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L-Cysteine Containing Vitamin Supplement Which Prevents or Alleviates Alcohol-related Hangover Symptoms: Nausea, Headache, Stress and Anxiety

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Abstract

Aims: Alcohol-related hangover symptoms: nausea, headache, stress and anxiety cause globally considerable amount of health problems and economic losses. Many of these harmful effects are produced by alcohol and its metabolite, acetaldehyde, which also is a common ingredient in alcohol beverages. The aim of the present study is to investigate the effect of the amino acid L-cysteine on the alcohol/acetaldehyde related aftereffects.

Methods: Voluntary healthy participants were recruited through advertisements. Volunteers had to have experience of hangover and/or headache. The hangover study was randomized, double-blind and placebo-controlled. Nineteen males randomly swallowed placebo and L-cysteine tablets. The alcohol dose was 1.5 g/kg, which was consumed during 3 h.

Results: The primary results based on correlational analysis showed that L-cysteine prevents or alleviates hangover, nausea, headache, stress and anxiety. For hangover, nausea and headache the results were apparent with the L-cysteine dose of 1200 mg and for stress and anxiety already with the dose of 600 mg.

Conclusions: L-cysteine would reduce the need of drinking the next day with no or less hangover symptoms: nausea, headache, stress and anxiety. Altogether, these effects of L-cysteine are unique and seem to have a future in preventing or alleviating these harmful symptoms as well as reducing the risk of alcohol addiction.

INTRODUCTION

Alcohol drinking and drunkenness commonly lead to hangover symptoms: nausea, headache, stress and anxiety, which are unpleasant experiences of various physical, physiological and psychological effects. These aftereffects may last and vary from <1 h up to several days, depending on numerous intrinsic and extrinsic factors. Globally, the alcohol-related aftereffects cause, e.g. impaired cognitive functions and performance of everyday tasks, e.g. such as driving (Gunn *et al*. 2018), as well as impaired work performance (presenteeism) and absence from work (absenteeism) (Thørrisen *et al*. 2019). Such impairments create a considerable amount of economic loss worldwide (Wiese *et al*. 2004).

In January 2020, there were >700 publications in PubMed in which hangover has been studied in different contexts. Of these publications, only 10 relevant studies have investigated various food supplements as possible cures for the aftereffects of alcohol drinking (Bang *et al*. 2015; Chauhan and Kulkarni 1991; George *et al*. 2019; Kim *et al*. 2017; Kim *et al*. 2018; Lee *et al*. 2013; Lee *et al*. 2014; Mammen *et al*. 2018; Takahashi *et al*. 2010; Wiese *et al*. 2004). In all of these 10 studies, plants, fruits and/or their extracts have been used, which complicates the evaluation of the real effective agents. Stress was not investigated in any of these studies. Anxiety was mentioned in four studies, two without response (Lee *et al*. 2014; Takahashi *et al*. 2010) and two with response (George *et al*. 2019; Mammen *et al*. 2018). Hangover, nausea and headache were the primary target for these 10 studies. Three of the studies displayed lower blood alcohol curves with the food supplements compared to placebo (Lee *et al*. 2013; Lee *et al*. 2014; Mammen *et al*. 2018). These effects may relate to slower gastric absorption. It is commonly known that virtually any sort of food may reduce the absorption of alcohol (Gentry 2000).

Alcohol hangover is a complex phenomenon affecting biochemical, inflammatory and neurochemical mechanisms (Palmer *et al*. 2019, 2020). Generally, alcohol is considered to be the agent for causing hangover and related symptoms. However, the truth is that many of these harmful effects are produced by alcohol and its metabolite, acetaldehyde (Eriksson 2001), which also is a common ingredient in alcohol beverages (Lachenmeier and Sohnius 2008). In addition, also cigarette smoking produces acetaldehyde (Seeman *et al*. 2002), which may explain why alcohol drinking and smoking are closely associated with each other. A study published in 1967 showed that acetaldehyde in cigarette smoke binds to L-cysteine and forms a 2-methyl-L-thiazolidine-4-carboxylic acid (MTCA) derivative (Braven *et al*. 1967). The hypothesis was that the protective strength of amino thiols (especially L-cysteine) would be reduced, due to the acetaldehyde, which could increase the possibility of carcinogenesis. Later studies have shown that alcohol-related acetaldehyde is carcinogenic (Secretan *et al*. 2009) and in addition, also causes harmful symptoms during a hangover (Eriksson 2001).

In our present study, we investigated the effect of the semi-essential amino acid, L-cysteine, on hangover symptoms: nausea, headache, stress and anxiety. L-cysteine, representing a single chemical molecule, is produced in the human body and is also an ingredient in the diet. This makes L-cysteine different from the other studied food supplements (plants, fruits and/or their extracts), in which there are a number of ingredients of unspecific nature. Our main hypothesis for the present study is that the oral administration of the L-cysteine leads to the elimination of acetaldehyde in the body, which in turn prevents or alleviates alcohol aftereffects. To our knowledge, our study is the first to prove the prevention and the alleviation of alcohol-related hangover symptoms: nausea, headache, stress and anxiety with L-cysteine as a food supplement.

MATERIALS AND METHODS

The recruitment and selection of volunteers

Voluntary healthy participants were recruited through advertisements (media, internet, message boards from the University of Helsinki). To all participants, which were interested in the study, we sent the first questionnaires, which were completed and sent back to us by mail before the first session. Altogether, 27 participants were enrolled, 8 women and 19 men, aged between 21 and 50 (women) and 21 and 60 (men). All volunteers had to have some experience of hangover and/or headache. The exclusion criteria also included pregnancy (tested before sessions), menopause, alcoholism, especially low tolerance to alcohol (highlighted intoxication and/or hangover), >6 h fasting, BMI more than 30 kg/m^2 and <18 kg/m^2, alcohol-related and non-related diseases and alcohol drinking related aggression. Also, all volunteers received a letter, in which the study was described, together with an informed consent document (to be signed before the first session).

A main problem was that only eight women participated; one attending one session. Three women had zero response to hangover symptoms in all three sessions. We were left with four women; one, unfortunately, participating at different stages of the normal menstrual cycle. One of the remaining three women using long-term steroids vomited and had nausea during all three sessions. These confounding factors prevent us from drawing reliable conclusions from the present women's data. Thus, the results of the present study are based solely on men's data.

Study design

The study protocol has been approved by the research ethics committee of the University of Eastern Finland (UEF) and by the coordinating ethics committee of Helsinki University Hospital (HUH). The present hangover study was randomized, double-blind and placebo-controlled. In all categories (hangover, nausea, headache, stress and anxiety), only the data of participants with a response were included. Two volunteers quit after the first session, one quit after two sessions, one could not finish the drinking in one session, one could not finish the drinking in two sessions and two volunteers did not respond in any of their three sessions. Twelve volunteers responded in all three sessions. Altogether, data were obtained from 43 participations in the five categories (hangover, nausea, headache, stress and anxiety). In addition, alcohol and acetaldehyde levels were also measured for two volunteers, who did not respond in any of the five categories, raising the number of participations to 49. All volunteers randomly swallowed during Friday evenings (August–September 2018) six placebo tablets, three placebos plus 3 L-cysteine tablets and/or six L-cysteine tablets (L-cysteine tablets containing 200 mg L-cysteine), every time about 15 min before 7, 8, 9, 10, 11 and 12 pm.

All tablets, excluding placebo tablets, contained also vitamin B1 (thiamine, 50 mg), B2 riboflavin, 1.4 mg), B3 (niacin, 16 mg), B6 (pyridoxine, 1.4 mg), B7 (biotin, 50 µg), B9 (folic acid, 200 µg), B12 (cobalamin 2.5 µg) and vitamin C (ascorbic acid, 80 mg). This L-cysteine tablet is a fast releasing food supplement (Catapult Cat^{TM} L-cysteine vitamin tablet), which cannot be distinguished with the placebo. The composition of all tablets also consists of filling agent (microcrystalline cellulose), anti-caking agent (magnesium salts of fatty acids and silicon dioxide), titanium dioxide, copper complexes

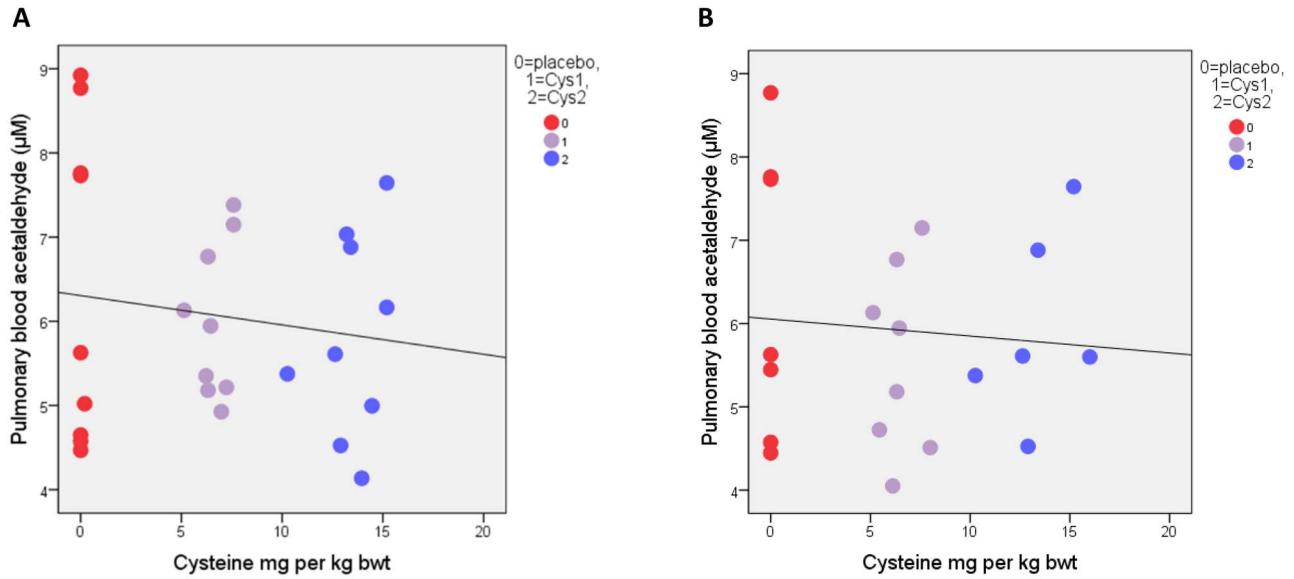

Fig. 1. The effect of L-cysteine on evening acetaldehyde in the categories of morning nausea (**A**) and stress (**B**). Individual data of nine men attending all three sessions are shown in (A) and six men attending all three sessions plus 3 single cases are shown in (B). Friedman-related samples analysis of variance by ranks shows differences between placebo (red dots) and L-cysteine (1200 mg, blue dots) with the significance of $P = 0.048$ (A) and $P = 0.051$ (B).

of chlorophyll and chlorophyllin, glycerol, hydroxypropyl methylcellulose and flavor (menthol).

All sessions were done at a private hotel, during six subsequent Fridays, started at 6 pm with an informal event during which the informed consents were signed and second questionnaires completed. First saliva samples were taken at about 6:30 pm. Alcohol drinking started just before 7 pm and was consumed evenly in three doses in the period of 3 h. The overall alcohol dose was 1.5 g/kg, which was served as 10%, v/v, mixed with lingonberry/blackcurrant juice (sucrose, 9 g/l, energy content 160 kJ). Second saliva samples were taken about half an hour after finishing drinking ca 10:30 pm, during which an intoxication questionnaire was completed. Sessions were closed around midnight after which participants went to sleep. Neither smoking nor eating was allowed during the evening and night. The next morning, around 8 to 9 am, the participants gathered in the same room as in the previous evening. After the third saliva sampling and completing, the rest of the questionnaires the participants were free to go for breakfast and other activities.

With the first questionnaire for the present study, we could assess the inclusion and exclusion criteria for the participation, and also using the Alcohol Use Disorders Identification Test (Saunders *et al.* 1993). The main morning questionnaires, with which the participants expressed their degree of hangover, nausea, headache and anxiety, were done with Likert Scales from 0 to 10. In addition, we also used a Likert Scale 1–4 in interviewing the degree of volunteers' stress.

Analytical procedures

Alcohol and acetaldehyde breath tests were performed before the session, at the end of sessions and in the morning using Proton Transfer Reaction Time-of-Flight Mass Spectrometry (PTR-TOF-MS) (PTR-TOF 1000, Ionicon Analytik, Innsbruck, Austria). Proton transfer reaction mass spectrometry is a very sensitive analytical methodology that can be used for online analysis of various volatile organic compounds in the gas phase (Blake *et al.* 2009). The sensitivity is high enough to enable the analysis of endogenous ethanol and acetaldehyde levels in human exhaled breath. A closely related technique, selected-ion flow-tube mass spectrometry (SIFT-MS), has previously been used to analyse acetaldehyde and ethanol from the exhaled breath (Turner *et al.* 2006).The PTR-TOF-MS operating conditions were as follows: field density ratio (E/N) of 127 Td; drift tube pressure of 2.20 mbar, H_2O flow of 5.0 standard cubic centimetres per minute (sccm); ion source current of 3.0 mA; inlet flow of 50 sccm and drift tube voltage of 551 V. Drift tube and inlet temperatures were kept at 70°C. Sampling frequency was 1 Hz, meaning one spectrum was recorded every second. Breath samples were obtained using Ionicon BET-med breath sampler. The breath sampler was connected to a device (Multiple Breath Gas Sampler, Loccioni) that measured the exhaled volume of air and CO_2 concentration. Breath samples were collected such that the volunteers exhaled a total of 1300 ml of air for each sample.

The acetaldehyde concentration was quantified at the protonated mass-to-charge ratio (m/z) signal of 46 that corresponds to the less abundant isotopologue of acetaldehyde. This was done to reduce the effect of signal saturation that takes place due to the high concentration of acetaldehyde after alcohol drinking. The signal at m/z 46 was multiplied by a factor of 47 to get the concentration of the most abundant acetaldehyde isotopologue. Regardless, the very high ethanol concentration in breath caused problems for the operation of the instrument and the acetaldehyde analysis. In practice, we observed that the mean acetaldehyde levels had significant differences between the six sessions. For this reason, the individual acetaldehyde measurements were normalized by multiplying with the following ratio: mean acetaldehyde concentration of all sessions/mean acetaldehyde concentration of session.

In addition, alcohol breath tests were also measured by the Dräger Alcometer, Alcotest 3000 (Drägerwerk AG & Co. KGaA, Lübeck, Germany). Breath alcohol and acetaldehyde concentrations were converted by the blood/breath ratio (2300:1) for alcohol (Jones 2000) and (190:1) acetaldehyde (Jones 1995), respectively. Cortisol and testosterone were measured from saliva samples before alcohol

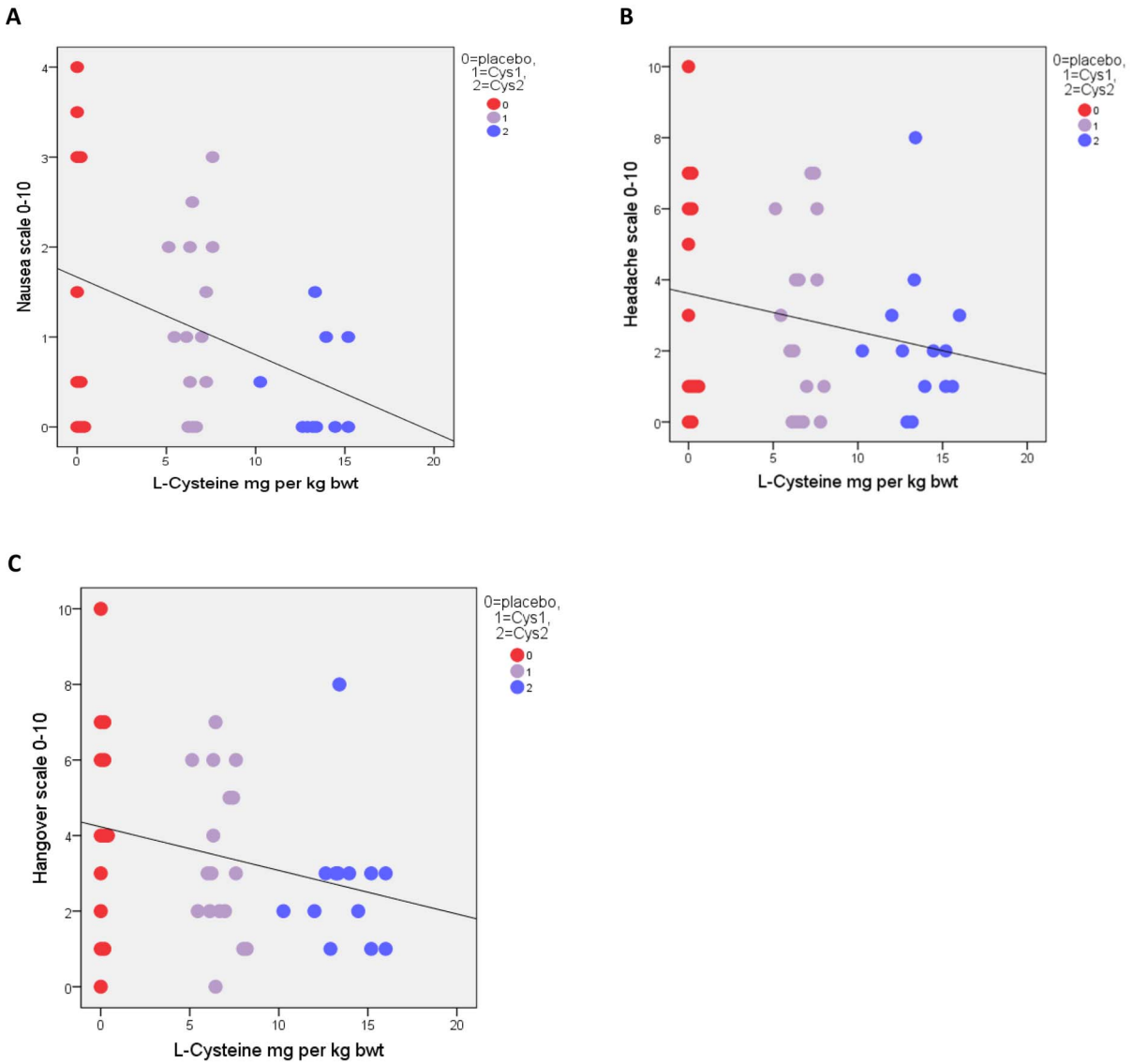

Fig. 2. The effect of evening L-cysteine on alcohol-related morning nausea (**A**), headache (**B**) and hangover (**C**). Individual data of men are shown, all of which displayed at least a hint of nausea (A), headache (B) and/or hangover (C) at some of the sessions. Altogether the participations were 34 with nine subjects attending all three sessions (A), 43 with 12 subjects attending all three sessions (B and C). Correlations analysis displayed significance with −0.287, $P = 0.050$ (A), negligible with −0.165, $P = 0.145$ (B) and significance with −0.258, $P = 0.047$ (C). Moreover, related-samples Wilcoxon sign rank test tests (median differences) displayed significant differences between placebo (red dots) and L-cysteine (1200 mg, blue dots), $P = 0.013$ (A), $P = 0.010$ (B) and $P = 0.043$.

drinking, after the drinking and next morning. Salivary cortisol and testosterone determinations were made by the enzyme-linked immunosorbent assay analysis (see Acknowledgements).

Statistical methods

The statistics were performed with the (IBM) SPSS software version 24. In the present study, all statistical significances associated with L-cysteine were one-tailed. This presumption is reasonable, since it is known that L-cysteine binds to acetaldehyde and consequently diminishes alcohol-related hangover symptoms: nausea, headache, stress and anxiety. For the other correlations without L-cysteine, the significances were two-tailed. Spearman's rho coefficients are used for all correlation analyses (all figures). Related-Samples Wilcoxon Sign Rank Test (for median differences), Related-Samples Friedman's Two-Way Analysis of Variance by Ranks and Paired Samples and t-test were used (see figures). Standard error of the mean was used in alcohol and acetaldehyde calculations.

RESULTS

Alcohol and acetaldehyde concentrations

In the present study, the overall mean alcohol concentration after 3 h evening drinking was 28.35 ± 0.69 mM (1.31 ± 0.03 ‰) ($N = 49$) without any significant differences between the placebo and L-cysteine groups. Neither were there any separate significant differences between evening alcohol concentration and the five categories hangover symptoms, nausea, headache, stress and anxiety, in

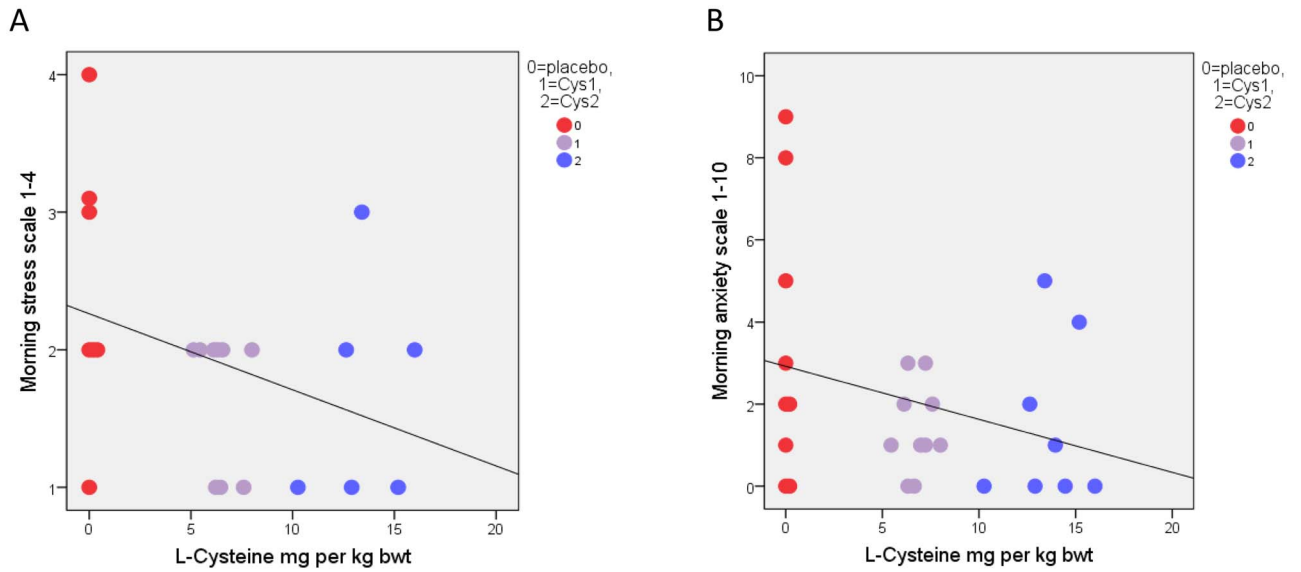

Fig. 3. The effect of L-cysteine on alcohol-related morning stress (**A**) and anxiety (**B**). Individual data of men are shown, all of which displayed at least a hint of stress (A) and anxiety (B) at some of the sessions. Altogether the participations were 22 with 6 subjects (A) and 27 with 7 subjects, attending all three sessions. Correlations analysis displayed significance with −0.382, $P = 0.039$ (A) and negligible with −0.250, $P = 0.104$. (B). In addition, paired samples t-test (with seven subjects) displayed a significance of $P = 0.039$ between placebo (red dots) and L-cysteine (600 mg, purple dots) (A). Moreover, related-samples Wilcoxon sign rank test (median differences) displayed a significance of $P = 0.052$ (B).

placebo and L-cysteine groups. Similarly, the overall average morning alcohol concentration was 3.45 ± 0.83 mM without any significant differences between the placebo and L-cysteine groups. Thus, in the present study, L-cysteine did not affect the evening absorption or the rate of alcohol elimination.

The evening mean acetaldehyde level was 6.31 ± 0.26 μM ($N = 49$) without any significant differences between the placebo and L-cysteine groups. However, in the category of nausea and stress, ingestion of L-cysteine (1200 mg) resulted in significant effects on evening acetaldehyde (Fig. 1). Morning acetaldehyde concentration was 4.47 ± 0.60 μM without any significant differences between placebo and L-cysteine.

Correlational analyses

Our correlational study is designed so that all the data points in the figures represent the original data. Although the number of volunteers was rather low, several significant results were obtained by L-cysteine when hangover symptoms: nausea, headache, stress and anxiety were examined the next morning, ca. 10 h after evening drinking was finished. One main hangover symptom is nausea, which was prevented or alleviated by L-cysteine (Fig. 2A). Nausea was also significantly positively correlated with a hangover (34 participations, with nine subjects attending all three sessions, 0.437, $P = 0.010$). However, the headache was more strongly correlated with a hangover than with nausea (participations were 43 with 12 subjects attending all three sessions, 0.690, $P = 0.000$). Nausea and headache symptoms may thus share some affecting parameters, but headache also seems to have an additional parameter in common with a hangover (participations were 34 with nine subjects attending all three sessions, 0.370, $P = 0.031$).

From the correlations between L-cysteine and hangover symptoms: nausea and headache, it could be seen that the dose of L-cysteine, 600 mg, had little effect on these symptoms, as compared to the dose of 1200 mg, (Fig. 2A, B and C). However, for stress and anxiety, a correlation with L-cysteine is present already at a dose level of 600 mg (Fig. 3). Moreover, both stress (headache correlation 0.574, $P = 0.005$; hangover correlation 0.503, $P = 0.017$) and anxiety (headache correlation 0.594, $P = 0.001$; hangover correlation 0.586, $P = 0.001$) were significantly associated with headache and hangover, as also with each other (stress vs anxiety correlation 0.806, $P = 0.000$).

We also studied the possible interrelations between the hangover and stress and anxiety symptoms, and the steroids cortisol and testosterone. The only trend effect was a positive correlation (0.304, $P = 0.086$) between cortisol and nausea. In fact, the positive cortisol/nausea correlation has been recognized in an earlier Finnish study by Ylikahri *et al.* (1974).

DISCUSSION

Alcohol and acetaldehyde

No differences in overall evening and morning alcohol concentrations were observed between placebo and L-cysteine groups. This is plausibly due to the strict control imposed on the volunteers' evening drinking which led to a very low variation in the blood alcohol levels. The lack of differences in morning alcohol levels showed that the L-cysteine did not change the rate of alcohol elimination. Altogether, it was impossible to detect any significant alcohol correlations within the different categories (hangover symptoms: nausea, headache, stress and anxiety) between the placebo and L-cysteine groups. Regarding the pulmonary acetaldehyde, the difficulty is that the exhaled breath sample may be contaminated by acetaldehyde derived by the oral microflora. Most likely, the real pulmonary acetaldehyde concentration is a bit lower than our measured concentrations. In addition, technical problems caused by the high ethanol content of exhaled breath during the sessions, most likely introduced additional noise into the acetaldehyde data. However, in spite of these problems,

with acetaldehyde and L-cysteine, two significant differences emerged between placebo and L-cysteine (see Result section, Fig. 1A and B).

Hangover, nausea, headache, stress and anxiety

In our present study, hangover represents disagreeable aftereffects of drunkenness involving physical, physiological and psychological experience. Instead of using a hangover scale that includes a number of hangover symptoms such as Hangover Symptoms Scale (Slutske *et al*., 2003), Acute Hangover Scale (Rohsenow *et al*. 2007) or Alcohol Hangover Severity Scale (Penning *et al*. 2013), we just used a single Likert scales for hangover, stress and anxiety symptoms. Earlier six food supplement studies demonstrate some success treating nausea (Bang *et al*. 2015; George *et al*. 2019; Kim *et al*. 2017; Mammen *et al*. 2018 Takahashi *et al*. 2010; Wiese *et al*. 2004), headache (Bang *et al*. 2015; George *et al*. 2019; Kim *et al*. 2017; Kim *et al*. 2018; Mammen *et al*. 2018) and hangover (Bang *et al*. 2015; Chauhan and Kulkarni 1991; Kim *et al*. 2017; Mammen *et al*. 2018). Anxiety has been treated only in two studies (George *et al*. 2019; Mammen *et al*. 2018). Interestingly, stress has not been treated in any of the earlier studies. In our present study, we observed statistically significant effects in all of the five categories.

Vitamins

The vitamins included in the L-cysteine tablets may or may not had an effect on the hangover symptoms. The neutralizing effect of L-cysteine on acetaldehyde (Fig. 1), which is a major factor promoting hangover symptoms, indicates that L-cysteine has a main impact in diminishing the alcohol-related hangover symptoms. Altogether, the present study was focused only on the effect of L-cysteine on a hangover and its symptoms. A separate study with alcohol-related hangover symptoms with all different vitamins would certainly be an interesting topic for further research.

Ethics and L-cysteine

In many parts of the world where alcohol drinking is legal, a widely held belief still exists, that hangover should not be cured because that would increase the risk of more alcohol consumption. However, this belief may be misinformed and not entirely correct. The fact of the matter is that higher degree of alcohol-related hangover and stress symptoms lead to more effort 'curing' the aftereffects by drinking alcohol. This is especially the case with individuals with predisposition for developing alcohol addiction (Earleywine 1999; Newlin and Pretorius 1990). Moreover, it seems that there is no evidence for why preventing or alleviating hangover would lead to increased alcohol consumption (Wiese *et al*. 2000). Finally, it has to be recognized that not all people who experience hangovers continue to drink.

Some of the previously studied food supplements, plants, fruits and/or their extracts may have some similar effects as L-cysteine, but possibly also various other unwanted effects as well. The advantage with L-cysteine is that this semi-essential amino acid already is present in the human body. This means that the addition of L-cysteine can directly and dose-dependently enter into the normal metabolism and help to neutralize the detrimental acetaldehyde, as well as prevent or alleviate the alcohol aftereffects.

Moreover, since acetaldehyde is carcinogenic, binding it by L-cysteine may also reduce the probability for the development of cancer (Hellström *et al*. 2017; Juliano *et al*. 2011). Thus, all these actions of L-cysteine are ethically sound.

CONCLUSION

The final conclusion is that L-cysteine reduces alcohol-related hangover symptoms: nausea, headache, stress and anxiety. Altogether, the effects of L-cysteine on hangover symptoms: nausea, headache, stress and anxiety are unique and seem to have a future in preventing or alleviating these harmful symptoms, as well as reducing the risk of alcohol addiction.

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CONFLICTS OF INTEREST STATEMENT

Authors have no conflict of interest. The authors were fully responsible for the study design and the funding agency had no role in the collection, analysis, interpretation of data and in writing of the manuscript.

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