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METHODS AND TECHNIQUES

ADDICTION SSA

Definition matters: assessment of tolerance to the effects of alcohol in a prospective cohort study of emerging adults

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Abstract

Background and aims: Tolerance to the effects of alcohol is an important element in the diagnosis of alcohol use disorders (AUD); however, there is ongoing debate about its utility in the diagnosis AUD in adolescents and young adults. This study aimed to refine the assessment of tolerance in young adults by testing different definitions of tolerance and their associations with longitudinal AUD outcomes.

Design: Prospective cohort study.

Settings: Australia.

Participants: A contemporary cohort of emerging adults across Australia (n = 565, mean age = 18.9, range = 18–21 at baseline).

Measurements: Clinician-administered Structured Clinical Interview for DSM-IV Research Version (SCID-IV-RV) assessed for AUD criteria across five interviews, at 6-month intervals over 2.5 years. Tolerance definitions were operationalized using survey-type response (yes/no), clinician judgement (SCID-IV-RV), different initial drinking quantity and percentage increase thresholds and average heavy consumption metrics. AUD persistence was operationalized by the number of times AUD was present across the 2.5-year study period (n = 491), and new-onset AUD was operationalized as any new incidence of AUD during the follow-up period (n = 461).

Findings: The (i) SCID-IV-RV clinician judgement [odds ratio (OR) = 2.50, P = 0.005], (ii) an initial drinking quantity threshold of four to five drinks and 50% minimum increase (OR = 2.48, P = 0.007) and (iii) 50% increase only (OR = 2.40, P = 0.005) were the tolerance definitions more strongly associated with any new onset of AUD throughout the four follow-up time-points than other definitions. However, these definitions were not associated with persistent AUD (Ps > 0.05). Average heavy consumption definitions of tolerance were most strongly associated with persistent AUD (OR = 6.66, P = 0.001; OR = 4.65, P = 0.004) but not associated with new-onset AUD (Ps > 0.05).

Conclusions: Initial drink and percentage change thresholds appear to improve the efficacy of change-based tolerance as an indicator for new-onset alcohol use disorder diagnosis in self-report surveys of young adults. When predicting persistent alcohol use disorder, average heavy consumption-based indicators appear to be a better way to measure tolerance than self-reported change-based definitions.

KEYWORDS
Adolescents, alcohol, alcohol use disorder, cohort study, tolerance, young adult

INTRODUCTION

Tolerance to the effects of alcohol is an important element in major diagnostic classifications of alcohol use disorders (AUD) [1, 2]. Broadly, tolerance refers to the need to consume larger amounts of alcohol to obtain the same effect, or a decrease in effect at the same dose. It is usually associated with chronic alcohol consumption and reflects neuroadaptation to alcohol's presence in the body[1] [1]. However, there is ongoing debate about the utility of the tolerance criterion in diagnosis of AUDs [5–7].

In the Diagnostic and Statistical Manual of Mental Disorders (DSM) and other diagnostic classification systems, tolerance is assessed by perceptions of changes in the effects of alcohol over time. For instance, in DSM-5, tolerance is assessed by (a) 'A need for markedly increased amounts of alcohol to achieve intoxication or desired effect' and (b) 'Markedly diminished effect with continued use of the same amount of alcohol' [2]. From here on we refer to this as a subjective change-based definition of tolerance, as respondents are required to reflect on their alcohol consumption history and determine whether the quantity required to feel an effect from alcohol has changed over time. This temporal comparison means that the tolerance criterion may be particularly sensitive to developmental stages wherein patterns of behaviour, such as drinking, are less stable, making it easier to endorse it early in one's drinking experience [6]. Moreover, these definitions also require respondents to use their own definition of 'effect' or 'intoxication'.

In adolescent treatment samples, as many as 40–50% endorsed past 12-month tolerance (e.g. [8, 9]), with similarly high endorsement of 40–50% in non-clinical young adult populations [10, 11]. In contrast, fewer than 12% endorsed tolerance in adult samples [12–14]. These high rates, and the tendency for them to significantly reduce in later adulthood, may indicate that tolerance to alcohol is a natural developmental phenomenon experienced by most emerging adult drinkers, and inclusion in diagnostic systems may increase false-positive AUD diagnoses [5, 7, 14, 15]. Nonetheless, the natural development of tolerance still needs to be assessed in the context of alcohol-related harms and risk factors to determine its significance for the individual. Moreover, defining tolerance in different ways could decrease the prevalence of tolerance in this population [5]. For this reason, there remains a pressing need to empirically evaluate alternative definitions of tolerance to accurately capture its experience in adolescent and young adult populations.

Harrison *et al*. found that the tolerance criterion had poor positive predictive value (< 50%) for DSM-IV alcohol dependence diagnosis in teenagers. That is, endorsing tolerance did not distinguish those with AUD from those without AUD [16]. Chung and colleagues concluded that tolerance has low specificity when identifying alcohol use problems in youth [17]. A study using cognitive interviewing in an adolescent clinical treatment sample found that the modal increase associated with endorsement of tolerance was only two to three drinks [18]. Ultimately, the authors concluded that the degree of tolerance reported was more closely aligned with normative developmental changes in sensitivity to alcohol than with clinically significant increases in alcohol consumption, indicating physiological dependence [18].

Tolerance has also been operationalized by explicitly applying percentage-change thresholds (e.g. > 50% increase in drinking quantity to feel effect) and by simply using alcohol consumption indices (e.g. [5, 19, 20]). For instance, Chung *et al*. operationalized tolerance as a minimum average drinking quantity of seven or more drinks for women or nine or more drinks for men per occasion, plus a minimum average drinking frequency of 8 or more drinking days per month [5]. They found that, in adolescents, consumption-based definitions had better sensitivity and specificity than any percentage-change definitions, and that a percentage-change approach to assigning tolerance was impacted by large individual variability in initial drinking quantities (i.e. number of drinks required to feel an effect from alcohol when the adolescents first started drinking) [5]. This variability led to over-assigning the tolerance symptom when the initial drinking quantities were low and potential under-assignment when the initial drinking quantities were high [5].

While these studies highlight the complex nature of tolerance endorsement in young adults, they are limited by their cross-sectional nature. Additionally, most research specifically investigating tolerance was undertaken nearly 2 decades ago (e.g. [5, 16]), and adolescent drinking trends have changed significantly since then [21]. It remains to be seen whether different definitions of tolerance are better at prospectively predicting the longitudinal course of AUD in contemporary emerging adults.

[1]There are multiple proposed neurobiological, pharmacokinetic and cognitive processes through which tolerance is thought to occur (e.g. [3, 4]). However, the focus of this paper is upon defining tolerance in the context of AUD diagnoses, and thus review of this literature is outside the scope of this paper.

The current study

The present study aimed to determine which definitions of tolerance were most strongly associated with newly developing AUD and chronic presentations of AUD. To do so, we created different definitions of tolerance and examined how these definitions endorsed during a baseline interview related to new-onset AUD and persistent AUD across a 2.5-year follow-up period. The types of definitions compared were based on (1) subjective change; (2) subjective change plus percentage increase and/or initial drinking quantity thresholds; and (3) alcohol consumption. The present study was not pre-registered and was exploratory in nature; thus, we did not have any a priori hypotheses regarding the performance of each definition.

METHOD

Participants

Study sample

The sample was derived from the RADAR study [22, 23]. RADAR participants were recruited in 2016–18 from an existing, and ongoing, cohort of 1603 adolescents participating in the Australian Parental Supply for Alcohol Longitudinal Study (APSALS) [24–26]. Participants [*n* = 565, mean age 18.9, range = 18–21 at baseline at entry to RADAR, 48.3% female] were eligible for the RADAR study if they reported frequent alcohol consumption—drinking at least 1–2 days per week and/or semi-frequent binge drinking—binge drinking two or more times per month). Institutional ethics approval was granted for the APSALS by the University of New South Wales Research Ethics Committee and ratified by the universities of Tasmania, Newcastle, and Queensland, and Curtin University. APSALS was registered with clinicaltrials.gov (NCT02280551). The RADAR study was approved by the University of New South Wales Research Ethics Committee (UNSW HREC 10144).

Study design

RADAR participants completed a total of 5 interviews. First, they completed a baseline telephone interview (*n* = 565) with a clinical psychologist, during which they were assessed for AUD criteria and diagnosis throughout their life-time using the Structured Clinical Interview for DSM-IV Research Version (SCID-IV-RV). Participants were subsequently invited to complete four follow-up telephone SCID-IV-RV interviews conducted at 6-month intervals each assessing alcohol consumption and AUD criteria, including tolerance, for the preceding 6-month period. Further information on the SCID-IV-RV and its reliability in our sample can be found in [23]. The primary research question and analyses were not pre-registered. As such, the results should be considered exploratory.

Measures and procedure

Alcohol consumption

Average quantity and frequency of alcohol consumption at each time-point was assessed using two questions, which differed at the baseline interview and 6-month follow-up interviews:

1. Since you were (age of first drink)[baseline]/in the last 6 months [follow-ups], how often have you had an alcoholic drink of any kind? Possible responses were: never, less often than any of these, about 1 day a month, 2–3 days a month, 1–2 days a week, 3–4 days a week, 5–6 days a week and every day.
2. Since you were (age of first drink) [baseline]/in the last 6 months [follow-ups], on a typical day you had an alcoholic drink, how many standard drinks did you usually have? Possible responses were: one to two drinks; three to four drinks, five to six drinks, seven to 10 drinks, 11–12 drinks 13 or more drinks.

Prior to deriving consumption-based definitions, these variables were coded to the mid-point, with every day coded as seven and 13+ drinks coded as 13.

DSM-5 alcohol use disorder

The RADAR study used a modified version of the SCID-IV-RV to assess symptoms of DSM-5 AUD criteria [27]. Each AUD criterion was assessed for clinical significance; specifically, whether a symptom occurred with the requisite severity and frequency (for further details see [23]). When assessing the predictive power of different tolerance definitions against longitudinal AUD diagnoses, tolerance was excluded from the overall AUD diagnosis. Hence, DSM-5 AUD was diagnosed as present if two or more of the remaining 10 criteria were endorsed within a 12-month period (for the baseline interview), or within the preceding 6-month period (for follow-up interviews).

Tolerance in the SCID-IV-RV

In the SCID-IV-RV, the tolerance criterion was assessed using two symptom questions. First, the interviewing clinician would ask: 'Have you ever [baseline]/in the last 6 months have you [follow-ups], found that you needed to drink more alcohol in order to get drunk than you did when you first started drinking?'. If a participant endorsed this symptom, the interviewing clinician would probe and record the initial and current drinking quantities required to feel drunk. They would also ask whether the participant themselves felt they had developed tolerance and whether they could drink more than their friends.[2] Secondly, participants were asked: 'What about finding that when you

[2]This information was questioned by the clinician and taken into account when making a judgement of clinical significance, but was not necessarily recorded in the data collection process.

drank the same amount, it had much less effect than before?'. In the SCID-IV-RV, the overall tolerance criterion was met if one or both symptom questions are rated as clinically significant by the interviewing clinician.

The new tolerance definitions and analyses focus only upon answers to the first question in the SCID-IV-RV. In the present study, of the 284 participants who endorsed SCID-IV-RV-defined clinically significant tolerance at the baseline interview, 241 (85%) met the criteria through their response to the first tolerance symptom question. It was also not possible to refine the definition of question 2 by applying the same kinds of thresholds and percentage change definitions as with question 1. If we were to attempt to change the definition of question 2 we would need to measure, in some reliable way, differences in the subjective effect of alcohol at a given amount. The subjective effect of alcohol is a much more difficult construct to measure. Other investigations into the tolerance criterion have taken a similar approach for similar reasons as taken by our study [5].

Change-based indicators of tolerance

The first definition was based on a simple 'yes' or 'no' answer to the tolerance question, before any additional probing or clinician judgement was applied. This reflects what would be expected from simple self-report surveys. The second definition took into account the clinician judgement of clinical significance. Next, we derived definitions based on combinations of the minimum percentage increase over time in the quantity of alcohol required to feel drunk and the minimum initial quantity of alcohol required to feel drunk. The minimum initial drinking quantity required to feel drunk was five standard drinks for men and four standard drinks for women [28]. Given concerns about over-assignment of tolerance in this population, our focus was to narrow the definition. As such, we only applied these new change-based definition rules to participants judged by clinicians as endorsing clinically significant tolerance.

Consumption-based indicators of tolerance

We also tested two non-normative consumption-based definitions of tolerance. The first definition was based on average frequency and quantity among the 'riskiest drinking 25%' of their age and gender cohort. Data for this came from the latest Young Australians' Alcohol Reporting System (YAARS) report (i.e. for 18–19-year-olds, drinking 2-+ days a month, 7+/9+ drinks per occasion for women and men) [29]. That is, people who were assigned this definition of tolerance drank more frequently and in larger quantities than three-quarters of a representative sample of Australian 18–19-year-olds. The second definition was based on the upper 25th percentile of average consumption within our own sample: that is, those people who drank more frequently and in larger quantities than three quarters of the RADAR cohort. Given the absence of sex differences in the frequency and quantity to define the upper 25th percentile, the same definition was applied to both genders. Table 1 provides descriptions of each of the tolerance definitions.

AUD outcomes

There is evidence that AUD itself can be time-limited (or developmentally limited) in presentation [30, 31]. That is, AUDs tend to emerge in adolescence, peak in prevalence in early adulthood

TABLE 1 Different definitions of tolerance tested in this study and prevalence of each at baseline.

Name of definition	Description of definition	Prevalence at baseline (*n* = 565)
Survey	Respondent answered yes to key tolerance question: 'Have you ever found that you needed to drink more alcohol in order to get drunk than you did when you first started drinking?'	414 (73.3%)
SCID	Survey definition plus clinician judgement regarding clinical significance	241 (42.7%)
50%	SCID definition plus 50% increase in consumption to feel drunk	238 (42.1%)
100%	SCID definition plus 100% increase in consumption to feel drunk	192 (34.0%)
4/5 + 50%	50% definition plus 4 (females)/5 (males) or more initial standard drinks to feel drunk at baseline interview	116 (20.5%)
4/5 + 100%	100% definition plus 4 (females)/5 (males) or more initial standard drinks to feel drunk at baseline interview	77 (13.6%)
Varied	If participant reported 5 or more initial drink quantity to feel drunk at baseline, then 100% self-reported increase in consumption to feel drunk; if less than 5 initial drinks to feel drunk, then 150% self-reported increase in consumption to feel drunk	145 (25.7%)
Population-average consumption	Consumes alcohol at least 2 days a month and at least 7–10 drinks per occasion—this equates to drinking pattern of top 25% of Australian 18–19-year-old drinkers (Lam *et al.* 2017)	181 (32.0%)
Sample-specific average consumption	Consumes alcohol at least 1–2 days a week and at least 7–10 drinks per occasion—this equates to drinking pattern of top 25% of RADAR participants (Slade *et al.* 2021)	109 (19.3%)

SCID = Structured Clinical Interview for DSM-IV.

and decline markedly thereafter [30, 32]). Many of those who are diagnosed with an AUD recover without treatment; however, those reporting more severe alcohol-related problems are less likely to recover [30, 33, 34]. We aimed to not only determine which definitions of tolerance endorsed at baseline were most strongly associated with newly developing AUD during a 2.5-year period, but also which were most strongly associated with chronic presentations of AUD. To assess incident AUD we derived a variable indicating, among those who did not already meet criteria for AUD at baseline and completed at least one follow-up (n = 461), whether participants newly developed AUD at any time across the four follow-up occasions (1 = new onset, 0 = no new onset). To capture chronicity of AUD, longitudinal AUD categories were constructed based on whether AUD was 'persistent', 'limited' or 'absent' across all time-points. Persistent AUD was defined as meeting criteria for AUD in at least three time -points (i.e. at least half the study period). Limited AUD was defined as meeting criteria for AUD at some time-points, but not reaching criteria for persistent (i.e. one or two AUD diagnoses, not present for more than 12 months in total). Finally, absent AUD was defined as cases where AUD was never present between the initial baseline interview and the final follow-up. The comparison of most importance for this variable was limited versus persistent AUD, as it distinguishes between levels of chronicity in AUD which may indicate those who will go on to require treatment from those with potentially time-limited AUD.

Statistical analyses

Separate binary logistic regression models investigated the odds of having incident AUD across the four follow-up time-points, dependent upon each tolerance definition endorsement at baseline interview. Separate multinomial logistic regression models investigated associations between longitudinal AUD severity categories (absent, limited, persistent) and each tolerance definition at baseline. *P*-values for each set of analyses were corrected for multiple tests using false discovery rate corrections [35]. The Akaike information criterion corrected for small sample size (AICc) was used to compare model fit (Supporting information, Tables S3 and S4). We tested diagnostic efficiency for each tolerance definition on both outcomes (i.e. incident and chronic AUD) using six different indices: sensitivity, specificity, positive and negative predictive value, diagnostic odds ratio (OR) and area under the curve (AUC). These analyses supported findings from our primary analyses and are provided in Supporting information, Tables S6 and S7.

The RADAR cohort had good retention, with 80.4% of participants remaining in the study at the final follow-up and 376 participants completing all four follow-up interviews (see [23] and Supporting information, Fig. S1). There were no significant differences in baseline demographics and drinking characteristics between those who completed follow-ups compared to those who dropped out after the baseline interview (see Supporting information, Table S1). The lack of difference in loss suggests that loss is completely at random, and therefore complete case analysis is not likely to be biased. If data were missing for initial and/or current drinking quantities, such that percentage increase could not be calculated or initial drinking quantity threshold applied, the clinician judgement of presence of tolerance at that time-point was assumed true and participants were coded as endorsing the change-based tolerance definitions (n = 10). One participant was missing data for tolerance from their baseline interview. This participant was coded as missing for all baseline tolerance definitions and were thus not included in the final analyses. If participants did not complete any follow-up interviews, they were also excluded from subsequent analyses (n = 47). A total of 518 participants completed at least one follow-up, and 491 participants completed at least two follow-ups. Participants were only included in the analyses for AUD chronicity if they completed at least two follow-ups (n = 491), as we could not determine the absence of persistent AUD with fewer than two follow-ups. Participants were included in the analyses for incident AUD if they (1) completed at least one follow-up and (2) did not report AUD at baseline (n = 461).

Analyses were conducted in R studio version 1.4.1106 (release 2021-02-11). Statistics were calculated using R version 4.0.3 [36]. Data were manipulated and descriptive statistics calculated using the *dplyr* (version 1.0.2) [37], *psych* (version 2.0.8) [38] and *tidyr* (version 1.3.0) [39] packages. Binary logistic regressions were estimated using the *stats* [36] package. Multinomial logistic regressions were estimated using the *nnet* [40] package. ORs were estimated using the *questionr* package [41]. False discovery rate *P*-values were estimated using the *p.adjust* function in the *stats* package [36].

RESULTS

Prevalence of tolerance definitions

More than 73% of participants endorsed the survey tolerance definition at baseline. Prevalence dropped to 42.7% for the clinician judgement definition of tolerance. Further applying initial drinking thresholds reduced the prevalence of change-based definitions to between 25.7 and 13.6%. Prevalence of consumption-based definitions was between 19.3 and 32.0% (Table 1). Of the participants who did not have AUD at baseline, 12.7% had a new-onset AUD throughout the 2-year follow-up period. Prevalence for the AUD chronicity categories was highest for absent (76.8%), followed by limited (18.5%) and persistent (4.7%) (Table 2).

Relationship between tolerance definitions and AUD

Based on ORs (Table 3) and model fit (Supporting information, Table S3), the SCID tolerance definition, closely followed by the 4/5 + 50% and 50% increase definitions were most strongly associated with having any new onset of AUD across the 24-month follow-up period. Participants who endorsed SCID tolerance at the baseline interview had 2.5 times greater odds of developing AUD throughout

TABLE 2 Number of people who met criteria for each longitudinal category of AUD chronicity (n = 491) and new-onset AUD (n = 461).

	n (%)	Mean (SD) number of diagnoses	Median (range) number of diagnoses	IQR (25th, 75th percentile)
Absent AUD	377 (76.8%)	0	0	0
Limited AUD	91 (18.5%)	1.26 (0.44)	1 (1–2)	1 (1, 2)
Persistent AUD	23 (4.7%)	3.74 (0.81)	4 (3–5)	1 (3, 4)
New-onset AUD	64 (12.7%)	1.39 (0.75)	1 (1–4)	1 (1, 2)

Alcohol use disorder (AUD) diagnosis scored not including the tolerance criterion; SD = standard deviation; IQR = interquartile range.

TABLE 3 Summary of binomial logistic regression models of different tolerance definitions at baseline interview predicting new onset AUD (without tolerance) across all 6-month follow-ups (n = 461).

Tolerance definition	*Z*-value	OR	OR 95% CI	*P*	FDR *P*-value
Survey	1.91	1.91	1.01, 3.86	0.056	0.095
SCID	3.34	2.50	1.47, 4.33	0.001*	0.005*
50%	3.20	2.40	1.41, 4.13	0.001*	0.005*
100%	2.00	1.74	1.00, 2.98	0.044*	0.095
4/5 + 50%	3.09	2.48	1.38, 4.39	0.002*	0.007*
4/5 + 100%	1.90	1.94	0.94, 3.75	0.057	0.095
Varied	2.18	1.82	0.94, 3.02	0.069	0.099
Population average consumption	1.08	1.36	0.77, 2.35	0.278	0.278
Sample average consumption	1.60	1.69	0.87, 3.14	0.109	0.121

AUD = Alcohol use disorder; SCID = Structured Clinical Interview for DSM-IV; OR = odds ratio; 95% CI = 95% confidence interval; FDR = false discovery rate adjusted.
*$P < 0.05$.

the four follow-up interviews, compared to those who did not (OR = 2.50, P = 0.005). Both consumption-based definitions performed poorly in comparison.

The sample-specific consumption-based definition (i.e. average quantity seven to 10 drinks, average frequency 1–2 nights/week) was the definition most strongly associated with having persistent (versus absent and limited) AUD throughout the whole 2.5-year study period (Table 4, Supporting information, Table S4). The odds of having persistent AUD compared to limited AUD were seven times higher among those who endorsed the sample-specific consumption-based definition compared to those who did not. Additionally, the odds of having persistent AUD compared to absent AUD were 11 times higher among those who did versus did not endorse this definition.

DISCUSSION

This study compared the utility of different definitions of tolerance against longitudinal AUD outcomes in a cohort of regularly drinking young adults. The prevalence of tolerance when using a subjective change survey response was excessive for a non-clinical sample (> 70%). The addition of clinician judgement as in the SCID definition lowered prevalence substantially (43%), but it remained arguably too high to be a sensitive or specific assessment of AUD. The addition of 50% increase and initial drinking thresholds to these change-based definitions maintained the level of predictive utility seen for clinician judgement for new-onset AUD, but reduced the prevalence substantially (~20%). These findings suggest that using quantitative thresholds in subjective change-based definitions could refine existing tolerance definition for use in young adult populations.

Results of regression analyses indicated that high-threshold consumption-based definitions were most strongly associated with persistent AUD presentations (versus limited or absent) throughout a 2.5-year period. Clinician judgement, as well as an additional refinement of 50% self-reported increase in quantity needed to get drunk, plus a four- or five-plus drink minimum initial quantity to feel drunk were more strongly associated with new onset AUD than other definitions. Finally, survey-type responses were not strongly associated with either AUD outcome. This pattern of findings suggests that if one is interested in predicting AUD in someone who does not already have the disorder, change-based definitions may be more useful than consumption-based definitions. That is, change-based definitions of tolerance may capture the very early developmental stages of a time-limited disorder, but not necessarily the maintenance or persistence of the disorder. In contrast, if interest is in predicting the persistence of AUD in someone who already shows symptoms, it may be less about the 'changes' in drinking patterns and become more about a relative tolerance that is maintained through a heavy consumption mechanism. Heavy consumption measures may imply the presence of other risk factors beyond tolerance [42]. As such, it is reasonable to

TABLE 4 Summary of multinomial logistic regression models of different tolerance definitions at baseline and their association with chronicity of AUD (without tolerance) measured longitudinally (n = 491).

	Survey		SCID		50%	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Limited versus absent AUD	2.14 (1.20, 3.83)	0.018	2.54 (1.59, 4.07)	< 0.001	2.61 (1.63, 4.16)	< 0.001
Persistent versus absent AUD	4.77 (1.11, 20.59)	0.060	4.94 (1.90, 12.83)	0.003	5.06 (1.95, 13.13)	0.003
Persistent versus limited AUD	2.24 (0.48, 10.53)	0.384	1.91 (0.70, 5.39)	0.265	1.94 (0.70, 5.40)	0.265
	100%		4/5 + 50%		4/5 + 100%	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Limited versus absent AUD	2.40 (1.50, 3.82)	0.001	2.31 (1.39, 3.85)	0.003	2.41 (1.35, 4.27)	0.006
Persistent versus absent AUD	3.18 (1.35, 7.48)	0.015	2.05 (0.81, 5.19)	0.192	1.59 (0.52, 4.89)	0.503
Persistent versus limited AUD	1.33 (0.53, 3.34)	0.584	0.89 (0.33, 2.39)	0.817	0.66 (0.20, 2.15)	0.546
	Varied		Population average consumption		Sample average consumption	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Limited versus absent AUD	2.58 (1.58, 4.19)	0.001	1.20 (0.74, 1.97)	0.527	1.61 (0.91, 2.85)	0.163
Persistent versus absent AUD	4.89 (2.07, 11.56)	0.001	5.60 (2.24, 13.99)	0.001	10.71 (1.34, 26.45)	< 0.001
Persistent versus limited AUD	1.90 (0.75, 4.78)	0.250	4.65 (1.73, 12.51)	0.004	6.66 (2.47, 17.39)	0.001

AUD = alcohol use disorder; SE = standard error; OR = odds ratio; 95% CI = 95% confidence interval. All P-values have Benjamini & Hochberg (1995) false discovery rate correction applied.

expect that sustained high consumption will not be present before other AUD criteria (thus, it may not predict new onset), but will predict persistence because it reflects dysfunction associated with other AUD criteria.

The above findings indicate a need to revisit the suggestion that indicators of alcohol consumption should be considered part of the diagnostic criteria for AUD. This was debated prior to the publication of DSM-5. For example, several studies used item response theory to investigate the utility of adding average consumption and frequency indicators to the DSM AUD diagnoses with some showing support [10, 43–45], while others finding that consumption-based indicators did not add any predictive power [46, 47]. Given the strong associations between our heavy average consumption definitions and persistent AUD, our findings suggest that it may be worthwhile considering heavy consumption either instead of or additional to traditional definitions of tolerance when assessing for AUD in adolescents and young adults.

Our findings are somewhat in line with past research comparing change-based and consumption-based definitions in adolescents. Like our study, Chung *et al*. found average heavy consumption definitions had higher specificity and sensitivity for baseline AUD than change-based definitions [5]. However, they also found that a 100% increase had the highest sensitivity and specificity of change-based definitions (although this was still not above chance). We did not find the same pattern. Indeed, 100% increase did not outperform 50% increase when predicting incident AUD, as found in Chung *et al.* [5]. These discrepancies in findings may reflect both methodological and sampling differences between the studies, as well as reductions in adolescent drinking during the two decades between studies [21].

Change-based definitions of tolerance have historically been limited by the relatively high degree of variability in initial drinking quantities in adolescents [5, 18]. We attempted to control this variability by assigning initial drinking quantity thresholds to some change-based definitions of tolerance. Adding a four- or five-plus initial drinking quantity threshold marginally improved the percentage change-based definitions strength of association with new onset AUD. However, the difference in effect sizes were very small, and should be replicated in larger, more diverse samples. Nonetheless, if clinician administered semi-structured interviews are not possible, inclusion of initial and current drinking quantities may refine the assessment of tolerance in a young adult population by reducing prevalence while retaining or potentially improving predictive value.

Strengths and limitations

Although this study fills an important gap in the existing literature, several limitations are worth noting. First, using SCID data both as independent (i.e. tolerance criterion) and dependent variables (i.e. AUD diagnosis) may limit the generalizability of results. Moreover, our scope for generalizing our findings to less frequent or clinical treatment young adult drinker populations is limited. However, our population is one of interest when investigating AUD outcomes, which has a peak age of onset at 18–24 years [48]. Similarly, the consumption definition based on our RADAR cohort drinking characteristics may not be generalizable to the general population. However, this definition was similar to the characteristics of the 18–19-year-old top 25% riskiest drinking representative Australian sample from the

YAARS study [29], who are also a population of interest when investigating AUD outcomes. The APSALS and RADAR samples are also not entirely probabilistic. As such, these findings will need to be replicated in larger and more generalizable samples, and across different contexts and countries, before researchers can recommend specific guidelines for refining the definition of tolerance in diagnostic systems.

The sample size for some of the tolerance definitions are small, limiting the robustness of some regressions. However, tolerance is generally endorsed at a much higher rate than most other AUD criteria [23]. Indeed, an AUD criterion that is endorsed by upward of 40% of a non-clinical sample is not likely to be a sensitive or specific assessment of AUD. As such, tolerance definitions that are more rare in this age group may be more reflective of pathological tolerance rather than normative early developmental changes.

A clear strength of this study is the use of longitudinal data from a contemporary cohort of emerging adults to assess the predictive validity of different tolerance definitions over time. This approach has extended past research by testing definitions based on limitations highlighted by previous findings (e.g. assigning initial drinking quantity thresholds, adding consumption-based definitions). Moreover, our comparison of different types of methods (e.g. survey response versus detailed clinical interview) also allows us to provide some indication of shortcomings of methods, and potential ways to improve the assessment of tolerance in young adults.

Future directions

Future research could replicate these findings with larger sample sizes, in different populations (e.g. clinical treatment samples), with wider age ranges and with longer-term follow-ups. Such research could provide more empirical guidelines for assessing tolerance in the context of AUD for adolescents and young adults. For prevention and intervention of AUD, sharpened clinical assessment and rating of tolerance could identify individuals at risk for new onset of AUD and persistence of AUD who might benefit from targeted intervention. Moreover, other AUD criteria may also suffer from issues of definition and/or interpretation with young adults (e.g. larger/longer [18, 49]) and deserve similar attention. Another important line of inquiry is to investigate differences between natural developmental tolerance and pathological tolerance in adolescents and young adults. For instance, do these different manifestations of tolerance have different risk factors and correlates? Answers to such questions could further inform which assessments of tolerance are important indicators of risk for AUD in young adults.

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DECLARATION OF INTERESTS

None.

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Siobhan M. O'Dean: Conceptualization (supporting); data curation (supporting); formal analysis (lead); methodology (equal); writing – original draft (lead); writing – review and editing (equal). **Louise Mewton:** Conceptualization (supporting); data curation (supporting); funding acquisition (supporting); investigation (supporting); methodology (supporting); writing – original draft (supporting); writing – review and editing (supporting). **Tammy Chung:** Investigation (supporting); methodology (supporting); writing – original draft (supporting); writing – review and editing (supporting). **Peter Clay:** Methodology (supporting); writing – original draft (supporting); writing – review and editing (supporting). **Philip J. Clare:** Data curation (supporting); formal analysis (supporting); writing – original draft (supporting); writing – review and editing (supporting). **Raimondo Bruno:** Conceptualization (supporting); funding acquisition (supporting); methodology (supporting); writing – original draft (supporting); writing – review and editing (supporting). **Wing See Yuen:** Data curation (supporting); writing – original draft (supporting); writing – review and editing (supporting). **Nyanda McBride:** Investigation (supporting); methodology (supporting); writing – original draft (supporting); writing – review and editing (supporting). **Wendy Swift:** Conceptualization (supporting); data curation (supporting); investigation (supporting); methodology (supporting); writing – original draft (supporting); writing – review and editing (supporting). **Ashling Isik:** Data curation (supporting); project administration (supporting); writing – original draft (supporting); writing – review and editing (supporting). **Emily Upton:** Data curation (supporting); project administration (supporting); writing – original draft (supporting); writing – review and editing (supporting). **Joel Tibbetts:** Data curation (equal); investigation (supporting); methodology (supporting); project administration (lead); writing – original draft (supporting). **Phoebe Johnson:** Data curation (supporting); project administration (supporting); writing – review and editing (supporting). **Kypros Kypri:** Conceptualization (supporting); data curation (supporting); funding acquisition (supporting); investigation (supporting); methodology (supporting).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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