# Delineating the Effects of Alcohol Use on Cognition in Individuals With Neurocognitive Disorders

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## Abstract

**Objective:** Excessive alcohol use is a recognized modifiable risk factor for the development of dementia; however, the neuropsychological profile of cognitive impairment seen with alcohol use is heterogeneous. We studied cognitive characteristics associated with alcohol use in a "real-world" memory clinic cohort of patients with neurocognitive disorders.

**Methods:** We used the Toronto Dementia Research Alliance memory clinic research database to generate an age, sex, and education matched sample of individuals with alcohol-related cognitive impairment (ARCI group; n = 51) and twice as many individuals without such history (Comparator group; n = 102). We compared cognitive domain and subdomain Toronto Cognitive Assessment scores between the two groups using linear regression while controlling for age, sex, education, concurrent psychiatric disorders, global cognition, and traumatic brain injury.

**Results:** Mean (SD) age was 67.67 (13.01) years for the ARCI group and 67.96 (12.82) years for the Comparator group. The ARCI and Comparator groups had 35% and 36% females, respectively. Neither global cognition nor other cognitive domains differed significantly between the two groups. Among cognitive subdomains, only the intrusion rates on the delayed recall task were higher (worse performance) in the ARCI group (mean [SD] = 0.79 [1.21]) relative to the Comparator group (mean [SD] = 0.34 [0.69]; $P_{corrected} = .018$).

**Conclusions:** Our study suggests that ARCI results in specific deficits involving cognitive control during delayed recall task. This may help advance development of markers to delineate ARCI from other causes of cognitive impairment. Future work may test these findings in larger, well-characterized samples.

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Chronic excessive alcohol use is a recognized modifiable risk factor for dementia.[1,2] Although excessive alcohol use increases the risk for cognitive impairment and all-cause dementia, it does not seem to increase the risk for Alzheimer's disease specifically.[3] This suggests a distinct pathophysiological mechanism, and indeed, the deleterious neurocognitive effects of alcohol are thought to arise from a combination of direct and indirect causes.[4] Alcohol has a direct neurotoxic effect, and chronically heavy levels of alcohol use result in smaller volumes across most brain regions, especially in older age.[5] Moreover, even low-to-moderate alcohol use may be associated with smaller brain volumes,[6] although the downstream cognitive effects of these changes are incompletely understood. Beyond the direct effects of alcohol on the brain, secondary or indirect consequences of chronic and excessive alcohol use, such as hepatic injury, cardiovascular disease, and acquired brain injury, can also contribute to cognitive decline.[7] Moreover, alcohol use disorder is associated with nutritional deficiencies, specifically thiamine, which can result in specific forms of alcohol-related cognitive impairment (ARCI) such as Wernicke encephalopathy and Korsakoff syndrome.[8] Alcohol may also interact synergistically with age-related neurodegeneration to promote accelerated aging and progression to dementia,[9] or even contribute directly to other common neurocognitive disorders.[10]

It is challenging to diagnose ARCI in routine clinical practice, particularly in the presence of other

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## Clinical Points

- There are unique cognitive characteristics associated with alcohol-related cognitive impairment (ARCI).
- Persons with ARCI may exhibit a greater number of intrusions during delayed recall, suggesting specific impairment in cognitive processes related to memory.
- There may be a tendency toward false memory generation in ARCI, which may help clinicians to distinguish ARCI from other cognitive disorders.

neurocognitive disorders.[11] The features of ARCI can also overlap with other neurocognitive disorders such as Alzheimer's disease. As a result, ARCI is often underdiagnosed, precluding timely intervention.[12]

Several studies have characterized the neuropsychological profile of ARCI. Memory impairment is especially prominent in those with Wernicke-Korsakoff syndrome, and confabulations frequently emerge as a prominent feature, manifesting as fabricated or distorted narratives intended to fill memory gaps.[8] In the absence of Wernicke-Korsakoff syndrome, ARCI presents with deficits across multiple cognitive domains.[13,14] A meta-analysis revealed significant cognitive impairments in individuals with alcohol use disorder in memory, executive function, and attention.[13] Another meta-analysis found executive dysfunction and impulsivity in alcohol use disorder.[14] Still another meta-analysis found cognitive deficits in virtually every cognitive domain that persist even after abstaining from alcohol, with the greatest deficits seen in the domains of processing speed, visual memory, spatial cognition, verbal learning, and executive function.[15] None of these studies compared ARCI with other causes of cognitive impairment or studied specific cognitive features attributable to alcohol in the presence of other neurocognitive disorders.

Thus, our objective was to delineate cognitive deficits related to ARCI in the presence of other neurocognitive disorders in a "real-world" memory clinic cohort. We compared cognitive domains in participants with neurocognitive disorders with and without ARCI. Further, to understand the cognitive processes related to ARCI, we compared cognitive subdomain scores in participants with neurocognitive disorders with and without ARCI.

# METHODS

## Participants

The Toronto Dementia Research Alliance (TDRA)[16] is a multicenter collaboration among academic hospitals in Toronto, Ontario, Canada, dedicated to research in understanding, preventing, and treating dementia. This study used the TDRA research database, which contains data from TDRA-affiliated memory clinics. The data include demographic, medical, psychiatric, and substance use histories, as well neuropsychological testing data including the Toronto Cognitive Assessment (TorCA).[17]

The TDRA research database comprised data from 2,154 participants seen in specialized memory clinics for cognitive concerns at hospitals affiliated with the University of Toronto between 2017 and 2022 at the time of analysis. Those without TorCA scores (n = 361) and those without information on alcohol use (n = 65) were excluded. Next, participants with schizophrenia spectrum disorders (n = 9) were excluded to reduce heterogeneity in cognitive profiles as these disorders result in neurocognitive deficits across a broad range. We then excluded participants who were not fluent in English (n = 68) as it can interfere with cognitive testing using TorCA. Lastly, individuals who did not have a diagnosis of either dementia (major neurocognitive disorder) or mild cognitive impairment (MCI) (mild neurocognitive disorder) were removed (n = 883). Of the remaining 768 participants, there were 51 for whom alcohol was identified as an "active contributing factor to cognitive impairment" (ARCI group). The determination of ARCI was a clinical diagnosis made by the evaluating physician based on history of excessive current or past drinking. Although there was not a specific threshold of alcohol consumption for this assignment, it was at a level such that alcohol was deemed a contributing factor to cognitive impairment and likely exceeded the recommended upper limit as per Canadian alcohol drinking guidelines (no more than 10 standard drinks per week for women and 15 standard drinks per week for men) at the time of the study. Comparator participants were selected from the remaining sample (n = 717) with matching performed using the "MatchIt" package version 4.5.4 in R.[18] We employed a 1:2 match to allow for a larger sample size and thus greater likelihood of detecting differences in outcome measures.[19] *Nearest* matching was performed for age, sex, and years of education variables. This yielded a well-matched sample of 51 individuals with ARCI and 102 individuals without alcohol as an active contributing factor to cognitive impairment (Comparator group; see Supplementary Table 1). The participant selection flowchart is presented in Supplementary Figure 1. Both groups comprised individuals diagnosed with either MCI or dementia and included varying underlying etiologies such as Alzheimer's disease, cerebral vascular disease, Parkinson's disease/Lewy body disease, frontotemporal lobar degeneration, and mixed etiologies.

## Neuropsychological Testing

TorCA is a broad cognitive screening test consisting of 27 subtests covering 7 cognitive domains.[17] Specifically, TorCA assesses orientation (Orientation), immediate verbal recall (Immediate Recall), delayed verbal and

visual recall (Delayed Recall), delayed verbal and visual recognition (Delayed Recognition), visuospatial function (Visuospatial), working memory/executive function (Executive Function), and language (Language). Each domain total score is calculated by summing the various subtests which assess each respective domain. For example, the sum of the 3 trials of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD)[20] constitute the total Immediate Recall composite domain score. Score ranges vary for each domain depending on the subtests of which they are composed, and higher scores indicate better cognitive performance. Normative scores exist for these tests as previously published.[17]

### Statistical Analysis

Analyses were conducted using Rstudio with R version 4.2.0.[21] Descriptive statistics were used to summarize demographic data (eg, age, sex, education), global cognition (measured by total TorCA score), and neurocognitive phenotype by group (ie, the ARCI or Comparator group). These values were compared between groups using 2-sample independent *t* test for continuous variables and $\chi^2$ for categorical variables. We created composite scores for the 7 cognitive domains by calculating the sum of the corresponding TorCA subtest scores (Figure 1). To assess for differences in cognitive test measures, linear regression models were used to compare TorCA composite domain scores (dependent variables) between the two groups (independent variables), controlling for age, sex, education, psychiatric illness (other than alcohol use), global cognition, and traumatic brain injury as covariates. We included these covariates in the regression models to account for remaining differences following nearest matching as described above.[22] Linear regression models were also generated for TorCA cognitive subdomain scores (within specific cognitive domains) following the same method as described above. To check assumptions of normality and model fit, diagnostic plots such as histograms and Q–Q plots were used.

Since the individual domains were part of the total TorCA score, which itself was included as a covariate, we conducted additional sensitivity analyses as follows. We generated linear models for both TorCA composite domain and subdomain scores both without controlling for global cognition and also using a partial total TorCA score as the global cognition covariate (adjusted global cognition score), whereby this score was the sum of all domains except for the domain being analyzed as the dependent variable.

The Benjamini-Hochberg false discovery rate (FDR) method was applied to account for multiple hypothesis testing.[23] Where data were missing, results were calculated for samples with missing data removed. Two-sided *P* values < .05 after FDR adjustment were declared as statistically significant.

### Ethical Approval

The study received institutional Research Ethics Board approval from Clinical Trials Ontario (Clinical Trials Ontario #1430), and all participants or their substitute decision-makers provided informed consent.

## RESULTS

### Results Overview

Following the matching, age, sex, and years of education between the ARCI and Comparator groups were not significantly different. Mean (SD) age was 67.67 (13.01) years for the ARCI group and 67.97 (12.82) years for the Comparator group. The ARCI group had 33 males and 18 females, and the Comparator group had 65 males and 37 females. Mean (SD) total TorCA scores were 259.14 (31.00) for the ARCI group and 248.76 (45.16) for the Comparator group and were not significantly different ($P = .10$). Regarding cognitive disorders, in the ARCI group, 27 (53%) were diagnosed with MCI, and 14 (27%) were diagnosed with dementia, with the remainder unspecified severity. In the Comparator group, 65 (64%) were diagnosed with MCI, and 37 (36%) were diagnosed with dementia. For those with defined etiologies, the majority in both groups were attributable to Alzheimer's disease, vascular, or mixed Alzheimer's disease/vascular. A greater proportion of individuals in the ARCI group were diagnosed with mixed Alzheimer's disease/vascular cognitive impairment and unspecified etiology ($P = .019$). Full demographic and clinical details are presented in Table 1.

### Cognitive Domain and Subdomain Analysis

Detailed group differences between the ARCI and Comparator groups across all composite domain and subdomain scores are shown in Tables 2 and 3. There were no statistically significant differences in the cognitive domains between the two groups. When comparing the memory subdomain, while the total score on the CERAD[20] delayed recall test did not differ between groups, intrusion rates on the CERAD delayed recall test were higher (worse performance) in the ARCI group (after correcting for multiple testing), with mean (SD) score of 0.79 (1.21), compared to 0.34 (0.69) in the Comparator group ($\beta = .66$, SE = .19, $t_{117} = 3.55$, $P_{corrected} = .018$). There were no other statistically significant differences in the remaining cognitive subdomains between the groups.

### Sensitivity Analysis

In the sensitivity analyses, when global cognition was excluded as a covariate, individuals in the ARCI group performed better on the Orientation domain; this was not significant, however, when controlling for the adjusted global cognition value as covariate

Figure 1.

**Toronto Cognitive Assessment (TorCA) Cognitive Domains and Subdomain Tests**

| ORIENTATION | IMMEDIATE RECALL | DELAYED RECALL | DELAYED RECOGNITION | VISUOSPATIAL FUNCTION | EXECUTIVE FUNCTION | LANGUAGE |
|---|---|---|---|---|---|---|
| Orientation | CERAD Trial 1<br>CERAD Trial 2<br>CERAD Trial 3 | CERAD Delayed Recall<br>Benson Figure Delayed Recall | CERAD Delayed Recognition<br>Benson Figure Delayed Recognition | Benson Figure Copy<br>Clock Draw | Serial 7s<br>Serial 3s<br>Forward Digit Span<br>Reverse Digit Span<br>Trails A<br>Trails B<br>Alternating Sequences<br>Similarities<br>Verbal Fluency – Phonemic | Verbal Fluency - Semantic<br>MINT Naming<br>Repetition<br>Single Word Comprehension<br>Single Word Reading Comprehension<br>Sentence Comprehension<br>Single Word Reading Semantic Knowledge |

Abbreviations: CERAD = Consortium to Establish a Registry for Alzheimer Disease, MINT = Multilingual Naming Test.

(Supplementary Table 2). As in the main analysis, intrusion rates on the CERAD delayed recall test remained higher (worse performance) in the ARCI group relative to Comparators in these additional sensitivity analyses, and this finding remained significant in all analyses after controlling for multiple testing (Supplementary Table 3).

## DISCUSSION

We delineated the cognitive deficits seen in ARCI in an understudied population of participants with cognitive disorders (MCI or dementia) from a memory clinic cohort. We studied the cognitive processes underlying these deficits through cognitive testing, and we found that while the overall cognitive performance and performance on memory domain were comparable between those with and without ARCI in the presence of other cognitive disorders, those with ARCI had a higher rate of intrusions in the CERAD delayed recall test (worse performance), a robust finding that remained significant after correcting for multiple comparisons and across a range of sensitivity analyses.

The finding of worse intrusion rate in those with ARCI has important implications for understanding processes underlying cognitive deficits related to alcohol. An intrusion is recorded when a respondent incorrectly recalls a word during the delayed recall test that was not previously provided during encoding and learning. Such intrusions reflect deficits in cognitive control, namely response inhibition, which is impaired by excessive alcohol use.[14] Also, intrusions in a delayed recall task can be viewed as an analogous measure of provoked confabulation, a tendency to unknowingly generate false memories filling gaps in recollection with fabricated details.[24] Confabulations are a notable cognitive manifestation observed in individuals with ARCI such as in Wernicke-Korsakoff syndrome.[25,26] It is possible that those with ARCI demonstrate reduced cognitive control specifically on tests of verbal delayed recall, even in the absence of Wernicke-Korsakoff syndrome. A recent meta-analysis suggested that alcohol use may predispose individuals toward developing false memories,[27] yet this domain was not explored in prior analyses.[13,14] This highlights the importance of more comprehensive cognitive testing instruments when considering ARCI. Both cognitive control and false memory deficits have been linked to early damage to the ventral medial prefrontal cortex (vmPFC) across neurodegenerative processes.[28,29] Our findings support an increased propensity toward intrusions on a test of delayed recall in those with ARCI which may be mediated by damage to specific brain structures secondary to alcohol use such as the vmPFC, and this represents an important area for further investigation in neurocognitive disorders cohorts with structural neuroimaging data.

We did not observe between-group differences between those with and without ARCI on tests of executive function domains such as working memory (eg, backward digit span) and set shifting (eg, alternating sequences).[29] Moreover, there were no between-group differences on tests of response inhibition (eg, false-positives on delayed recognition tasks). This implies specific deficits in cognitive control tested through verbal recall in those with ARCI. Executive function deficits are frequently observed in ARCI, and although those with ARCI demonstrated executive function deficits in our sample, they did not differ from those with other neurocognitive disorders. The Comparator group in our study comprised predominantly individuals with cognitive impairment due to Alzheimer's disease and/or vascular

Table 1.

## Demographic and Clinical Characteristics of the Matched Sample[a]

| Variable | ARCI group (n = 51) | Comparator group (n = 102) | P[b] |
|---|---|---|---|
| **Age, mean (SD), y** | 67.67 ± 13.01 | 67.96 ± 12.82 | .89 |
| **Female sex** | 18 (35%) | 37 (36%) | 1.0 |
| **Education, mean (SD), y** | 15.00 ± 2.66 | 15.43 ± 2.66 | .38 |
| **Total TorCA score, mean (SD)** | 259.14 ± 31.00 | 248.76 ± 45.16 | .10 |
| **Neurocognitive phenotype** | | | |
| Mild cognitive impairment | 27 (53%) | 65 (64%) | <.001 |
| Dementia | 14 (27%) | 37 (36%) | |
| Unspecified | 10 (20%) | 0 | |
| **Neurocognitive etiology** | | | |
| Alzheimer's | 9 (18%) | 35 (34%) | .019 |
| Vascular | 3 (6%) | 13 (13%) | |
| Mixed | 12 (24%) | 18 (18%) | |
| Lewy body/Parkinson's | 0 | 6 (6%) | |
| Frontotemporal | 4 (8%) | 5 (5%) | |
| Unspecified | 23 (45%) | 25 (25%) | |

[a]Values shown as n (%) unless otherwise noted.
[b]*P* values calculated using either *t* test or $\chi^2$ as appropriate.
Abbreviations: ARCI = alcohol-related cognitive impairment, TorCA = Toronto Cognitive Assessment.

Table 2.

## Comparison of Cognitive Domain Scores Between ARCI and Comparator Groups

| TorCA cognitive domain | ARCI group | | Comparator group | | | | |
|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Adj. β | Adj. SE | $P_{corrected}$* |
| **Orientation (/12)** | 11.16 | 1.07 | 10.53 | 2.01 | 0.48 | 0.23 | .29 |
| **Immediate Recall (/30)** | 14.84 | 3.83 | 14.92 | 4.60 | −0.65 | 0.58 | .94 |
| **Delayed Recall (/27)** | 11.59 | 6.43 | 10.33 | 6.46 | −0.29 | 0.86 | .95 |
| **Delayed Recognition (/21)** | 18.76 | 1.87 | 18.26 | 2.84 | 0.05 | 0.37 | .95 |
| **Visuospatial (/32)** | 28.86 | 2.47 | 28.43 | 4.28 | −0.16 | 0.50 | .95 |
| **Executive Function**[a] | 98.41 | 14.55 | 93.85 | 22.22 | −0.08 | 1.34 | .95 |
| **Language**[a] | 75.51 | 10.29 | 72.43 | 12.26 | 0.63 | 1.19 | .95 |

[a]No maximum score.
**P* value after applying the Benjamini-Hochberg false discovery rate (FDR) correction for 7 tests.
Abbreviations: ARCI = alcohol-related cognitive impairment, TorCA = Toronto Cognitive Assessment.

disease. Executive dysfunction is also commonly observed in those with neurocognitive disorders due to Alzheimer's, vascular, or mixed etiologies.[30,31] Thus, future studies may replicate these findings in prospective longitudinal cohorts.

The finding of higher prevalence of neurocognitive disorders with unspecified etiology in the ARCI group in this study is expected, and it may reflect the inherent challenge in diagnosing and characterizing cognitive impairment in individuals with excessive alcohol use. ARCI may present with a range of clinical manifestations, such as concussions, nutritional deficiencies, and mental health symptoms, which further complicates the accurate diagnosis of etiology of cognitive impairment in this population. It is important to accurately diagnose and delineate ARCI from other causes of cognitive impairment, especially in the context of recent jurisdictional changes to recommended safe drinking limits for alcohol. In 2023, Canada changed their safe upper limit for alcohol from 10 standard drinks (defined as 13.45 g ethanol/standard drink) per week for women or elderly and 15 standard drinks per week for men to a maximum of 2 standard drinks per week.[32] This change was largely driven by the risks related to cardiovascular disease and cancer, and the risk of cognitive impairment was not emphasized in these changes. Similarly, the Australian guidelines published in 2017 reduced the safe upper limit for alcohol to 10 standard drinks (defined as 10 g ethanol/standard drink) per week.[33] Other countries stand to develop new

Table 3.

## Comparison of Cognitive Subdomain Scores Between ARCI and Comparator Groups

| | ARCI group | | Comparator group | | | | |
|---|---|---|---|---|---|---|---|
| Cognitive subdomain | Mean | SD | Mean | SD | Adj. β | Adj. SE | $P_{corrected}$* |
| CERAD trial 1 (/10) | 3.43 | 1.39 | 3.63 | 1.53 | −0.32 | 0.23 | .93 |
| CERAD trial 2 (/10) | 5.24 | 1.37 | 5.28 | 1.82 | −0.25 | 0.24 | .93 |
| CERAD trial 3 (/10) | 6.18 | 1.58 | 6.01 | 1.90 | −0.09 | 0.25 | .93 |
| CERAD delayed recall (/10) | 3.18 | 2.36 | 2.86 | 2.40 | −0.13 | 0.36 | .93 |
| CERAD delayed recall intrusions[a,b] | 0.79 | 1.21 | 0.34 | 0.69 | 0.66 | 0.19 | **.018** |
| CERAD delayed recall repetitions[a,c] | 0.22 | 0.85 | 0.18 | 0.61 | −0.071 | 0.15 | .93 |
| Benson figure recall (/17) | 8.41 | 4.78 | 7.47 | 4.55 | −0.16 | 0.64 | .93 |
| CERAD delayed recognition (/20) | 18.06 | 1.80 | 17.55 | 2.70 | 0.087 | 0.37 | .93 |
| Benson figure recognition (/1) | 0.71 | 0.46 | 0.72 | 0.45 | −0.033 | 0.08 | .93 |
| Benson figure copy (/17) | 15.43 | 1.42 | 15.18 | 2.24 | −0.024 | 0.30 | .98 |
| Clock draw (/15) | 13.43 | 1.93 | 13.25 | 2.60 | −0.13 | 0.35 | .93 |
| Serial 7's (/13) | 10.73 | 3.51 | 9.95 | 4.04 | −0.25 | 0.53 | .93 |
| Serial 3's (/13) | 11.57 | 2.78 | 11.25 | 3.37 | −0.15 | 0.45 | .93 |
| Longest forward span recalled correctly (/9) | 6.43 | 1.22 | 6.30 | 1.41 | 0.004 | 0.22 | .98 |
| Longest backward span recalled correctly (/8) | 4.31 | 0.99 | 4.19 | 1.38 | 0.006 | 0.19 | .98 |
| Trails A (/24) | 23.14 | 2.80 | 22.10 | 4.65 | 0.50 | 0.58 | .93 |
| Trails B (/24) | 19.96 | 6.73 | 18.26 | 8.16 | 0.39 | 0.90 | .93 |
| Alternating sequences (/2) | 1.67 | 0.62 | 1.58 | 0.74 | 0.041 | 0.12 | .93 |
| Similarities (/10) | 8.96 | 1.83 | 8.84 | 1.90 | −0.20 | 0.28 | .93 |
| Verbal fluency score[a] | 11.65 | 3.70 | 11.37 | 5.06 | −0.41 | 0.70 | .93 |
| Verbal fluency intrusions[a] | 0.22 | 0.92 | 0.21 | 0.71 | 0.020 | 0.15 | .98 |
| Verbal fluency repetitions[a] | 0.55 | 0.83 | 0.85 | 1.21 | −0.31 | 0.20 | .93 |
| Semantic fluency score[a] | 15.80 | 6.34 | 14.12 | 6.44 | 0.63 | 0.80 | .93 |
| Semantic fluency intrusions[a] | 0.06 | 0.24 | 0.03 | 0.17 | 0.051 | 0.04 | .93 |
| Semantic fluency repetitions[a] | 0.33 | 0.68 | 0.71 | 1.24 | −0.45 | 0.20 | .41 |
| Mint naming (/15) | 13.29 | 2.74 | 13.07 | 2.45 | −0.12 | 0.35 | .93 |
| Sentence repetition (/10) | 8.76 | 1.49 | 8.73 | 2.19 | −0.24 | 0.33 | .93 |
| Single-word comprehension (/8) | 7.84 | 0.61 | 7.83 | 0.92 | −0.052 | 0.15 | .93 |
| Single-word reading comprehension (/2) | 1.86 | 0.49 | 1.90 | 0.41 | −0.036 | 0.08 | .93 |
| Sentence comprehension (/8) | 6.69 | 1.71 | 6.25 | 1.87 | 0.073 | 0.29 | .93 |
| Single-word reading (/12) | 11.76 | 0.95 | 11.35 | 1.53 | 0.24 | 0.23 | .93 |
| Semantic knowledge (/10) | 9.49 | 1.14 | 9.18 | 1.42 | 0.14 | 0.21 | .93 |

[a]No maximum score.
[b]After omitting missing values, n = 8 for the alcohol-related cognitive impairment (ARCI) group; n = 20 for the Comparator group.
[c]After omitting missing values, n = 10 for the ARCI group; n = 22 for the Comparator group.
*$P$ value after applying the Benjamini-Hochberg false discovery rate (FDR) correction for 32 tests.
Abbreviations: ARCI = alcohol-related cognitive impairment, CERAD = Consortium to Establish a Registry for Alzheimer Disease, MINT = Multilingual Naming Test.

or revised guidelines, and they may enact similar changes to safe drinking limits for alcohol.[34] In contemplating such changes, it would be important to consider not only cancer and cardiovascular health but also the neurocognitive effects of alcohol use, particularly in those with cognitive disorders. Future studies should aim to quantify the burden of ARCI in people with cognitive disorders in large population-based cohorts.

## Limitations

Our study has several limitations. First, the sample size was small; however, our sample was well matched in terms of age, gender, and education. Second, the assignment of ARCI was a binary decision by the physicians taking into account Canadian alcohol drinking guidelines at that time; however, we did not have quantitative data on alcohol use. Thus, it is likely that only those with significant alcohol use clearly impacting their cognition were considered in the ARCI group. It is also possible that the excessive alcohol use phenotype was missed in certain individuals, especially those with more advanced disease who may be unable to provide a reliable self-history; however, the clinical assessment was also developed with the input of an informant. Third, our comparator group was mixed in terms of the etiology of cognitive impairment. However, mixed dementias are common in clinical practice, and our sample is thus representative of individuals seen in "real-world" memory clinics.[35] Lastly, given that we studied a memory clinic sample and not a deeply phenotyped research

cohort, we relied on clinical diagnosis for cognitive disorders without the use of biomarkers, but again this is representative of the real-world setting.

Alcohol use is a recognized modifiable risk factor for dementia, but in routine clinical practice, it is challenging to distinguish the contribution of ARCI from other causes of cognitive impairment. In this study, using a memory clinic cohort of mixed cognitive disorders population, we found specific impairments in delayed recall process (higher rate of intrusions) in those with ARCI, which may represent a tendency toward cognitive control deficits and false memory generation in those with ARCI. Future studies should verify these findings in well-characterized longitudinal cohorts and characterize the impact of alcohol use on trajectories of cognitive disorders. Future studies may also aim to understand mechanisms of ARCI in those with cognitive disorders by using brain imaging and other biomarkers. These efforts could have significant impact on differentiating and understanding the impact of alcohol consumption in individuals with cognitive disorders, eventually leading to precision-based preventive and management strategies for ARCI.

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