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Article

The Self-Rated Effects of Alcohol Are Related to Presystemic Metabolism of Alcohol

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Abstract

Aims: A high number of alcohol units required to feel a subjective effect of alcohol predicts future alcohol use disorders (AUDs). The subjective response to alcohol can be measured using the validated retrospective self-rated effects of alcohol (SRE) questionnaire. Few studies have investigated the specific relationship between SRE and blood alcohol concentration (BAC) in an experimental setting.
Methods: Twenty healthy young adult male volunteers who had experience with binge drinking, but did not have AUD, filled out the SRE-questionnaire and were served with a fixed amount of alcohol per body weight. BACs were measured throughout a 12-hour period, reaching a maximum BAC of ∼0.13%. Median split of SRE-scores was utilized to compare BACs among participants with relatively high effects (low SRE) and relatively low effects (high SRE) of alcohol.
Results: Participants reporting a relatively low SRE-score had a statistically significant higher measured BAC at all time points until alcohol was eliminated. This was especially pronounced during the first 2 hours after alcohol ($P = 0.015$) without a significant difference in the alcohol elimination rate being detected.
Conclusion: The study indicates that a self-ated SRE-score is related to BACs after the ingestion of a standardized amount of alcohol per body weight. Reporting a higher number of alcohol units before feeling an effect was related to a lower BAC. As the differences in BAC between relatively high and low self-rated effects appeared rapidly after intake, this could be interpreted as an effect of presystemic metabolism of alcohol.

INTRODUCTION

Studies have shown that sensitivity to the effects of alcohol predicts the risk of heavy drinking and of developing alcohol problems (Heath *et al.*, 1999; Schuckit and Smith, 2000). This is thought to be because a low level of response (low LR) to alcohol may lead to heavier drinking with subsequently increased risk for alcohol use disorder (AUD) (Schuckit *et al.*, 2019). Low LR is considered as a moderately heritable trait (Heath *et al.*, 1999; Kalu *et al.*, 2012) and is thought to be different from the more acquired phenomenon of tolerance (Schuckit *et al.*, 2009a). Low LR has further been proposed to result from innate low central nervous sensitivity to alcohol rather than from alcohol metabolism (Roberts and Dollard, 2010). However, the relation between LR and alcohol metabolism is an under-researched area.

Research on the level of response to alcohol has been performed experimentally by administrating oral alcohol and by measuring people's reactions both subjectively and objectively (Boyd and Corbin, 2018). Sensitivity to the effects of alcohol can also be investigated using self-report instruments that ask people retrospectively about their experience with alcohol intoxication. One questionnaire, named self-rated effects of alcohol (SRE), a 12-item questionnaire asking how many units a person had to drink to feel certain effects, has been found to tap into the same information as subjectively reported effects after an alcohol challenge and has demonstrated to predict future AUD (Schuckit *et al.*, 1997b, 2009b).

Alcohol is predominantly metabolized in the liver by alcohol dehydrogenase (ADH). A smaller part is metabolized by ADH-isoform in the gastric mucosa and subsequently also in the liver before it reaches the systemic circulation, known as first-pass metabolism (Cederbaum, 2012). Heavy drinkers regularly have higher alcohol elimination rates (Keiding *et al.*, 1983; Jones, 2008) due to acquired metabolic tolerance, an increased hepatic metabolism of alcohol (Wright and Cameron, 1998) following enzyme induction after heavy drinking and other mechanisms (Whitfield and Martin, 1994; Jones, 2010; Cederbaum, 2012). Also, genetic polymorphisms in certain ADH isoforms are related to reduced metabolism rate of alcohol, rapid emergence of subjective effects of alcohol (Cook and Wall, 2005) and reduced risk of developing AUD (Higuchi *et al.*, 2006; Edenberg and McClintick, 2018), all

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indicating that subjective effects of alcohol could be related to metabolism.

While some studies have measured blood alcohol concentration (BAC) in relation to the SRE questionnaire (Junger *et al.*, 2016; Boyd and Corbin, 2018), to the best of our knowledge, no studies have directly compared alcohol metabolism rates in those with low or high LR to alcohol in an experimental setting. Such a study could provide further information about the relationship between the effects of alcohol and alcohol metabolism.

In the current experimental study, we hypothesized that alcohol metabolism rates were associated with SRE and could explain parts of the mechanisms of low LR. To investigate this, we examined the relationship between people with high and low SRE and BAC measured on different times after alcohol intake.

MATERIALS AND METHODS

Study participants and design

Data for the current study were taken from a previously performed double-blind cross-over experimental study where the effects of added nutritional phosphate on alcohol pharmacokinetics and alcohol abstinence were investigated (Neupane *et al.*, 2016; Bramness *et al.*, 2022). The participants were therefore given a high dose of alcohol (see below). The results presented here are based on the analyses of data taken from the day that the participants received the placebo condition.

Healthy volunteers were recruited among prison officer students through an open advertisement to the University College of Norwegian Correctional Service. Inclusion criteria were male gender, age of 20–45 years and Caucasian origin. Due to the high dose of alcohol administered, participants needed to have experience of drinking more than five units of alcohol in at least one occasion in the past. Exclusion criteria were significant medical illness, alcohol or other substance use disorders and metabolic disorders. Twenty volunteers were included.

Demographic information, as well as physical and psychological health, was recorded. The volunteers were screened for alcohol dependence (AUD) using the Alcohol Use Disorder Identification Test (AUDIT) (Saunders *et al.*, 1993). All individuals scored <15 on the AUDIT scale, where15 is considered as a threshold for probable alcohol dependence. This was corroborated by measuring the serum carbohydrate-deficient transferrin (CDT) value at baseline, which was <1.7%, in a venous blood drawn after an overnight fast prior to the study day in all participants, showing no indication of AUD.

Participants arrived at the experiment location at 7:00 a.m. in the morning following an overnight fast. Baseline blood samples were taken 15 minutes after arrival and then a light breakfast was served. Thirty minutes after the breakfast, participants were served oral alcohol in the form of vodka (38% by volume but diluted to 0.5 l of fluid) in a dose of 1.37 g alcohol/kg body weight, which they drank over a period of 30 minutes. Participants were allowed standard meals (lunch after 4 hours and dinner after 9 hours) and indoor activities throughout the experiment.

Measured variables

Blood samples were taken 10 days prior to the experimental day at ~2:00 p.m. to determine the eligibility and to assess the baseline values. Pre-experimental biochemical tests included blood hemoglobin (Hb), mean corpuscular volume (MCV) and mean hemoglobin (MCH), C-reactive protein (CRP), serum glucose, creatinine, alanine aminotransferase (ALAT), gamma-glutamyl transferase (γ-GT) and CDT assays. Body mass index (BMI) was calculated as [weight (Kg)/height (m)^2].

Subjective effects of alcohol were measured before baseline using the instrument SRE, a 12-item questionnaire asking how many units a person had to drink to feel any effect, produce dizziness or slurred speech, be associated with stumbling or to have contributed to unintentionally falling asleep. Units required for each of these four experiences were registered for three different time points (Schuckit *et al.*, 1997a): the first five times when the participant ever drank (SRE early), during the last period when drinking at least once a month for three consecutive months (SRE lately) and in periods of heaviest drinking (SRE heavy). The SRE has mostly been used in English-speaking countries and was for the purpose of this study, translated into Norwegian and then back translated. A SRE score was generated by totaling the number of drinks required for each effect and dividing it by the number of reported effects for each of the three time points indicated, resulting in three composite scores: SRE_{early}, SRE_{lately} or SRE_{heavy} (Schuckit *et al.*, 1997a, 1997b). As the participants were given a rather high dose of alcohol, we analyzed the SRE_{heavy} measure as this would most closely resemble the experimental setting. Given the sample size, the SRE-measure was dichotomized using a median split, creating one group with relatively high effects of alcohol (SRE below the median) and a group with relatively low effects of alcohol (SRE above the median).

Analyses

BACs were measured 10 times during the experimental study: at 0:00 H, 1:00 H, 1:30 H, 2:00 H, 3:30 H, 5:00 H, 6:30 H, 8:00 H, 10:00 H and 12.00 H. Based on these measures of BAC, different measures were calculated. First, the maximum BAC (BAC_{max}) was measured at 2 hours after start of intake. Second, the BAC area under the curve (BAC-AUC) for the two first hours was calculated using the trapezoidal rule ($BAC\text{-}AUC_{2H}$). The BAC-AUC for the whole experimental period was also calculated ($BAC\text{-}AUC_{total}$). Alcohol elimination follows zero-order kinetics at concentrations above approximately BAC of 0.02%, and the elimination rate could thus be calculated by subtracting BAC at 6.5 hours from BAC at 3.5 hours and dividing by 3 hours. The denomination is % per hour.

The statistical analysis was performed using IBM SPSS Statistics for Windows version 25 (IBM Corp, Armonk, NY). Bivariate statistical tests were done using Mann–Whitney U-test for comparing continuous variables across two groups or Pearson's correlation for looking at the relationship between two continuous variables. Exact *P*-values are given.

Ethics

The study protocol was approved by the Norwegian Regional Ethics Committee (REK case ref. 2013/1563). Prior to inclusion, written informed consent was obtained from all participants. Participants were fully entitled to withdraw their consent at any time during the study. They received a bank transfer amounting to 2000 Norwegian Kroner (~€ 200) in compensation for the time incurred for the experiment, and their taxi fare was paid to return home after the experiment.

Table 1. Background variables measured at baseline for those reporting high or low SRE in periods of heavy drinking (SRE_{heavy})

			SRE (SRE_{heavy})		
			Relatively high effects	**Relatively low effects**	***P*-value[a]**
Background variables					
Age	Years	Mean (SD)	28.9 (5.8)	28.8 (5.0)	1.000
BMI	kg/m^2	Mean (SD)	25.7 (2.9)	25.0 (2.1)	0.739
Background biochemistry					
Hb	g/dl	Mean (SD)	15.6 (0.6)	15.4 (0.7)	0.684
MCH	pg	Mean (SD)	30.6 (1.4)	31.0 (1.6)	0.436
CRP	mg/l	Mean (SD)	1.1 (1.1)	2.2 (4.9)	0.579
s-glucose	mmol/l	Mean (SD)	4.8 (0.3)	4.56 (0.4)	0.280
Creatinine	μmol/l	Mean (SD)	86.6 (10.7)	84.9 (11.7)	0.631
Alcohol use measures					
AUDIT		Mean (SD)	9.0 (3.4)	9.3 (3.1)	1.000
MCV	fl	Mean (SD)	87.4 (3.7)	89.9 (3.7)	0.165
ALAT	U/l	Mean (SD)	34.0 (10.8)	32.2 (8.9)	0.684
γ-GT	U/l	Mean (SD)	27.1 (15.5)	26.8 (9.6)	0.912
CDT	%	Mean (SD)	0.75 (0.27)	0.74 (0.23)	0.912

[a]Independent samples Mann–Whitney U-test.

Table 2. BAC measures in those reporting high or low SRE in periods of heavy drinking (SRE_{heavy})

[a]			SRE (SRE_{heavy})			
			Relatively high effects	**Relatively low effects**	**Effect size (η^2)**	***P*-value[b]**
BAC_{max} (2 h)	% alcohol	Mean (SD)	**0.141 (0.017)**	**0.114 (0.026)**	**0.31**	**0.015**
BAC-AUC_{2h}	% alcohol * hour	Mean (SD)	**0.195 (0.020)**	**0.159 (0.042)**	**0.23**	**0.035**
BAC-AUC_{total}	% alcohol * hour	Mean (SD)	**0.832 (0.155)**	**0.550 (0.178)**	**0.51**	**0.001**
BAC elimination rate	% alcohol/hour	Mean (SD)	0.019 (0.004)	0.022 (0.002)	0.08	0.247

[a]Abbreviations: AUC: area under curve. [b]Independent samples Mann–Whitney U-test. Signficant values are shown in bold.

All participants were insured as part of the project leader's membership of the Norwegian Drug Liability Association (ref. 5041916/1), which covers eventualities in connection with a clinical drug trial. The study was not preregistered.

RESULTS

Scores on SRE_{heavy} ranged from 5 to 12 with a median of 9.8 (Supplementary Fig. 1). Mean (SD) SRE_{heavy} score was 8.2 (1.5) in those with relatively high level of response and 10.7 (0.7) in those with a relatively low LR. Table 1 displays the background variables, baseline medical biochemistry parameters and alcohol use measures in the volunteers in the relatively high SRE group versus those in the relatively low SRE group during heavy drinking periods (SRE_{heavy}). The groups did not differ on alcohol use measures like AUDIT, MCV, ALAT, γ-GT or CDT. The three different measures of SRE (early, lately and heavy) were highly correlated (Supplementary Table 1).

Table 2 compares the median split groups on blood alcohol parameters measured during the experimental study, showing that volunteers with high SRE had a higher BAC_{max} ($\eta^2 = 0.31$; $P = 0.015$), a higher BAC-AUC_{2h} ($\eta^2 = 0.23$; $P = 0.025$) and a higher BAC-AUC_{total} ($\eta^2 = 0.51$; $P = 0.001$) than those with low SRE. As displayed in Fig. 1, those rating effects of alcohol as high had significantly higher BAC concentrations at all time points (except at baseline and after 12.0 hours) than those who rated their effects of alcohol as low. There was no statistically significant difference in the alcohol elimination rate between the two groups ($\eta^2 = 0.08$; $P = 0.247$).

When analyzing SRE_{heavy} as a continuous variable (Supplementary Table 1), SRE trended to be more related to the BAC elimination rate (Supplementary Fig. 2) and BAC-AUC_{12h} (Supplementary Fig. 3) than BAC-AUC_{2h}.

The AUDIT score was not related to any measure of BAC (BAC-AUC_{2h}: Spearman's $\rho = 0.241$, $P = 0.321$, BAC_{max}: $\rho = 0.277$, $P = 0.251$). The same lack of association to BAC at any timepoint was also found for γ-GT ($\rho = -0.129$, $P = 0.588$ and $\rho = 0.060$, $P = 0.801$, respectively) and CDT ($\rho = -0.260$, $P = 0.268$ and $\rho = -0.259$, $P = 0.270$ respectively). The same negative findings were true for MCV and ALAT and all the measured BAC parameters. These data are not shown in a table.

DISCUSSION

In this experimental study among healthy, male volunteers, given a standardized amount of alcohol, we found that the group with low self-rated effects of alcohol (SRE), in periods of high consumption of alcohol, had a significantly lower systemic exposure to alcohol (BAC-AUC_{total}) than the group with high self-rated effects. This lower exposure appeared to be mostly due to the lower BAC levels in the time close to intake on the rising part of the BAC-curve (BAC-AUC_{2h} and BAC_{max}). The difference in the systemic elimination rate between the groups was non-significant.

The difference in BAC between the median split SRE-groups was most pronounced in the beginning of the BAC versus time curve. The differences found in the later stages could mostly be explained by this initial discrepancy. In general, the

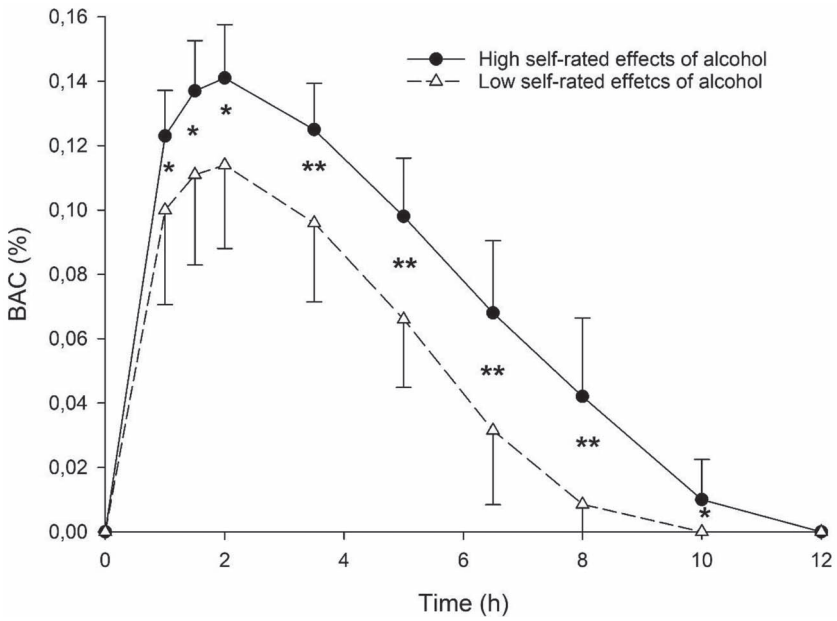

Fig. 1. The blood alcohol level (BAC) curves for the subjects with high SRE-scores (low SRE) (open triangles and dotted lines) or low SRE-scores (high SRE) (filled dots and whole lines) to alcohol in heavy drinking periods (SRE_{heavy}); the difference in BAC between low- and high-sensitivity groups is at all time points statistically significant (*$P < 0.05$ and **$P < 0.01$; Mann–Whitney U-test).)

systemic exposure to alcohol after oral intake will depend on re-systemic metabolism, which takes place in the gastric mucosa (Seitz *et al.*, 1993; Birley *et al.*, 2008) and the liver before reaching the systemic circulation, determining the ethanol C_{max} and the AUC_{2h}. The magnitude of exposure will then depend on the systemic elimination rate. The largest portion of alcohol metabolism takes place in the liver (Frezza *et al.*, 1990; Cederbaum, 2012), and hepatic metabolism rates may increase in periods of high consumption due to enzyme induction and other mechanisms, which is referred to as metabolic tolerance (Whitfield and Martin, 1994; Jones, 2010; Cederbaum, 2012). It could be argued that the observed relation between the low systemic exposure to alcohol and low SRE is a consequence of increased hepatic alcohol metabolism due to the higher alcohol intake in the group with high SRE scores over time. However, in the current study, we observed no relationship between SRE and the alcohol elimination rate in the two groups. Furthermore, we detected no differences in other measures that could indicate that one group had a substantially different drinking pattern than the other, which could have pointed to the increased hepatic metabolism. The groups had similar AUDIT, γ-GT and CDT-scores. Both γ-GT (van Beek *et al.*, 2014; Dixit and Singh, 2015) and CDT (Salaspuro, 1999; Golka and Wiese, 2004) are considered as reliable markers of alcohol intake.

Our findings could indicate a more pronounced presystemic elimination rate among those with low SRE. Previous research has demonstrated that as much as one-third of ethanol can be eliminated by this first-pass metabolism before it reaches systemic circulation (Frezza *et al.*, 1990; Bramness *et al.*, 2022; Pfützner *et al.*, 2022). As there were only marginal differences related to SRE and alcohol elimination, as calculated from the descending limb of the BAC versus time curve, the results could further be interpreted to stem from the differences in the gastric rather than the hepatic step of presystemic elimination of alcohol. Gastric metabolism is the most prominent in men (Baraona *et al.*, 2001) and may be influenced by the speed of gastric alcohol transfer (Oneta *et al.*, 1998), which is delayed after meals. The volunteers in this experimental study were given a standardized meal prior to the alcohol challenge, which could explain the relatively marked role of presystemic elimination to the systemic exposure to alcohol in this study. However, this effect would be equally distributed among the two groups.

When treating SRE_{heavy} as a continuous rather than a dichotomous variable, there was a tendency for the difference to be more skewed to the latter part of the BAC curve, possibly indicating a larger contributing role of alcohol elimination in relationship to SRE. However, there was still a tendency that those with higher SRE_{heavy} scores experienced a lower BAC_{max}.

The role of a substantial gastric elimination has recently been debated (Jones, 2010, 2019), however, recent evidence from gastric operations for obesity indicates a significant gastric metabolism of alcohol (Seyedsadjadi *et al.*, 2022). The isomer of ADH mostly expressed in the gastric tract is ADH7 (Jelski *et al.*, 2002; Birley *et al.*, 2008), and the genetic variation in the enzyme is related to the risk of AUD (Całka *et al.*, 2016). More broadly, heritable traits of alcohol metabolism have also been linked to AUD (Tawa *et al.*, 2016; Edenberg and McClintick, 2018). A follow-up study to investigate shared heritability between SRE and alcohol metabolism would therefore be relevant to further bridge the knowledge gap surrounding alcohol sensitivity.

To the best of our knowledge, this is the first study comparing the SRE directly with differences in BAC levels at fixed time points. A few have measured BAC and subjective effects in relation to within-session tolerance, a process that leads to less effect of alcohol on the descending limb of the curve compared with similar BAC on the ascending curve (Morris *et al.*, 2017; Anthenelli *et al.*, 2021). In the study by Anthenelli and colleagues, which did not find support for a relationship between an increased acute tolerance and low LR, SRE scores were used to divide participants into two groups where they subsequently recorded the subjective effects experienced during an oral alcohol challenge. They

found no difference between the SRE groups and BAC at peak in the absorption phase, which was measured by the breath alcohol concentration. Their study included women and men but found no effect of sex on the results. Our results demonstrated a difference in peak BAC, and a possible explanation for the different findings could be that it was a male sample, where gastric metabolism is considered to be more pronounced (Frezza *et al.*, 1990).

This study was a well-controlled experimental study, including a wide range of biochemical measures and close monitoring of BAC in subjects, given the same amount of alcohol per kg body weight. The participants consisted of a quite small ($n = 20$) homogenous group of well-trained Caucasian men in their 20s. This limits the generalizability of our results to other populations and gender, which needs to be confirmed in future studies with larger sample sizes. Participants were also given a higher dose of alcohol than in other experimental studies (Wetherill *et al.*, 2012; Pfützner *et al.*, 2022), which also affects gastric emptying and first-pass metabolism (Oneta *et al.*, 1998) and might complicate comparisons with other studies. However, the BACs reached in the present study could be more representative for real life than other experimental studies with lower exposure to alcohol (Clapp *et al.*, 2009; Rossheim *et al.*, 2017). The experiment was part of a hangover study and the rationale behind the high bolus was the intent to induce a BAC that at least had some chance of producing hangover. The study was approved by the regional ethics committee and no adverse effects were reported, including no hangover effects. It is worth keeping in mind that while SRE enquires about the effects of alcohol without specifying in what situation the drinking occurred (relation to food, social drinking, drinking alone, activities during drinking, etc.), there will be a contextual difference between the drinking experiences recorded by the SRE and that experienced in an unnatural experimental setting. Additional studies with more participants will thus be required to confirm results. Another potential limitation is that the interpretation of our findings cannot exclude the possibility that the participants reporting a high SRE had acquired an increased gastric metabolism of alcohol through higher intake of alcohol. While the contribution of gastric metabolism is possibly minimal in social drinkers (Ammon *et al.*, 1996), the gastric ADH activity increases with increasing moderate alcohol intake. By contrast, it is found to be substantially decreased in severe AUD (Seitz *et al.*, 1993). However, considering the lack of difference in alcohol measures, which could indicate different consumption patterns, we consider this interpretation to be less likely. The study could have profited from the inclusion of more alcohol intake measurements, such as phosphatidylethanol (PEth) as this is considered as a more accurate measure of recent alcohol intake (Simon, 2018; Årving *et al.*, 2021), however, this was not feasible due to the analysis cost at the time of the study. We would also have liked to include the family history of AUD, which has been shown to relate to both SRE and alcohol metabolism. In addition, the study, being hypothesis-driven, should have been preregistered. Lastly, the study did not control for speed of gastric emptying, which is known to affect first-pass metabolism (Oneta *et al.*, 1998). These are limitations which future studies should consider.

Conclusion

This experimental study demonstrates that relatively low self-rated effect of alcohol is related to the lower systemic exposure to alcohol, which could be related to the increased gastric presystemic metabolism of alcohol. Considering the limitations mentioned for the current study, it is of high importance to conduct additional studies on the pharmacokinetic aspects of SRE to elucidate further the role of alcohol metabolism in SRE.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *Alcohol and Alcoholism* online.

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AUTHORS' CONTRIBUTIONS

The original idea for the study was developed by Knut R. Skulberg and Andreas Skulberg. Jørgen G. Bramness, Knut R. Skulberg and Andreas Skulberg developed the protocol and organized the study. Jørgen G. Bramness was PI of the experimental study. All authors interpreted the data. Jørgen G. Bramness drafted the manuscript in collaboration with Jenny Skumsnes Moe, Jørg Mørland and Andreas Skulberg, and all authors participated in writing the manuscript and approving the final version. Jørgen G. Bramness (PI of experimental study, developed study protocol, interpreted data, drafted manuscript, revised manuscript, approved final version); Knut R. Skulberg (original idea for the study, developed study protocol, interpreted data; drafted manuscript, revised manuscript, approved final version); Andreas Skulberg (original idea for the study, developed study protocol, interpreted data, revised manuscript, approved final version); Jenny Skumsnes Moe (interpreted data, drafted manuscript, revised manuscript, approved final version) and Jørg Mørland (interpreted data, drafted manuscript, revised manuscript, approved final version).

CONFLICT OF INTEREST STATEMENT

Knut R. Skulberg and Andreas Skulberg owned and ran the commercial firm Primo Inc, which produces the sports drink 'c-Foz', and were paid for this experimental study with an unrestricted grant. Jørgen G. Bramness was also paid with a one-time advisory honorarium of 10,000-Norwegian Kroner (~€ 1100,-) for work on designing the project from Primo Inc. Primo Inc was sold in 2021. None of the authors are currently owners of or have any collaboration with the new firm. There is therefore no current conflict of interest by any of the authors and none of the other authors have any conflicts of interest to report.

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