2016a, 2016b). When self-reported information about sex or age was missing, information from the household roster was drawn.

## 2.4. Analysis

In the initial analysis step, we estimated sex- and age-group-specific odds ratios linking major depressive symptoms with drinking onset. Based on the theoretical model for major depression and due to the nature of the assessment, two sets of regressions were conducted to assess the association between (a) either depressed mood or anhedonia and drinking onset among all participants under study, and (b) each of the 13 additional items relating to major depressive symptoms and drinking onset among those who had either depressed mood or anhedonia ( $n = 33,991$ ). We used logistic regression to estimate the

association between depressed mood/anhedonia and drinking onset. For the second set of regressions, we used generalized estimation equations (GEE) with a robust estimator to take into account the inter-correlation of the 13 items relating to major depressive symptoms, (Liang and Zeger, 1986).

In subsequent analysis steps, we conducted exploratory factor analysis using a random 10% of the sample to investigate the factor structure of the 13 items among individuals who had depressed mood or anhedonia. The best fitting model was determined by jointly considering the substantive meaning of the factor structure and fit indices (i.e., the eigenvalue; Root Mean Square Error Of Approximation, RMSEA; Tucker Lewis Index, TLI; Comparative Fit Index, CFI; Standardized Root Mean Square Residual, SRMR; and correlation coefficient across factors). Previous studies suggest that  $RMSEA < 0.08$ ,  $TLI/CFI > 0.95$ , and  $SRMR < 0.08$  are indications of good model fit (Bentler, 1990; Hu and Bentler, 1999; Vuong, 1989).

After assessing the fitting of the chosen factor structure using confirmatory factor analysis, we estimated the association between each dimension of major depressive symptoms and drinking onset by sex and age among individuals who experienced depressed mood or anhedonia using structural equation models. Both confirmatory factor analysis and structural equation models were conducted using the remaining 90% of sample. Due to small numbers of new drinkers in the 22–25 and 26+ group, we combined the two oldest groups for factor analysis and structural equation models.

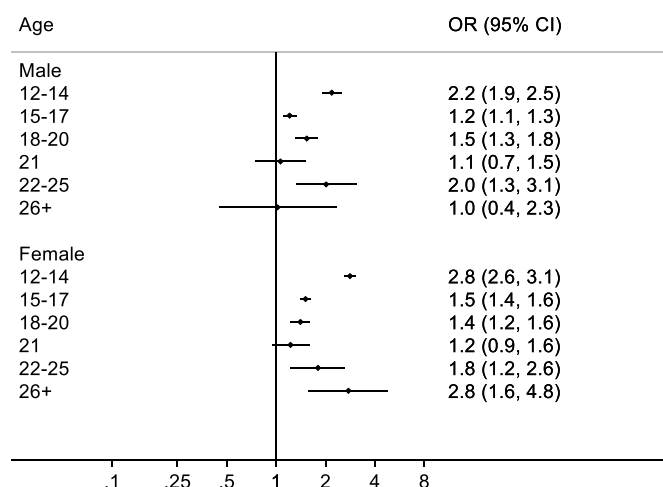
In this study, all analyses were weighted using NSDUH year-specific analysis weights that account for sample selection probabilities and post-stratification adjustment factors based upon US Census sub-population counts. (The depression module was administered to a random half sample in 2004. Therefore, a weight generated specifically for depression-related analysis was used for 2004 data.) Standard errors and 95% confidence intervals (CI) for drinking incidence and logistic regression were from Taylor Series linearization. A robust weighted least squares estimator was used for factor analysis and structural equation models to account for the stratified sample design. A probit link was used for estimation in structural equation models.

## 3. Results

Table 1 shows estimated sex- and age-specific drinking incidence for individuals who had and had not experienced low mood or anhedonia during the 12 months prior to the assessment, and Fig. 1 presents the association between low mood or anhedonia and drinking onset. For females, higher drinking incidence was observed for those who experienced low mood or anhedonia compared to those who did not although the difference was not statistically significant for the 21-year-old age group. The strength of association showed a U-shaped pattern

**Table 1**  
Incidence (%) of drinking onset stratified by the presence of depressed mood or anhedonia. Data from National Survey on Drug Use and Health 2004–2018.

Age (years)	Depressed mood or anhedonia	Male			Female		
		Drinking incidence			Drinking incidence		
		n	%	95% CI	n	%	95% CI
12–14	No	50,004	6.6	6.3, 6.9	43,907	7.5	7.2, 7.9
	Yes	3395	13.4	12.0, 14.9	8205	18.6	17.6, 19.7
15–17	No	34,971	20.5	20.0, 21.1	28,743	21.6	20.9, 22.2
	Yes	4451	23.8	22.2, 25.4	8741	29.3	28.0, 30.7
18–20	No	13,727	22.9	22.0, 23.9	13,267	23.7	22.7, 24.7
	Yes	1430	31.4	28.3, 34.7	2353	30.4	28.0, 33.0
21	No	3012	50.8	48.3, 53.3	3365	54.3	51.9, 56.6
	Yes	290	52.3	43.9, 60.7	484	59.2	53.3, 64.9
22–25	No	4805	6.3	5.3, 7.4	6510	6.5	5.7, 7.5
	Yes	430	11.9	8.3, 16.7	699	11.1	8.1, 15.1
26 +	No	11,486	0.6	0.4, 0.8	23,260	0.4	0.3, 0.5
	Yes	761	0.6	0.3, 1.2	1988	1.1	0.7, 1.8



**Fig. 1.** Association between Depressive Mood or Anhedonia and Newly Incident Alcohol Drinking. Data from National Survey on Drug Use and Health 2004–2018. OR, odds ratio; CI, confidence interval.

with stronger associations for younger and older age groups compared to the 21-year age groups (i.e., when drinking onset was at its peak). For males, robust positive associations were observed for 12–14, 15–17, 18–20, and 22–25 year olds, and null associations were observed for 21 and 26+ groups.

Next, we examined the factor structure of the 13 clinical features of depression among individuals who experienced low mood or anhedonia in the prior 12 months. Based on results from exploratory factor analyses using the 10% of sample, a 3-factor model fitted data well for all sex- and age-subgroups. The three factors/dimensions were (a) neurovegetative problems ('neurovegetative symptoms'; symptoms i to iv, as listed in Section 2.3), (b) low mood or energy ('Mood'; symptoms iv to ix), and (c) suicide-related thoughts/behaviors ('Suicide-related'; symptoms ix to xiii). Of note, "fatigue or loss of energy" and "feelings of worthlessness or excessive or inappropriate guilt" were allowed to cross-load on two dimensions. Confirmatory factor analysis showed good fitness of the 3-factor model for all subgroups using the 90% of sample (i.e., RSMEA < 0.06; CFI/TLI > 0.95; SRMR < 0.08).

Estimated relationships between the three major depression dimensions and drinking onset among individuals with depressed mood or anhedonia are shown in Fig. 2. We observed similarities and heterogeneity across dimensions of depression, across age groups, and between males and females. Specifically, among individuals with low mood or anhedonia, the most common pattern linking the three major depressive dimensions and drinking onset is characterized by positive associations for Neurovegetative and Suicide-related symptoms and inverse associations for Mood symptoms. This pattern was observed for 12–14 year old females, 15–20 year old males and females, as well as 22+ males. Among 12–14 year old males, the Suicide-related factor was positively associated with drinking onset whereas null associations were found for Neurovegetative and Mood factors. For at-age drinking onset (i.e., among 21 year olds), null associations were found for all depressive symptom dimensions and drinking onset among both males and females.

Supplementary Figure 1 presents odds ratios linking item-level depressive symptoms and drinking onset for each sex- and age-subgroup among individuals with low mood or anhedonia. Based on the reported age of onset of first major depressive episode and the first full drink, a small proportion (0.8%) of individuals had their first major depressive episode and drinking onset in the same year. (Major depressive episode preceded drinking onset for the rest of the sample.) Statistical inference remained the same when these individuals were excluded from analysis.

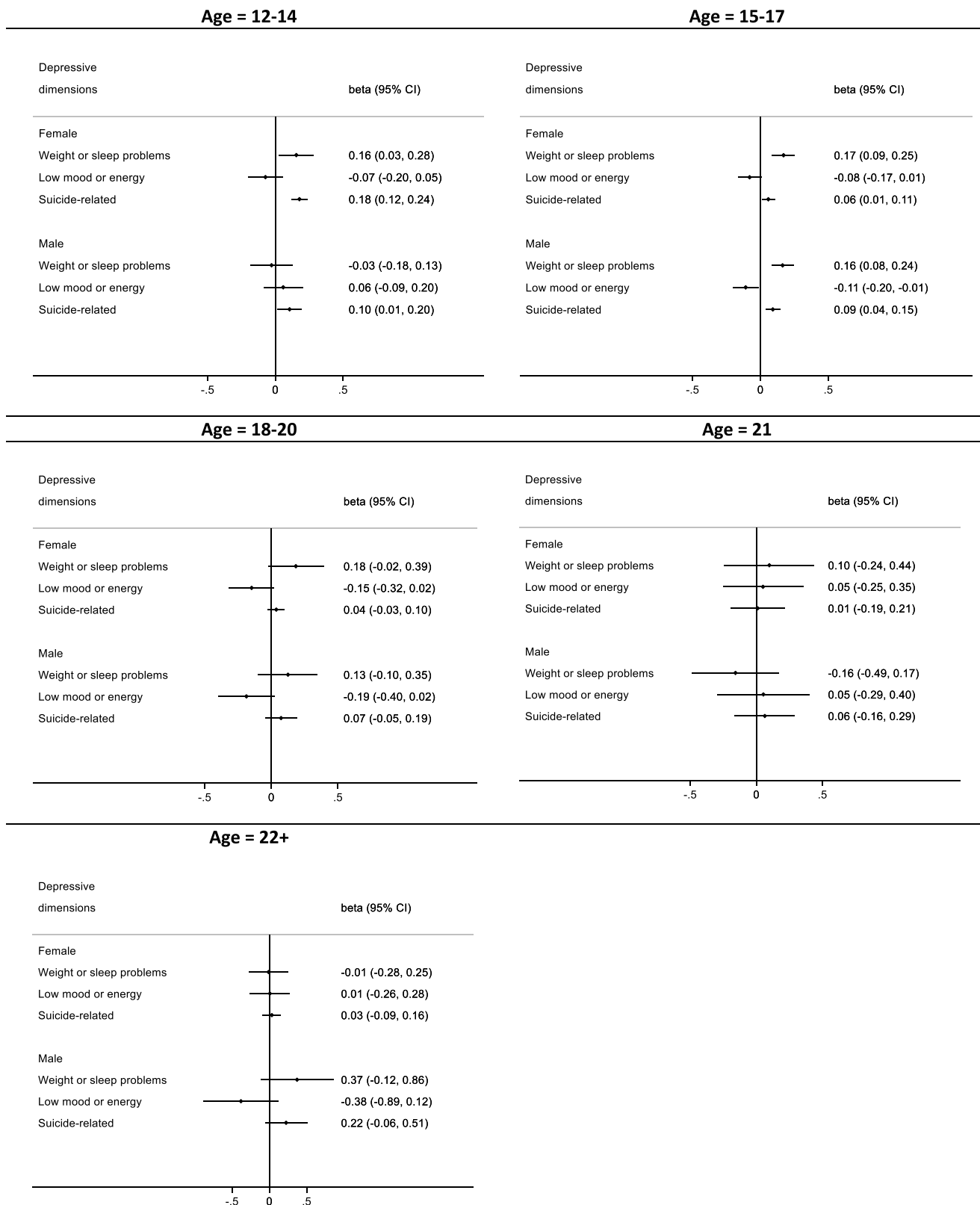
#### 4. Discussion

In this study, we found that the direction and strength of depressive symptoms predicting drinking onset varies across age groups and between males and females. Specifically, depressed mood or anhedonia were associated with increased risk of drinking onset among females and underage males. Among individuals with depressed mood or anhedonia, those with neurovegetative symptoms were more likely to start underage drinking, whereas those with low mood or energy were less likely to start underage drinking, except for early-adolescent boys 12–14 years of age where null associations were observed. Null relationships were the dominant pattern among individuals 21 years of age and older. Suicide-related symptoms were positively associated with underage drinking but not at- or over-legal-age drinking onset. Our findings underscore the importance of the symptomatic variation in how major depression manifests when considering its relationship to risk of drinking onset, and they suggest that this relationship shifts as a function of development and differs between males and females.

Our results are based on nationally representative samples and therefore are readily generalizable to US civilian household dwelling individuals 12 years of age and older. In this study, we used recalled information about recent onset of drinking (i.e., during the 12 months prior to the assessment) from cross-sectional surveys to construct drinking incidence. Two major advantages of this approach are (a) it minimizes recall bias because participants were only required to recall whether they took their first full drinking during the past 12 months, and (b) by excluding past-onset drinkers, we were able to construct drinking incidence which represented the risk of starting to drink without any interference from the persistence of drinking (Cheng et al., 2016a). Particularly useful to this study, we were able to clarify that the onset of major depressive symptoms precedes the onset of drinking. Compared to prospective studies, this novel approach has several robust advantages, including the absence of attrition and the absence of response reactivity, both of which can introduce biases and can be influenced by drinking and depressive symptoms (Cheng et al., 2016a; Thygesen et al., 2008). Moreover, by combining multiple years of nationally representative data, we are able to produce finely grained sex- and age-specific estimates.

The study findings are of interest because they demonstrate that relationships between major depressive symptoms and drinking onset vary based on (1) phenotypic dimensions (latent constructs), (2) sex, and (3) age. These findings suggest that the identification of high-risk individuals for underage drinking should be tailored for boys and girls and for different age groups. For example, experiencing depressed mood or anhedonia, the defining feature of depression, strongly predicted early-adolescent drinking onset. In contrast, depressed mood or anhedonia does not predict drinking onset at legal age for males. Among females, the U-shaped relationship between depressed mood or anhedonia and drinking onset across age groups merits further consideration. Multiple competing mechanisms underlie drinking onset with complex interplay between genetic and socioenvironmental factors (Agrawal and Lynskey, 2008). During early adolescence, familial or psychopathologic influences may play more important roles in drinking onset, whereas peers and other social forces may exert greater influence for older adolescents and young adults as drinking incidence sharply increases and drinking becomes normative (Cheng et al., 2016a, 2016b). The U-shaped curve can be a reflection of this shift in underlying mechanisms.

Among individuals with depressed mood or anhedonia, we observed pronounced heterogeneity across major depressive dimensions in predicting underage drinking onset. Neurovegetative symptoms are the most robust positive predictors for underage drinking, whereas low mood or energy are inversely associated with underage drinking onset except for early adolescent boys. When parents, teachers, peers, and clinicians become aware of concurrent weight or sleep changes and depressed mood or anhedonia among underage individuals, they should



**Fig. 2.** Estimated relationships linking three latent major depressive symptom constructs with drinking onset among individuals with depressed mood or anhedonia. Data from National Survey on Drug Use and Health 2004–2018.

be prepared to discuss drinking with underage teens or emerging adults. Reoccurring suicidal thoughts and behaviors can lead to life-threatening events, and drinking can exacerbate or accelerate these conditions (Schilling et al., 2009). The finding that suicidal thoughts or

behaviors predicted drinking onset among underage individuals suggests that prevention and intervention programs should include drinking prevention in the curriculum for these teens to prevent life-threatening events.



Sex differences were observed for early adolescents and post-legal-age drinking onset. Among early adolescents who experienced depressed mood or anhedonia, positive association was found for neuro-vegetative symptoms and drinking onset among girls whereas null association was observed for boys. This difference is likely to be a result of an interplay of multiple factors including developmental stages (girls generally begin puberty earlier than boys), social expectations (e.g., self-image, peer affiliation, etc.), and biological differences. Among post-legal-age individuals with depressed mood or anhedonia, major depressive symptom dimensions are not predictive of female drinking onset in these age groups, whereas the association pattern resembled the one among underage individuals for males. In addition, antecedent depressed mood or anhedonia was not associated with drinking onset among males 26 or older whereas it predicted female drinking onset in the same age group. Given that most individuals in the US have had their first full drink by the age of 21 (Cheng et al., 2016a), these observed differences are intriguing. Again, these observed differences are likely rooted in multiple aspects. Post-legal-age is a stage when many individuals graduate from college and enter the work force, where they go through significant changes in their social environment. Male- and female-specific changes may contribute to the observed differential patterns among those who did not drink until after the legal drinking age. Future studies that collect a wide range of these social changes are required to disentangle potential sex-specific pathways for these observed male-female differences. Here, we provide benchmarking population estimates to help colleagues in the depression-alcohol field generate hypotheses.

Our findings should be interpreted with the following limitations in mind. Of central concern is the observational nature of the study which precludes any inference of causal relationships. Feedback loops and potential confounders likely exist between drinking onset and depression-related variables studied here. Nonetheless, our goal is to investigate the prediction structure linking depressive symptoms and drinking onset rather than inferring causal relationships. Of note, we use ‘predict’ here simply to refer to increased or decreased likelihood of drinking onset based on the level of antecedent major depressive symptoms studied here, but not to imply any underlying mechanisms.

Despite a large overall sample size, estimated drinking incidence for older groups are less precise due to the limited number of newly incident drinkers in the 22 and older group. Therefore, we combined all individuals 22 years of age and older in the latent variable analysis, which may mask differences between younger and older adults. Future studies with an over sampling of adults will provide more insights on potential differences for adults.

Due to skip patterns in the assessment of major depressive symptoms (e.g., anhedonia was not assessed among individuals with depressed mood), we were not able to estimate specific relationships linking depressed mood or anhedonia with drinking onset, individually. Future studies without such skip patterns will provide further insights on this issue. In addition, the 13 additional symptoms were only assessed among those who had depressed mood or anhedonia. Therefore, the prediction structure linking the 3 dimensions of major depressive symptoms to drinking onset can only be generalized to individuals who had experienced depressed mood or anhedonia.

In this study, we assessed the fitness of the 3-dimension depression measurement model for each sex- and age-subgroup but did not hold constant the measurement model parameters. That is, we did not formally assess potential measurement invariance of the depression measurement model across sex and age groups. Our focus for this study is the prediction structure of depressive symptoms and drinking onset for each sex- and age-group with a parsimonious model to account for intercorrelation between depressive symptoms. Therefore, we consider measurement invariance to be beyond the scope of the current study.

In sum, we focused on the first milestone of drinking, the onset of first drink, in this study, and found differential patterns linking antecedent major depressive symptoms with drinking onset across sex, age,

and depressive symptom dimensions. Future studies on the trajectory of drinking after the first drink can provide more insights about whether individuals with major depressive symptoms have an accelerated progression to problematic drinking.

## Contributors

HGC and ACE designed the study. HGC conducted the literature review, data analysis, and wrote the first draft. ACE and KSK critically reviewed and substantially revised the manuscript. All authors have contributed significantly to the work and agrees to the submission.

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## Declaration of Competing Interest

Authors declare no competing interest related to this study. HGC is a full-time employee of Altria Client Services, LLC. This work is not associated with or sponsored by Altria Client Services, LLC.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.jad.2020.01.176](https://doi.org/10.1016/j.jad.2020.01.176).

## References

- Agrawal, A., Lynskey, M.T., 2008. Are there genetic influences on addiction: evidence from family, adoption and twin studies. *Addiction*. <https://doi.org/10.1111/j.1360-0443.2008.02213.x>.
- Association, A.P., 2013. *American psychiatric association. Diagnostic and Statistical Manual of Mental Disorders, 5th Edition*. American Psychiatric Association, Arlington, VA.
- Anthony, J.C., Warner, L.A., Kessler, R.C., 1994. Comparative epidemiology of dependence on tobacco, alcohol, controlled substances, and inhalants: basic findings from the national comorbidity survey. *Exp. Clin. Psychopharmacol.* 2, 244–268. <https://doi.org/10.1037/1064-1297.2.3.244>.
- Bentler, P.M., 1990. Comparative fit indexes in structural models. *Psychol. Bull.* 107, 238–246. <https://doi.org/10.1037/0033-2909.107.2.238>.
- Blumenthal, H., Taylor, D.J., Cloutier, R.M., Baxley, C., Lasslett, H., 2019. The links between social anxiety disorder, insomnia symptoms, and alcohol use disorders: findings from a large sample of adolescents in the united states. *Behav. Ther.* <https://doi.org/10.1016/j.beth.2018.03.010>.
- Breslau, J., Gilman, S.E., Stein, B.D., Ruder, T., Gmelin, T., Miller, E., 2017. Sex differences in recent first-onset depression in an epidemiological sample of adolescents. *Transl. Psychiatry*. <https://doi.org/10.1038/tp.2017.105>.
- Brown, S.A., McGue, M., Maggs, J., Schulenberg, J., Hingson, R., Swartzwelder, S., Martin, C., Chung, T., Tapert, S.F., Sher, K., Winters, K.C., Lowman, C., Murphy, S., 2009. Underage alcohol use: summary of developmental processes and mechanisms: ages 16–20. *Alcohol Res Heal* 32, 41–52.
- Center for Behavioral Health Statistics and Quality, 2018. Results from the 2017 national survey on drug use and health: detailed tables prevalence estimates. 2017 National Survey on Drug Use and Health.
- Center for Behavioral Health Statistics and Quality, 2018b. 2017 National survey on drug use and health: methodological summary and definitions. Rockville, MD.
- Cheng, H.G., Cantave, M.D., Anthony, J.C., 2016a. Alcohol experiences viewed microscopically: newly incident drinking of twelve- to twenty-five-year-olds in the united states, 2002–2013. *J. Stud. Alcohol Drugs* 77, 405–412. <https://doi.org/10.15288/jsad.2016.77.405>.
- Cheng, H.G., Cantave, M.D., Anthony, J.C., 2016b. Taking the first full drink:

- epidemiological evidence on male-female differences in the united states. *Alcohol. Clin. Exp. Res.* 40, 816–825. <https://doi.org/10.1111/acer.13028>.
- Cheng, H.G., Lopez-Quintero, C., Anthony, J.C., 2017. Age of onset or age at assessment—that is the question: estimating newly incident alcohol drinking and rapid transition to heavy drinking in the united states. *Int. J. Methods Psychiatr. Res.* 2002–2014. <https://doi.org/10.1002/mpr.1587>.
- Hallfors, D.D., Waller, M.W., Bauer, D., Ford, C.A., Halpern, C.T., 2005. Which comes first in adolescence - Sex and drugs or depression? *Am. J. Prev. Med.* <https://doi.org/10.1016/j.amepre.2005.06.002>.
- Hasin, D.S., Goodwin, R.D., Stinson, F.S., Grant, B.F., 2005. Epidemiology of major depressive disorder: results from the national epidemiologic survey on alcoholism and related conditions. *Arch. Gen. Psychiatry.* <https://doi.org/10.1001/archpsyc.62.10.1097>.
- Hasin, D.S., Stinson, F.S., Ogburn, E., Grant, B.F., 2007. Prevalence, correlates, disability, and comorbidity of dsm-iv alcohol abuse and dependence in the united states: results from the national epidemiologic survey on alcohol and related conditions. *Arch. Gen. Psychiatry* 64, 830–842. <https://doi.org/10.1001/archpsyc.64.7.830>.
- Hu, L., Bentler, P.M., 1999. Cutoff criterion for fit indexes in covariance structure analysis: conventional criteria versus new alternatives. *Struct. Equ. Model.* 6, 1–55. <https://doi.org/10.1080/10705519909540118>.
- Johannessen, E.L., Andersson, H.W., Bjørngaard, J.H., Pape, K., 2017. Anxiety and depression symptoms and alcohol use among adolescents - a cross sectional study of norwegian secondary school students. *BMC Public Health.* <https://doi.org/10.1186/s12889-017-4389-2>.
- Johnston, L.D., Miech, R.A., O'Malley, P.M., Bachman, J.G., Schulenberg, J.E., Patrick, M.E., 2019. Monitoring the future national survey results on drug use 1975–2018: 2018 Overview- Key Findings on adolescent drug use. Monitoring the FUTURE National Survey Results on Drug Use. <https://doi.org/10.1017/CBO9781107415324.004>.
- Kaplow, J.B., Curran, P.J., Angold, A., Costello, E.J., 2001. The prospective relation between dimensions of anxiety and the initiation of adolescent alcohol use. *J. Clin. Child Psychol.* 30, 316–326. [https://doi.org/10.1207/S15374424JCCP3003\\_4](https://doi.org/10.1207/S15374424JCCP3003_4).
- Kessler, R.C., Chiu, W.T., Demler, O., Walters, E.E., Merikangas, K.R., Walters, E.E., 2005. Prevalence, severity, and comorbidity of 12-month dsm-iv disorders in the national comorbidity survey replication. *Arch. Gen. Psychiatry* 62, 617–627. <https://doi.org/10.1001/archpsyc.62.6.617>.
- Kessler, R.C., Crum, R.M., Warner, L.A., Nelson, C.B., Schulenberg, J., Anthony, J.C., 1997. Lifetime co-occurrence of dsm-iii-r alcohol abuse and dependence with other psychiatric disorders in the national comorbidity survey. *Arch. Gen. Psychiatry* 54, 313–321. <https://doi.org/10.1001/archpsyc.1997.01830160031005>.
- King, S.M., Iacono, W.G., McGue, M., 2004. Childhood externalizing and internalizing psychopathology in the prediction of early substance use. *Addiction.* <https://doi.org/10.1111/j.1360-0443.2004.00893.x>.
- Koob, G.F., Volkow, N.D., 2016. Neurobiology of addiction: a neurocircuitry analysis. *The Lancet Psychiatry.* [https://doi.org/10.1016/S2215-0366\(16\)00104-8](https://doi.org/10.1016/S2215-0366(16)00104-8).
- Kramer, M., 1957. A discussion of the concepts of incidence and prevalence as related to epidemiologic studies of mental disorders. *Am J Public Heal. Nations Heal.* 47, 826–840.
- KUO, P.-H., GARDNER, C.O., KENDLER, K.S., PRESCOTT, C.A., 2006. The temporal relationship of the onsets of alcohol dependence and major depression: using a genetically informative study design. *Psychol. Med.* <https://doi.org/10.1017/s0033291706007860>.
- Lapouse, R., 1967. Problems in studying the prevalence of psychiatric disorder. *Am J Public Heal. Nations Heal.* 57, 947–954.
- Liang, K.-Y., Zeger, S.L., 1986. Longitudinal data analysis using generalized linear models. *Biometrika* 73, 13–22. <https://doi.org/10.1093/biomet/73.1.13>.
- McGue, M., Iacono, W.G., Legrand, L.N., Malone, S., Elkins, I., 2001. Origins and consequences of age at first drink. I. associations with substance-use disorders, disinhibitory behavior and psychopathology, and P3 amplitude. *Alcohol. Clin. Exp. Res.* <https://doi.org/10.1111/j.1530-0277.2001.tb02330.x>.
- Meier, M.H., Caspi, A., Houts, R., Slutske, W.S., Harrington, H., Jackson, K.M., Belsky, D.W., Poulton, R., Moffitt, T.E., 2013. Prospective developmental subtypes of alcohol dependence from age 18 to 32 years: implications for nosology, etiology, and intervention. *Dev. Psychopathol.* <https://doi.org/10.1017/s0954579413000175>.
- Merikangas, K.R., He, J.P., Burstein, M., Swanson, S.A., Avenevoli, S., Cui, L., Benjet, C., Georgiades, K., Swendsen, J., 2010. Lifetime prevalence of mental disorders in U.S. adolescents: results from the national comorbidity survey replication-adolescent supplement (NCS-A). *J. Am. Acad. Child Adolesc. Psychiatry.* <https://doi.org/10.1016/j.jaac.2010.05.017>.
- Miller, T.R., Levy, D.T., Spicer, R.S., Taylor, D.M., 2015. Societal costs of underage drinking. *J. Stud. Alcohol.* <https://doi.org/10.15288/jsa.2006.67.519>.
- Mojtabai, R., Olfson, M., Han, B., 2016. National trends in the prevalence and treatment of depression in adolescents and young adults. *Pediatrics* 138, e20161878. <https://doi.org/10.1542/peds.2016-1878>.
- Murray, C.J.L., Mokdad, A.H., Ballesteros, K., Echko, M., Glenn, S., Olsen, H.E., Mullany, E., Lee, A., Khan, A.R., Ahmadi, A., Ferrari, A.J., Kasaeian, A., Werdecker, A., Carter, A., Zipkin, B., Sartorius, B., Serdar, B., Sykes, B.L., Troeger, C., Fitzmaurice, C., Rehm, C.D., Santomauro, D., Kim, D., Colombaro, D., Schwebel, D.C., Tsoi, D., Kolte, D., Nsoesie, E., Nichols, E., Oren, E., Charlson, F.J., Patton, G.C., Roth, G.A., Hosgood, D., H., W., H.A., K., H., E., H.E., Erskine, H.E., Huang, H., M., I., S., J.A., N., J.B., S., J.R., A., K., O., K., T., K., Tabb, K., Krohn, K.J., C., L., D., L., M., M., F., M., G., M., C., M., B., M., N., M., W., M., Wallin, M., Mirarefin, M., Q., M., Y., M., F., N., L., P., B., P., G., P., H., R., L., R., K., R., B.-H., S., H., S.I., Y., S., B., S., V., S.E., A., T., F., T., F., T., M., T., V., T., B., T., G., T.T., Y., Y., A.-A., Z., M., A., H., A., K., A., A., B., B., B., M., D., R.D., E., Ray Dorsey, E., Ding, E.L., P., E.K., W., G., H., G., C., H., S., J.E., K., J., L., J., L., J., S., J., U., J., C., L., C., L., H., M., B., M., B., N., H., P., T.-M., R., S., S., S., J., S., A., S., J., S., P., T., A., T., S., V., K., Y., B., Z., J., J.B., M., C.J., L., 2018. The state of us health, 1990–2016: burden of diseases, injuries, and risk factors among us states. *JAMA - J. Am. Med. Assoc.* <https://doi.org/10.1001/jama.2018.0158>.
- Saraceno, L., Heron, J., Munafò, M., Craddock, N., van den Bree, M.B.M., 2012. The relationship between childhood depressive symptoms and problem alcohol use in early adolescence: findings from a large longitudinal population-based study. *Addiction.* <https://doi.org/10.1111/j.1360-0443.2011.03662.x>.
- Schilling, E.A., Aseltine, R.H., Glanovsky, J.L., James, A., Jacobs, D., 2009. Adolescent alcohol use, suicidal ideation, and suicide attempts. *J. Adolesc. Heal.* <https://doi.org/10.1016/j.jadohealth.2008.08.006>.
- Stice, E., Myers, M.G., Brown, S.A., 1998. A longitudinal grouping analysis of adolescent substance use escalation and de-escalation. *Psychol. Addict. Behav.* <https://doi.org/10.1037/0893-164X.12.1.14>.
- Thygesen, L.C., Johansen, C., Keiding, N., Giovannucci, E., Grønbaek, M., 2008. Effects of sample attrition in a longitudinal study of the association between alcohol intake and all-cause mortality. *Addiction* 103, 1149–1159. <https://doi.org/10.1111/j.1360-0443.2008.02241.x>.
- Vuong, Q.H., 1989. Likelihood ratio tests for model selection and non-nested hypotheses. *Econometrica* 57, 307. <https://doi.org/10.2307/1912557>.
- Wu, P., Bird, H.R., Liu, X., Fan, B., Fuller, C., Shen, S., Duarte, C.S., Canino, G.J., 2006. Childhood depressive symptoms and early onset of alcohol use. *Pediatrics.* <https://doi.org/10.1542/peds.2006-1221>.
- Zucker, R.A., Donovan, J.E., Masten, A.S., Mattson, M.E., Moss, H.B., 2008. Early developmental processes and the continuity of risk for underage drinking and problem drinking. *Pediatrics.* <https://doi.org/10.1542/peds.2007-2243b>.