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The relation between moderate alcohol consumption and cognitive function in older women with type 2 diabetes

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Abstract

Aims: To examine the association between moderate drinking, cognitive function, and cognitive decline in women with type 2 diabetes.

Methods: From 1995–2001, we assessed cognitive function in 1,698 women aged 71–80 years with type 2 diabetes in the Nurses' Health Study. Assessments were repeated twice at 2-year intervals. We used linear regression to estimate multivariable-adjusted mean differences in initial cognitive function and longitudinal models to estimate cognitive decline over 4 years, according to average alcohol intake between diagnosis with diabetes and the initial cognitive measurement.

Results: At the initial assessment, the mean score on our test of general cognition was 0.31 (95% CI 0.02, 0.60) points higher in women who were moderate alcohol drinkers (those consuming 1.0–9.9 grams of alcohol, or about 1 drink, per day) compared with abstainers. However, moderate alcohol was not associated with cognitive decline. Higher alcohol consumption (10.0–30.0 grams of alcohol per day) was not associated with initial cognition or cognitive decline, although there was no apparent harm either.

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Conclusions: Among women with type 2 diabetes, moderate alcohol was associated with better initial cognition, but not reduced rates of cognitive decline. Thus, we found no clear and consistent cognitive benefits of moderate alcohol in diabetes.

Keywords

Alcohol consumption; Cognitive function; Type 2 diabetes

1. Introduction

The burden of type 2 diabetes is growing worldwide. In the United States, one study has estimated that the number of people with diagnosed diabetes will increase 165%, from approximately 11 million in 2000 to 29 million in 2050 [1].

A large body of evidence has identified type 2 diabetes as a strong risk factor for cognitive decline and dementia. For example, a meta-analysis of prospective studies found that a history of type 2 diabetes conferred a significant 20-70% increased risk of cognitive decline and a significant 60% increased risk of dementia [2]. Thus, identifying strategies to reduce cognitive decline in this high-risk group is a public health priority.

In studies of mostly healthy adults, moderate alcohol intake has been consistently associated with decreased risk of cognitive impairment, cognitive decline, and dementia, compared with abstinence [3,4]. In addition, alcohol improves insulin resistance [5,6], and there is evidence that, compared with non-drinkers, adults with type 2 diabetes who are moderate drinkers have a lower risk of cardiovascular disease [7], also a strong risk factor for cognitive decline [4]. Thus, it is plausible that moderate alcohol consumption may reduce cognitive decline in those with type 2 diabetes.

We examined the association between moderate levels of alcohol consumption and cognitive function and cognitive decline over 4 years of follow-up in 1,698 women with type 2 diabetes enrolled in the Nurses' Health Study.

2. Subjects, Materials and Methods

2.1 Study population

The Nurses' Health Study was established in 1976 when 121,701 female nurses aged 30 to 55 years gave informed consent to participate in the study by responding to a mailed questionnaire about their health and lifestyle. Information is updated using biennial questionnaires. To date, the follow-up rate in the cohort is approximately 90%. The Institutional Review Board of Brigham and Women's Hospital approved this study.

The analyses presented here were restricted to participants in the cognitive function subcohort with prevalent type 2 diabetes at their first cognitive interview. The cognitive function subcohort includes 19,514 Nurses' Health Study participants aged 70 years and older and free of diagnosed stroke who completed a telephone cognitive assessment between 1995 and 2001. On each biennial questionnaire since 1976, all participants were asked to report a diagnosis of diabetes and a supplementary questionnaire regarding date of diagnosis, symptoms, diagnostic tests, and treatment was mailed to each participant who reported diabetes. Based on the information provided on the supplementary questionnaire, we confirmed type 2 diabetes using the criteria of the National Diabetes Data Group [8] because 90% of our participants were diagnosed before the American Diabetes Association released their criteria in 1997 [9]. In a validation study of 62 Nurses' Health Study participants with self-reported type 2 diabetes, 98% of the reports were confirmed by medical record reviews [10].

There were 2,101 participants who reported a type 2 diabetes diagnosis and also completed a cognitive interview. We excluded 374 women with missing data on alcohol consumption. In addition, because we were interested only in moderate alcohol consumption, we excluded 29 women reporting consumption of more than 30.0 g of alcohol per day. Thus, there were 1,698 women available for analysis of which 92% were white. Women with missing data on alcohol consumption were similar to the population for analysis in key characteristics, such as mean age and body mass index and prevalence of hypertension and heart disease. In addition, mean scores on tests of general cognition were identical among those with and without missing alcohol consumption data, indicating that substantial bias due to missing data is highly unlikely.

Follow-up cognitive assessments were administered twice, at approximately 2-year intervals. Among the 1,698 women included in this analysis, 5% died before the first follow-up. Of those who were alive, 93% completed the second cognitive assessment, 6% refused, and 1% were lost to follow-up. Of those who completed the second assessment, 8% died before the third assessment and, of those who were alive, 93% completed the third assessment, 5% refused, and 2% were lost to follow-up.

2.2 Telephone Cognitive Assessment

Trained interviewers who were unaware of the study hypothesis administered cognitive tests by telephone to participants in the cognitive study. In early interviews, we used only the Telephone Interview for Cognitive Status (TICS) [11], a telephone adaptation of the Mini-Mental State Examination (n=1,698). We gradually added five other tests; thus, the sample size differs somewhat for each cognitive test. The additional tests were: immediate and delayed recalls of the East Boston Memory Test (immediate recall: n=1,674; delayed recall: n=1,671) [12]; a delayed recall of the TICS 10-word list (n=1,608); a test of category fluency in which women name animals during 1 minute (n=1,672) [13]; and digit span-backwards, in which women repeat backwards increasingly long series of digits (n=1,609).

The primary outcomes of this study were general cognition and verbal memory; the latter is a strong predictor of Alzheimer's disease development [14,15]. To assess general cognition, we used the TICS score and also a global score, calculated by averaging the z-scores of the six cognitive tests. We assessed verbal memory by averaging the z-scores from the immediate and delayed recalls of the East Boston Memory Test and the TICS 10-word list. For each test, z-scores were calculated by dividing the difference between the participant's score and the mean score in the population for analysis by the standard deviation. The global and verbal memory scores were calculated only for women who completed all component tests (n=1,607 for global score; n=1,608 for verbal memory).

In a validation study we conducted among 61 high-functioning women similar to our nurses in age and level of education, global scores from telephone assessments and those from in-person assessments were highly correlated ($r=0.81$). In addition, we found a correlation of 0.70 between scores on two administrations of the TICS 31 days apart among a subset of nurses, indicating high test-retest reliability. Finally, in a study of inter-reviewer reliability, correlations across 10 interviewers for scoring of each test in our battery were greater than 0.95.

2.3 Measurement of Alcohol Consumption

Information on alcohol consumption was collected using a semi-quantitative food frequency questionnaire administered in 1980, 1984, 1986, and every 4 years thereafter. Participants were asked how often, on average, they consumed beer (12 ounces), wine (4-ounce glass), or liquor (1 shot) during the past year. Response options were: none or less than 1/month, 1-3/month, 1/week, 2-4/week, 5-6/week, 1/day, 2-3/day, 4-5/day, and 6 or more/day. We calculated total

grams of alcohol consumed per day by multiplying the consumption frequency of each beverage and its ethanol content (12.8 g for beer, 11.0 g for wine, and 14.0 g for liquor) and summing across beverages.

To assess the validity and reliability of our alcohol consumption measurement, 173 Nurses' Health Study participants living in the Boston area were asked to keep a written record of all food and beverages consumed over four 1-week periods approximately 3 months apart. High correlations were observed between average alcohol intake estimated by the diet records and average intake estimated by the food frequency questionnaire ($r=0.90$) and between 2 food frequency questionnaires administered approximately 1 year apart ($r=0.90$) [16].

2.4 Statistical Analysis

In primary analyses, we estimated alcohol consumption by averaging all available alcohol intake reports after participants' type 2 diabetes diagnosis and before their first cognitive interview. Alcohol consumption was categorized as 0.0 g/day (reference), 1.0-9.9 g/day (roughly equivalent to ≤ 1 drink/day; mean 2.2 (SD 2.3) g/day), or 10.0-30.0 g/day (roughly equivalent to more than 1, but no more than 3 drinks/day; mean 17.0 (SD 5.7) g/day). To compare baseline characteristics across alcohol consumption categories, we used one-way analysis of variance for continuous variables and chi-square tests for proportions. We used multivariable linear regression models to estimate the mean difference in initial cognitive score between women in each category of alcohol consumption compared with abstainers, adjusted for potential confounding factors. To examine the multivariable-adjusted association between alcohol consumption and rate of change in cognitive function over 3 repeated assessments, we used linear mixed effects models with person-specific random effects for baseline cognitive score (random intercept) and rate of change in cognitive function (random slope) [17]. Multivariable models included the following potential confounding factors assessed from the questionnaire administered immediately before the baseline cognitive interview: age at cognitive interview (continuous), highest attained education (registered nurse, bachelor's degree, master's degree or higher), history of myocardial infarction or angina pectoris (yes, no), use of postmenopausal hormone therapy (current, past, missing, never), body mass index (continuous), physical activity level (metabolic-equivalent tasks [METs] per week, continuous), duration of type 2 diabetes (years from diagnosis to date of first cognitive interview, continuous), regular use of insulin (yes, no), regular use of oral hypoglycemic medication (yes, no), and history of antidepressant use (yes, no). Adjustment for cigarette smoking, use of vitamin E, history of hypertension, and history of hypercholesterolemia did not change associations, and thus, were not included in the multivariable models.

Since long-term alcohol intake may be important in addition to alcohol intake after diabetes diagnosis, we performed a secondary analysis in which we averaged alcohol consumption from 1980 (the first time alcohol information was collected) through the first cognitive interview (i.e., both before and after type 2 diabetes diagnosis). In addition, since we were concerned about possible differential changes in alcohol intake just after the diagnosis of type 2 diabetes, we conducted a secondary analysis excluding women who reported a major reduction in their alcohol intake on the questionnaire following their type 2 diabetes diagnosis (i.e., from 5 or more grams of alcohol per day, or about 3 drinks per week, to none; $n=30$).

All statistical tests were two-sided and p values <0.05 were considered statistically significant. Analyses were performed with SAS version 9.1 (SAS Institute, Cary, NC, USA).

3. Results

Among these women aged 71 to 80 years, the mean duration of type 2 diabetes at the initial cognitive assessment was 13 years and 54% were regularly using insulin or oral hypoglycemic

medication. Women who consumed at most 1 drink (1.0-9.9 g of alcohol) per day were the most physically active and the most likely to have a Master's degree or higher (Table 1). A history of heart disease and use of insulin or oral hypoglycemic medications were least common in women consuming more than one, but no more than 3 drinks (10.0-30.0 g of alcohol) per day. The percentage of women with a history of antidepressant use was similar across alcohol consumption categories ($p=0.76$). Mean baseline scores on the TICS, mean global cognitive scores, and mean verbal memory scores were highest among women consuming at most 1 drink per day.

In multivariable-adjusted analyses, we found that the mean TICS score at the initial cognitive assessment was 0.31 (95% CI 0.02, 0.60) points higher among women who consumed at most 1 drink per day than the score among women who did not consume any alcohol (Table 2). To help interpret this mean difference, we considered the mean difference in TICS score associated with one year of age. In our data, a 1 year increase in age was associated with a 0.14 (95% CI 0.08, 0.20) point decrease in mean TICS score; thus, consumption of at most 1 drink per day could be considered as cognitively equivalent to being approximately 2 years younger in age. For verbal memory and the global cognitive score, the point estimates for the mean differences also indicated better performance in women who consumed at most 1 drink per day; however, these associations were not statistically significant after multivariable adjustment. Consumption of more than 1, but no more than 3 drinks per day compared with abstinence was not associated with mean TICS, verbal memory, or global scores at the first cognitive interview.

In longitudinal analyses of cognitive decline (mean follow-up=4.1 yrs), we did not observe associations between the level of alcohol consumption and changes in TICS, verbal memory, or global score (Table 3). For example, on the global score, the mean difference in decline was -0.01 (95% CI -0.03 , 0.01) standard units among women who consumed at most 1 drink per day and -0.01 (95% CI -0.04 , 0.03) standard units among women who consumed more than 1, but no more than 3 drinks per day compared with abstainers.

We conducted several secondary analyses for both initial cognitive function and for cognitive decline to further explore several issues. To consider possible effects of very long-term alcohol consumption, we repeated the analyses using the average of all available reports of alcohol intake, both before and after type 2 diabetes diagnosis. The relation of long-term moderate alcohol consumption (1.0-9.9 g per day) with the initial TICS score was similar to the primary analysis, although not statistically significant (mean difference 0.27, 95% CI -0.02 , 0.56). Estimates of the mean difference in global score (0.07, 95% CI 0.01, 0.13) and verbal score (0.09, 95% CI 0.01, 0.16) comparing long-term moderate consumers with abstainers were also positive, and they also reached statistical significance. In secondary analyses excluding women who decreased their alcohol intake after their type 2 diabetes diagnosis, the associations with initial TICS, verbal memory, and global scores were nearly identical to those in the primary analyses. For example, comparing moderate drinkers with abstainers, the mean difference in TICS score was 0.31 (95% CI 0.02, 0.61) points and the mean difference in the global score was 0.06 (95% CI -0.00 , 0.13) standard units.

When we conducted each of these secondary analyses longitudinally, in relation to change in cognitive function over time, results were similar to those in the main analysis, with no clear associations between alcohol consumption and cognitive decline.

4. Discussion

Among women with type 2 diabetes, consumption of at most 1 alcoholic drink per day compared with abstinence was related to better initial general cognition, but not with reduced rates of cognitive decline over four years of follow-up. Additionally, very long-term moderate

intake of alcohol before and after diabetes diagnosis was positively associated with both general cognition and verbal memory at the initial interview, but there was no association with cognitive decline. Thus, there was not a clear and consistent relation between alcohol intake and cognition.

Limitations of our study should be considered. First, our findings may reflect a true null association between moderate alcohol consumption and change in cognitive function. However, it is also possible that a relation with cognitive decline may not be evident within the relatively short follow-up period (of four years) for measuring cognitive decline. This may be especially pertinent considering the fairly small sample size in this subgroup of women with type 2 diabetes, limiting our power to detect the modest changes in cognition which are generally observed in non-demented populations. In addition, information on alcohol consumption was self-reported. However, a previous validation study demonstrated high validity and reliability of self-reported alcohol intake [16]. Furthermore, our measure of alcohol consumption is correlated with serum high density lipoprotein levels [16] and has been associated with risks of several chronic diseases, including cognitive function and cognitive decline in the entire cohort [4,18]. To address potential confounding, we conducted our study within a relatively homogeneous cohort of health professionals and performed multivariable-adjusted analyses. Also, results of age- and education-adjusted analyses were nearly identical to results of fully-adjusted analyses, suggesting that residual confounding is unlikely to explain most of the observed associations. However, the possibility of residual confounding cannot be ruled out in an observational study. Finally, our findings may not be generalizable to broader populations of adults with type 2 diabetes, including men and minorities. In addition, our participants were less likely to be regular users of insulin or oral hypoglycemic medication than adults in the general population with type 2 diabetes [19]. Thus, our findings may not be applicable to adults with more severe or less controlled type 2 diabetes.

Among the few existing studies that have examined alcohol intake and cognitive function specifically among adults with type 2 diabetes, study populations were restricted to men and participants' alcohol intakes were measured at one time, limiting comparisons with our analyses of long-term moderate alcohol intake in women. Nonetheless, in a cross-sectional study of 119 men with type 2 diabetes, Fan et al. found that overall performance on a battery of 5 cognitive tests was significantly better in moderate alcohol drinkers, defined as those usually consuming at least 1 drink per month to no more than 2 drinks per day, compared with abstainers, after adjusting for potential confounding factors ($p=0.02$), similar to our cross-sectional results [20]. Also, in a cross-sectional analysis of 187 men with cardiovascular disease or type 2 diabetes, Launer et al. reported significant decreased risks of poor cognitive function (Mini-Mental State Examination score <26) among men who drank <1 (OR 0.3, 95% CI 0.2-0.7) or 1-2 drinks per day (OR 0.2, 95% CI 0.1-0.4) compared with non-drinkers [21]. In the same study, there was no association between alcohol intake and change in cognitive function over 3 years of follow-up. Similar to our study, power to assess a relation with cognitive decline was likely limited given the very small sample size and short follow-up period. Overall, although these findings and ours are suggestive of a cross-sectional relation between moderate drinking after diagnosis with type 2 diabetes and better cognitive function, null results from longitudinal analyses do not support a potential role for moderate alcohol consumption in preserving cognitive function in adults with type 2 diabetes. However, clearly, additional data on associations with changes in cognitive function over time are needed from studies with long follow-up and larger samples.

Several lines of evidence support our finding of a relation between moderate alcohol intake and initial cognition. For example, among adults with type 2 diabetes, moderate alcohol consumption has been associated with decreased atherosclerotic progression [22], decreased levels of markers of inflammation and endothelial dysfunction [23], and decreased risk of

coronary heart disease [7]. These findings suggest that moderate alcohol may help preserve vascular health in type 2 diabetes, and thus might also preserve cognitive health. More directly, several studies have reported an association between moderate alcohol consumption and improved insulin sensitivity [5,6,24]. Maintenance of normal insulin levels in the brain may help prevent intraneuronal accumulation of amyloid beta and the formation of neurofibrillary tangles, which have been implicated in Alzheimer's disease development [25]. Together, these data support the plausibility of an intervening role of moderate alcohol consumption on the pathway between type 2 diabetes and cognitive impairment; however, as noted above, more longitudinal data are needed from epidemiologic studies.

In conclusion, considering the inconsistencies of our findings in analyses of initial cognitive function and change in cognitive function over time, our results do not clearly support a relation between moderate alcohol consumption after diagnosis with type 2 diabetes and cognition. However, further large-scale, longitudinal studies with long follow-up are needed to assess the association between moderate alcohol consumption and cognitive decline in adults with type 2 diabetes to better understand relations.

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Table 1

Characteristics of participants in the Nurses' Health Study with type 2 diabetes according to alcohol intake at baseline

Variable	Alcohol intake (g/day)			P-value ^a
	0.0 (N = 976)	1.0-9.9 (N = 609)	10.0-30.0 (N = 113)	
Participant characteristics (mean ± SD)				
Age at interview (years)	74.5 ± 2.4	74.2 ± 2.3	74.6 ± 2.4	0.02
Body mass index (kg/m ²)	29.4 ± 5.9	28.5 ± 5.3	26.7 ± 5.1	<0.01
Physical activity (METs/wk)	12.5 ± 13.1	14.3 ± 12.2	14.0 ± 11.3	0.02
Highest attained education (%)				0.06
Registered Nurse	82.6	77.5	77.0	
Bachelor's	13.6	16.3	18.6	
Master's or higher	3.8	6.2	4.4	
History of heart disease (%)	28.3	29.6	23.0	0.36
Postmenopausal hormone use (%)				0.05
Never	32.9	29.1	38.1	
Past	30.0	31.2	34.5	
Current	23.4	28.4	17.7	
Missing	13.7	11.3	9.7	
Antidepressant use (%)	11.0	11.2	13.3	0.76
Type 2 diabetes severity/control (mean ± SD)				
Type 2 diabetes duration (years)	11.8 ± 8.1	14.4 ± 8.8	14.1 ± 9.1	<0.01
Insulin use (%)	19.1	17.7	11.5	0.14
Oral hypoglycemic medication use (%)	43.0	42.2	22.1	<0.01
Baseline cognitive scores (mean ± SD)				
TICS score (n=1,698)	33.0 ± 2.8	33.4 ± 2.8	32.9 ± 3.7	0.02
Verbal score (n=1,608)	−0.02 ± 0.7	0.05 ± 0.7	−0.11 ± 0.7	0.05
Global score (n=1,607)	−0.02 ± 0.6	0.06 ± 0.6	−0.09 ± 0.7	0.02

^aFor tests of differences between the 3 groups, one-way analysis of variance was used for continuous variables and chi-square tests were used for categorical variables.

Table 2

Mean difference (95% CI) in initial cognitive test performance by category of alcohol intake

Cognitive test	Alcohol intake (g/day)		
	0.0 (ref)	1.0-9.9	10.0-30.0
TICS (n=1,698)			
Age-education adjusted	0	0.31 (0.02, 0.60)	-0.13 (-0.68, 0.42)
Multivariable adjusted ^a	0	0.31 (0.02, 0.60)	-0.01 (-0.57, 0.54)
Verbal score (n=1,608)			
Age-education adjusted	0	0.05 (-0.02, 0.12)	-0.09 (-0.23, 0.05)
Multivariable adjusted ^a	0	0.05 (-0.02, 0.12)	-0.06 (-0.21, 0.08)
Global score (n=1,607)			
Age-education adjusted	0	0.06 (-0.00, 0.12)	-0.06 (-0.19, 0.06)
Multivariable adjusted ^a	0	0.06 (-0.00, 0.12)	-0.04 (-0.16, 0.09)

^a Adjusted for age at interview, highest attained education, history of heart disease, postmenopausal hormone use, body mass index, antidepressant use, physical activity, type 2 diabetes duration, insulin use, and oral hypoglycemic medication use.

Table 3Multivariable-adjusted mean difference (95% CI) in rate of cognitive decline per year by category of alcohol intake^a

Cognitive test	Alcohol intake (g/day)		
	0.0 (ref)	1.0-9.9	10.0-30.0
TICS (n=1,698)	0	-0.03 (-0.12, 0.07)	-0.04 (-0.22, 0.15)
Verbal score (n=1,608)	0	-0.01 (-0.03, 0.01)	0.01 (-0.04, 0.05)
Global score (n=1,607)	0	-0.01 (-0.03, 0.01)	-0.00 (-0.04, 0.03)

^a Mean duration of follow-up is 4 years. Associations are adjusted for age at interview, highest attained education, history of heart disease, postmenopausal hormone use, body mass index, antidepressant use, physical activity, type 2 diabetes duration, insulin use, and oral hypoglycemic medication use.