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***Basic Study***

**Alcohol intolerance and myalgic encephalomyelitis/chronic fatigue syndrome**

Maciuch J *et al*. Alcohol intolerance and ME/CFS

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**Abstract**

BACKGROUND

The literature is mixed about the occurrence of alcohol intolerance among patients with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Surveys that asked respondents with ME/CFS whether they experienced alcohol intolerance within a recent time frame might produce inaccurate results because respondents may indicate that the symptom was not present if they avoid alcohol due to alcohol intolerance.

AIM

To overcome this methodologic problem, participants in the current study were asked whether they have avoided alcohol in the past 6 mo, and if they had, how severe their alcohol intolerance would be if they were to drink alcohol.

METHODS

The instrument used was a validated scale called the DePaul symptom questionnaire. Independent *t*-tests were performed among the alcohol intolerant or not alcohol intolerant group. The alcohol intolerant group had 208 participants, and the not alcohol intolerant group had 96 participants.

RESULTS

Using specially designed questions to properly identify those with alcohol intolerance, those who experienced alcohol intolerance *vs* those who did not experience alcohol intolerance experienced more frequent/severe symptoms and domains. In addition, using a multiple regression analysis, the orthostatic intolerance symptom domain was related to alcohol intolerance.

CONCLUSION

The findings from the current study indicated that those with ME/CFS are more likely to experience alcohol intolerance. In addition, those with this symptom have more overall symptoms than those without alcohol intolerance.

**Key Words:** Myalgic encephalomyelitis/chronic fatigue syndrome; Alcohol intolerance; Orthostatic intolerance; DePaul symptom questionnaire; Symptom burden; Methodology

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**Core Tip:** The findings from the current study indicated that those with myalgic encephalomyelitis/chronic fatigue syndrome are more likely to experience alcohol intolerance.

**INTRODUCTION**

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a chronic illness characterized by persistent debilitating fatigue, post-exertional malaise, cognitive impairment, and sleep dysfunction[1].In addition to these core symptoms, individuals with ME/CFS may also present with a variety of other symptoms. Symptom occurrence patterns have been previously proposed as a method of determining ME/CFS subtypes[2,3].

In response to anecdotal observation of alcohol avoidance in individuals with ME/CFS, several studies have attempted to quantify alcohol intake. The majority of these studies reported decreased alcohol intake in ME/CFS, but results are inconsistent across studies. Woolley *et al*[4] reported that 66% of respondents chose to reduce alcohol intake, with the most common justifications being “increased tiredness after drinking (67%), increased nausea (33%), exacerbated hangovers (23%) and sleep disturbance (24%).” The same study also reported increased impairment in the ability to work, engage in social or leisurely activities, and memory function in those with reduced alcohol intake[4]. Weigel *et al*[5] and van't Leven *et al*[6] also reported reduced alcohol intake in ME/CFS compared to the general population and non-fatigued controls, respectively. In contrast, Hamaguchi *et al*[7] reported no significant difference in alcohol intake in participants with ME/CFS.

Studies focusing on alcohol intolerance or sensitivity as a potential symptom of ME/CFS have produced similarly inconsistent findings. Jason *et al*[8] found a statistically significant higher prevalence of alcohol intolerance in participants with ME/CFS compared to non-fatigued controls. Within ME/CFS populations, De Becker *et al*[9] found that 59%-64% of participants who met either the Holmes or Fukuda diagnostic criteria for ME/CFS reported alcohol intolerance. Chu *et al*[10] found that 66% of participants with ME/CFS reported an increased sensitivity to alcohol after becoming ill. However, Nisenbaum *et al*[11] found no significant difference in alcohol intolerance between fatigued and non-fatigued respondents.

Surveys that ask respondents with ME/CFS whether they experienced alcohol intolerance within a recent time frame might produce inaccurate results since respondents may indicate that the symptom was not present if they have avoided alcohol in the designated time frame[12]. Due to this concern, in research there is a need to ask participants whether they have avoided alcohol in the past 6 mo, and if they have, how severe their alcohol intolerance would be if they were to drink alcohol. The failure to account for the effect of question wording may partially explain the inconsistency in findings related to alcohol intolerance in ME/CFS.

Despite inconsistent findings in the literature, alcohol intolerance has been identified as a clinically relevant feature of ME/CFS by Bansal[13], even suggesting that the ability to tolerate four or more drinks in one sitting should prompt healthcare practitioners to rethink an ME/CFS diagnosis. Chu *et al*[10] previously speculated that alcohol intolerance in ME/CFS might be related to underlying autonomic dysfunction, which would also explain the high prevalence of orthostatic intolerance and impaired temperature regulation in ME/CFS. Baraniuk[14] speculated that alcohol intolerance in ME/CFS may be related to the effect of acetate (a byproduct of ethanol breakdown) on mitochondrial function, which is already known to be impaired in ME/CFS[15,16]. The added stress of high acetate levels during alcohol consumption may cause more severe dysfunction in areas of the brain that are highly metabolically active[14]. However, to our knowledge, neither hypothesis has been directly investigated.

The present study aimed to provide insight into the role of alcohol intolerance in ME/CFS by identifying correlations between alcohol intolerance and other common symptoms. We hypothesized that alcohol intolerance correlates with measures of autonomic dysfunction (such as orthostatic and temperature intolerance), measures of neurocognitive dysfunction, and higher severity of physical impairment. Further, we investigated whether alcohol intolerance may be used to distinguish a clinically relevant subtype of ME/CFS.

**MATERIALS AND METHODS**

***Participants***

The present study utilized a previously collected cross-sectional sample of adults with various chronic illnesses from a larger study[17]. Participant recruitment was conducted *via* email requests to national foundations as well as posts to social media outlets, research forums, and support group websites. Participants were directed to complete an online questionnaire after establishing informed consent. Approval was provided by the DePaul University Institutional Review Board for all study methods.

For the purposes of this investigation, participants were included if they reported a diagnosis of CFS, ME, or ME/CFS, and if they responded to the DePaul symptom questionnaire-2 (DSQ-2) questions used to classify alcohol intolerance (*n* = 304). Exclusion criteria consisted of a diagnosis of cancer, lupus, multiple sclerosis, post-polio syndrome, HIV/AIDS, or Gulf War syndrome.

***Measures***

Participants completed the DSQ-2[12], a self-report questionnaire that assesses ME/CFS symptomatology as well as social, occupational, and medical history, and demographic information. The DSQ-2 constitutes an addition of 34 items to the DePaul Symptom Questionnaire-1 (DSQ-1), which has previously shown favorable results for construct, convergent, and discriminant validity[18] and test-retest reliability[19]. The DSQ-2 is publicly available in the shared library of the Research Electronic Data Capture (REDCap)[20,21] and can be accessed at https://redcap.is.depaul.edu/surveys/?s=4NJ9CKW7JD.

Participants were asked to rate the frequency and severity of each symptom over the past 6 mo on 5-point Likert scales. For frequency, participants chose between the following options: 0 = none of the time; 1 = a little of the time; 2 = about half the time; 3 = most of the time; and 4 = all of the time. For severity, participants chose between the following options: 0 = symptom not present; 1 = mild; 2 = moderate; 3 = severe; and 4 = very severe. Composite scores were generated for each symptom by averaging respective scores for frequency and severity and multiplying by 25 for a 100-point scale. Higher scores indicate a higher burden of the designated symptom. Symptom domain scores were calculated by averaging the composite scores for each item within the following symptom domains, previously determined by exploratory factor analysis on DSQ-2 data, including post-exertional malaise, cognitive impairment, fever and flu, pain, sleep disruption, orthostatic intolerance, genitourinary, and temperature intolerance[12].

Table 1 lists the DSQ-2 questions used to classify alcohol intolerance. The DSQ-2 question relating to frequency of alcohol intolerance over the past 6 mo was omitted due to ambiguity as to whether responses reflected the frequency of drinking alcohol or the frequency of experiencing alcohol intolerance when drinking alcohol.

Participants were classified as alcohol intolerant if they met either condition: (1) Reported a severity of moderate or higher on alcohol intolerance within the past 6 mo (options 2-4 on question 1 in Table 1); or (2) Reported that they were avoiding alcohol (“Yes” on question 2), and their alcohol intolerance would be moderate or higher if they were to drink alcohol (options 2-4 on question 3 in Table 1).

Participants were classified as “not alcohol intolerant” if they met either condition: (1) Reported alcohol intolerance severity within the past 6 mo as “symptom not present” or “mild” (options 0-1 on question 1 in Table 1); or (2) Reported that they were avoiding alcohol (“Yes” or “No, I do not drink alcohol for other reasons” on question 2), and their alcohol intolerance would be mild or not present if they were to drink alcohol (options 0-1 on question 3).

For the linear regression, alcohol intolerance was coded as a linear variable based on the following conditions: (1) If the participant answered that they were avoiding alcohol (“Yes” on question 2), alcohol intolerance was coded as the score of how severe alcohol intolerance would be if they were to drink alcohol (question 3); and (2) If the participant was NOT avoiding alcohol, alcohol intolerance was coded as the score of alcohol intolerance severity in the past 6 mo (question 1).

In addition to the DSQ-2, participants were also asked to complete the MOS 36-item Short-Form Health Survey (SF-36)[22]. The SF-36 is a self-report measure that assesses health across eight general domains: physical functioning; role limitations due to physical health problems (role physical); bodily pain; general health functioning; vitality; role limitations due to personal or emotional problems (role emotional); and mental health. Responses to each of the 36 items are recoded to a 100-point scale, and items are grouped together based on the eight domains. Subscale scores are then generated by averaging item scores within each domain, with higher scores indicating better functioning in the domain. Adequate psychometric properties have been demonstrated for SF-36 across diverse patient groups[23], and it has previously been shown to perform well in measuring fatigue-related functional impairment in ME/CFS[24].

***Statistical analyses***

Independent *t*-tests were performed using SPSS 26 for all DSQ-2 symptoms and SF-36 items. Participants were divided into a binary classification of “alcohol intolerant” or “not alcohol intolerant.” Due to the large number of items that were tested, we only considered findings significant if *P* ≤ 0.01, and we used two-tailed significance levels.

Multiple linear regression was conducted to determine if composite symptom scores in the eight DSQ-2 domains were predictors of alcohol intolerance severity scores. Age and sex (coded in the data set as: 1 = male; 2 = female; and 3 = other) were also evaluated in the regression model.

**RESULTS**

***Demographics***

Table 2 describes the demographic characteristics of the sample separated by the binary alcohol intolerance classification. The alcohol intolerant group (*n* = 208) had a mean age of 45.48 (standard deviation = 16.49), and the not alcohol intolerant group (*n* = 96) had a mean age of 45.54 (standard deviation = 17.40). Both groups were predominantly female and Caucasian/White. The majority of the sample reported being on disability (50.0% for the alcohol intolerant group; 40.6% for the not alcohol intolerant group) and married/living with a partner (45.2% for the alcohol intolerant group; 55.2% for the not alcohol intolerant group).

*t*-tests were conducted on mean composite scores for 79 individual symptoms, mean composite scores for the 8 symptom domains (calculated by averaging composite scores for items within the symptom domain), and subscale scores for 8 SF-36 domains. Results of the independent *t-*tests for DSQ-2 symptoms are available in Table 3. Out of 79 individual symptoms, 33 (41%) were significantly different (*P* ≤ 0.01). For every statistically significant symptom, mean composite scores were higher for the alcohol intolerant group, indicating a higher symptom burden (in terms of frequency and severity of the symptom).

Of the eight symptom domains, five domain scores were significantly higher for the alcohol intolerant group, including post-exertional malaise, cognitive impairment, pain, orthostatic intolerance, and temperature intolerance. The fever and flu, sleep disruption, and genitourinary domains were not significantly different between the two groups.

Results of the *t*-tests for the SF-36 are presented in Table 4. The alcohol intolerant group scored significantly lower on physical functioning and bodily pain. Higher scores indicate better functioning on the SF-36, so lower scores for the alcohol intolerant group would indicate worse functioning.

Results of the multiple linear regression are available in Table 5. The overall multiple linear regression was statistically significant [*R*2 = 0.14, F (10, 233) = 3.64, *P* ≤ 0.001]. Sex, age, and seven out of eight symptom domains did not significantly predict alcohol intolerance severity (*P* ≤ 0.05). Only the orthostatic intolerance domain significantly predicted alcohol intolerance severity (𝛽 = 0.21, *P* = 0.01). We did not use the SF-36 domains as predictors as our interest was in assessing which symptoms might be related to alcohol intolerance rather than physical or mental functioning.

**DISCUSSION**

Prior research assessed alcohol intolerance, but respondents could indicate that the symptom was not present if they have avoided alcohol in the designated time frame. When participants were asked whether they have avoided alcohol in the past 6 mo, and if they had how severe their alcohol intolerance would be if they were to drink alcohol, those designated in the alcohol intolerant group evidenced a higher symptom burden (in terms of frequency and severity of the symptoms). A second unique finding was that the orthostatic intolerance symptom domain predicted alcohol intolerance.

The fact that orthostatic intolerance was the only variable related to alcohol intolerance is of theoretical importance. Others have suggested that alcohol intolerance might be related to underlying autonomic dysfunction, which might help explain the high levels of orthostatic intolerance and impaired temperature regulation in ME/CFS[10]. It is also possible that the added stress of high acetate levels, which are a byproduct of ethanol breakdown, may cause more severe dysfunction in areas of the brain that are highly metabolically active[14].

A strength of the current study was using a validated questionnaire, the DePaul Symptom Questionnaire, that differentiates the frequency and severity of symptoms as well as specifies threshold values for determining whether symptoms meet a necessary threshold of being a burden for the patient. When symptoms are measured only using occurrence as a binary outcome, patients who experience the symptom at relatively low frequencies and/or severities are counted, even if the symptom might not represent any burden to the respondent. It is only by using more differentiated surveys that allow these important characteristics to be assessed and using questionnaires that have been validated that more assurance can occur that symptoms such as alcohol intolerance are being accurately identified in patients.

There are several limitations in this study. First, all analyses relied on self-report data. Thus, there was no biological confirmation of alcohol intolerances in the respondents. In addition, the designation of ME/CFS was also based on self-report. Therefore, there was not an independent assessment of this illness by a medical health care professional. Finally, the sample was somewhat biased toward women who were White, and the outcomes of a more sociodemographic sample is unclear.

**CONCLUSION**

In general, the findings from the current study indicated that those with ME/CFS are more likely to experience alcohol intolerance. It is very likely that this subtype of patients might have other biologic differences, and future research is needed to explore this hypothesis. The contribution of the current study was assessing the construct of alcohol intolerance in a more sophisticated way than has been attempted in previous investigations.

**ARTICLE HIGHLIGHTS**

***Research background***

There is a need to objectively measure alcohol intolerance among those with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).

***Research motivation***

There is a need to determine if those with ME/CFS with alcohol intolerance are more symptomatic than those without alcohol intolerance.

***Research objectives***

We aimed to carefully measure alcohol intolerance and determine its effects on those with ME/CFS.

***Research methods***

We collected data from patients with ME/CFS using a validated symptom questionnaire.

***Research results***

We were able to determine that those with alcohol intolerance were more symptomatic than those without it among a sample of patients with ME/CFS.

***Research conclusions***

It is important to measure alcohol intolerance carefully among patients who are not going to report using alcohol over the preceding months.

***Research perspectives***

It is possible to reliably and validly measure alcohol intolerance among those with ME/CFS, and this should guide future research in this area.

**REFERENCES**

1 Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness. Washington (DC): National Academies Press (US); 2015-Feb-10 [PMID: 25695122 DOI: 10.17226/19012]

2 **Jason LA**, Corradi K, Torres-Harding S, Taylor RR, King C. Chronic fatigue syndrome: the need for subtypes. *Neuropsychol Rev* 2005; **15**: 29-58 [PMID: 15929497 DOI: 10.1007/s11065-005-3588-2]

3 **Huber KA**, Sunnquist M, Jason LA. Latent class analysis of a heterogeneous international sample of patients with myalgic encephalomyelitis/chronic fatigue syndrome. *Fatigue* 2018; **6**: 163-178 [PMID: 31435490 DOI: 10.1080/21641846.2018.1494530]

4 **Woolley J**, Allen R, Wessely S. Alcohol use in chronic fatigue syndrome. *J Psychosom Res* 2004; **56**: 203-206 [PMID: 15016579 DOI: 10.1016/s0022-3999(03)00077-1]

5 **Weigel B**, Eaton-Fitch N, Passmore R, Cabanas H, Staines D, Marshall-Gradisnik S. A preliminary investigation of nutritional intake and supplement use in Australians with myalgic encephalomyelitis/chronic fatigue syndrome and the implications on health-related quality of life. *Food Nutr Res* 2021; **65** [PMID: 34262415 DOI: 10.29219/fnr.v65.5730]

6 **van't Leven M**, Zielhuis GA, van der Meer JW, Verbeek AL, Bleijenberg G. Fatigue and chronic fatigue syndrome-like complaints in the general population. *Eur J Public Health* 2010; **20**: 251-257 [PMID: 19689970 DOI: 10.1093/eurpub/ckp113]

7 **Hamaguchi M**, Kawahito Y, Takeda N, Kato T, Kojima T. Characteristics of chronic fatigue syndrome in a Japanese community population : chronic fatigue syndrome in Japan. *Clin Rheumatol* 2011; **30**: 895-906 [PMID: 21302125 DOI: 10.1007/s10067-011-1702-9]

8 **Jason LA**, Torres-Harding SR, Carrico AW, Taylor RR. Symptom occurrence in persons with chronic fatigue syndrome. *Biol Psychol* 2002; **59**: 15-27 [PMID: 11790441 DOI: 10.1016/s0301-0511(01)00120-x]

9 **De Becker P**, McGregor N, De Meirleir K. A definition-based analysis of symptoms in a large cohort of patients with chronic fatigue syndrome. *J Intern Med* 2001; **250**: 234-240 [PMID: 11555128 DOI: 10.1046/j.1365-2796.2001.00890.x]

10 **Chu L**, Valencia IJ, Garvert DW, Montoya JG. Onset Patterns and Course of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. *Front Pediatr* 2019; **7**: 12 [PMID: 30805319 DOI: 10.3389/fped.2019.00012]

11 **Nisenbaum R**, Reyes M, Mawle AC, Reeves WC. Factor analysis of unexplained severe fatigue and interrelated symptoms: overlap with criteria for chronic fatigue syndrome. *Am J Epidemiol* 1998; **148**: 72-77 [PMID: 9663406 DOI: 10.1093/oxfordjournals.aje.a009562]

12 **Bedree H**, Sunnquist M, Jason LA. The DePaul Symptom Questionnaire-2: A Validation Study. *Fatigue* 2019; **7**: 166-179 [PMID: 32685281 DOI: 10.1080/21641846.2019.1653471]

13 **Bansal AS**. Investigating unexplained fatigue in general practice with a particular focus on CFS/ME. *BMC Fam Pract* 2016; **17**: 81 [PMID: 27436349 DOI: 10.1186/s12875-016-0493-0]

14 **Baraniuk JN**. Review of the Midbrain Ascending Arousal Network Nuclei and Implications for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), Gulf War Illness (GWI) and Postexertional Malaise (PEM). *Brain Sci* 2022; **12** [PMID: 35203896 DOI: 10.3390/brainsci12020132]

15 **Tomas C**, Elson JL, Strassheim V, Newton JL, Walker M. The effect of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) severity on cellular bioenergetic function. *PLoS One* 2020; **15**: e0231136 [PMID: 32275686 DOI: 10.1371/journal.pone.0231136]

16 **Fluge Ø**, Mella O, Bruland O, Risa K, Dyrstad SE, Alme K, Rekeland IG, Sapkota D, Røsland GV, Fosså A, Ktoridou-Valen I, Lunde S, Sørland K, Lien K, Herder I, Thürmer H, Gotaas ME, Baranowska KA, Bohnen LM, Schäfer C, McCann A, Sommerfelt K, Helgeland L, Ueland PM, Dahl O, Tronstad KJ. Metabolic profiling indicates impaired pyruvate dehydrogenase function in myalgic encephalopathy/chronic fatigue syndrome. *JCI Insight* 2016; **1**: e89376 [PMID: 28018972 DOI: 10.1172/jci.insight.89376]

17 **Ohanian D**, Brown A, Sunnquist M, Furst J, Nicholson L, Klebek L, Jason LA. Identifying Key Symptoms Differentiating Myalgic Encephalomyelitis and Chronic Fatigue Syndrome from Multiple Sclerosis. *Neurology (ECronicon)* 2016; **4**: 41-45 [PMID: 28066845]

18 **Brown AA**, Jason LA. Validating a measure of myalgic encephalomyelitis/chronic fatigue syndrome symptomatology. *Fatigue* 2014; **2**: 132-152 [PMID: 27213118 DOI: 10.1080/21641846.2014.928014]

19 **Jason LA**, So S, Brown AA, Sunnquist M, Evans M. Test-Retest Reliability of the DePaul Symptom Questionnaire. *Fatigue* 2015; **3**: 16-32 [PMID: 26973799 DOI: 10.1080/21641846.2014.978110]

20 **Harris PA**, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009; **42**: 377-381 [PMID: 18929686 DOI: 10.1016/j.jbi.2008.08.010]

21 **Obeid JS**, McGraw CA, Minor BL, Conde JG, Pawluk R, Lin M, Wang J, Banks SR, Hemphill SA, Taylor R, Harris PA. Procurement of shared data instruments for Research Electronic Data Capture (REDCap). *J Biomed Inform* 2013; **46**: 259-265 [PMID: 23149159 DOI: 10.1016/j.jbi.2012.10.006]

22 **Ware JE Jr**, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992; **30**: 473-483 [PMID: 1593914]

23 **McHorney CA**, Ware JE Jr, Lu JF, Sherbourne CD. The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. *Med Care* 1994; **32**: 40-66 [PMID: 8277801 DOI: 10.1097/00005650-199401000-00004]

24 **Buchwald D**, Pearlman T, Umali J, Schmaling K, Katon W. Functional status in patients with chronic fatigue syndrome, other fatiguing illnesses, and healthy individuals. *Am J Med* 1996; **101**: 364-370 [PMID: 8873506 DOI: 10.1016/S0002-9343(96)00234-3]

**Footnotes**

**Institutional review board statement:** Approval obtained from the DePaul Institutional Review Board.

**Institutional animal care and use committee statement:** Animals were not used in this study.

**Conflict-of-interest statement:** There are no conflicts of interest to report.

**Data sharing statement:** Data will be shared when investigators contact the corresponding author.

**ARRIVE guidelines statement:** The authors have read the ARRIVE guidelines, and the manuscript was prepared and revised according to the ARRIVE guidelines.

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**Table 1 DePaul symptom questionnaire-2 questions used to classify alcohol intolerance**

|  |  |
| --- | --- |
| **Question** | **Response options** |
| Severity: Throughout the past 6 months, how much has alcohol intolerance bothered you? | 0 = symptom not present |
| 1 = mild |
| 2 = moderate |
| 3 = severe |
| 4 = very severe |
| Over the last 6 months, did you avoid alcohol due to an alcohol intolerance (feeling sick after drinking alcohol)? | Yes |
| No, I drank alcohol |
| No, I do not drink alcohol for other reasons |
| If you were to drink alcohol, how severe would the intolerance be? | 0 = symptom not present |
| 1 = mild |
| 2 = moderate |
| 3 = severe |
| 4 = very severe |

**Table 2 Demographic characteristics of the sample (*n* = 304) separated by binary alcohol intolerance classification**

|  |  |  |
| --- | --- | --- |
| **Characteristic** | **Alcohol intolerant, *n* = 208** | **Not alcohol intolerant, *n* = 96** |
| **mean (%)** | **SD or *n*** | **mean (%)** | **SD or *n*** |
| **Age** | 48.07  | 12.26 | 49.57 | 13.50 |
| **Sex** |  |  |  |  |
|  Male | 11.1 | 23 | 8.3 | 8 |
|  Female | 87.5 | 182 | 88.5 | 85 |
| **Race** |  |  |  |  |
|  White | 95.2 | 198 | 99.0 | 95 |
|  Asian or Pacific Islander | 1.4 | 3 | 1.0 | 1 |
|  Other | 2.9 | 6 | 0 | 0 |
| **Latinx** |  |  |  |  |
|  No | 98.1 | 204 | 96.9 | 93 |
|  Yes | 1.4 | 3 | 3.1 | 3 |
| **Education** |  |  |  |  |
|  High school diploma or less | 12.0 | 25 | 9.4 | 9 |
|  College degree or partial college | 46.2 | 96 | 55.3 | 53 |
|  Graduate degree | 41.3 | 86 | 34.4 | 33 |
| **Work status** |  |  |  |  |
|  On disability | 50.0 | 104 | 40.6 | 39 |
|  Working (full-time or part-time) | 25.5 | 53 | 29.2 | 28 |
|  Retired | 8.7 | 18 | 13.5 | 13 |
|  Unemployed | 16.3 | 34 | 11.5 | 11 |
|  Student or homemaker | 9.6 | 20 | 12.6 | 12 |
| **Marital status** |  |  |  |  |
|  Married or living with partner | 45.2 | 94 | 55.2 | 53 |
|  Never married | 31.7 | 66 | 25.0 | 24 |
|  Divorced | 16.8 | 35 | 14.6 | 14 |
|  Widowed | 1.9 | 4 | 3.1 | 3 |
|  Separated | 2.9 | 6 | 2.1 | 2 |

**Table 3 Differences in composite DePaul symptom questionnaire-2 symptom scores**

|  |  |  |  |
| --- | --- | --- | --- |
| **Symptom** | **Alcohol intolerant** | **Not alcohol intolerant** | ***P* value** |
| **mean (SD)** | **mean (SD)** |
| **Post-exertional malaise** | 79.53 (15.46) | 71.99 (17.07) | < 0.01 |
|  Feeling drained | 74.70 (21.53) | 67.06 (23.31) | 0.01 |
|  Minimum exercise | 78.99 (20.48) | 72.27 (20.62) | 0.01 |
|  Worse after physical activity | 80.83 (21.42) | 74.22 (21.83) | 0.01 |
|  Soreness | 77.84 (19.87) | 70.96 (20.40) | 0.01 |
|  Fatigue | 81.86 (15.10) | 77.47 (15.88) | 0.02 |
|  Heavy feeling | 83.87 (22.56) | 69.53 (30.82) | < 0.01 |
|  Muscle fatigue | 76.80 (24.01) | 64.32 (26.03) | <0 .01 |
|  Unrefreshing sleep | 81.52 (18.83) | 80.08 (20.80) | 0.57 |
| **Cognitive impairment** | 61.53 (18.28) | 54.92 (18.39) | < 0.01 |
|  Difficulty remembering | 68.84 (22.51) | 64.58 (25.17) | 0.14 |
|  Difficulty finding right word | 61.78 (23.69) | 54.56 (23.02) | 0.01 |
|  Difficulty understanding | 51.02 (24.93) | 44.14 (24.33) | 0.02 |
|  Absent-mindedness | 62.74 (24.94) | 57.50 (22.73) | 0.08 |
|  Slowness of thought | 60.34 (24.78) | 52.99 (25.70) | 0.02 |
|  Only focus on one thing | 68.96 (23.14) | 59.38 (24.60) | < 0.01 |
|  Difficulty paying attention | 72.84 (23.31) | 66.97 (23.77) | 0.04 |
|  Slowed speech | 35.75 (27.80) | 29.61 (24.33) | 0.07 |
|  Mental tiredness | 71.32 (21.74) | 64.19 (23.55) | 0.01 |
| **Fever and flu** | 37.71 (19.81) | 33.74 (19.55) | 0.10 |
|  Fever | 16.36 (21.41) | 14.71 (20.52) | 0.53 |
|  High temperature | 33.82 (26.14) | 29.43 (26.09) | 0.18 |
|  Flu-like symptoms | 52.84 (25.87) | 49.22 (27.97) | 0.27 |
|  Prolonged viral illness recovery | 38.16 (32.95) | 35.68 (33.88) | 0.55 |
|  Fluctuations in temperature | 47.18 (31.83) | 39.76 (31.38) | 0.06 |
| **Pain** | 54.84 (22.94) | 46.30 (21.86) | < 0.01 |
|  Stomach pain | 45.11 (28.08) | 36.33 (25.14) | 0.01 |
|  Irritable bowel | 51.98 (31.39) | 44.01 (31.88) | 0.04 |
|  Bloating | 50.79 (28.83) | 41.45 (25.80) | 0.01 |
|  Muscle pain | 71.45 (25.12) | 63.15 (29.43) | 0.02 |
| **Sleep disruption** | 57.63 (23.80) | 51.52 (25.12) | 0.04 |
|  Problems staying asleep | 61.29 (28.62) | 54.04 (29.16) | 0.04 |
|  Waking up early | 52.40 (28.64) | 44.53 (30.07) | 0.03 |
|  Problems falling asleep | 61.29 (28.62) | 54.04 (29.16) | 0.39 |
| **Orthostatic intolerance** | 39.99 (23.21) | 27.86 (22.93) | < 0.01 |
|  Graying or blacking out after standing | 28.14 (29.39) | 17.63 (24.90) | < 0.01 |
|  Blurred or tunnel vision after standing | 35.52 (31.01) | 25.13 (28.51) | 0.01 |
|  Heart beats quickly after standing | 50.12 (31.11) | 35.66 (33.37) | < 0.01 |
|  Dizziness | 45.91 (26.21) | 33.85 (26.34) | < 0.01 |
| **Genitourinary** | 43.06 (26.18) | 36.81 (23.43) | 0.05 |
|  Urinary urgency | 41.95 (30.88) | 38.03 (31.99) | 0.31 |
|  Bladder problems | 36.96 (31.91) | 29.82 (27.29) | 0.05 |
|  Nighttime urinary urgency | 50.18 (31.51) | 42.37 (30.20) | 0.04 |
| **Temperature intolerance** | 39.45 (22.76) | 28.60 (19.98) | < 0.01 |
|  Chills or shivers | 37.38 (26.16) | 27.34 (24.01) | < 0.01 |
|  Low temperature | 29.41 (28.02) | 17.45 (20.80) | < 0.01 |
|  Cold limbs | 51.02 (28.65) | 41.02 (28.89) | 0.01 |
| **Other** |
|  Needing to nap daily | 58.74 (28.63) | 53.39 (30.80) | 0.14 |
|  Sleep inversion | 21.80 (30.09) | 16.28 (26.85) | 0.11 |
|  Joint pain | 60.33 (31.88) | 56.64 (30.99) | 0.35 |
|  Eye pain | 34.24 (29.25) | 25.52 (25.32) | 0.01 |
|  Chest pain | 28.32 (23.57) | 19.79 (24.24) | < 0.01 |
|  Headaches | 53.32 (26.10) | 45.18 (24.69) | 0.01 |
|  Twitching | 38.28 (26.15) | 30.34 (24.25) | 0.01 |
|  Muscle weakness | 68.15 (25.56) | 57.81 (25.92) | < 0.01 |
|  Sensitivity to noise | 64.12 (25.50) | 57.55 (27.95) | 0.04 |
|  Sensitivity to light | 58.53 (28.25) | 51.04 (29.00) | 0.03 |
|  Unable to focus vision | 41.35 (26.21) | 33.06 (22.82) | 0.01 |
|  Unable to focus attention | 56.63 (21.10) | 53.89 (20.75) | 0.31 |
|  Loss of depth perception | 31.10 (31.76) | 17.63 (24.22) | < 0.01 |
|  Nausea | 39.42 (24.74) | 26.04 (25.76) | < 0.01 |
|  Feeling unsteady | 49.70 (28.00) | 36.85 (25.48) | < 0.01 |
|  Shortness of breath | 38.88 (27.26) | 35.81 (26.07) | 0.36 |
|  Irregular heartbeat | 32.91 (26.82) | 28.26 (26.79) | 0.16 |
|  Losing weight | 19.04 (25.04) | 17.34 (19.65) | 0.60 |
|  Gaining weight | 52.70 (33.53) | 47.58 (31.51) | 0.30 |
|  Loss of appetite | 30.37 (24.52) | 31.12 (25.84) | 0.81 |
|  Sweating hands | 15.99 (23.28) | 15.89 (24.97) | 0.97 |
|  Night sweats | 37.44 (29.32) | 35.55 (30.20) | 0.61 |
|  Feeling hot or cold | 53.93 (26.88) | 45.96 (26.93) | 0.02 |
|  Sore throats | 37.50 (25.00) | 32.16 (24.11) | 0.08 |
|  Lymph nodes | 39.54 (28.82) | 34.08 (27.50) | 0.12 |
|  Sensitivity to smells | 53.43 (30.68) | 37.50 (30.99) | < 0.01 |
|  Sensitivity to mold | 29.89 (37.74) | 21.45 (29.94) | 0.04 |
|  Temperature intolerance | 72.52 (26.97) | 55.60 (31.93) | < 0.01 |
|  Worse after mental activity | 66.41 (24.31) | 59.87 (28.53) | 0.06 |
|  Feeling disoriented | 40.44 (25.23) | 33.68 (23.36) | 0.03 |
|  Difficulty reading | 50.96 (32.42) | 39.34 (30.89) | < 0.01 |
|  Eye aching | 40.44 (29.61) | 30.66 (28.47) | 0.01 |
|  Sensitivity to pain | 53.50 (31.78) | 44.35 (36.19) | 0.04 |
|  Pain from pressure | 27.00 (34.21) | 24.87 (33.73) | 0.62 |
|  Daytime drowsiness | 64.24 (26.74) | 60.53 (27.85) | 0.27 |
|  Sensitivity to vibrations | 36.34 (35.50) | 21.68 (31.39) | < 0.01 |
|  Poor coordination | 51.68 (28.56) | 38.42 (25.08) | < 0.01 |
|  Sinus infections | 25.00 (28.84) | 23.68 (25.36) | 0.69 |
|  Upright position intolerance | 51.98 (32.87) | 44.08 (32.86) | 0.05 |

**Table 4 Differences for short form-36 domain scores**

|  |  |  |  |
| --- | --- | --- | --- |
| **Domain** | **Alcohol intolerant** | **Not alcohol intolerant** | ***P* value** |
|  | **mean (SD)** | **mean (SD)** |  |
| Physical functioning | 23.91 (20.45) | 34.27 (21.86) | < 0.01 |
| Role physical | 2.00 (9.39) | 4.39 (11.22) | 0.12 |
| Bodily pain | 34.30 (22.50) | 43.82 (26.36) | < 0.01 |
| General health | 23.28 (15.02) | 25.51 (14.36) | 0.29 |
| Vitality | 8.98 (10.74) | 12.47 (13.75) | 0.06 |
| Social functioning | 18.34 (20.03) | 25.51 (22.38) | 0.02 |
| Role emotional | 69.54 (42.15) | 63.01 (43.94) | 0.29 |
| Mental health | 67.08 (18.84) | 66.48 (20.00) | 0.83 |

**Table 5 Linear regression for symptom domain scores, sex, and age**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Feature** | **Unstandardized coefficients** | **Standardized coefficients** | ***t*** | ***P*** | **95%CI** |
|  | **B** | **SE** | **Beta** |  |  | **LL** | **UL** |
| (Constant) | 0.90 | 0.70 | < 0.01 | 1.29 | 0.20 | -0.47 | 2.27 |
| Sex | -0.27 | 0.27 | -0.06 | -1.01 | 0.31 | -0.79 | 0.25 |
| Age | < 0.01 | 0.01 | 0.04 | 0.57 | 0.57 | -0.01 | 0.02 |
| PEM domain | 0.01 | 0.01 | 0.15 | 1.82 | 0.07 | 0.00 | 0.02 |
| Cognitive impairment domain | < 0.01 | 0.01 | -0.04 | -0.54 | 0.59 | -0.01 | 0.01 |
| Fever/flu-like symptoms domain | -0.01 | 0.01 | -0.11 | -1.39 | 0.16 | -0.02 | 0.00 |
| Pain domain | < 0.01 | < 0.01 | 0.07 | 0.89 | 0.37 | 0.00 | 0.01 |
| Sleep disruption domain | < 0.01 | < 0.01 | -0.03 | -0.43 | 0.67 | -0.01 | 0.01 |
| Orthostatic intolerance domain | 0.01 | < 0.01 | 0.21 | 2.57 | 0.01 | 0.00 | 0.02 |
| Genitourinary domain | 0.01 | < 0.01 | 0.12 | 1.73 | 0.08 | 0.00 | 0.01 |
| Temperature intolerance domain | 0.01 | < 0.01 | 0.09 | 1.11 | 0.27 | 0.00 | 0.01 |

CI: Confidence interval; LL: Lower limit of the confidence interval; PEM: Post-exertional malaise; UL: Upper limit of the confidence interval.