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Reported alcohol consumption and cognitive decline: the Northern Manhattan Study

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Abstract

Background—Moderate alcohol intake may slow cognitive decline and both vascular and neurodegenerative mechanisms have been implicated.

Methods—We examined reported alcohol intake and cognitive decline in a community-based cohort of Hispanic, black, and white individuals (N=1,428). The role of the APOE-4 allele as a modifier was also studied.

Results and Conclusions—Reported drinking was as follows: 300 participants (21%) were "never" drinkers, 622 "past" drinkers (44%), 145 (10%) reported taking less than one drink weekly, 330 (23%) one drink weekly up to two daily, and 31 (2%) more than two drinks daily. A positive relationship was seen between reported alcohol intake and cognition. Drinking less than one drink a week (P=0.09), between one drink weekly up to two drinks daily (P=0.001), and more than two drinks daily (P=0.003) were associated with less cognitive decline on the modified Telephone Interview for Cognitive Status (TICS-m) compared to never drinkers. This dose-response relationship was not modified by the presence of an APOE-4 allele in a subsample.

Keywords

Alcohol drinking; cognition disorders; apolipoprotein E-4

Evidence is accumulating that moderate alcohol consumption may lower the risk of cognitive decline and dementia.[1-7] The benefit may be mediated in part by a protective effect against vascular disease, as moderate alcohol consumption has been shown to lower the risk of stroke as well as subclinical infarcts and white matter disease on brain imaging.[8,9] However, moderate alcohol intake has also been found to lower the risk of Alzheimer disease (AD) in two studies.[2,10] Few studies have examined the apolipoprotein E ε4 (APOE-4) allele, a strong risk factor for cognitive decline and AD, as a potential mediator of the effect of alcohol

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on cognition.[11] Results of studies that have been done are mixed, with some reporting that the allele was a modifier and others not finding an association.[5,10,12,13]

Alcohol consumption in moderation may provide an opportunity for prevention or delay of cognitive dysfunction if it is found to be protective. To answer this question, data from longitudinal studies using sensitive measures to detect early cognitive changes are needed. Many studies on alcohol intake and cognition to date have been cross-sectional, limiting inferences about causality. Though several longitudinal studies have found that moderate alcohol consumption was associated with less cognitive decline, most have been limited to older subjects[1,6,14] or used less sensitive measures of cognition.[5,7,15] Additional data are also needed in diverse populations; most studies have been limited to white subjects, only a few studies have included blacks,[7,16,17] and none have included a significant proportion of Hispanic participants. Hispanics are the largest growing segment of the US population, having increased by 58% in the last decade of the 20th century.[22] Blacks and Hispanics may be at higher risk than whites since they have higher rates of cerebral small vessel disease and intracranial atherosclerosis and may be at higher risk of dementia and AD.[18,19] The purpose of this study was to measure the effect of alcohol intake on cognitive performance over time in a younger multiethnic community-based sample and to assess the effect of having an APOE-4 allele.

Methods

The Northern Manhattan Study (NOMAS) included 3,298 stroke-free participants at baseline identified through random digit dialing using dual-frame sampling as described previously.[20] Community participants were eligible if they had never been diagnosed with a stroke, were ≥ 40 years of age, and had been residents of Northern Manhattan for ≥3 months in a household with a telephone. Subjects were recruited from the telephone sample for an in-person assessment and the overall response rate was 68%. After enrollment, all subjects have been followed annually by telephone to determine changes in vital status, detect neurological and cardiac symptoms and events, and note interval hospitalizations. Loss to follow-up from the cohort has been less than one percent. The ethics committee of Columbia University Medical Center approved the study and all subjects signed informed consent.

Data were collected through interviews by trained bilingual research assistants using standardized data collection instruments, review of medical records, physical and neurological examinations by study physicians, and fasting blood samples. Standardized questions about vascular risk factors were adapted from the Centers for Disease Control and Prevention Behavioral Risk Factor Surveillance System as defined previously.[21] Hypertension was defined as a systolic blood pressure >140 mm Hg or a diastolic blood pressure >90 mm Hg based on the mean of two blood pressure measurements, self report of a diagnosis of hypertension, or medical treatment thereof. Diabetes was defined as a fasting blood glucose ≥127 mg/dL, subject self-report of a diagnosis of diabetes, or insulin or oral hypoglycemic use. Cardiac disease was defined as a history of coronary artery disease, atrial fibrillation, or myocardial infarction. Race-ethnicity was based on self-identification and the distribution at enrollment was approximately 63% Hispanic, 21% black, 15% white, and 2% other groups. Depression was defined as a score on the Hamilton Depression Rating Scale of > 10 or a history of antidepressant use at time of enrollment or follow-up.

Cognitive Assessment

The modified Telephone Interview for Cognitive Status (TICS-m) has been administered annually to the prospective cohort since 2001 during telephone follow-up. The original version (TICS) assesses orientation, attention, immediate recall of a ten-word list, calculations, judgment, language, finger tapping, and antonyms.[22] The modified version (TICS-m)

additionally requires delayed recall of the ten-word list resulting in a total score of 51 points and has scores that are normally distributed without ceiling effects.[23] The TICS-m has good reliability and validity in this multi-ethnic community.[24]

Alcohol Consumption Assessments

Alcohol use was assessed using structured interviews adapted from food frequency questionnaires as previously described, to create a defined frequency response set.[8,25,26] At enrollment, we asked about the average amount consumed in the past year, and on average during the participant's drinking lifetime. The follow-up alcohol assessment at the time of the baseline cognitive examination with the TICS-m asked about intake over the prior six months. In both cases, there were nine possible responses from none to 7 or more drinks per day of wine (120 mL or 11 g), beer (360 mL or 12.8 g), and liquor (45 mL or 14 g). Responses for each beverage type were summed to obtain an overall quantity that was divided into categories as described below.

Laboratory Assessments

Baseline fasting blood samples were drawn into serum tubes and spun within one hour at 3000g and 4°C for 20 minutes and immediately frozen at −70°C. High density lipoprotein cholesterol (HDL-C) levels were measured using an automated spectrometer (Hitachi 705, Boehringer, Mannheim, Germany). The number of APOE-4 alleles carried by each subject was determined by HhaI digestion of PCR products amplified from genomic DNA as described previously. [27]

Statistical Analyses

Statistical analyses were carried out using SAS software (version 8.2, SAS Institute, Cary, NC). We excluded participants with a history of stroke prior to their first TICS-m and censored scores acquired after strokes. We initially excluded participants with a history of an alcohol-related hospitalization, but also carried out a separate analysis that included these individuals.

As the TICS-m was not instituted in this cohort until 2001 we used the follow-up questions about alcohol intake closest to the first assessment (90% occurred on the same day). We created five categories of alcohol intake: 1) never (reference group); 2) past; 3) less than one drink weekly; 4) one drink weekly up to two daily; and 5) more than two drinks daily. As noted above, the follow up questions referred to alcohol intake in the six months prior to the interview; however we took into account their reported consumption at enrollment as well. Patients that reported drinking at enrollment but not at follow-up were considered past drinkers, whereas those that reported no alcohol intake at follow-up were considered never drinkers only if they had been never drinkers at enrollment. Those whose alcohol intake at follow-up differed by two categories from enrollment were excluded, to ensure stable drinking patterns over time (N=10).

We measured the association between reported alcohol intake at the time of the first TICS-m and changes in TICS-m scores over time. We employed generalized estimating equations (GEE), a multivariate regression method that uses changes of TICS-m scores from the baseline exam as a vector of outcome. An advantage of GEE is that even when the covariance structure is unspecified, the correlation among change scores is taken into account. We adjusted for sociodemographic and health-related potential confounders associated with cognition or alcohol intake: time between TICS-m administrations, age in years, education, gender, race-ethnicity, health insurance status, high density lipoprotein (HDL-C) level, body mass index (BMI), history of hypertension, diabetes, cardiac disease, current smoking, depression, and physical inactivity. We tested for interaction in separate models. We also investigated the effect

of alcohol on cognition stratified by APOE-4 allele status in a sub-sample of participants for whom these data were available (N=600).

Not all participants had a complete TICS-m done every year during their telephone follow-up. Differential dropout would be a source of bias only if those that dropped out differed by performance on the TICS-m. To assess for potential bias in the estimates of the relationship between alcohol intake and the outcome of TICS-m change scores, we fitted a logistic regression model using an indicator for those that dropped out after the first TICS-m as the outcome. TICS-m score, reported alcohol intake, and the interaction between the two were included in the model along with other relevant covariates.

Results

Of 3,298 stroke-free participants enrolled between 1993 and 2001, we excluded 31 due to a prior history of an alcohol related hospitalization. In addition, 508 died and 80 suffered strokes prior to the initiation of annual cognitive assessment with the TICS-m. Of the 2,631 remaining subjects 304 died and 48 suffered strokes after the initial TICS-m leaving 2,279 potentially available for this study. There were 1,428 participants with data on reported alcohol intake and at least two TICS-m scores available (mean age 66, range 40-98; see table 1 for other characteristics). Compared to those not included in this study, the present sample had more Hispanics (62 vs. 54%, $P<0.05$), fewer blacks (20 vs. 25%, $P<0.05$), and more diabetics (22 vs. 19%, $P<0.05$). There was no difference in TICS-m scores or in the interaction between TICS-m scores and alcohol intake comparing those that dropped out after the first TICS-m with those that had complete follow-up assessments.

At the follow-up closest to the baseline TICS-m, 300 participants (21%) were classified as “never” drinkers and 622 as “past” drinkers (44%). For current drinkers, 145 (10%) reported drinking less than one drink weekly, 330 up to two drinks daily (23%), and 31 (2%) more than two drinks daily. Performance on the TICS-m (mean 31; interquartile range 27 to 35) differed by drinking category at baseline: past drinkers ($P<0.05$) and both categories of current drinkers had higher TICS-m scores than never drinkers in univariate analysis ($P<0.0001$). Past drinkers had average TICS-m scores one point better (mean=30), those who drank up to two drinks daily four points better (mean=33), and those who drank more than two drinks daily six points better (mean 35) than never drinkers (mean=29).

Over 6,913 person-years of follow-up (mean 2.2 years, range 0.5-4.4 years), the mean decline in scores comparing the first to the last TICS-m was 0.4 points (SD 5.6). There was a positive relationship between the amount of reported alcohol intake and performance on the TICS-m over time adjusting for age and educational attainment (table 2, model 1). All three categories of current drinkers, but not past drinkers, had significantly less cognitive decline than never drinkers. Adjusting for gender, race-ethnicity, and insurance status attenuated the estimates, but the association between current drinking and less decline was still significant (table 2, model 2). After adjusting for vascular risk factors and depression the dose-response relationship remained, although the association between drinking less than one drink weekly and cognitive decline remained only a trend. However, taking more than one drink weekly was still associated with less cognitive decline in the fully adjusted model (table 2, model 3). In a sensitivity analysis we included those with a history of an alcohol related hospitalization (N=31) and the protective effect against cognitive decline in those reporting more than two drinks daily was attenuated somewhat, but remained significant.

There was no significant difference in baseline TICS-m scores between APOE-4 allele carriers (mean 31.5, SD 6.8, N=155) and non-carriers (mean 32.1, SD 6.4, N=445). In addition, the change over time did not differ significantly between carriers and non-carriers ($P=0.1$). The effect of alcohol intake on cognitive performance was not modified by APOE-4 allele status.

Conclusions

In this stroke-free community-based cohort we found that current drinkers had less cognitive decline on a telephone cognitive assessment than never drinkers, adjusting for sociodemographic and vascular risk factors. In addition, there was no interaction by APOE-4 status on the beneficial effect of alcohol intake on cognitive function. This study has several strengths including the prospective design, allowing for measurement of cognitive decline. Also, our multi-ethnic urban population includes Hispanics and blacks at greater risk of dementia than their white counterparts.[40]

Our findings are in agreement with other recent prospective studies showing that alcohol intake may decrease the risk of cognitive decline.[1,13,28] One prospective study found no effect but they used the Mini Mental State Exam, which lacks sensitivity.[14] Some studies have found a graded association between reported alcohol intake and cognition,[29-31] although U-shaped relationships have also been found.[32,33] Other prospective studies have found a benefit for those who consumed less than one drink a day or an equal benefit among all categories of intake.[1,13] We found a dose-response effect against cognitive decline for those that reported current drinking. There was no difference in cognitive decline between past drinkers and never drinkers, but this is a heterogeneous group that includes a wide range of both past alcohol intake and time since becoming abstinent. Therefore, we felt it was important to keep them separate. Participants that reported drinking more than two drinks daily showed incrementally less cognitive decline than never drinkers. Given that the heavier drinking group was small (N=31), and the potential harm of excessive alcohol intake considerable, larger studies are needed to clarify the effects of this level of alcohol intake on cognition. In this study 70% of those in the highest category drank less than or equal to 4 drinks daily (N=22 of 31). Thus, most were not heavy drinkers.

We did not find a difference at baseline or over time in TICS-m scores between APOE-4 carriers and non-carriers. Results of other studies have been mixed, with two studies showing a benefit of alcohol intake in APOE-4 non-carriers in relation to cognitive decline and dementia, respectively.[5,10] In the NHLBI twin study, only drinkers that were APOE-4 carriers appeared to benefit. Interestingly, the Nurses' Health Study also used the TICS-m, as well as other tests, and likewise found APOE-4 status had no effect. One possible explanation of our findings is that the smaller sample size combined with the relatively short mean follow-up (2.2 years) may have limited our ability to detect differences between the groups in this smaller sample. The mechanism by which alcohol might mediate the effect of APOE-4 on cognition is not clear. However, APOE4 is known to be less effective at membrane repair and as an antioxidant than other isoforms.[34] Given that APOE-4 binds beta amyloid and is involved in its deposition in the plaques of AD, alcohol may decrease oxidation and deposition of beta-amyloid in the brains of those at risk.[35] Separately, evidence from animal studies suggests alcohol may increase brain acetylcholine.[36] Since this neurotransmitter is depleted in AD, alcohol could improve cognition in those affected even in the early stages.

Many if not most cases of dementia may be due to Alzheimer disease *with* vascular disease. In such cases, alcohol may have a benefit through its effects on the vascular system. We find it of note that adjusting for vascular risk factors had little effect on the change in TICS-m scores. Thus, alcohol may act on the vascular system independently of other risk factors. Moderate alcohol consumption appears to be protective against stroke and subclinical cerebrovascular disease, which may explain part of any beneficial effect of moderate alcohol consumption on cognition.[8,9] In a cross-sectional study we did not find carotid plaque to be a mediator of this relationship.[37] But, in the Cardiovascular Health Study moderate alcohol consumption was associated with less subclinical brain disease.[9] Thus, microangiopathy may be more relevant and additional studies are needed to clarify the importance of small vessel disease in

this relationship. One potential mechanism is through raising HDL-C levels.[38] In this study, HDL-C levels did not differ significantly by alcohol category and were not associated with cognitive performance in multivariate analysis. Moderate alcohol consumption also has inhibitory effects on platelet aggregation, degranulation, and formation of thromboxane A-2.[39] We did not systematically gather information on non-steroidal anti-inflammatory drug use, although we did ask about aspirin use. Excluding aspirin users in a post-hoc analysis had no effect on our results (data not shown).

This study has several limitations. In this and other studies involving self-reported alcohol use and cognition, current drinkers may be healthier than nondrinkers. This may be because the latter have stopped drinking due to health problems or because they lack social or other attributes possessed by the drinkers. Such bias is minimized by examining changes in scores. Also, factors in our cohort known to be associated with lower socio-economic status such as having Medicaid, no insurance, or being Hispanic or black compared to white were more common among nondrinkers, which would tend to minimize our findings. Another potential source of bias is differential drop out from the repeated TICS-m assessments that is dependent on alcohol intake. However, we found that drop-outs did not differ by TICS-m score or the interaction between TICS-m and alcohol intake. Another limitation is our reliance on cognitive assessment done over the telephone. While the TICS-m may not be as valid as in-person neuropsychological testing, scores on the TICS-m correlate well with in-person testing in a somewhat healthier sample of 323 NOMAS participants that have received both. In addition, the TICS-m has been found to be sensitive in detecting mild cognitive impairment in other studies.[41]

In this longitudinal study of cognitive performance, we found that current drinkers suffered less decline on a cognitive test compared to never drinkers. This effect was not modified by APOE-4 allele status. A larger sample of heavier drinkers is needed to clarify the dose of alcohol that may protect against cognitive decline without causing damage. Future studies in a larger sample from this cohort may clarify this and race-ethnic differences in drinking patterns and cognitive performance. In addition, brain imaging studies will help determine the relative importance of subclinical vascular disease in the causal pathway between alcohol consumption and cognition.

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Table 1

Characteristics of study sample by reported alcohol intake

Variable		Overall %	Reported Drinking Behavior at baseline TICS-m				
			Never	Past	1/ month – <1/ week	1/week – 2 drinks/ day	>2/day*
		N= 1,428	N=300	N=622	N=145	N=330	N=31
Age mean (SD)		71 (9)	72 (9)†	71 (9)	68 (9)	69 (9)	68 (7)
Women (%)		67	28†	44	9	18	<1
Education							
<8 years (%)		42	30†	48	8	13	1
>8 and <12 years (%)		13	19	42	12	26	<1
High school grad. (%)		16	16	45	11	24	3
Some college (%)		12	17	39	11	30	3
Graduate degree (%)		17	9	34	13	40	4
Insurance status							
None (%)		12	23†	48	8	19	2
Medicaid (%)		45	27	47	8	16	2
Private (%)		43	14	39	13	31	3
Race-ethnicity							
Hispanic (%)		62	25†	46	9	18	2
Black (%)		19	16	44	11	27	2
White (%)		19	11	35	13	37	4
Hypertension (%)		82	23†	45	9	21	2
Diabetes (%)		25	26†	47	10	17	<1
Cardiac disease (%)		19	21	45	9	24	1
Current smokers (%)		13	11†	44	9	32	4
BMI*							
>30 (%)		30	20†	41	11	26	2
25 to 30 (%)		43	18	44	11	24	3
<25 (%)		27	20	41	11	26	2
Depression (%)		3	21†	49	6	23	0
Any physical activity (%)		59	21†	39	11	27	2
tHcy	mean (SD)	9.9 (3.0)	9.2 (2.7)		9.9 (7.5)‡	9.0 (3.1)	10.7 (4.2)‡
HDL-C	mean (SD)	47 (14)	47 (13)	46 (14)	46 (14)	48 (15)	47 (16)
TICS-m	mean (SD)	31 (6)	29 (6)		30 (6)	33 (6)‡	35 (6)‡

TICS-m – modified Telephone Interview for Cognitive Status

†P<0.0001 for trend.

‡P<0.05 compared to never drinkers

Table 2

Relation between reported alcohol intake and performance on repeated measures of TICS-m*

MODEL	Reported alcohol intake								
	Never	Past		1 drink/month to < 1 drink/ week		1 drink/week up to 2 drinks/ day		>2 drinks/day	
		β (95% CI)	P	β (95% CI)	P	β (95% CI)	P	β (95% CI)	P
Model 1	Ref	β =0.6 (−0.2,1.3)†	0.14	β =1.5 (0.5,2.5)	0.003	β =2.2 (1.3,3.0)	<0.0001	β =2.9 (1.4,4.4)	0.0002
Model 2	Ref	β =0.3 (−0.4,1.1)	0.40	β =1.0 (0.03,1.9)	0.04	β =1.6 (0.7,2.4)	0.0003	β =2.1 (0.6,3.6)	0.008
Model 3	Ref	β =0.4 (−0.4,1.2)	0.36	β =0.9 (-1.2,1.9)	0.09	β =1.5 (0.6,2.4)	0.001	β =2.4 (0.8,4.0)	0.003

Model 1 – Adjusted for age and education.

Model 2 – Model 1 + gender, race-ethnicity, and insurance status.

Model 3 – Model 2 + history of hypertension, diabetes, cardiac disease, physical inactivity, depression, current smoking, HDL-C level, and BMI.

*TICS-m – modified Telephone Interview for Cognitive Status.

†Beta coefficient represents the change in points on the TICS-m over time compared to never drinkers; positive denotes better scores.