The role of alcohol response phenotypes in the risk for alcohol use disorder

Andrea C. King, Dingcai Cao, Harriet deWit, Sean J. O’Connor and Deborah S. Hasin

Summary
Heavy alcohol use is pervasive and one of our most significant global health burdens. Early theories posited that certain alcohol response phenotypes, notably low sensitivity to alcohol (‘low-level response’) imparts risk for alcohol use disorder (AUD). However, other theories, and newer measures of subjective alcohol responses, have challenged that contention and argued that high sensitivity to some alcohol effects are equally important for AUD risk. This study presents results of a unique longitudinal study in 294 young adult non-dependent drinkers examined with alcohol and placebo testing in the laboratory at initial enrolment and repeated 5 years later, with regular follow-up intervals assessing AUD (trial registration: http://clinicaltrials.gov/ct2/show/NCT00961792). Findings showed that alcohol sedation was negatively correlated with stimulation across the breath alcohol curve and at initial and re-examination testing. A higher rather than lower alcohol response phenotype was predictive of future AUD. The findings underscore a new understanding of factors increasing vulnerability to AUD.

Declaration of interest
None.

Keywords
Alcohol; stimulation; sedation; differentiator model; low-level response theory.

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Method
Participants were healthy young non-alcohol-dependent drinkers (42% female; mean age 25.4, s.d. = 2.9) who were at high or low risk for AUD based on their alcohol consumption patterns. High-risk drinkers (n = 208) were defined as those who consumed ≥5 standard drinks (≥4 for women) per occasion 1–4 times/week, >14 units weekly and low-risk, light drinker (n = 86) were defined as those who consumed 1–6 drinks/weekly with no/rare heavy drinking. After providing informed consent, participants were individually tested in two 5 h afternoon laboratory sessions in which they consumed either 0.8 g/kg alcohol or placebo in random order under double-blind conditions. They were told the beverage could contain a stimulant, sedative, alcohol or placebo or a combination of two substances. Beverages were consumed in two 5 min intervals separated by 30, 60 and 120 min after beverage initiation home with instructions not to drive or operate machinery for 12 h, provided the BrAC was ˂0.04 g/L with no overt signs of intoxication.

As part of a larger study, the first cohort of 190 participants (104 heavy and 86 light drinkers) were re-tested between 5 and 6 years...
after initial testing in identical sessions to the initial testing.10 The majority (88%) of the 178 deemed eligible for re-examination agreed to participate (86 high-risk and 70 low-risk drinkers). For all participants, follow-up interviews were conducted at 1, 2, 5 and 6 years after initial testing to ascertain the number of AUD symptoms met in the prior year. Those who met mild, moderate or severe AUD by DSM-5 criteria11 in two or more of these inter-symptoms met in the prior year. Those who met mild, moderate and 6 years after initial testing to ascertain the number of AUD met in the prior year. Those who met mild, moderate or severe AUD by DSM-5 criteria11 in two or more of these symptoms were deemed AUD+. Through follow-up, AUD+ was evident in 53% (110/208) of high-risk drinkers and 1% (1/86) of low-risk drinkers.

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The high-risk drinkers in the two cohorts had similar BrAC levels and alcohol responses,11 so their initial testing data were combined. Regression analyses determined the association between stimulation and sedation across the BrAC and for the whole sample and drinker subgroups, and persisted for 5 years. In addition, higher rather than lower-level responses to alcohol predicted the development of AUD, challenging the conventional notion of the exclusive role of low-level response to alcohol as the key alcohol risk response pattern. High responders were >5 times more likely (P<0.001 from a binomial test against a 50% chance likelihood) to develop AUD than low responders.8

Scores on the BAES sedation and stimulation scales were consistently inversely related at rising, peak and declining BrAC limbs (r ≥ -0.37, P < 0.001) in both light and heavy drinkers, and at initial and 5-year re-examinations (see Fig. 1(a) for peak BrAC; and supplementary Fig. 1 available at https://doi.org/10.1192/bjo.2019.18 for all BrAC limbs and study phases). Of participants meeting AUD+ during follow-up, at initial testing peak BrAC, very few were low-level alcohol responders (low stimulation and low sedation; 8%, n = 9/111; Fig. 1(b), quadrant III), in contrast to 46% who exhibited a high-level alcohol response (n = 51/111; Fig. 1(b), quadrant I). This difference in the frequency of low and high-level responders was also evident during ascending and descending BrAC limbs and persisted through re-examination (2% low-level responders, n = 1/47 vs. 51% high-responders, n = 24/47). Thus, drinkers developing AUD were about five times more likely to be high rather than low alcohol responders (P<0.001) and this did not change over time.

**Results**

Scores on the BAES sedation and stimulation scales were consistently inversely related at rising, peak and declining BrAC limbs (r ≥ -0.37, P < 0.001) in both light and heavy drinkers, and at initial and 5-year re-examinations (see Fig. 1(a) for peak BrAC; and supplementary Fig. 1 available at https://doi.org/10.1192/bjo.2019.18 for all BrAC limbs and study phases). Of participants meeting AUD+ during follow-up, at initial testing peak BrAC, very few were low-level alcohol responders (low stimulation and low sedation; 8%, n = 9/111; Fig. 1(b), quadrant III), in contrast to 46% who exhibited a high-level alcohol response (n = 51/111; Fig. 1(b), quadrant I). This difference in the frequency of low and high-level responders was also evident during ascending and descending BrAC limbs and persisted through re-examination (2% low-level responders, n = 1/47 vs. 51% high-responders, n = 24/47). Thus, drinkers developing AUD were about five times more likely to be high rather than low alcohol responders (P<0.001) and this did not change over time.

**Discussion**

Lower alcohol sedation was consistently inversely associated with higher stimulation across the BrAC, for the whole sample and drinker subgroups, and persisted for 5 years. In addition, higher rather than lower-level responses to alcohol predicted the development of AUD, challenging the conventional notion of the exclusive role of low-level response to alcohol as the key alcohol risk response phenotype. Conflicting theories of the role of alcohol response in the risk for future AUD may have resulted from inconsistencies in examining alcohol effects relative to placebo, and lack of attention to the higher stimulation that is associated with AUD.4-10

Our findings from the most extensive repeated alcohol challenge study to date warrant a new understanding of the risk for AUD. Sensitivity to both the stimulating and sedating effects of alcohol may underlie its reinforcing properties4 and foster heavy...
drinking and development of AUD. Early identification of this alcohol response phenotype may provide information for interventions that could reduce the burden of heavy drinking and AUD in society.

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Supplementary material
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