EFFECTS OF ALCOHOL USE ON COGNITION DURING LATER ADULTHOOD

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DEDICATION

To Bill W. and Dr. Bob

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Alcohol is one of the most widely used psychoactive substance in the world, yet there are conflicting findings related to its long-term effect on cognition. Some research has identified a U-shaped relationship between alcohol consumption and cognition, while negative relationships have been identified in other studies. Methodological issues, particularly the time at which alcohol consumption was measured relative to when cognition was measured, wide variability in definitions of "moderate" alcohol consumption, and selecting appropriate comparison groups, have made exploring the effects of alcohol on cognition during aging difficult. The current study examined the relationship between drinking at three separate time points (between the ages of 50 and 74) and cognition in older adulthood. Results revealed that the quantity of self-reported drinks over the three time points was a significant predictor of cognition in older adulthood

(*b*=0.001; *p*<.001), although the effect sizes were very small and not meaningful. Subsequent analyses examined this relationship among heavy drinkers and binge drinkers compared to moderate drinkers and non-binge drinkers, but heavy and binge drinking were not significant predictors of cognition in older adulthood (all *ps*>0.05). Overall, the results suggest no that there is not a meaningful relationship between alcohol consumption and cognitive functioning in older adulthood in this sample. There were few consistent heavy drinkers (*n*=71), but a large number of consistent moderate drinkers (*n*=1,847), although even the moderate drinkers did not consume much alcohol (mean alcohol consumption = 15.3 drinks/month; median alcohol consumption = 5.0 drinks/month). This may have limited the ability to detect clinically meaningful differences. Future studies should rely on more standardized alcohol measures, large, diverse samples, and inclusion of cognitive measures assessing visuospatial abilities and executive functioning, in order to better explore the relationship of alcohol in the aging brain.

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LIST OF ABBREVIATIONS

AUD: Alcohol Use Disorder

BMI: Body Mass Index

CERAD: Consortium to Establish a Registry for Alzheimer disease

CVD: Cardiovascular Disease

DSST: Digit-Symbol Substitution Test

LOESS: Locally Estimated Scatter-Plot Smoother

MMSE: Mini Mental Status Examination

NSDUH: The National Survey on Drug Use and Health 2002-2018

SILS: Shipley Institute of Living Scale

TMT A & B: Trail Making Test A & B

WAIS–R: Weschler Adult Intelligence Scale – Revised

WCST: Wisconsin Card Sorting Test

WLS: Wisconsin Longitudinal Study

SECTION ONE

Journal Ready Manuscript

1.0 INTRODUCTION

As the global population continues to live longer, dementia research has focused on identifying modifiable risk factors. Alcohol is the most widely used psychoactive substance in the world (Sun et al., 2018); however, investigation of the long-term effects of moderate alcohol consumption and cognition has yielded mixed results (Baumgart et al., 2015; Neafsey & Collins, 2011). In a recent large scale investigation (N = 19,887), low to moderate drinking (7-14 drinks/week) was associated with lower odds of cognitive decline, as measured by performance on a mental status exam, a word recall task, and a vocabulary task, compared to individuals who reported never consuming alcohol (Zhang et al., 2020). Another investigation reported that older adults who occasionally (defined as less than daily) consumed two alcoholic beverages or less had a lower risk of dementia compared to individuals who did not drink (Liu et al., 2019). Similarly, older adults who consumed one to three drinks per week had significantly lower risk of developing dementia compared to nondrinkers (Ruitenberg et al., 2002). While these studies demonstrated a reduced risk of cognitive decline and dementia with moderate alcohol consumption, other studies have found no relationship (Lobo et al., 2010; Peters, Peters, Warner, Beckett, & Bulpitt, 2008), or an increased risk of cognitive decline associated with alcohol consumption (Edelstein, Kritz-Silverstein, & Barrett-Connor, 1998; Topiwala et al., 2017).

In a 2008 systematic review of 23 studies examining the relationship between alcohol and cognition, there was no protective effect of moderate alcohol consumption on cognitive decline (Peters et al., 2008). Similarly, low-to-moderate alcohol consumption was not associated with rate of cognitive decline in a large (N=3,888) population based study (Lobo et al., 2010). In

contrast, moderate alcohol consumption (14-21 drinks/week) was associated with greater cognitive decline and increased right sided hippocampal atrophy compared to abstainers (Topiwala et al., 2017). Similarly, consumption of greater than 14 drinks per week was associated with a 17% increase in dementia compared to those drinking less than 14 drinks per week (Sabia et al., 2018).

While these studies were conducted in large populations, they still have some limitations which may account for the variation in results between studies. As detailed in the meta-analysis by Neafsey and Collins (2011), many of the studies that identified protective effects of moderate alcohol consumption relied on use of cognitive screeners, such as the Mini Mental Status Examination (MMSE). These are frequently used measures in clinical practice, but are mainly a means to identify gross cognitive impairment or individuals who should receive a full neuropsychological evaluation (Roebuck-Spencer et al., 2017). Studies that include more sensitive cognitive measures would be better at detecting subtle cognitive changes. Another limitation is that many of the studies mentioned above rely on single points of data collection for alcohol use and/or retrospective accounts of alcohol use. This limits the ability to explore a long-term dose dependent relationship between alcohol consumption and cognition. With so many varied findings, it is difficult for clinicians to provide appropriate recommendations regarding alcohol consumption; thus, there is a need to better understand the role of alcohol in the aging brain.

Longitudinal databases where alcohol consumption is assessed at multiple time points with multiple cognitive measures allow for more detailed examination of the long-term effect of alcohol consumption on cognition in older adulthood. The Wisconsin Longitudinal Study (WLS) is a database with nearly 20 years of sociodemographic, medical, psychiatric, psychological,

alcohol, and cognitive data. Using data from the WLS, the aim of this study was to examine the relationship between alcohol consumption (assessed at three separate time points over the course of 19 years) in later adulthood (i.e., early 50s) and cognition in older adulthood (i.e., early 70s). It was hypothesized that greater alcohol consumption over the course of follow up would be associated with poorer cognition in older adulthood and that greater alcohol consumption at baseline would be a stronger predictor of cognition in older adulthood compared to alcohol consumption in older adulthood.

2.0 METHODS

2.1 Sample

The present study was conducted using secondary data from the WLS, a large longitudinal, de-identified, publicly available database collected by researchers at the University of Wisconsin – Madison (Hauser, Sewell, & Herd, 1957-2019; Herd, Carr, & Roan, 2014). Data collection began in 1957 as a state-sponsored questionnaire completed by every high school senior in Wisconsin. In 1964, a random 1/3 sampling of those surveyed in 1957 was taken and this sample became the cohort followed during the WLS. This cohort (*n*=10,317) consisted of men and women from Wisconsin born between 1938 and 1940. The original aim of the study was to understand the factors (e.g., parental support and finance for education, occupational aspirations and plans, marriage and military plans, etc.) that contributed to high school seniors' decision to seek higher education, although over time the aim of the study became focused on psychosocial factors in an aging population. The cohort was followed over the course of 54 years, with data collection occurring in 1957 (in school), 1964 (phone and mail), 1975 (phone), 1992 (phone and mail), 2004 (phone and mail), and 2011 (in-person, phone, and mail). The sample is rather

homogenous with regards to sociodemographic variables, with 99% of the sample being Caucasians who graduated high school in Wisconsin in 1957.

During the 1992 data collection period WLS participants were asked a series of questions regarding their personality, cognition, and health. Additionally, a random 80% sample were administered two separate sections that included questions regarding depression history and alcohol use. In the 2004 data collection period the cognition and health sections were expanded to include more detailed information. During the 2011 data collection period even more cognitive measures were added including a memory task, a digit ordering task, a phonemic fluency task, and six items from the Weschler Adult Intelligence Scale – Revised (WAIS–R) Similarities subtest.

Participants for the current study were drawn from the random sample selected for depression and alcohol during the 1992 data collection (n=6,636). Between the 1992 and the 2004 (n=5,316) data collection periods, 1,320 participants were lost to follow-up, and between the 2004 and 2011 (n=4,431) data collection periods 885 participants were lost to follow up. Exclusion criteria for the current study included individuals who denied ever consuming alcohol (n=353) and those with history of Parkinson's disease (n=1), multiple sclerosis (n=26), stroke (n=0), or epilepsy (n=0). Some participants (n=724) were missing alcohol data at one of the time points or did not have complete cognitive data at the 2011 data collection; thus, only participants with complete cognitive and alcohol data (N= 3,327) were used.

2.2 Measures

2.2.1 Demographic information

Participants provided demographic information including, sex, age, and years of education. In 2004 less than 1% of participants identified as "non-white" (Herd et al., 2014); thus, ethnicity was not included as a covariate in the present study.

2.2.2 Alcohol

Alcohol use information was collected in the WLS via self-report in 1992, 2004 and 2011. Participants were asked a series of questions regarding their alcohol consumption. If participants responded "no" to the question "Have you ever drunk alcoholic beverages, such as beer, wine, liquor, or mixed alcoholic drinks?" at any timepoint they were excluded from the study. If they responded "yes" to the previous question they were then asked, "During the last month, on how many days did you drink any alcoholic beverages, such as beer, wine, or liquor?" and "About how many drinks did you have on average on those days?". Total number of drinks over the past month was calculated based on their responses to these questions, which was used in the analysis as the measure of alcohol consumption.

2.2.3. Cognition

For the current study, only the cognitive tasks completed in 2011 were used. Each time point included the addition of more cognitive measures (with the most in 2011); therefore, it was decided to only use those measures in order to maximize the ability to assess each participant's cognitive performance. The four tasks included: a letter fluency task, six items from the WAIS–R Similarities subtest, a digit ordering task, and a verbal learning and memory task. For the letter fluency task, participants were asked to generate as many words as possible that begin with a certain letter (L or F) in one minute, with none of the words being proper names of people or places. This verbal fluency task is modeled off of the controlled oral word association task, a commonly used measure in neuropsychological evaluations (Ross et al., 2007). It involves an

array of cognitive functions such as attention, vocabulary knowledge, and aspects of executive functioning (Kreutzer, DeLuca, & Caplan, 2018; Whiteside et al., 2016). For the Similarities task, a measure of abstract reasoning (Kreutzer et al., 2018), participants were asked to describe the way in which two words, usually representing a concept, are alike. To assess attention, working memory and sequencing, participants were read a series of numbers (beginning with two digits and increasing the digit by one after each successful ordering) and asked to arrange them from smallest to largest. Memory was assessed by reading a ten-item word list to the participants, asking them to immediately repeat the words, and then recall them again after a ten-minute delay. This task is similar to other verbal memory tasks commonly used in neuropsychological evaluations (e.g., Hopkins Verbal Learning Test, Rey Auditory Verbal Learning Test, etc.), although participants were only read the list once. Only participants who had complete data for each cognitive measure were included in this study.

2.2.4 Covariates

Several variables were used as covariates based upon their potential contribution to changes in cognitive functioning with age. These variables included years of education (Baumgart et al., 2015; Campbell, Unverzagt, LaMantia, Khan, & Boustani, 2013), cardiovascular risk (Ciobica, Padurariu, Bild, & Stefanescu, 2011), and history of depression (Almeida, Hankey, Yeap, Golledge, & Flicker, 2017). Education was defined by the number of years of education (range 12-22 years of education). Cardiovascular risk was assessed using several factors, including history of hypertension, history of high cholesterol, and body mass index (BMI). For history of hypertension and high cholesterol, if participants responded “yes” to the questions “Has a doctor ever told Participant they have high cholesterol?” or “Has a doctor ever told Participant they have high blood pressure or hypertension?” they were categorized as

"history of high cholesterol" or "history of hypertension", respectively. BMI was calculated based upon the participant's reported height (cm) and weight (kg) at the 2011 data collection period. History of depression was assessed based upon the participant's response to the question, "Have you ever had a time in life lasting two weeks or more when nearly every day you felt sad, blue, depressed or when you lost in interest in most things like work, hobbies, or things you usually liked to do for fun?" Individuals who responded "yes" at any timepoint were categorized as "history of lifetime depression."

2.3 Statistical Analysis

Descriptive statistics, including means and standard deviations for continuous variables, and frequencies and percentages for categorical variables, were examined. To determine the predictive ability of alcohol use at each time point on cognition, a panel data analysis with an auto-regressive correlation structure was performed, which allows for data to be analyzed in a temporal manner (Finkel, 1995). In this analysis, alcohol use was examined as a continuous variable. An overall cognitive composite score was calculated in order to characterize each participant's cognition in a single metric. To create the cognitive composite score, a total mean *z*-score was calculated for each cognitive measure, after which, the four *z*-scores were averaged to form a single metric.

A local quadratic polynomial regression lines, specifically locally estimated scatter-plot smoother (LOESS) lines, were fit to the scatterplot to explore the possibility that the relationship between alcohol and cognition was non-linear and to identify possible inflection points. That is, the value at which alcohol use has the least or greatest effect on cognition at each time point. Structure coefficients were also calculated to determine at which time point alcohol consumption explained the largest amount of variance in cognition. The normality assumption was checked

and not met, as drinks over the past month was significantly right- skewed at each time point (kurtosis =38.36, 37.05, and 16.44 at each time point, respectively). Results were deemed statistically significant at $p < 0.05$. Statistical analyses were conducted using SPSS version 26.0 (SPSS Inc., Chicago, IL).

3.0 RESULTS

3.1 Descriptive Statistics

The study sample (N=3,327) had a mean age of 71.2 with a mean of 13.9 years of education and a mean BMI of 28.8 kg/m^2 (See Table 1). Mean drinks consumed in the past month (across all three time points) was 15.0 (SD = 23.8) drinks, with a mean of 13.6 (SD = 21.2) drinks at baseline (i.e., 1992, the initial year of assessment), a mean of 15.2 (SD = 23.7) drinks at time point two, and a mean of 16.31 (SD = 26.0) drinks at time point three (See Table 2). Overall, 53.98% of the sample (n=1,796) was female, and 37.2% (n=1,239) endorsed a history of depression, 52.7% endorsed a history of high cholesterol (n=1,754), and 58.5% endorsed a history of hypertension (n=1,947).

3.2 Panel Regression Analysis

A panel regression analysis was conducted to evaluate the relationship between quantity of alcohol consumed at three separate time points (1992, 2004, 2011) and global cognition at the final timepoint (2011). The predictors in the model were total drinks in the past month, sex, time (which accounts for 19-year period over which the three data collections occurred), years of education, history of hypertension (yes/no), history of high cholesterol (yes/no), BMI (kg/m^2), and history of depression (yes/no), while the dependent variable was the global cognition composite score. Total drinks past month (b = 0.001; p<.001), time (b = 0.000; p = .005), sex (b = 0.301; p < .001), years of education (b = 0.094; p < .001), history of hypertension (b = 0.060; p

= 0.006) were statistically significant predictors of the global cognition score, whereas history of high cholesterol (b = –0.150; p = 0.476), BMI (b = 0.001; p = 0.605), and history of depression (b = 0.033; p = 0.113) were non-significant predictors (Table 3).

A scatterplot with fitted LOESS lines depicting the relationship between alcohol consumption and global cognition was created cross-sectionally for each time point (Figure 1). This was done to determine whether there were meaningful inflection points in the data, for which the least or most influential levels of alcohol consumption on global cognition could be ascertained. Structure coefficients (r_s) were calculated using Spearman rank-order correlation coefficients (used opposed to Pearson's correlation, since time is an ordinal variable) to describe the unique relationship between alcohol consumption and the predicted global cognition score at each time point; the aim of which was to determine at which time point, alcohol consumption explained the largest amount of variance in the global cognition. The structure coefficient at baseline was non-significant (r_s^2 = 0.0002, p = 0.30), whereas the structure coefficients at time point two (r_s^2 = 0.002, p = 0.004) and time point three (r_s^2 = 0.005, p < 0.001) were statistically significant.

4.0 DISCUSSION

It was hypothesized that greater average cumulative quantity of alcohol consumption would be associated with poorer cognitive functioning in older adulthood. This was based upon previous research that identified poorer cognitive functioning in older adulthood as alcohol consumption increased. This hypothesis was not supported. There was a significant positive relationship between the quantity of alcohol consumed and the global cognition index score later in life; however, the effect sizes were very small. It was also hypothesized that consumption of alcohol in later adulthood would be the strongest predictor of cognition in older adulthood.

Contrary to what was hypothesized, greater alcohol consumption in later adulthood (i.e., early 50s) was not a significant, nor stronger predictor, of cognitive functioning in older adulthood (i.e., early 70s). Instead, alcohol consumption in older adulthood was the strongest predictor (albeit, with a very small effect size) of cognition and alcohol consumption at baseline was not a significant predictor of cognition. The findings from the current study are consistent with others, which identified a positive relationship with alcohol consumption and cognition.

Results from the Rotterdam Study (Ruitenberg et al., 2002) and the Okayama Study (Liu et al., 2019), two large, population-based, longitudinal investigations, found a *protective* effect of moderate alcohol consumption. These studies included multiple measures of alcohol consumption over relatively short periods of follow-up (6-7 years). Those findings were somewhat supported by the current study, as current alcohol consumption and alcohol consumption at time point two (approximately seven years between follow-up) were significant positive predictors of global cognition at time point three. The effect size ($r_s^2 = 0.005$) of the current result was very small and lower than those from the Rotterdam Study or the Okayama Study, and less meaningful than the average ratio of risk (RR = 0.77) for cognitive decline associated with moderate drinking found in the meta-analysis by Neafsey and Collins (2011). In other words, there was an approximately 25% less risk of cognitive decline with moderate drinking in the meta-analysis by Neafsey and Collins (2011).

The differences in findings between the current study and some prior ones may be related to several factors. The population in the current study did not consume as much alcohol as studies that have found inverse relationships. For example, Parker and Noble (1977) found significant negative (albeit small effect size [*r*'s=0.22-0.33]) relationships between moderate (55% of the sample [*n*=56]; 1.5 drinks/occasion; 4 occasions/week) drinking and recent cognitive

functioning, and heavy (36% of the sample [*n*=37]; 3-4 drinks/occasion; 3 occasions/week) drinking and recent cognitive functioning. In the present study, mean drinks/month was 15 (median drinks/month was 5), roughly four drinks per week on average, which is similar to the six drinks per week on average reported by Parker and Noble (1977); however, the present study had a much larger sample (*N*=3,197) and included multiple measurements of alcohol use over a 19- year period, allowing for greater ability to detect differences. The larger sample size in the present study was a clear strength, but in another large population- based sample (*N*=3,021) consuming greater than 14 drinks per week compared to less than one drink per week was associated with lower MMSE scores (Koch et al., 2019). However, in both those studies alcohol was only assessed at one time point (in older adulthood) which limits the ability to explore the long-term effects of alcohol use on cognition. Another common limitation of studies exploring the relationship between alcohol consumption and cognition is grouping participants based upon drinking patterns.

When participants are grouped based upon drinking patterns (e.g., moderate drinkers, heavy drinkers, etc.) it limits the ability to examine the effect of changing drinking patterns. For example, in both Parker and Noble (1977) and Koch et al. (2019) participants were categorized into groups based upon drinking patterns, whereas the present study examined alcohol as a continuous variable. Examining alcohol as a continuous variable takes into account an individual's variation in drinking at each time point, whereas categorization of participants into groups makes exploring changing patterns more difficult.

Another possible explanation for the variation in results is the time at which alcohol use was measured relative to when cognition was assessed. In Koch et al. (2019), the effects of alcohol consumption in older adulthood related to recent cognitive functioning as the study did

not include reports of previous drinking behavior. Having multiple measures of alcohol consumption increased the ability to detect differences related to long-term effects of alcohol consumption on cognitive functioning, a clear strength of the study. The findings suggest that while there was a statistically positive relationship between alcohol consumption and cognition it does not appear to be a meaningful one.

Limitations

There were several limitations to the current study which should be noted. First, the sample consisted of a non-diverse population, primarily Caucasian high school graduates. Second, the sample did not drink much compared to other studies which found negative effects on cognition as alcohol consumption increased. For example, median alcohol consumption was 11.5 drinks per week for men and 6.4 drinks per week for women in the sample of participants used by Topiwala et al. (2017), which showed right-sided hippocampal atrophy and poorer cognition as alcohol consumption increased. The median number of drinks in that sample is far higher than the median of five drinks in the current sample, which may have limited the ability to detect more meaningful differences. Third, not using a standardized method to quantify number of drinks consumed may result in an underestimation of actual alcohol consumption. A "standard" drink is any drink that contains 14 grams of pure alcohol (National Institute on Alcohol Abuse & Alcoholism, 2017). When participants were asked about alcohol consumed there was no definition of what a standard drink consists of, or the type of alcohol consumed. Use of more standardized measures of alcohol consumption can be used to better capture true drinking behavior, an important consideration as population studies typically produce a 40%-50% underrepresentation of alcohol consumption (Livingston & Callinan, 2015). The Timeline Follow Back method is widely used in alcohol and substance use research and is a quick and

efficient means of improving estimates of total amounts consumed (Sobell & Sobell, 1992). Participants are provided the definition of a standard drink and a calendar and asked how much they drank on each day, including the type of beverages consumed. Fourth, there were no cognitive measures of visuospatial abilities or executive functioning included in the WLS, two areas known to be directly impacted by alcohol use, particularly when consuming high levels. This may have limited the ability to detect subtle differences related to alcohol. Inclusion of cognitive measures that assess visuospatial abilities or executive functioning is an important consideration for future studies.

Conclusions

No meaningful relationship between quantity of alcohol consumed throughout the lifespan and cognition in older adulthood was found in this large sample of otherwise healthy aging individuals. Based upon these findings, moderate alcohol consumption does not appear to be a significant risk factor for cognitive impairment in older adulthood. Continuing to study the relationship between alcohol consumption and cognition is an important endeavor, as there is a wide array of findings and because this is a clinically relevant issue, as alcohol is the most widely consumed psychoactive substance. The use of standardized methods for quantifying alcohol consumption and inclusion of cognitive measures that assess a variety of cognitive abilities in more detail are crucial to include in future studies.

Table 1. Demographic Characteristics for Entire Sample

Demographic Characteristics

	Mean	SD
Age	71.19	0.90
Years of Education	13.90	2.43
Body Mass Index	28.76	5.54
	Frequency	**Percent**
Sex–Female/Male	1,796/1,531	53.98/46.02
History of Hypertension	1,947	58.52
History of High Cholesterol	1,754	52.72
History of Depression	1,239	37.24
History of Multiple Sclerosis	34	1.02
History of Parkinson's Disease	58	1.74
History of Stroke	148	4.45

Note. n = 3,327.

Table 2. Mean Number of Drinks for Past Month at Each Time Point

Descriptive Statistics

	Mean	SD
Total Drinks (over past 30 days) – Baseline	13.62	21.15
Total Drinks (over past 30 days) – Time 2	15.22	23.74
Total Drinks (over past 30 days) – Time 3	16.31	25.97
Total Drinks (over past 30 days) – Cumulative	15.07	23.75

Table 3. Results from Panel Regression Looking at Alcohol and Cognition

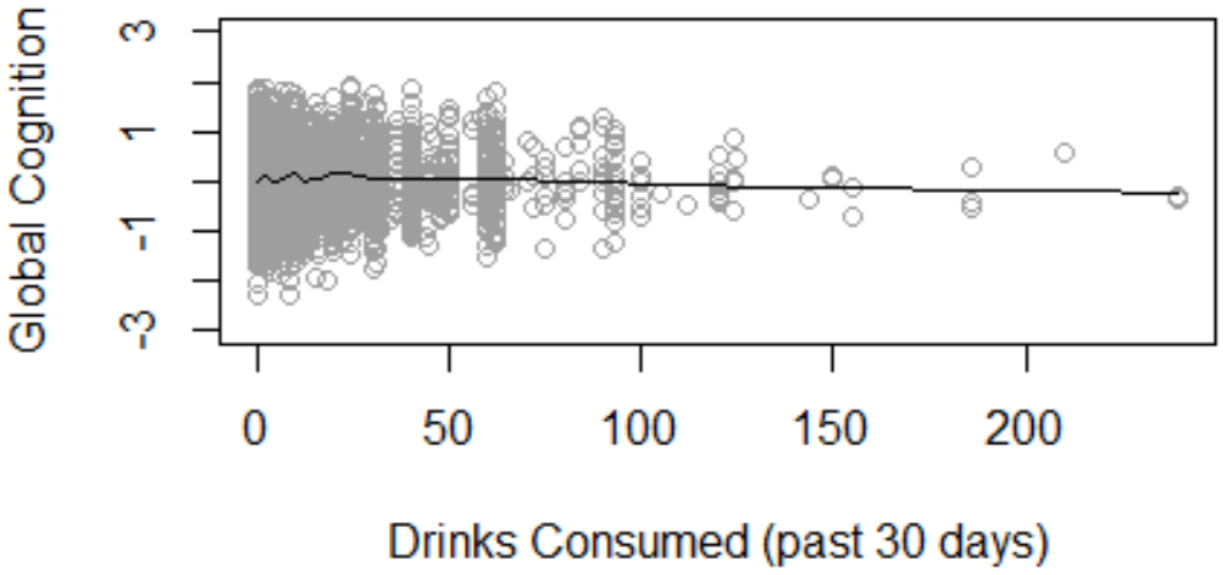
Panel Regression Results

			95% CI				
	B	**S.E.**	**Lower**	**Upper**	**Wald χ^2**	***df***	***p***
Total Drinks (over past 30 days)	.001	.0004	.001	.002	14.049	1	< .001
Time	.000	.0001	-.001	.000	7.940	1	.005
Sex	.301	.0206	.260	.341	212.743	1	< .001
Years of Education	.094	.0041	.086	.101	532.662	1	< .001
History of Hypertension	.060	.0215	.017	.102	7.676	1	.006
History of High Cholesterol	-.015	.0203	-.054	.025	.509	1	.476
Body Mass Index	.001	.0019	-.003	.005	.267	1	.605
History of Depression	.033	.0207	-.008	.073	2.513	1	.113

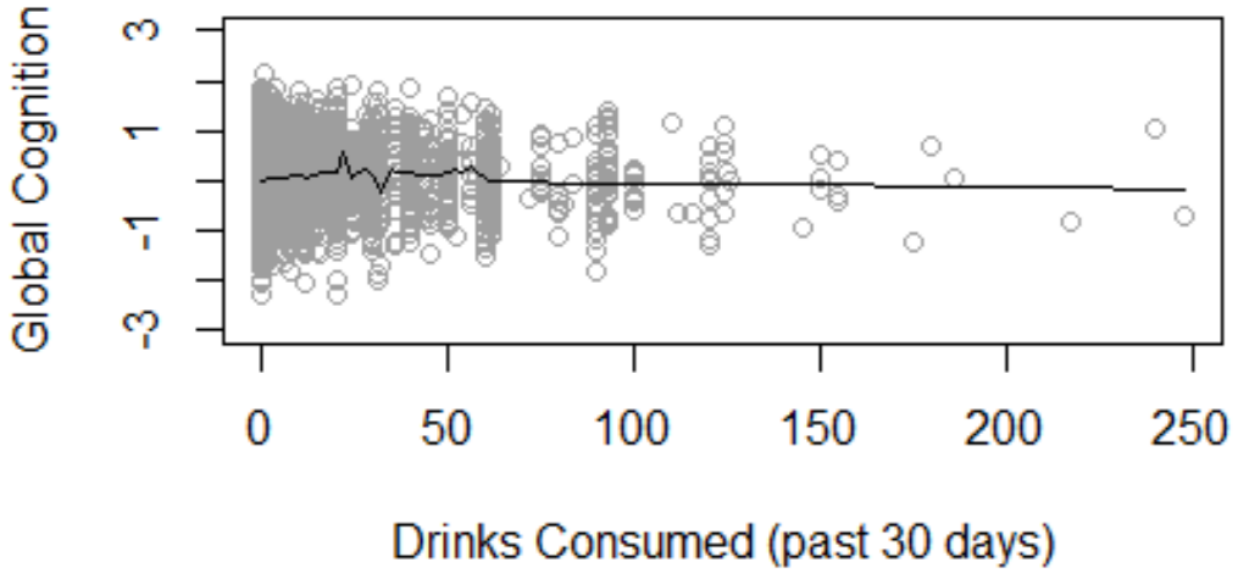
Note. n = 3,327.

Figure 1

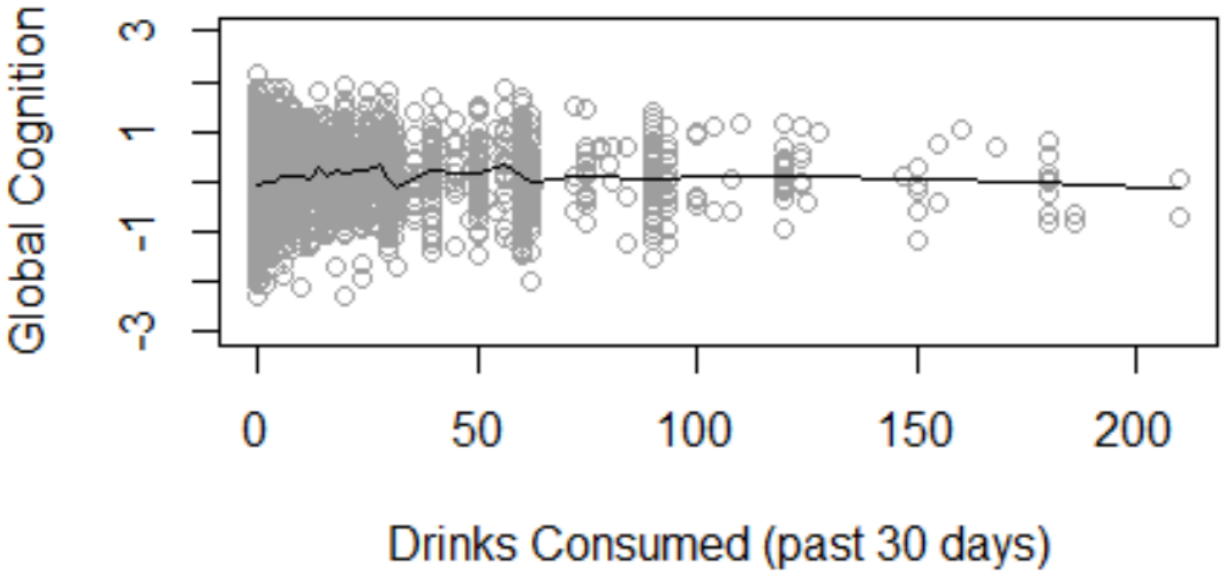
Association between drinks consumed and global cognition at time points (a) 1, (b) 2, and (c) 3 with fitted Loess line



(a)



(b)


Global Cognition
3
1
-1
-3
0
50
100
150
200
Drinks Consumed (past 30 days)

(c)

SECTION TWO
Appendices

APPENDIX A: ADDITIONAL BACKGROUND

Additional Background

Introduction

Modifiable risk factors of dementia and cognitive decline receive special attention as treatments for dementia are limited once a diagnosis is made. Research in this field have identified numerous modifiable risk factors (e.g., cardiovascular health, social activity, education attainment, history of depression or traumatic brain injury, and the importance of a balanced diet with regular exercise), yet research on the relationship between alcohol consumption and dementia risk continues to produce mixed results (Baumgart et al., 2015; Neafsey & Collins, 2011).

The mechanisms through which moderate alcohol consumption has positive or negative effects on health are poorly understood. Various methodological issues, including reliance on self-report measures, inconsistencies in how varying levels of alcohol consumption are defined, and lack of longitudinal studies examining the long-term effects of alcohol consumption on cognition, make this area of research challenging.

The present study was designed to investigate the long-term effects of alcohol consumption on cognition in older adulthood. Use of a longitudinal database with nearly 60 years of total data collection and 19 years of alcohol, psychosocial, and cognitive data allows for examination of the potential effects of varying levels of alcohol consumption on cognition in older adulthood. Clarifying the relationship between alcohol and cognition in the aging brain can help clinicians make informed recommendations regarding the potential positive or negative effects and potentially provide another early access point to aid in prevention of dementia

ALCOHOL USE AND ASSOCIATED HEALTH OUTCOMES

Epidemiology

Rates of alcohol consumption vary throughout the lifespan. Data from The National Survey on Drug Use and Health 2002-2018 (NSDUH) found that 26.3% of the population surveyed between the ages of 12 to 17 endorsed having used alcohol, with 9% consuming in the past month. Of those reporting alcohol consumption in the past month, 4.7% endorsed binge drinking, which is defined by the NSDUH as consuming five or more drinks on a single occasion at least once in the past month. An additional 0.5% endorsed heavy drinking, which is defined by the NSDUH as at least 5 binge drinking days in the past month. For individuals 18 to 25 years old, 79.7% endorsed having used alcohol, with 55.1% consuming alcohol in the past month. Of those consuming alcohol in the past month, 34.9% endorsed binge drinking and 9% endorsed heavy drinking. For individuals aged 26 and older, 87.3% endorsed having consumed alcohol in their life, with 55.3% consuming alcohol in the past month. A total of 25.1% % of individuals reporting consuming alcohol in the past month endorsed binge drinking and 6.2% endorsed heavy drinking. As people age, there tends to be a reduction in binge drinking and heavy drinking, with 18.1% of persons 50 or older endorsing binge drinking in the past month, and 4.6% endorsing heavy drinking. Per the Diagnostic and Statistical Manual of Mental Disorders – 5th Edition (DSM-*5*), Alcohol Use Disorder (AUD) is diagnosed by presence of behavioral and physical symptoms, which may include craving, tolerance, and withdrawal (American Psychiatric Association, 2013). The twelve-month prevalence of AUD varies by age, with 12- to 17-year-olds at 4.6% and nearly doubles 8.5% t for those 18 and older(American Psychiatric Association, 2013). Rates of AUD for men (12.4%) are consistently much higher than for women (4.9%). Similar to rates of consumption across the lifespan, twelve-month prevalence of

AUD decreases in middle age, with greatest rates in people 18- to 29-years-old (16.2%) and lowest among people age 65 years and older with only 1.5% (American Psychiatric Association, 2013).

HEALTH OUTCOMES ASSOCIATED WITH ALCOHOL CONSUMPTION

Recent epidemiological studies have established a positive linear relationship between alcohol consumption and an increased risk of disease or death, with over 40 ICD-10 diagnoses being attributable to alcohol (Rehm et al., 2017). A U-shaped relationship between alcohol consumption and some health outcomes (e.g., cardiovascular disease, gastrointestinal disease, hepatic disease, etc.) is generally accepted, although there is variability among studies regarding the amount of alcohol consumption that leads to poor health outcomes (Gronbaek, 2009). Individuals who have never consumed alcohol, or lifetime abstainers, tend to have slightly higher all-cause mortality rates than those who consumed alcohol even after adjusting for age and other confounding variables (smoking status, diabetes, cardiovascular disease, etc.), and these individuals also have greater rates of cardiovascular disease compared to drinkers (Bernards, Graham, Kuendig, Hettige, & Obot, 2009; Choi, DiNitto, Marti, & Choi, 2016; de Labry et al., 1992; Wannamethee & Shaper, 1997).

Heavy alcohol consumption is not a uniformly defined term. It may refer to greater than five drinks consumed per day (*2018 National Survey on Drug Use and Health: Methodological summary and definitions*, 2019), although it is defined elsewhere as greater than >7 drinks/week for women and >14 drinks/week for men . Heavy consumption of alcohol can lead to a number of diseases including steatosis, alcoholic hepatitis, fibrosis, cirrhosis, pancreatitis, cardiomyopathy, arrhythmias, stroke, hypertension, compromised immune system, and an increased risk of cancer (García, Blasco-Algora, & Fernández-Rodríguez, 2015; Schuckit, 2006).

In persons with AUD, a threefold higher risk of death has been identified (Schwarzinger, Thiebaut, Baillot, Mallet, & Rehm, 2017). Chronic AUD can affect nearly every organ system, especially the liver and central and peripheral nervous systems (García et al., 2015; Suzanne & Kril, 2014). Findings from the Global Burden of Disease Study, which examined data from 195 countries from 1990-2016, revealed that alcohol use alone accounted for 2.2% of age-standardized female deaths and 6.6% of age-standardized male deaths, with alcohol being the leading risk factor globally in 2016 for individuals between the ages of 15-49 (Griswold et al., 2018). Those data also demonstrated that risk of all-cause mortality, especially related to cancers, rises as alcohol consumption increases, and that only abstinence was associated with minimizing health risk (Griswold et al., 2018). Similarly, binge drinking at least one day per week was associated with an increased risk of all-cause and cancer-specific mortality (Xi et al., 2017). Individuals engaging in binge drinking are also more likely to use other illicit substances, have higher rates of depression, and more mental health related hospitalizations (Han, Moore, Sherman, Keyes, & Palamar, 2017). Despite data regarding potential deleterious effects of alcohol consumption on health outcomes (particularly binge drinking or heavy alcohol consumption) it continues to be widely used across the lifespan.

Not all alcohol consumption is associated with poor health outcomes, however, as there is a sizeable body of literature suggesting potential beneficial effects of moderate alcohol consumption. According to the latest data from the U.S. Department of Health and Human Services and the U.S. Department of Agriculture's Dietary Guidelines for Americans 2015-2020, moderate drinking is defined as up to one drink per day for women and up to two drinks per day for men. A meta-analysis of 15 studies found that moderate alcohol consumption may have some benefit for health outcomes, largely thought to be related to positive cardiovascular effects

(Anstey, Mack, & Cherbuin, 2009). Similarly, in a large scale investigation (*N*=333,247) moderate alcohol consumption was associated with a lower risk of mortality for all causes and cardiovascular disease (Xi et al., 2017).

ALCOHOL USE AND COGNITION

A meta-analysis (Neafsey & Collins, 2011) that reviewed 143 papers spanning from 1977 to 2011 detailed the research on alcohol use and cognition, dividing it into two different phases: studies conducted between 1977-1997 (Phase I) and those done between 1998-2011 (Phase II). Studies conducted in Phase I used robust neuropsychological measures, a younger age population (ages 18-50 years), and were concerned more with determining current effects on cognition. Phase I studies revealed mixed findings, with earlier studies indicating moderate drinking impaired cognition, while later studies failing to replicate the findings, and instead finding no differences between drinkers and non-drinkers. For example, cognitive performance on tests of executive functioning and abstraction (e.g., Wisconsin Card Sorting Test [WCST], Halstead Category Test) was negatively associated with the amount of alcohol consumed in a sample of 102 men from rural California (Parker & Noble, 1977). This effect was particularly strong in heavy drinkers, although a modest effect was found in non-heavy drinkers. A common issue in studies such as this one is that drinking patterns are poorly defined. The mean alcohol consumption in the study conducted by Parker and Noble (1977) was 42 ± 23 mL of "absolute alcohol" (which is roughly equivalent to one standard drink) per drinking occasion, with the mean number of drinking occasions at 204 ± 222 per year. The authors provide little detail on what constitutes a "drinking occasion," although it appears there may be multiple drinking occasions per day based upon the standard deviation reported. In a replication study, similar results were found for the overall sample (*N*=106 men), but different from the original study,

individuals whose drinking consumption was greater than "alcoholic" levels (defined as less than 58 L/year, or roughly 25 drinks per week or 3.5 drinks per day) were excluded, providing further evidence to support the negative relationship described in the original study was more due to moderate drinking (MacVane, Butters, Montgomery, & Farber, 1982). While these two studies established a negative relationship between moderate drinking and recent cognitive performance, the effect sizes were small (*r*'s = .22–.33), and the studies were conducted in relatively small samples (MacVane et al., 1982; Parker & Noble, 1977).

Later investigations in Phase I (from the Neafsey and Collins [2011] review) that used larger samples failed to replicate the findings from the earlier studies. In a sample of 1,367 male and female drinkers (mean age of 38±13 years; mean years of education 13±3 years) residing in Detroit, participants were selected using a random digit dialing procedure that screened households for eligible respondents (those 18 years or older and employed at least 30 hours per week). There was no relationship between total amount of alcohol consumed over the lifetime and recent cognitive abilities, as measured by performance on the Shipley Institute of Living Scale (SILS); however, there was a significant negative relationship between current alcohol consumption and cognitive performance, but only in men (Parker, Parker, Brody, & Schoenberg, 1983). Alcohol use was self-reported during an interview with a trained interviewer, in which participants were asked about their current and past drinking behavior. In another large, community based study examining correlates of cognitive functioning in older adults (*n*=3,682) there was no significant relationship between alcohol consumption and current cognitive functioning (Scherr et al., 1988). Cognition domains tested included memory, attention, and orientation, with each domain consisting of one measure. This study lacked reports of previous drinking behavior, as found in Parker et al. (1983), MacVane et al. (1982), and Parker and Noble

(1977), which is an important consideration in an elderly population, as alcohol consumption typically decreases with age. Not all studies conducted in the later part of Phase I relied on fewer cognitive measures, which may reduce the specificity of identifying cognitive domains that could be differentially affected.

In a larger sample, 1,308 participants from a prospective longitudinal study (Rutgers Health and Human Development Project) were examined to further explore the relationship between moderate drinking and cognition (Bates & Tracy, 1990). The findings revealed no effect of moderate drinking on cognitive performance in young adults. This study had two strengths: first, eight cognitive tests were used including, measures from the Halstead-Reitan Neuropsychological Test Battery (Category Test and Trail Making Test A & B [TMT A & B]), the SILS (Vocabulary and Verbal Abstraction), the Wechsler Adult Intelligence Scale – Revised (Block Design and Digit Span), Thurstone's Primary Ability Tests (Spatial Relations test), and Digit-Symbol Substitution Test (DSST), which is important as the domains these tests measure have previously shown to be affected by alcohol use (e.g., executive functioning, visuospatial abilities, and memory); second, alcohol use was examined as a continuous variable, a technique not widely used due to smaller samples and less specific questions related to alcohol consumption. While this study found no relationship between moderate alcohol consumption and cognition, it was conducted in a younger population which limited the generalizability to older populations and of exploring the longer-term effects of moderate alcohol consumption. Longer term effects of alcohol consumption on cognition were explored more in Phase II studies.

In Phase II, as Neafsey and Collins (2011) define it, neuropsychological measures were replaced with mental status examinations and older populations (aged greater than 55 years) were used. These studies relied mostly on hazards ratios to determine relative risk for

development of dementia or cognitive impairment. These studies provide conflicting information, with some studies finding beneficial effects from moderate consumption and other studies finding no effect or even deleterious effects of moderate levels of alcohol consumption with regards to cognition. The Rotterdam Study is a large (*N*=14,926; as of 2008) ongoing (since 1990), prospective population–based study of men and women (aged 45 years or older), targeting factors (e.g., alcohol consumption, physical activity, social activity, genetics, etc.) that contribute to development of cardiovascular, endocrine, hepatic, neurological, ophthalmic, psychiatric, dermatological, oncological, and respiratory diseases (Hofman et al., 2007; Hofman et al., 2013). Individuals without a diagnosis of dementia at baseline (1990-1993) and who had complete alcohol data (*n*=5,359), from the first cohort (*N*=7,983; all aged 55 years or older) who regularly consumed alcohol were compared to those who did not consume alcohol to compare risk of developing dementia (Ruitenberg et al., 2002). Cognitive performance was measured using the MMSE, and diagnosis of dementia was based upon MMSE score, examination by a neurologist, and interview with a caregiver. Results revealed that participants who consumed one to three drinks per day had significantly lower risk of developing dementia, even after adjusting for age, sex, cardiovascular factors (e.g., BMI, blood pressure), and smoking status.

Similar results were found in The Cardiovascular Health Study (CHS) a large, population-based, multisite, longitudinal study consisting of (*N*=5,888) men and women aged 65 years or older who were not institutionalized, did not require a proxy for consent, and were not in a wheelchair at the time of enrollment (1989-1990) that were followed over the course of three years in order to identify new risk factors for cardiovascular disease (CVD), with particular interest in modifiable or protective factors (e.g., BMI, alcohol consumption), and quantify the relative impact of known risk factors (e.g., hyperlipidemia, hypertension, etc.) on development

and severity of CVD (Fried et al., 1991). Using a nested case-control method, 373 participants that developed dementia over the course of follow up were compared with 373 participants without dementia to explore the relationship between alcohol consumption and risk for dementia (Mukamal et al., 2003). Cognition was assessed using the MMSE at baseline and the 100-point Modified Mini-Mental State Examination and the DSST at follow-up. Compared to abstainers, consumption of one to six alcoholic beverages per week was associated with a reduced risk of incident dementia (Mukamal et al., 2003). Similar results were found using a sample of participants (*n*=972) from the Cardiovascular Risk Factors Aging and Dementia (CAIDE) Study, which revealed positive relationships between alcohol consumption in midlife (between ages 47-48) and later (between ages 70-72), and better cognitive performance (in late life) on measures of short-term memory (measured by immediate recall of a 10-item verbal word list), psychomotor speed (measured using a grooved peg board task and a digit substitution task), and executive functioning (measured using the difference in times between the interference trial and the color trial on a Stroop test), compared to non-drinkers (Ngandu et al., 2007). Consumption of alcohol was categorized in three groups: those who never drank (not clearly defined if this group included former drinkers), those who drank infrequently (defined as "less frequently than once per month"), and those who drank frequently (defined as "once per month or more often"). Alcohol consumption was measured slightly differently at follow-up, as the participants were additionally asked the quantity and type of alcohol consumed over the previous week, but no comparisons could be made between the baseline questions as they were different.

In a sub-sample (*n*=1,098) of the Monogahela Independent Elders Survey (*N*=1,681), a prospective epidemiologic study of dementia in a rural community in Pennsylvania, participants were categorized based upon six different drinking patterns (not drinking currently, less than

once a month, once a month or more but less than weekly, weekly (including weekends only), more than weekly but less than daily, and daily) in order to explore the relationship between alcohol consumption and cognition in older adulthood (Ganguli, Vander Bilt, Saxton, Shen, & Dodge, 2005). There were very few heavy drinkers (e.g., defined in this study as daily drinking >1) in this cohort. Based upon results from a trajectory analysis, participants were grouped into one of three groups: no drinking, minimal drinking (once a month or less), and moderate drinking (more than once a month). Cognitive functioning was assessed using neuropsychological tests from the Consortium to Establish a Registry for Alzheimer disease (CERAD), which is used to measure cognitive performance in multiple domains known to be affected in dementia. The neuropsychological measures included the following: the MMSE, TMT A & B, Word List Learning and Delayed Recall, Story Immediate Retell and Delayed Recall, Initial Letter and Category Fluency, 15-item CERAD version of the Boston Naming Test, CERAD Constructional Praxis, and Clock Drawing. Compared to no drinking, minimal drinking and moderate drinking were associated with less decline on the MMSE and TMT A&B, and when former drinkers were compared to life-long abstainers, the results former drinkers had greater decline (Ganguli et al., 2005). The practice to re-run the analyses by separating the former drinkers from the life-long abstainers, a practice that is not frequently done, is an issue that has been raised as a criticism of research in this field, and one possibility for variation in findings across studies (Mukamal et al., 2003; Neafsey & Collins, 2011).

Deciding to include former drinkers, some of which are referred to as “sick quitters” (e.g., individuals who abstain from alcohol use because of high medical burden) in the same category as abstainers has raised questions regarding the generalizability and interpretation of results from studies which use abstainers as a reference group. Mukamal et al. (2003) completed

separate analyses comparing former drinkers and quitters (i.e., participants that quit drinking during the course of follow-up) to lifetime abstainers in participants from the CHS cohort and found that former drinkers and quitters had between 20% and 60% higher odds of dementia. However, Neafsey and Collins (2011) found that even when former drinkers were excluded from the reference group there was still a protective effect of drinking with regard to risk of dementia or cognitive decline.

Similar to cardiovascular health outcomes, a U-shaped association between alcohol and cognition was found by Anstey et al. (2009). Moderate alcohol consumption has been associated with a reduced risk of dementia, especially for men (Liu et al., 2019). In a large study examining the relationship between alcohol consumption and cognitive functioning (measured with the MMSE, a visual memory task, a 10-list word learning task, and TMT-B) in a cohort of community dwelling older adults (N = 1624, mean age ± SD = 73.2 ± 9.3 years) alcohol data were collected over the course of four years (Reas, Laughlin, Kritz-Silverstein, Barrett-Connor, & McEvoy, 2016). Results revealed an inverted U-shaped association with alcohol intake and visual memory, with those consuming alcohol moderately performing better on the Heaton Visual Reproduction Test and TMT-B relative to those abstaining or consuming heavy amounts of alcohol (Reas et al., 2016). Midlife drinking was related to the risk of mild cognitive impairment (MCI) in older age in a U-shaped fashion, yet no significant relationship was found for dementia (Anttila et al., 2004; Rehm, Hasan, Black, Shield, & Schwarzinger, 2019). Similarly, individuals who were abstinent from alcohol or who consumed alcohol heavily in their midlife were twice as likely to have MCI compared to those who drank moderately (Hui et al., 2019). Changes in brain structure have been observed in heavy alcohol use, which may account for the increased risk of dementia (Rehm et al., 2019; Sullivan & Pfefferbaum, 2019). Reduced

total brain volume, hippocampal atrophy, and white matter integrity, specifically in the anterior corpus callosum, was associated with higher levels of alcohol consumption, even after accounting for demographic variables, history of depression, and cardiovascular risk (Topiwala et al., 2017). Similarly, in a large community cohort (*n*=1848), alcohol consumption was associated with hippocampal volume reduction, in participants aged 50 years or older (Naglich, Van Enkevort, Adinoff, & Brown, 2018)

HEAVY ALCOHOL USE AND ASSOCIATED NEUROCOGNITIVE DISORDERS

People with alcohol related liver dysfunction are at an increased risk of developing a serious and potentially fatal neurologic disorder known as hepatic encephalopathy (HE) (Butterworth, 2003). The liver is responsible for purifying blood by removing toxins, including neurotoxins. Over the course of time, in patients with chronic heavy alcohol use, the number of hepatocytes, the liver cells responsible for removing toxic substances, decreases, thus resulting in an increase of toxic substances in the body (Butterworth, 1995; Butterworth, 2003). Two specific neurotoxic substances have been identified and studied thoroughly, ammonia and manganese (Butterworth, 2002; Lockwood, Weissenborn, & Butterworth, 1997). Build-up of these chemicals leads to the development of HE. Patients with hepatic encephalopathy suffer from changes in mood and personality, psychiatric conditions such as depression and anxiety, sleep disturbances, severe cognitive deficits, and motor dysfunction, specifically asterixis, a type of myoclonus primarily affecting the hand and wrist (Agarwal & Baid, 2016; Butterworth, 2003). In patients with HE the severe neurocognitive and motor deficits usually resolve as the disease is treated, although some cognitive deficits may still be present after remission.

Several investigators have described the neurocognitive characterization of and detection of HE both acutely and chronically. McCrea et al. examined differences in performance on

neuropsychological tests in 20 patients with liver disease and age, sex, education, and 20 alcohol use history matched controls (McCrea, Cordoba, Vessey, Blei, & Randolph, 1996). Results revealed deficits in complex attention and fine motor skills in individuals with liver disease compared to controls. A review of the literature by Weissenborn, Ennen, Schomerus, Rückert, and Hecker (2001) found similar results, with the addition of visuospatial deficits. Deficits in memory have also been observed in patients with hepatic encephalopathy, although these findings are inconsistent across studies (Bahceci, Yildirim, Karincaoglu, Dogan, & Sipahi, 2005; Randolph et al., 2009).

Memory impairments in chronic heavy alcohol use can also associated with a specific neurocognitive disorder. Korsakoff syndrome (KS) is a severe neurocognitive disorder that is most commonly associated with a long history of heavy AUD. The etiology of KS is related to a deficiency of thiamine, while the neuropathology of KS involves atrophy of the mammillary bodies and damage to the thalamus and hypothalamus (Kril & Harper, 2012). As a result of damage to these areas, affected patients present with dense amnesia and a tendency to confabulate on tests of memory (Butters, 1985). Korsakoff syndrome is usually preceded by a case of Wernicke encephalopathy (WE), with 80-90% of people with WE developing KS, referred to as Wernicke-Korsakoff syndrome (WKS) (Martin, Singleton, & Hiller-Sturmhofel, 2003). WKS is characterized by a clinical triad, including changes in mental status (e.g., confusion), ataxia, and the presence of nystagmus (Arts, Walvoort, & Kessels, 2017). Additionally, patients with WKS may experience peripheral neuropathy, tachycardia, and orthostatic hypotension, which could result in syncope (Arts et al., 2017). If WKS is detected early enough and treatment of thiamine is provided, patients usually recover some cognitive functioning, although impairments in memory, visuospatial, and attention often persist to some

degree (Butters & Brandt, 1985; Day, Bentham, Callaghan, Kuruvilla, & George, 2013). Alcohol related deficits in visuospatial and attention may not be exclusive WKS patients, as these are seen in patients with long-term heavy alcohol use (Butters & Brandt, 1985; Sullivan & Pfefferbaum, 2019).

Binge drinking has also been associated with changes in brain structure and poorer cognitive outcomes (Sun et al., 2018), though it may have different effects on cognition and brain structure compared to other rates of consumption. Higher rates of binge drinking are typically seen in males, and in young adulthood, although recently there has been a reported increase in binge drinking in older adulthood (Han et al., 2017). In young adults, binge drinking is associated with thinner and lower volumes in prefrontal cortex and cerebellar regions (Cservenka & Brumback, 2017) and areas of the temporal lobe (Thayanukulvat & Harding, 2015). Performance on cognitive measures has also been found to be poorer in binge drinkers, as many perform worse on executive functioning and memory tasks compared to moderate drinkers (Amrani, De Backer, & Dom, 2013; Sun et al., 2018). Less is known about the cognitive effects of binge drinking in older adult populations (Rehm et al., 2019), and it is an area that needs to be explored further.

There are a wide range of findings related to the effects of alcohol on cognitive outcomes. Many of the studies detailed above rely on single points of data collection for alcohol use, or retrospective accounts of alcohol use. Amounts of alcohol consumed are quantified in different manners depending on the study, with little consistency. In order to address some of the conflicting findings, use of a comprehensive longitudinal database is most suited to investigate the discrepancies. The Wisconsin Longitudinal Study is a database with almost 60 years of sociodemographic, medical, psychiatric, psychological, alcohol, and cognitive data. Use of this

database allowed for an examination of alcohol's role on cognition and to contribute to a topic that is of great clinical importance but has very mixed findings.

APPENDIX B: HYPOTHESES AND AIMS

Overall Aim: To determine the relationship between the amount of alcohol consumption in middle to later adulthood and cognition in older adulthood.

Aim 1: To investigate the relationship between quantity of alcohol consumed in middle adulthood to later adulthood and cognitive functioning in older adults

Hypothesis 1.1: Greater average cumulative quantity of alcohol consumption will be associated with poorer cognitive functioning in older adulthood.

Hypothesis 1.2: Greater alcohol consumption in middle adulthood will be associated with poorer cognitive functioning in older adulthood.

Aim 2: To investigate the relationship between consistent drinking patterns throughout the lifespan and cognition in older adulthood.

Hypothesis 2.1: Individuals who consistently consumed heavier amounts of alcohol throughout adulthood will have poorer cognitive functioning compared to individuals who consistently consumed lower levels of alcohol throughout adulthood.

Hypothesis 2.2: Individuals who never consumed alcohol will have poorer cognitive functioning compared to individuals consistently consuming moderate levels of alcohol throughout their adulthood.

Hypothesis 2.3: Individuals who consistently consumed heavier amounts of alcohol throughout their lifespan will have poorer cognitive functioning compared to individuals who have never consumed alcohol

Hypothesis 2.4: Individuals who reported binge drinking episodes will have poorer cognitive functioning compared to individuals who did not binge.

Aim 3: To investigate the relationship between changing drinking patterns during the lifespan and cognition in older adulthood.

Hypothesis 3.1: Participants who reported heavy drinking at either time point one or time point two but abstinence at time point three will have better cognitive functioning than consistent heavy drinkers.

Hypothesis 3.2: Participants who had never consumed alcohol at time point one but reported drinking at time point two or three will have better cognitive functioning than lifetime abstainers.

APPENDIX C: ADDITIONAL ANALYSES, AND RESULTS

Additional Analyses

Data Analysis

Descriptive statistics, including means and standard deviations for continuous variables, and frequencies and percentages for categorical variables, were examined to determine if statistically significant differences in demographics (e.g., sex, years of education, BMI, histories of hypertension, high cholesterol, or depression) existed between groups in 1992, considered the first year of data collection or "baseline" for the present study. Additionally, prior to conducting the primary analyses, a power analysis was performed. Results from the power analysis on an *F* test, suggested that for a small effect size ($f^2 = 0.10$), holding alpha = 0.05 and power = 0.80, the minimum sample size required is $n = 159$. As such, the study was well powered.

Aim 2: *To investigate the relationship between consistent drinking patterns throughout the lifespan and cognition in older adulthood.*

To further quantify and categorize the relationships between varying amounts of alcohol consumption throughout the lifespan on cognition in older adulthood, groups were formed based upon amounts of alcohol consumption. Participants who denied ever consuming alcohol at each timepoint were classified as "lifetime abstainers." Use of this classification will serve as means to compare participants who have never consumed alcohol to participants that have consumed alcohol in order to explore possible group differences in drinkers and lifetime abstainers.

For this study, consumption between 1-56 drinks/month, regardless of sex, was categorized as "moderate drinking." Participants who reported this pattern of drinking at each time point were grouped together and classified as "consistent moderate drinkers." Participants

that consumed more than 56 drinks per month were classified as “heavy drinkers,” and those that reported that level of drinking at each time point were classified as “consistent heavy drinkers.”

A multiple linear regression analysis was used to determine the relationship between alcohol consumption group and global cognition. Two dummy variables were created with lifetime moderate drinkers serving as the reference group for both, and lifetime abstainers and lifetime heavy drinking as the comparisons. Sex, years of education, BMI, and history of depression, history of hypertension, and history of high cholesterol were added as covariates. Results were deemed statistically significant at $p < 0.05$. Statistical analyses were conducted using SPSS version 26.0 (SPSS Inc., Chicago, IL).

In order to evaluate the relationship between consistent drinking patterns and performance on individual measures of cognition a multivariate analysis of covariance (MANCOVA) was used. The predictor in the model was drinking pattern and the outcome variables were each of the cognitive measures (i.e., Similarities, immediate recall, delayed recall, digit ordering, and categorical fluency) with sex, years of education, BMI, history of depression, history of hypertension, and history of high cholesterol added as covariates.

Binge drinking behavior was assessed separately using the question “Number of times you had five or more drinks on the same occasion during the last month?” Participants that endorsed this item at least once were classified as “binge drinkers” based on data from the 2018 National Survey on Drug Use and Health (NSDUH), where binge drinking was defined as having one day of consuming five or more drinks in a single occasion during the past month.

A multiple linear regression analysis was used to determine the relationship between binge drinking and global cognition. Binge drinkers were compared to non-binge drinkers, and sex, years of education, BMI, and history of depression, history of hypertension, and history of

high cholesterol were added as covariates. In order to evaluate the relationship between binge drinking and performance on individual measures of cognition a MANCOVA was used. The predictor in the model was history of binge drinking and the outcome variables were each of the cognitive measures (i.e., Similarities, immediate recall, delayed recall, digit ordering, and categorical fluency) with sex, years of education, BMI, history of depression, history of hypertension, and history of high cholesterol added as covariates.

Aim 3: *To investigate the relationship of changing drinking patterns during the lifespan and cognition older adulthood.*

A major area of interest concerns participants who endorse heavy drinking at one point and then report abstinence at a later point. These participants were categorized as "former heavy drinkers" and were compared with lifetime heavy drinkers to determine if there is a cognitively beneficial effect of abstinence. Similarly, participants that reported never consuming alcohol at time point one but reported any drinking at time point two or three were categorized as former abstainers and compared to lifetime abstainers to determine if there was any effect of changing their drinking pattern.

A multiple linear regression analysis was used to determine the relationship between changing drinking patterns and global cognition. Two separate regressions were performed, with one comparing former heavy drinkers to lifetime heavy drinkers and the other comparing former abstainers to lifetime abstainers. Sex, years of education, BMI, history of depression, history of hypertension, and history of high cholesterol were added as covariates. In order to evaluate the relationship between changing drinking patterns and performance on individual measures of cognition a MANCOVA was used for both former abstainers and former heavy drinkers. The

predictor in each model was drinking pattern and the outcome variables were each of the cognitive measures (i.e., Similarities, immediate recall, delayed recall, digit ordering, and categorical fluency) with sex, years of education, BMI, history of depression, history of hypertension, and history of high cholesterol added as covariates.

Results

Aim 2: To investigate the effect of consistent drinking patterns throughout the lifespan on cognition in older adulthood

A random sample of 100 participants from the consistent moderate drinking group (*n*=1,874) was taken and used for comparisons because group sizes were disproportionate. The random sampled was made by using a random number generator and assigning the values (1-100) randomly to 100 participants in the consistent moderate drinking group and assigning those 100 participants to a new group to use in subsequent analyses. This was done so as to create a more balanced model. As Shaw and Mitchell-Olds (1993) suggested, when there are more observations for a particular cell in the design matrix (or group) relative to another group, there is more information on its effect. As such, the estimates of effects cannot be assumed to be independent and main effects cannot be clearly distinguished. Independent samples *t*-tests and chi-square analyses were conducted using the random sample of moderate drinkers (*n*=100) and the consistent moderate drinkers to ensure that the random sample of *n* = 100 moderate drinkers did not differ in a statistically significant way from the entire "consistent moderate drinking" group of *n* = 1874. There were no significant differences on any variables (all *ps*>0.05) between the random sample of consistent moderate drinkers and the consistent moderate. The consistent heavy drinkers, consistent moderate drinkers and the lifetime abstainers did not differ in any

variable (all *ps*>0.05) except for sex (p<0.001), as there were more females in the lifetime abstainer group and fewer female in the consistent heavy drinking group (See Table 4).

A multiple linear regression analysis was conducted to evaluate the relationship between consistent heavy drinking (n=71), lifetime abstinence (n=50) and consistent moderate drinking (n=78) on global cognition compared. Omnibus results were statistically significant (F[8,190]=5.374, p<0.001, R^2=0.185). The predictors in the model were history of drinking, sex, years of education, history of hypertension, history of high cholesterol, history of depression, and body mass index. Years of education (b=0.101; p<.001) and sex (b=0.194; p=0.035) were statistically significant predictors of global cognition, whereas lifetime abstinence compared to consistent moderate drinking (b= –0.131; p=0.220, d=0.33), consistent heavy drinking compared to consistent moderate drinking (b= –0.086; p=0.395. d=0.46), history of depression (b=0.093; p=0.310), body mass index (b=0.015; p=0.050), history of hypertension (b= –0.042; p=0.639), and history of high cholesterol (b=-0.000; p=0.969) were not non-significant predictors of global cognition (See Table 5).

A multiple linear regression analysis was conducted to evaluate the relationship between reported heavy drinking (n=71) at all three time points compared to reported lifetime abstinence (n=50) on global cognition. Omnibus results were statistically significant (F[7,113]=3.695, p=0.001, R^2=.186). The predictors in the model were history of drinking, sex, years of education, history of hypertension, history of high cholesterol, history of depression, and body mass index. Years of education (b=0.118; p<.0001) was a statistically significant predictor of global cognition, whereas consistent heavy drinking compared to lifetime abstinence (b= –0.28; p=0.830, d=0.74), history of depression (b= –0.005; p=0.966), sex (b=0.072; p=0.050), body mass index (b=0.015; p=0.163), history of hypertension (b= –0.071; p=0.566), and history of

high cholesterol (b= –0.001; p=0.966) were not non-significant predictors of global cognition (See Table 6).

In order to determine if consistent drinking patterns had an effect on cognitive performance at the individual test level a MANCOVA was conducted. The dependent variables in the model were categorical fluency, digit span, similarities, immediate word recall, and delayed word recall with drinking pattern (lifetime abstainers [n=50] and consistent heavy drinkers [n=71] compared to consistent moderate drinkers [n=78]), years of education, sex, history of hypertension, history of high cholesterol, body mass index, and history of depression as predictors. Pillai's Trace criterion suggested that years of education had a statistically significant effect (V = 0.21, F[5, 186] = 9.86, p <0.001) on performance on each cognitive task, while drinking pattern (V = 0.03, F[10, 374] = 0.506, p =0.89, η^2 = 0.13), sex (V = 0.06, F[5, 186] = 2.17, p = 0.06), BMI (V = 0.03, F[5, 186] = 0.90, p = 0.49), history of depression (V = 0.03, F[5, 186] = 1.18, p = 0.32), history of hypertension (V = 0.02, F[5, 186] = 0.90, p = 0.49), and history of high cholesterol (V = 0.02, F[5, 186] = 0.64, p = 0.89) had a statistically non-significant effect on cognitive performance, while (Table 7).

A MANCOVA was conducted in order to determine if consistent heavy drinking compared to lifetime abstinence had any effect on performance on individual cognitive tasks. The dependent variables in the model were categorical fluency, digit span, similarities, immediate word recall, and delayed word recall with consistent heavy drinkers (n=71) compared to lifetime abstinence (n=50), years of education, sex, history of hypertension, history of high cholesterol, body mass index, and history of depression as predictors. Pillai's Trace criterion suggested that years of education had a statistically significant effect (V = 0.238, F[5, 109] = 6.793, p <0.001) on performance on each cognitive task, while consistent heavy drinking

compared to lifetime abstinence (V = 0.003, F[5, 109] = 0.073, p = 0.996, η^2 = 0.003), sex (V = 0.015, F[5, 109] = .342, p = 0.886), BMI (V = 0.026, F[5, 109] = 0.575, p = 0.719), history of depression (V = 0.028, F[5, 109] = .638, p = 0.671), history of hypertension (V = 0.038, F[5, 109] = 0.872, p = 0.502), and history of high cholesterol (V = 0.037, F[5, 109] = 0.832, p = 0.530) had a statistically non-significant effect on cognitive performance, while (Table 8).

A multiple linear regression analysis was conducted to evaluate the relationship between a history of binge drinking (i.e., if the participant ever endorsed a binge episode; [n=720]) on global cognition compared to participants without history of binge drinking (n=2,728; See Table 9). Omnibus results were statistically significant (F[7,3400]=100.74, p<0.001, R^2=0.110). The predictors in the model were history of binge drinking, history of depression, sex, years of education, body mass index, history of hypertension, and history of high cholesterol. Years of education (b = 0.10; p<.001), sex (b = 0.29; p<0.001), and history of hypertension (b = 0.05; p = 0.02) were found to be significant predictors of global cognition, while history of binge drinking compared to non-history of binge drinking (b = 0.03; p = 0.31, d=0.27), history of depression (b = 0.04; p = 0.05), body mass index (b = 0.001; p = 0.68), and history of high cholesterol (b = 0.004; p = 0.11) were non-significant predictors of global cognition (See Table 10).

A MANCOVA was conducted in order to determine if history of binge drinking compared to non-history of binge drinking had any effect on performance on individual cognitive tasks (Table 11). The dependent variables in the model were categorical fluency, digit span, similarities, immediate word recall, and delayed word recall with history of binge drinking (binge drinkers [n=720] compared to non-binge drinkers [n=2,728]), history of depression, sex, years of education, history of hypertension, history of high cholesterol, and body mass index as predictors. Pillai's Trace criterion suggested that history of depression (V = 0.003, F[5, 3436] =

72.6, $p < 0.001$), sex ($V = 0.08$, $F[5, 3436] = 58.8$, $p < 0.001$) years of education ($V = 0.18$, $F[5, 3436] = 149.58$, $p < 0.001$), body mass index ($V = 0.008$, $F[5, 3436] = 5.4$, $p < 0.001$), and history of hypertension ($V = 0.004$, $F[5, 3436] = 3.00$, $p = 0.01$) had significant effect on cognitive performance whereas, history of binge drinking ($V = 0.002$, $F[5, 3436] = 1.42$, $p = 0.22$) and history of high cholesterol ($V = 0.002$, $F[5, 3436] = 1.06$, $p = 0.38$) were not statistically significant.

Aim 3: To investigate the effect of changing drinking patterns during the lifespan on cognition in older adulthood

A multiple linear regression was conducted in order to evaluate the relationship between ceasing heavy drinking and becoming abstinent (n=31) at either time point two or time point three compared to consistent heavy drinking (n=71) on global cognition (See Table 12). Omnibus results were statistically significant ($F[7,94]=3.071$, p=0.006, R^2=.186). The predictors in the model were drinking pattern, years of education, history of depression, sex, body mass index, history of hypertension, and history of high cholesterol. Years of education (b = 0.10; p<.001) was a statistically significant predictor of global cognition, whereas former heavy drinking compared to consistent heavy drinking (b = -0.25; p=.0.07, d=0.39), history of depression (b = 0.10; p=0.47), sex (b = 0.09; p = 0.54), body mass index (b = -0.006; p = 0.64), history of hypertension (b = -0.12; p = 0.41), and history of high cholesterol (b = -0.005; p = 0.65) were not non-significant predictors of global cognition (See Table 13).

In order to evaluate the relationship between ceasing heavy drinking compared to consistent heavy drinking on cognitive performance at the individual test level a MANCOVA was conducted. The dependent variables in the model were categorical fluency, digit span, similarities, immediate word recall, and delayed word recall with drinking pattern (former heavy

drinkers [*n*=31] compared to consistent heavy drinkers [*n*=71]), years of education, sex, history of hypertension, history of high cholesterol, body mass index, and history of depression as predictors. Pillai's Trace criterion suggested that years of education ($V = 0.209$, $F[5, 90] = 4.767$, $p = 0.001$) had a statistically significant effect on performance on each cognitive task, while drinking pattern ($V = 0.049$, $F[5, 90] = 0.925$, $p = 0.468$), sex ($V = 0.026$, $F[5, 90] = 0.480$, $p = 0.79$), body mass index ($V = 0.011$, $F[5, 90] = 0.195$, $p = 0.964$), history of depression ($V = 0.028$, $F[5, 90] = 0.520$, $p = 0.760$), history of hypertension ($V = 0.032$, $F[5, 90] = 0.598$, $p = 0.702$), and history of high cholesterol ($V = 0.014$, $F[5, 90] = 0.258$, $p = 0.935$) had a statistically non-significant effect on cognitive performance (See Table 14).

A multiple linear regression was conducted in order to evaluate the relationship between ceasing abstinence and drinking (*n*=47) at either time point two or time point three compared to lifetime abstinence (*n*=50) on global cognition (See Table 15). Omnibus results were statistically significant ($F[7,89]=4.207$, $p<0.001$, $R^2=0.249$). The predictors in the model were drinking pattern, years of education, history of depression, sex, body mass index, history of hypertension, and history of high cholesterol. Years of education ($b = 0.122$; $p<0.001$), sex ($b = 0.311$; $p = 0.024$), and history of high cholesterol ($b = 0.035$; $p = 0.019$) were statistically significant predictors of global cognition, whereas former abstinence compared to lifetime abstinence ($b = 0.019$; $p=0.0.886$, $d=0.61$), history of depression ($b = –0.050$; $p=0.710$), body mass index ($b = 0.008$; $p = 0.524$), and history of hypertension ($b = –0.024$; $p = 0.862$) were not non-significant predictors of global cognition (See Table 16).

In order to evaluate the relationship between ceasing abstinence and drinking (*n*=47) at either time point two or time point three compared to lifetime abstinence (*n*=50) on cognitive performance at the individual test level a MANCOVA was conducted. The dependent variables

in the model were categorical fluency, digit span, similarities, immediate word recall, and delayed word recall with drinking pattern (former abstainers [*n*=74] compared to lifetime abstainers [*n*=50]), years of education, sex, history of hypertension, history of high cholesterol, body mass index, and history of depression as predictors. Pillai's Trace criterion suggested that years of education ($V = 0.278$, $F[5, 85] = 6.538$, $p < 0.001$) and sex ($V = 0.122$, $F[5, 85] = 2.364$, $p = 0.046$) had a statistically significant effect on performance on each cognitive task, while drinking pattern ($V = 0.047$, $F[5, 85] = 0.846$, $p = 0.521$), body mass index ($V = 0.015$, $F[5, 85] = 0.251$, $p = 0.938$), history of depression ($V = 0.043$, $F[5, 85] = 0.759$, $p = 0.582$), history of hypertension ($V = 0.009$, $F[5, 85] = 0.161$, $p = 0.976$), and history of high cholesterol ($V = 0.106$, $F[5, 85] = 2.007$, $p = 0.86$) had a statistically non-significant effect on cognitive performance (See Table 17).

APPENDIX D: DISCUSSION, CLINICAL IMPLICATIONS, AND FUTURE DIRECTIONS

Discussion

There were no statistically significant relationships between consistent drinking patterns throughout the lifespan and global cognition or performance on individual cognitive tasks in older adulthood. Similarly, when accounting for changes in drinking patterns (i.e., heavy drinking to abstinent or abstinent to drinking) there were no statistically significant relationships between changes in drinking patterns and global cognition or performance on individual cognitive tasks in older adulthood. There was also no statistically significant relationship between binge drinking compared to non-binge drinking on global cognition or at the individual cognitive task level. When examining alcohol consumption as a continuous variable at each time point there was a statistically significant positive relationship between the amount of alcohol consumed and global cognition, however the findings were likely not clinically significant as the effect size was extremely small (b=0.001; p<.001, effect sizes r_s^2 = 0.0002, p = 0.30; (r_s^2 = 0.002, p = 0.004; r_s^2 = 0.005, p < 0.001).

Results from the current analysis are consistent with previous findings that identified non-significant relationships between alcohol consumption and cognition in adulthood (Bates & Tracy, 1990; Elwood et al., 1999; Heffernan et al., 2016; Scherr et al., 1988; Schinka et al., 2002). When total alcohol consumption over the previous month was used as a predictor of cognitive functioning there was no significant relationship (Scherr et al., 1988). Using multiple assessments of alcohol consumption over a six-year period, Elwood et al. (1999) found no relationship between alcohol consumption and cognitive functioning, as measured by

performance on four different measures, even in the heaviest of drinkers. This finding is consistent with the findings the current study, and the design was similar to that used in aim two.

When participants were categorized into groups based upon consistent drinking patterns there were no significant relationships between drinking patterns and global cognition or performance on individual cognitive tests. Similar to Elwood et al. (1999), this was true even in the heavy drinking group when compared to moderate drinkers and to abstainers, suggesting that consistently consuming heavy amount of alcohol, at least at the level in the current sample (approximately three drinks per day), does not appear to be related to changes in cognition compared to drinking moderately (less than half a drink per day) or abstaining completely. This finding is in direct contradiction of the continuity hypothesis proposed by Ryback (1971) which states that cognitive effects of alcohol consumption are on a spectrum with the most severe forms of impairment seen in Wernicke-Korsakoff Syndrome on one end to subtle deficits in social drinking. Others have questioned the validity of the continuity hypothesis (Parsons & Nixon, 1998) and the meta-analysis by Neafsey and Collins (2011) provided further evidence to negate this hypothesis, as a large number of studies (n=43) conducted between 1977 and 2011 found no statistically significant differences between drinkers and non-drinkers. Bates and Tracy (1990) found similar results, but in a college aged sample, and argued that a longitudinal study, following middle aged adults, was needed in order to validate the original findings for Parker and Noble (1977), as cognitive changes in younger populations may be too subtle, if present at all.

The present study used an older population from a longitudinal study and still failed to replicate the findings from earlier studies. It was hypothesized that there would be a negative relationship between binge drinkers and cognition when compared to non-binge drinkers based upon previous findings which revealed that binge drinkers were almost twice as likely to have

cognitive impairment in older adulthood (Virta et al., 2010) and worse performance on measures of executive functioning and memory (Amrani et al., 2013). Binge drinkers typically consume more alcohol than non-binge drinkers, even after accounting for reduced frequency, and have more negative health outcomes (Han, Moore, Ferris, & Palamar, 2019). Binge drinkers did not have a statistically significant difference in cognition compared to non-binge drinkers in the current study. This brings Ryback's continuity hypothesis more into question, as even in this group there were no significant differences in cognition.

Quality of cognitive measures used is also a consideration that needs to be taken into account when examining the results from the current study. As detailed in the meta-analysis by Neafsey and Collins (2011) many of the older studies, or "Phase I" studies, relied on more robust and sensitive measures of cognitive functioning that had been shown to be specifically impacted in studies of alcohol consumption at levels of an alcohol use disorder (e.g., memory, visuospatial abilities, executive functioning). Five total measures of cognition were used in the current study, and on analyses examining the relationship between consistent drinking patterns (e.g., consistent heavy drinking compared to consistent moderate drinking, consistent heavy drinking compared to lifetime abstinence, and history of binge drinking compared to no history of binge drinking) and performance on individual measures of cognition, no drinking patterns were statistically significant predictors of cognitive performance. Even using less robust measures has allowed for identification of meaningful relationships, as many of the studies predicting risk for cognitive decline as a function of alcohol consumption have used mental status examinations, such as the MMSE (Neafsey & Collins, 2011).

Future Directions

Continuing to study the relationship between alcohol consumption and cognition is an important endeavor as the research has identified such varied findings. Many of the previous studies, especially the larger ones, lack robust cognitive measures and measures of alcohol consumption. These factors would need to be considered and added to the study at inception, rather than in the middle of, or at the end of, the study as so many studies, including the present one has done. Inclusion of cognitive measures sensitive to detection of differences related to alcohol consumption (e.g., executive functioning, visuospatial) need to be included. Multiple points alcohol consumption also needs to be included. Use of technology, such as an app, to record alcohol consumption would provide more accurate alcohol data. Finally, having a diverse sample of participants (e.g., ethnically, educationally, etc.) would further enhance the generalizability of the findings.

TABLES

Table 4. Demographic Characteristics and Descriptive Statistics – Lifetime Abstainers, Consistent Moderate Drinkers and Consistent Heavy Drinkers

Demographic Characteristics and Descriptive Statistics

	Consistent Moderate Drinkers		Lifetime Abstainers		Consistent Heavy Drinkers	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
Age	71.09	0.87	71.14	0.90	71.07	0.88
Years of Education	13.69	2.12	13.86	2.34	14.27	2.43
Total Drinks (over past 30 days) – Baseline	13.52	19.96	-	-	78.84	33.51
Total Drinks (over past 30 days) – Time 2	16.44	24.61	-	-	88.87	39.22
Total Drinks (over past 30 days) – Time 3	17.08	28.19	-	-	92.28	39.40
Body Mass Index	28.39	4.85	29.28	6.18	28.11	5.21
	Frequency	**Percent**	**Frequency**	**Percent**	**Frequency**	**Percent**
Sex – Female/Male	43/35	55.1/44.9	35/15	70.0/30.0	20/51	28.2/71.8
History of Hypertension	47	62.7	26	52.0	22	31.0
History of High Cholesterol	39	53.3	23	46.0	38	53.5
History of Depression	27	36.0	20	40.0	21	29.6
History of Multiple Sclerosis	0	0.0	0	0.0	1	1.4
History of Parkinson's Disease	1	1.3	1	2.1	1	1.4
History of Stroke	4	5.3	0	0.0	2	2.8

Note. Total *n* (consistent moderate drinkers) = 75; Total *n* (lifetime abstainers) = 50; Total *n* (consistent heavy drinkers) = 71.

Table 5. Results from Regression Comparing Consistent Moderate Drinkers to Consistent Heavy Drinkers and Lifetime Abstainers

Regression Results

	B	**S.E.**	**ß**	***p***
Abstainers	-.131	.107	-.091	.220
Heavy Drinkers	-.086	.100	-.065	.395
History of Depression	.093	.091	.069	.310
Sex	.194	.091	.154	.035
Years of Education	.101	.017	.399	.000
BMI	.015	.008	.135	.055
History of Hypertension	-.042	.089	-.033	.639
History of High Cholesterol	.000	.009	.003	.969

Note. Model: $F(8,190) = 5.374$, $p < .001$, $R^2 = 0.185$

Table 6. Results from Regression Comparing Consistent Heavy Drinkers to Lifetime Abstainers

Regression Results

	B	**S.E.**	**ß**	***p***
Heavy Drinkers	-.028	.129	-.021	.830
History of Depression	-.005	.121	-.004	.966
Sex	.072	.128	.055	.576
Years of Education	.118	.024	.429	.000
BMI	.015	.011	.129	.163
History of Hypertension	-.071	.123	-.052	.566
History of High Cholesterol	-.001	.014	-.004	.966

Note. Model: $F(7,113) = 3.695$, $p < .001$, $R^2 = 0.186$

Table 7. Results from MANCOVA Comparing Consistent Moderate Drinkers to Consistent Heavy Drinkers and Lifetime Abstainers

Multivariate Tests[a]

Effect		Value	F	Hypothesis df	Error df	Sig.	Partial Eta Squared
History of Depression	Pillai's Trace	.031	1.179[b]	5	186	.321	.031
Sex	Pillai's Trace	.055	2.174[b]	5	186	.059	.055
Years of Education	Pillai's Trace	.210	9.860[b]	5	186	.000	.210
BMI	Pillai's Trace	.033	1.288[b]	5	186	.271	.033
History of Hypertension	Pillai's Trace	.024	.897[b]	5	186	.485	.024
History of High Cholesterol	Pillai's Trace	.017	.636[b]	5	186	.672	.017
Drinking Pattern	Pillai's Trace	.027	.506	10	374	.886	.013

Note. Total *n* (consistent moderate drinkers) = 75; Total *n* (lifetime abstainers) = 50; Total *n* (consistent heavy drinkers) = 71.

Table 8. Results from MANCOVA Comparing Consistent Heavy Drinkers to Lifetime Abstainers

Multivariate Tests[a]

Effect		Value	F	Hypothesis df	Error df	Sig.	Partial Eta Squared
History of Depression	Pillai's Trace	.028	.638[b]	5	109	.671	.028
Sex	Pillai's Trace	.015	.342[b]	5	109	.886	.015
Years of Education	Pillai's Trace	.238	6.793[b]	5	109	.000	.238
BMI	Pillai's Trace	.026	.575[b]	5	109	.719	.026
History of Hypertension	Pillai's Trace	.038	.872[b]	5	109	.502	.038
History of High Cholesterol	Pillai's Trace	.037	.832[b]	5	109	.530	.037
Heavy Drinking	Pillai's Trace	.003	.073[b]	5	109	.996	.003

Total *n* (lifetime abstainers) = 50; Total *n* (consistent heavy drinkers) = 71.

Table 9. Demographic Characteristics and Descriptive Statistics – Binge Drinkers and Non-Binge Drinkers

Demographic Characteristics and Descriptive Statistics

	Binge Drinkers		Non-Binge Drinkers	
	Mean	**SD**	**Mean**	**SD**
Age	71.29	0.91	71.09	0.91
Years of Education	13.69	2.12	13.93	2.45
Total Drinks (over past 30 days) – Baseline	34.04	31.65	8.04	12.25
Total Drinks (over past 30 days) – Time 2	35.12	35.43	9.82	15.52
Total Drinks (over past 30 days) – Time 3	37.81	39.14	10.56	17.11
Binge Episodes (Time Point 1)	2.83	4.29	-	-
Binge Episodes (Time Point 2)	2.17	4.68	-	-
Binge Episodes (Time Point 3)	2.53	6.19	-	-
Body Mass Index	28.87	5.01	28.73	5.70
	Frequency	**Percent**	**Frequency**	**Percent**
Sex – Female/Male	191/531	26.50/73.50	1,688/1,042	61.80/38.20
History of Hypertension	469	65.10	1629	59.70
History of High Cholesterol	397	55	1466	53
History of Depression	232	32.10	1089	39.90
History of Multiple Sclerosis	10	1.40	28	1
History of Parkinson's Disease	14	1.9	48	1.80
History of Stroke	46	6.4	120	4.40

Note. Total *n* (binge drinkers) = 722; Total *n* (non-binge drinkers) = 2,730

Table 10. Results from Regression Comparing Binge Drinkers to Non-Binge Drinkers

Regression Results

	B	SE	ß	*p*
History of Binge Drinking	.025	.025	.016	.313
History of Depression	.039	.020	.031	.052
Sex	.286	.021	.229	.000
Years of Education	.096	.004	.371	.000
BMI	.001	.002	.007	.674
History of Hypertension	.047	.021	.037	.021
History of High Cholesterol	.004	.002	.025	.114

Note. Model: $F(7,3440) = 100.738$, $p < .001$, $R^2 = 0.170$

Table 11. Results from MANCOVA Comparing Binge Drinkers to Non-Binge Drinkers

Multivariate Tests[a]

Effect		Value	F	Hypothesis df	Error df	Sig.	Partial Eta Squared
History of Depression	Pillai's Trace	.003	2.289	5	3436	.043	.003
Sex	Pillai's Trace	.079	58.825	5	3436	.000	.079
Years of Education	Pillai's Trace	.179	149.577	5	3436	.000	.179
BMI	Pillai's Trace	.008	5.390	5	3436	.000	.008
History of Hypertension	Pillai's Trace	.004	2.982	5	3436	.011	.004
History of High Cholesterol	Pillai's Trace	.002	1.060	5	3436	.381	.002
History of Binge Drinking	Pillai's Trace	.002	1.415	5	3436	.215	.002

Note. Total *n* (binge drinkers) = 722; Total *n* (non-binge drinkers) = 2,730

Table 12. Demographic Characteristics and Descriptive Statistics – Former Heavy Drinkers and Consistent Heavy Drinkers

Demographic Characteristics and Descriptive Statistics

	Former Heavy Drinkers		Consistent Heavy Drinkers	
	Mean	**SD**	**Mean**	**SD**
Age	71.32	0.95	71.07	0.88
Years of Education	13.45	2.13	14.27	2.43
Total Drinks (over past 30 days) – Baseline	64.07	34.91	78.84	33.51
Total Drinks (over past 30 days) – Time 2	62.24	50.01	88.87	39.22
Total Drinks (over past 30 days) – Time 3	0	0	92.28	39.40
Body Mass Index	27.97	5.22	28.11	5.21
	Frequency	**Percent**	**Frequency**	**Percent**
Sex – Female/Male	9/22	29.03/70.97	20/51	28.17/71.83
History of Hypertension	23	74.2	22	31
History of High Cholesterol	16	51.61	38	53.50
History of Depression	13	41.94	21	29.60
History of Multiple Sclerosis	0	0	1	1.4
History of Parkinson's Disease	1	3.4	1	1.4
History of Stroke	4	12.9	2	2.8

Note. Total *n* (former heavy drinkers) = 31; Total *n* (consistent heavy drinkers) = 71

Table 13. Results from Regression Comparing Former Heavy Drinkers to Consistent Heavy Drinkers

Regression Results

	B	S.E.	ß	*p*
Former Heavy Drinkers	-.251	.138	-.175	.072
History of Depression	.097	.134	.069	.473
Sex	.091	.147	.062	.539
Years of Education	.101	.027	.360	.000
BMI	-.006	.013	-.049	.639
History of Hypertension	-.119	.142	-.082	.406
History of High Cholesterol	-.005	.012	-.043	.653

Note. Model: $F(7,94) = 3.071$, $p = .006$, $R^2 = 0.186$

Table 14. Results from MANCOVA Comparing Former Heavy Drinkers to Consistent Heavy Drinkers

Multivariate Tests

Effect		Value	F	Hypothesis df	Error df	Sig.	Partial Eta Squared
History of Depression	Pillai's Trace	.028	.520	5	90	.760	.028
Sex	Pillai's Trace	.026	.480	5	90	.790	.026
Years of Education	Pillai's Trace	.209	4.767	5	90	.001	.209
BMI	Pillai's Trace	.011	.195	5	90	.964	.011
History of Hypertension	Pillai's Trace	.032	.598	5	90	.702	.032
History of High Cholesterol	Pillai's Trace	.014	.258	5	90	.935	.014
Former Heavy Drinkers	Pillai's Trace	.049	.925	5	90	.468	.049

Note. Total *n* (former drinkers) = 31; Total *n* (consistent heavy drinkers) = 71

Table 15. Demographic Characteristics and Descriptive Statistics – Former Abstainers and Lifetime Abstainers

Demographic Characteristics and Descriptive Statistics

	Former Abstainers		Lifetime Abstainers	
	Mean	**SD**	**Mean**	**SD**
Age	71.23	1.03	71.14	0.90
Years of Education	13.45	2.13	13.86	2.34
Total Drinks (over past 30 days) – Baseline	0	0	0	0
Total Drinks (over past 30 days) – Time 2	7.90	17.34	0	0
Total Drinks (over past 30 days) – Time 3	11.54	26.81	0	0
Body Mass Index	28.74	4.48	29.28	6.18
	Frequency	**Percent**	**Frequency**	**Percent**
Sex – Female/Male	25/22	53.20/46.80	35/15	70/30
History of Hypertension	30	63.80	26	52
History of High Cholesterol	19	40.40	23	46
History of Depression	15	31.90	20	40
History of Multiple Sclerosis	0	0	0	0
History of Parkinson's Disease	0	0	1	2.1
History of Stroke	3	6.40	0	0

Note. Total *n* (former abstainers) = 47; Total *n* (lifetime abstainers) = 50

Table 16. Results from Regression Comparing Former Abstainers to Lifetime Abstainers

Regression Results

	B	S.E.	ß	*p*
Former Abstainers	.019	.131	.014	.886
History of Depression	-.050	.134	-.035	.710
Sex	.311	.135	.219	.024
Years of Education	.122	.029	.410	.000
BMI	.008	.013	.063	.524
History of Hypertension	-.024	.138	-.017	.862
History of High Cholesterol	.035	.015	.222	.019

Note. Model: $F(7,89) = 4.207$, $p < .001$, $R^2 = 0.249$

Table 17. Results from MANCOVA Comparing Former Abstainers to Lifetime Abstainers

Multivariate Tests

Effect		Value	F	Hypothesis df	Error df	Sig.	Partial Eta Squared
History of Depression	Pillai's Trace	.043	.759	5	85	.006	.171
Sex	Pillai's Trace	.122	2.364	5	85	.046	.122
Years of Education	Pillai's Trace	.278	6.538	5	85	.000	.278
BMI	Pillai's Trace	.015	.251	5	85	.938	.015
History of Hypertension	Pillai's Trace	.009	.161	5	85	.976	.009
History of High Cholesterol	Pillai's Trace	.106	2.007	5	85	.086	.106
Former Abstainers	Pillai's Trace	.047	.846	5	85	.521	.047

Note. Total *n* (former abstainers) = 47; Total *n* (lifetime abstainers) = 71

APPENDIX F – WLS PROTOCOLS

Appendix I – Original Questionnaire from 1957

HSR _____
HN _____

Do not write in this col.

MY PLANS BEYOND HIGH SCHOOL

Name _____ Age _____ M _____ F _____ 1-6 _____ 7-8 _____ 9-10 _____ 11 _____

School _____ Home address _____ 12 _____

_____ Father's name _____
(or other parent or guardian)

1. I plan: (Place a cross (x) before the statement which describes what you plan to do next year)

_____ To continue going to school
_____ To get a job
_____ To become an apprentice
_____ To go into military service
_____ To work at my home
_____ I have no definite plans
_____ (Other, specify) _____ 13 _____

If the plan you have checked is not what you would really like to do, place an (L) in front of the statement above which described what you would most like to do, then state what circumstances prevent you from doing what you would most like to do. _____ 14 _____ 15 _____

How sure are you that you will be doing what you plan? _____ certain _____ uncertain 16 _____

2. If you checked that you plan to go to school next year, what kind of school do you plan to attend?

Public	Private
_____ Vocational school	_____ Liberal arts college
_____ County teachers college	_____ University
_____ State college	_____ Business or trade school
_____ University	_____ Other _____ (Specify)

17 _____

Do you plan to attend school outside Wisconsin? _____ yes _____ no 18 _____

I plan to attend school _____ full-time _____ part-time 19 _____

3. If you plan to continue your schooling or training, answer the items below. If not, go to question 4.

I plan to enter the following courses or fields:

In trade or vocational school _____
Specify field or training

Apprenticeship _____
Specify field or trade

College or university: (check the field of your interest)

____ Agriculture	____ Engineering	____ Liberal Arts
____ Architecture	____ Fine Arts	____ Medicine
____ Aeronautics	____ Forestry	____ Nursing
____ Business	____ Home Economics	____ Pharmacy
____ Chemistry	____ Journalism	____ Social Work
____ Dentistry	____ Law	____ Teaching
____ Undecided	____ _____ (Other)	____ Veterinary

20-21 _____

4. If you plan to get a job next year, check the statement below which applies to you.

____ I have applied, but do not yet have a job
____ I have applied and have been accepted
____ I have not applied
____ I will continue in a job I now have
____ Other _____

My job will be: (describe) _____ 22-23 _____

(Name of firm) _____

It will pay about _____ per week 24 _____

5. To what extent have you discussed your plans with your teachers or school counselors?

_____ not at all _____ some _____ very much

How much did they influence your plans?

_____ not at all _____ some _____ very much 25 _____

6. To what extent have you discussed your plans with your parents?
_____ not at all _____ some _____ very much

How much did they influence your plans?
_____ not at all _____ some _____ very much

26.

7. Education of father and mother (check highest level attained)

	Father	Mother
High School		
did not attend	____	____
attended	____	____
graduated from	____	____
Trade or business school:		
attended	____	____
College:		
attended	____	____
graduated from	____	____
has master's or Ph.D. degree	____	____
Do not know	____	____

27.
28.

8. Education of older brother and sister who have had most schooling. (Check the highest level reached; if more than one, show number at each level.)

	Brother	Sister
Some high school	____	____
High school graduate	____	____
Some college	____	____
Attending college	____	____
College graduate	____	____
Attending graduate school (or attended)	____	____
None older	____	____

29.
30.

9. (a) My father is engaged in the type of occupation checked in the left hand column below.
(b) I hope eventually to enter the type of occupation checked in the right hand column below.

Father	Me
____ Office work (cashier, clerk, secretary, bookkeeper, etc.)	____
____ Professional (doctor, lawyer, minister, teacher, etc.)	____
____ Executive (manages large business, industry, firm)	____
____ Factory worker (laborer, janitor, farm hand, etc.)	____
____ Salesman (insurance, real estate, auto, store, etc.)	____
____ Owns, rents, manages small business (store, station, newspaper, cafe, etc.	____
____ Owns, rents, manages farm	____
____ Other occupation (be specific) _____	____

31.
32.

(c) If your mother has a job outside the home, place an (M) before the type of occupation in which she works.

33.

10. How much do you think it costs per school year to attend college away from home?

____ Less than $1000 ____ Between $1500 and $2000
____ Between $1000 and $1500 ____ More than $2000

34.

11. How do you estimate the ability of your parents to help you go to college, if you desire to go?

____ can easily afford it ____ cannot afford it
____ can afford it, but with much sacrifice ____ I must work to help support the family

35.

12. In terms of income or wealth of families in my community, I think my family is:

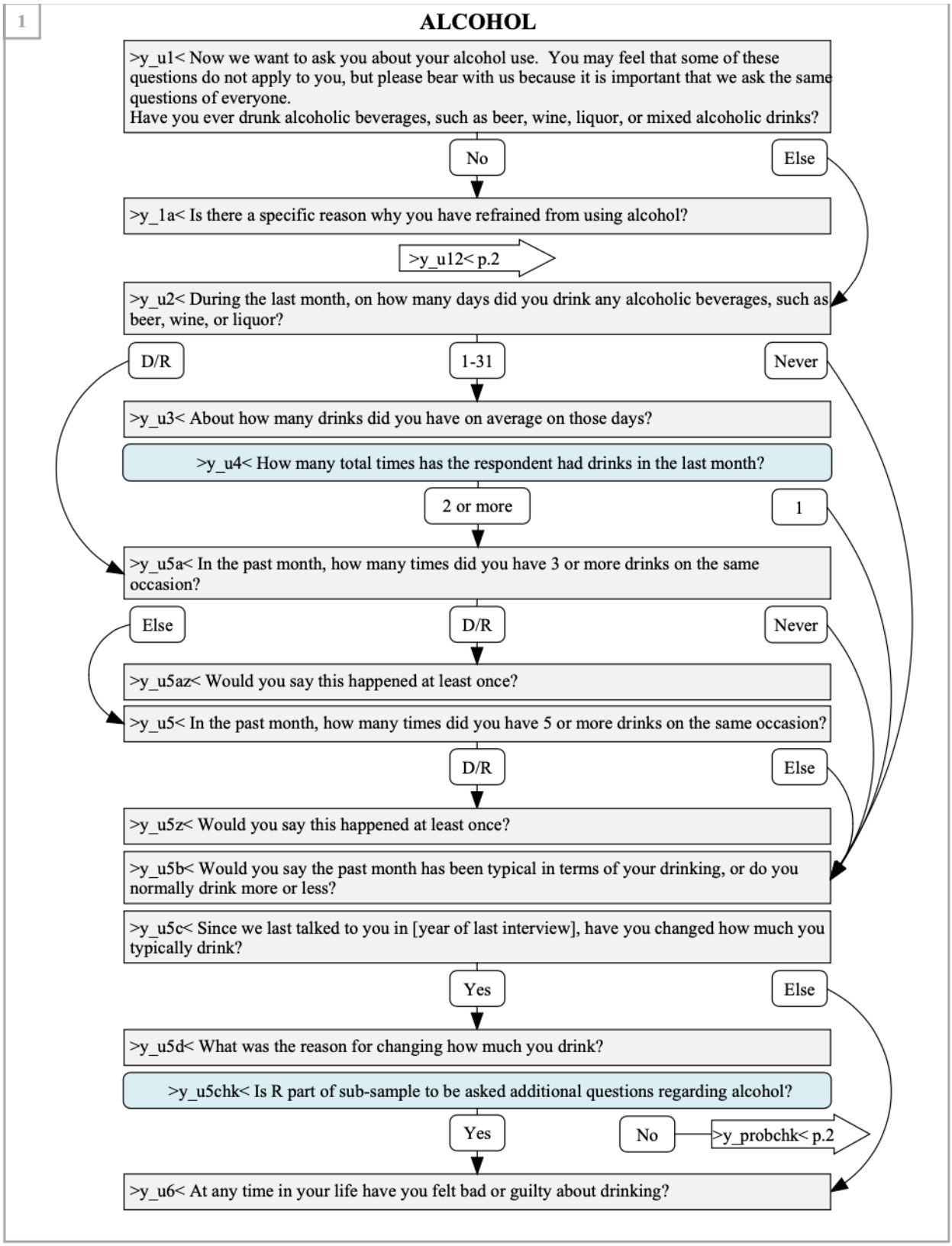
____ considerably above average ____ average
____ somewhat above average ____ somewhat below average
____ considerably below average

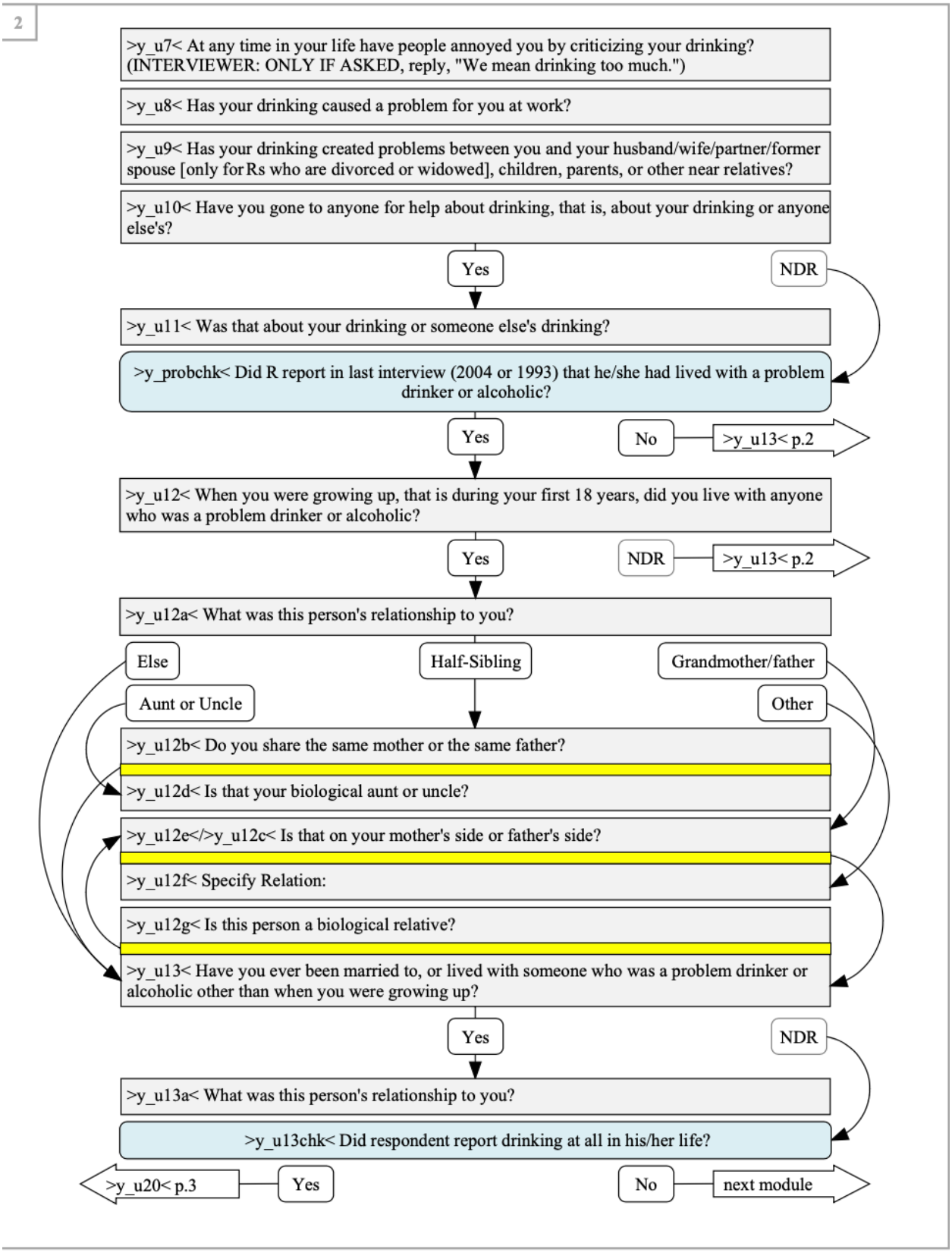
36.

13. (a) Have you ever considered attending college? ____ yes ____ no
(b) If no, would you consider it if you had the money ____ yes ____ no
(c) Would you borrow money for college expenses if you could pay it back on the installment plan after leaving college ____ yes ____ no
(d) About how much could you or your family contribute to your college expenses next year (if you were going)?
____ none ____ less than $500 ____ Between $500 and $1000
____ between $1000 and $1500 ____ all my expenses

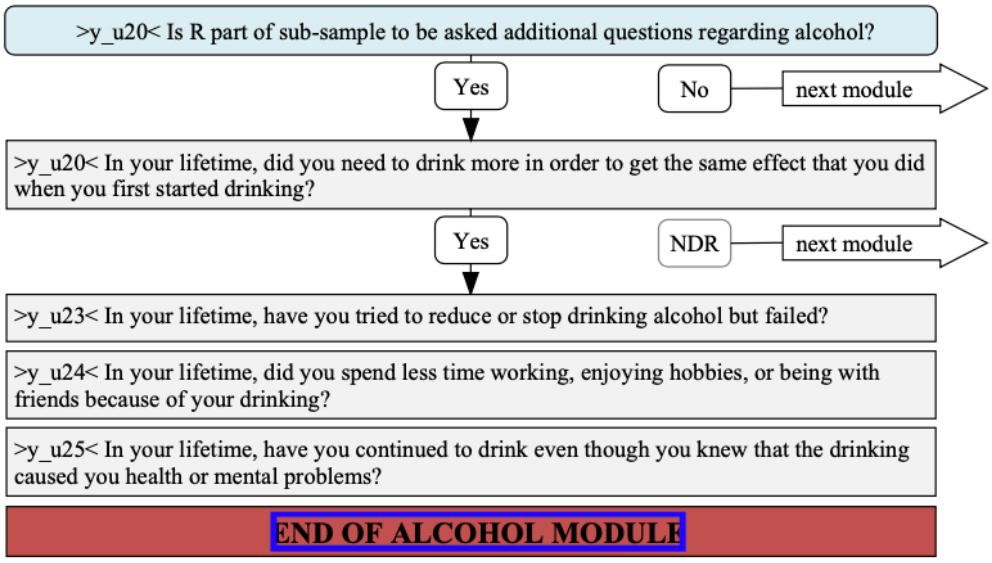
37.
38.
39.

Appendix II – Alcohol Questions

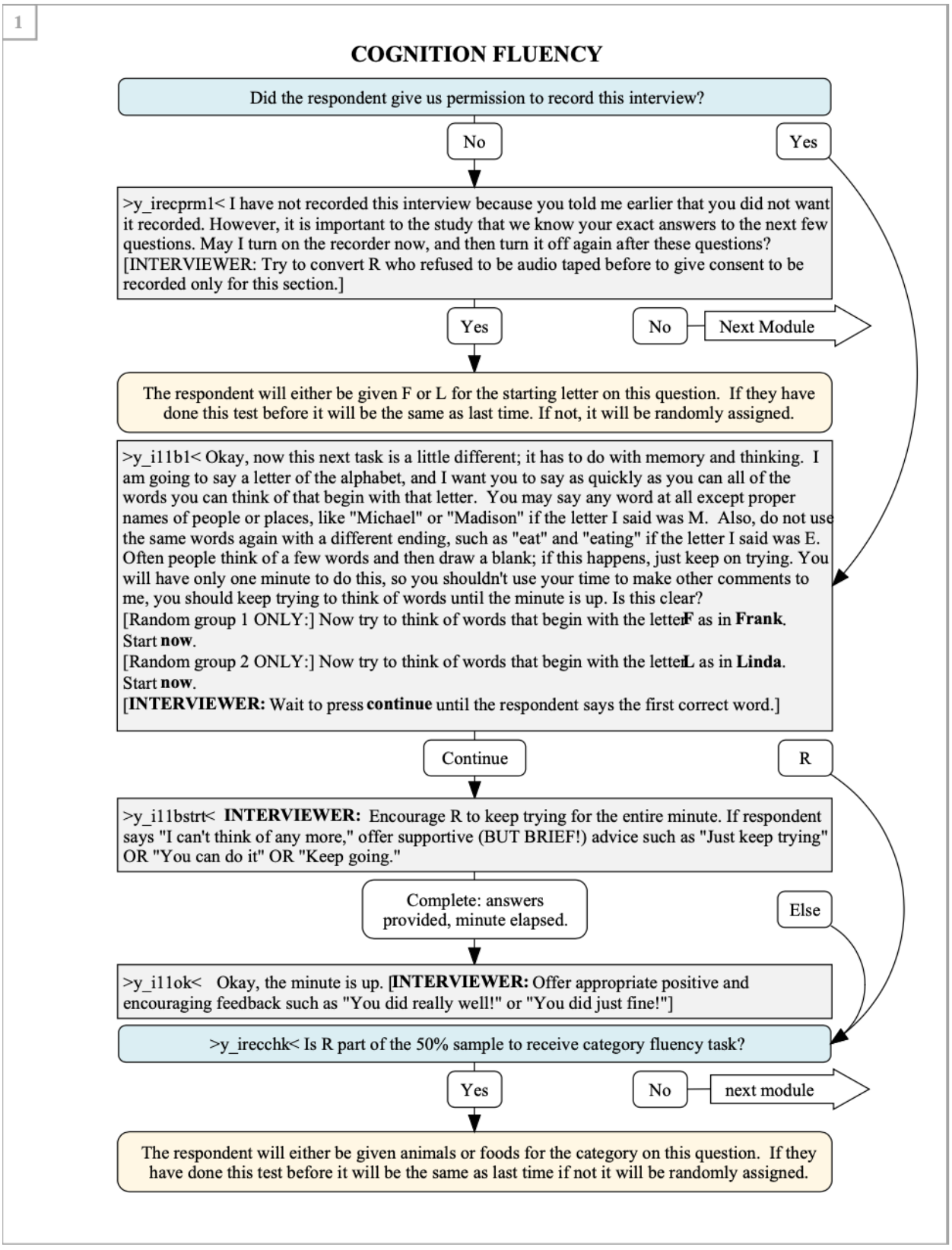


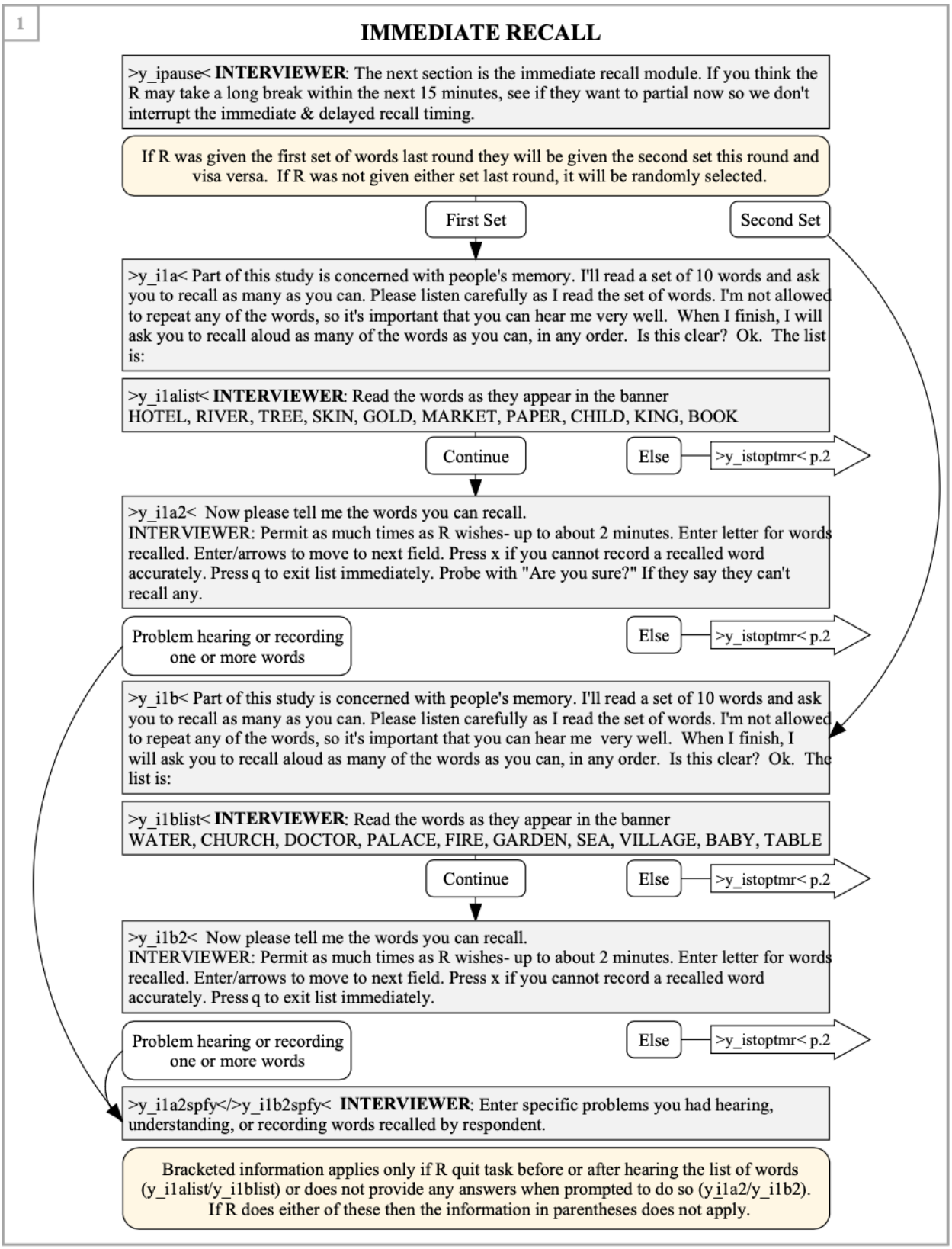

2
>y_u7< At any time in your life have people annoyed you by criticizing your drinking? (INTERVIEWER: ONLY IF ASKED, reply, "We mean drinking too much.")
>y_u8< Has your drinking caused a problem for you at work?
>y_u9< Has your drinking created problems between you and your husband/wife/partner/former spouse [only for Rs who are divorced or widowed], children, parents, or other near relatives?
>y_u10< Have you gone to anyone for help about drinking, that is, about your drinking or anyone else's?
Yes
NDR
>y_u11< Was that about your drinking or someone else's drinking?
>y_probchk< Did R report in last interview (2004 or 1993) that he/she had lived with a problem drinker or alcoholic?
Yes
No
>y_u13< p.2
>y_u12< When you were growing up, that is during your first 18 years, did you live with anyone who was a problem drinker or alcoholic?
Yes
NDR
>y_u13< p.2
>y_u12a< What was this person's relationship to you?
Else
Half-Sibling
Grandmother/father
Aunt or Uncle
Other
>y_u12b< Do you share the same mother or the same father?
>y_u12d< Is that your biological aunt or uncle?
>y_u12e</>y_u12c< Is that on your mother's side or father's side?
>y_u12f< Specify Relation:
>y_u12g< Is this person a biological relative?
>y_u13< Have you ever been married to, or lived with someone who was a problem drinker or alcoholic other than when you were growing up?
Yes
NDR
>y_u13a< What was this person's relationship to you?
>y_u13chk< Did respondent report drinking at all in his/her life?
>y_u20< p.3
Yes
No
next module

3


>y_u20< Is R part of sub-sample to be asked additional questions regarding alcohol?
Yes
No
next module
>y_u20< In your lifetime, did you need to drink more in order to get the same effect that you did when you first started drinking?
Yes
NDR
next module
>y_u23< In your lifetime, have you tried to reduce or stop drinking alcohol but failed?
>y_u24< In your lifetime, did you spend less time working, enjoying hobbies, or being with friends because of your drinking?
>y_u25< In your lifetime, have you continued to drink even though you knew that the drinking caused you health or mental problems?
END OF ALCOHOL MODULE

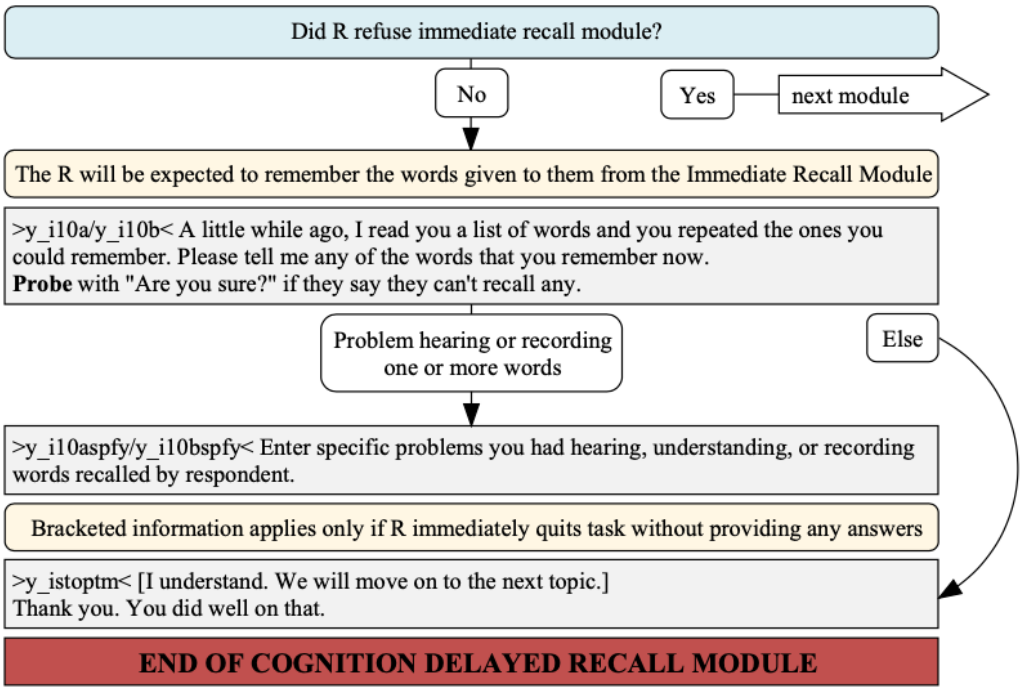
Appendix III – Sample of Cognitive Measures

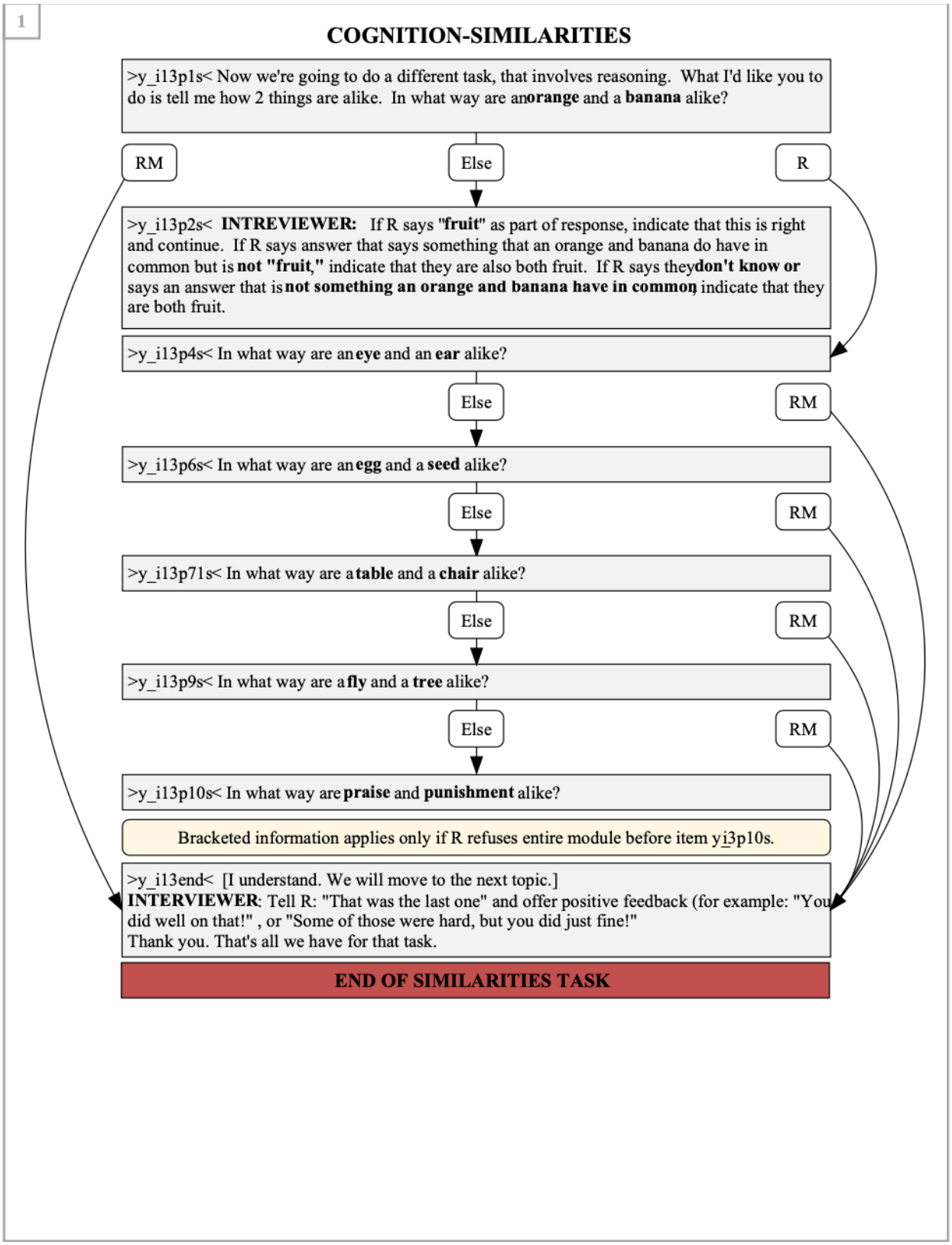



1
IMMEDIATE RECALL
>y_ipause< INTERVIEWER: The next section is the immediate recall module. If you think the R may take a long break within the next 15 minutes, see if they want to partial now so we don't interrupt the immediate & delayed recall timing.
If R was given the first set of words last round they will be given the second set this round and visa versa. If R was not given either set last round, it will be randomly selected.
First Set
Second Set
>y_i1a< Part of this study is concerned with people's memory. I'll read a set of 10 words and ask you to recall as many as you can. Please listen carefully as I read the set of words. I'm not allowed to repeat any of the words, so it's important that you can hear me very well. When I finish, I will ask you to recall aloud as many of the words as you can, in any order. Is this clear? Ok. The list is:
>y_i1alist< INTERVIEWER: Read the words as they appear in the banner
HOTEL, RIVER, TREE, SKIN, GOLD, MARKET, PAPER, CHILD, KING, BOOK
Continue
Else
>y_istoptmr< p.2
>y_i1a2< Now please tell me the words you can recall.
INTERVIEWER: Permit as much times as R wishes- up to about 2 minutes. Enter letter for words recalled. Enter/arrows to move to next field. Press x if you cannot record a recalled word accurately. Press q to exit list immediately. Probe with "Are you sure?" If they say they can't recall any.
Problem hearing or recording one or more words
Else
>y_istoptmr< p.2
>y_i1b< Part of this study is concerned with people's memory. I'll read a set of 10 words and ask you to recall as many as you can. Please listen carefully as I read the set of words. I'm not allowed to repeat any of the words, so it's important that you can hear me very well. When I finish, I will ask you to recall aloud as many of the words as you can, in any order. Is this clear? Ok. The list is:
>y_i1blist< INTERVIEWER: Read the words as they appear in the banner
WATER, CHURCH, DOCTOR, PALACE, FIRE, GARDEN, SEA, VILLAGE, BABY, TABLE
Continue
Else
>y_istoptmr< p.2
>y_i1b2< Now please tell me the words you can recall.
INTERVIEWER: Permit as much times as R wishes- up to about 2 minutes. Enter letter for words recalled. Enter/arrows to move to next field. Press x if you cannot record a recalled word accurately. Press q to exit list immediately.
Problem hearing or recording one or more words
Else
>y_istoptmr< p.2
>y_i1a2spfy</>y_i1b2spfy< INTERVIEWER: Enter specific problems you had hearing, understanding, or recording words recalled by respondent.
Bracketed information applies only if R quit task before or after hearing the list of words (y_i1alist/y_i1blist) or does not provide any answers when prompted to do so (y_i1a2/y_i1b2). If R does either of these then the information in parentheses does not apply.

1

Cognition Delayed Recall




1
COGNITION-SIMILARITIES
>y_i13p1s< Now we're going to do a different task, that involves reasoning. What I'd like you to do is tell me how 2 things are alike. In what way are an orange and a banana alike?
RM
Else
R
>y_i13p2s< INTREVIEWER: If R says "fruit" as part of response, indicate that this is right and continue. If R says answer that says something that an orange and banana do have in common but is not "fruit," indicate that they are also both fruit. If R says they don't know or says an answer that is not something an orange and banana have in common, indicate that they are both fruit.
>y_i13p4s< In what way are an eye and an ear alike?
Else
RM
>y_i13p6s< In what way are an egg and a seed alike?
Else
RM
>y_i13p71s< In what way are a table and a chair alike?
Else
RM
>y_i13p9s< In what way are a fly and a tree alike?
Else
RM
>y_i13p10s< In what way are praise and punishment alike?
Bracketed information applies only if R refuses entire module before item yi3p10s.
>y_i13end< [I understand. We will move to the next topic.]
INTERVIEWER: Tell R: "That was the last one" and offer positive feedback (for example: "You did well on that!" , or "Some of those were hard, but you did just fine!"
Thank you. That's all we have for that task.
END OF SIMILARITIES TASK

SECTION THREE
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