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TEA DRINKING AND COGNITIVE FUNCTION IN OLDEST-OLD CHINESE

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Abstract: *Objective:* We examined the longitudinal association between tea drinking frequency and cognitive function in a large sample of oldest-old Chinese. *Design:* population-based longitudinal cohort study. *Setting:* The Chinese Longitudinal Healthy Longevity Survey (CLHLS). *Participants:* 7139 participants aged 80 to 115 (mean age 91.4 years) who provided complete data at baseline (year 1998). *Measurements:* Current frequency of tea drinking and past frequency at age 60 were ascertained at baseline, and baseline and follow-up cognitive assessments were performed in the years 1998 (n=7139), 2000 (n=4081), 2002 (n=2288) and 2005 (n=913) respectively. Verbal fluency test was used as measure of cognitive function. *Results:* Tea drinking was associated at baseline with higher mean (SD) verbal fluency scores: daily=10.7 (6.6), occasional=9.2 (5.8), non-drinker=9.0 (5.5). In linear mixed effects model that adjusted for age, gender, years of schooling, physical exercise and activities score, the regression coefficient for daily drinking (at age 60) and occasional drinking was 0.72 (P<0.0001) and 0.41(P=0.01) respectively. Tea drinkers had higher verbal fluency scores throughout the follow-up period but concurrently had a steeper slope of cognitive decline as compared with non-drinkers (coefficient for the interaction term Time*Daily drinking= -0.12, P=0.02; 'Time' was defined as the time interval from baseline to follow-up assessments in years). Similar results were found for current tea drinking status at study baseline year (1998) as predictor variable. *Conclusion:* Regular tea drinking is associated with better cognitive function in oldest-old Chinese.

Key words: Tea, cognition, dementia, oldest-old, Chinese.

Introduction

Tea drinking originated in China 4000-5000 years ago, and today is consumed by people in nearly every country of the world. Tea consumption is reportedly associated with various health benefits including lowered risk of cardiovascular diseases (1), stroke (2) and all cause mortality (3). More recently, results from population-based studies suggest that tea drinking could have cognitive benefits for elderly persons (4-7).

The potential neuroprotective effect of tea on cognitive function is important. Cognitive impairment is a major attributable cause of disability and significantly affects the quality of life in the elderly population. As well, severe cognitive impairment from dementia contributes hugely to high health care costs and societal burden of care. Current knowledge about modifiable risk factors for cognitive decline or Alzheimer's disease is still not firmly grounded (8). Population based longitudinal studies are urgently needed and could provide vital clues to potential preventive measures or therapeutic agents.

The present study used longitudinal data collected from a large sample of oldest-old Chinese in the Chinese Longitudinal Healthy Longevity Survey (CLHLS) to examine the association between tea drinking frequency and cognitive function in old age. We hypothesized that tea consumption would be associated with better cognitive function and slower cognitive decline.

Methods

Participants

The subjects were 7139 participants aged 80 to 115 who had complete data on tea consumption at the baseline (year 1998) of the Chinese Longitudinal Healthy Longevity Survey (CLHLS). Cognitive function data were collected at baseline (n=7139), year 2000 (n=4081), year 2002 (n=2288) and year 2005 (n=913) respectively. Details of the Chinese Longitudinal Healthy Longevity Survey (CLHLS) could be found at the website: http://www.geri.duke.edu/china_study/index.htm . To our knowledge, the CLHLS has the largest sample of the oldest-old with compatible young-old groups in the world (9).

Tea Consumption Information

Self-reported information on tea consumption habit was collected through face-to-face interview by trained research staffs. The subjects were asked to report their past frequency of tea drinking at around age 60 as well as their current frequency of tea drinking. The frequency was recorded as "almost every day" or "occasionally" or "rarely or never". Tea here includes all types of tea made from the plant Camellia sinensis.

Evaluation of Cognitive Function

Verbal fluency test was used to evaluate cognitive function. The subject was asked to "name as many kinds of food as possible in 1 minute." The same test was repeated at follow-up assessments. Since very poor cognitive performance indicates dementia, we excluded all subjects who scored less than 3 in

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the verbal fluency test at baseline in the present study.

Covariates

Age, sex, years of schooling, physical exercise (regular exercise vs. others) and activities score were considered as covariates. The summed scores of activities were obtained from the frequency (0=never, 1=sometimes, 2=almost every day) of participation in each of the following activities: housework, grow vegetables and other field work, garden work, read newspapers/books, raise domestic animals, play cards and/or mahjong, watch TV and/or listen to radio, religious activities.

Statistical Analysis

In order to examine the effects of tea drinking at age 60 on cognitive function measured by verbal fluency scores and incorporate the correlation of repeated measurements, we considered a linear mixed effects model: $y_{ij}= \beta_0+\beta_1 ED_i+\beta_2 OD_i +\beta_3 Time_{ij}+\beta_4 ED_i*Time_{ij}+\beta_5 OD_i*Time_{ij}+b_i+\varepsilon_{ij}$, where y_{ij} is the response variable for the ith subject at the jth visit, EDi is the indicator whether the ith subject drinks tea everyday at age 60, ODi is the indicator whether the ith subject drink tea occasionally at age 60 and Time is the time interval from baseline to follow-up assessments in years. We included a random effect bi to address the within-subject correlation. We then considered including additional confounding variables in the above linear mixed effects model. Specifically, we considered: $y_{ij}= \beta_0+\beta_1 ED_i+\beta_2 OD_i +\beta_3 Time_{ij}+\beta_4 ED_i*Time_{ij}$ $\beta_5 OD_i*Time_{ij}+\beta Z_{ij} +b_i+\varepsilon_{ij}$, where Z is a multi-dimensional vector including age, sex, years of schooling, physical exercise and summed activities score of the subject. We repeated the above analyses and fit the above two models by replacing the variable of tea drinking at age 60 by the variable of tea drinking at the baseline survey conducted in year 1998. All numerical analyses were carried out in SAS by using PROC MIXED.

Results

The characteristics of the study subjects at baseline are summarized in Table 1, categorized by tea drinking status in year 1998. Daily tea drinkers and occasional tea drinkers compared to non-drinkers had higher verbal fluency scores at baseline and there was a clear linear trend across tea consumption categories in mean scores (10.7, 9.2 and 9.0 respectively). However, tea drinkers were also found to be younger in age, include less women, have more years of schooling, exercise more and have higher activities scores (all p values<0.001). For example, 42.5% of the daily tea drinkers and 26.1% of occasional tea drinkers reported that they exercise regularly while the percentage for non tea drinkers was only 25.0%. As these factors are known to be associated with cognitive function in late life, they were considered as confounding factors and controlled in multivariate analysis.

Of note, most subjects did not change their tea consumption habit during the period from the time when they were 60 years old to the study baseline year in 1998. For example, 3952 subjects reported that they never or rarely drink tea in year 1998 and 3585 (90.7%) of them also reported that they never or rarely drink tea at around age 60. (Table 1)

Table 1
Characteristics of the study subjects by tea consumption status in year 1998

Characteristic	Tea consumption status in year 1998			
	Rarely or never (n=3952)	Occasionally (n=1281)	Daily (n=1906)	P value
Age in year, mean (SD)	92.0 (7.6)	91.4 (7.2)	90.0 (7.3)	<0.001
Women, N (%)	2549 (64.5)	690 (53.9)	835 (43.8)	<0.001
Years of schooling, mean (SD)	1.4 (3.1)	1.9 (3.6)	3.0 (4.5)	<0.001
Exercise, N (%)	987 (25.0)	334 (26.1)	810 (42.5)	<0.001
Activities score, mean (SD)	2.6 (2.4)	2.8 (2.4)	3.6 (2.6)	<0.001
Tea consumption at age 60				
Rarely or never	3585 (90.7)	289 (22.6)	181 (9.5)	<0.001
Occasionally	258 (6.5)	914 (71.4)	255 (13.4)	
Daily	109 (2.8)	78 (6.1)	1470 (77.1)	
Verbal fluency score (1998), mean (SD)	9.0 (5.5)	9.2 (5.8)	10.7 (6.6)	<0.001

P values were calculated with analysis of variance for continuous variables and Chi-squared test for categorical variables.

The characteristics of the study subjects were also summarized based on study visits. As shown in Table 2, there were statistically significant differences on baseline age, physical exercise, and mean activities score (P<0.001). This indicates that subjects who deceased or dropped out at each visit were different from those subjects who remained in the cohort.

Table 2
Characteristics of the study subjects based on study visits

Baseline characteristic	Year 1998 (n=7139)	Year 2000 (n=4081)	Year 2002 (n=2288)	Year 2005 (n=913)	P value
Age, in year, mean (SD)	91.4 (7.5)	89.9 (7.3)	88.5 (6.8)	86.3 (5.8)	<0.001
Women, N (%)	4074 (57.1)	2332 (57.1)	1284 (56.1)	530 (58.1)	0.76
Years of schooling, mean (SD)	1.9 (3.7)	1.9 (3.5)	2.0 (3.5)	2.1 (3.6)	0.28
Exercise, N (%)	2131 (29.9)	1390 (34.1)	815 (35.6)	346 (37.9)	<0.001
Activities score, mean (SD)	2.9 (2.5)	3.3 (2.5)	3.6 (2.6)	4.0 (2.5)	<0.001
Tea consumption					
Rarely or never	3952 (55.4)	2190 (53.7)	1215 (53.1)	485 (53.1)	0.19
Occasionally	1281 (17.9)	730 (17.9)	410 (17.9)	158 (17.3)	
Daily	1906 (26.7)	1161 (28.4)	663 (29.0)	270 (29.6)	

P values were calculated with analysis of variance for continuous variables and Chi-squared test for categorical variables.

Table 3 shows results from linear mixed effects models with tea drinking frequency at age 60 as the predictor variable. Based on the unadjusted model, at the start of the study (year 1998), daily drinkers on average had a 1.84 points higher verbal fluency score than non-drinkers (coefficient=1.84, P<0.0001); occasional drinkers in average had a 0.83 higher verbal fluency score than non-drinkers (coefficient=0.83, P<0.0001). The

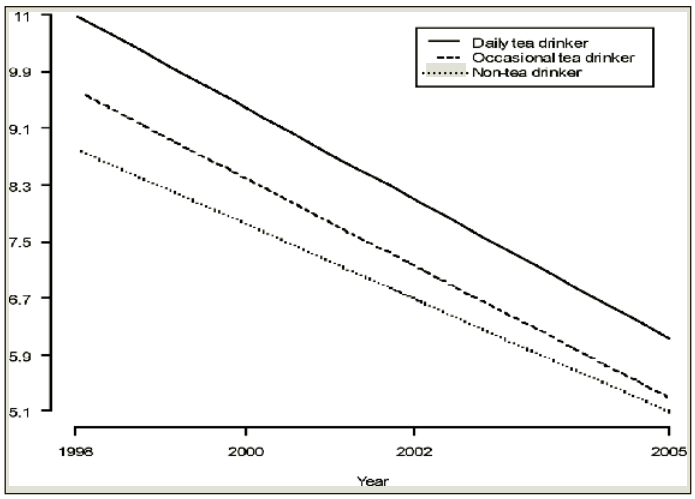
mean verbal fluency value decreased over time for all three groups (coefficient for time=-0.54, P<0.0001). It was noted that daily drinkers had a slightly steeper slope than Non-drinkers (coefficient for the interaction term Time * Daily drinker= -0.13, P=0.02) while the occasional drinkers had a non-significantly different slope from non-drinkers. From inspection of Fgure 1, it can be clearly seen that daily drinkers had consistently higher mean verbal fluency scores than occasional drinkers and occasional drinkers had consistently higher mean scores than non-drinkers across the follow-up period.

Table 3
The longitudinal association between tea drinking frequency at age 60 and verbal fluency scores

Parameter	Unadjusted model		Adjusted model	
	Coefficient	P-value	Coefficient	P-value
Daily drinker	1.84	<0.0001	0.72	<0.0001
Occasional drinker	0.83	<0.0001	0.41	0.01
Time	-0.54	<0.0001	-0.65	<0.0001
Time * Daily drinker	-0.13	0.02	-0.12	0.02
Time * Occasional drinker	-0.09	0.16	-0.08	0.16

In the adjusted model, the following variables were controlled for: age, gender, years of schooling, exercise, activities score.

Figure 1
The Decline in verbal fluency scores during follow-up period according to tea drinking frequency at age 60



The strength of the associations was attenuated when confounding factors were accounted for in the adjusted model but the main effect of Daily drinker, Occasional drinker and the interaction term Time * Daily drinker were still statistically significant at alpha=0.05 level. The coefficient was 0.72 (P<0.0001), 0.41(P=0.01) and -0.12 (P=0.02) respectively.

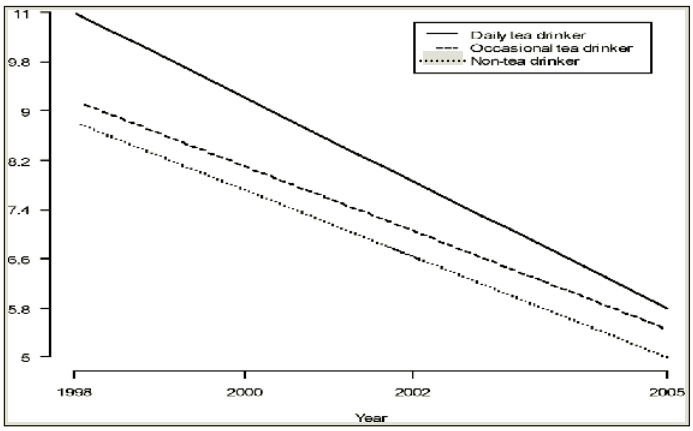
Similar results were obtained when tea drinking frequency at year 1998 was used as the predictor variable (Table 4, Figure 2). In the adjusted model, the regression coefficient for Daily drinker and the interaction term Time * Daily drinker was 0.65 (P<0.0001) and -0.13 (P=0.01) respectively. The main effect of Occasional-drinker was not statistically significant (P=0.61)

Table 4
The longitudinal association between tea drinking frequency in year 1998 and verbal fluency scores

Parameter	Unadjusted model		Adjusted model	
	Coefficient	P-value	Coefficient	P-value
Daily drinker	1.74	<0.0001	0.65	<0.0001
Occasional drinker	0.37	0.03	0.08	0.61
Time	-0.55	<0.0001	-0.67	<0.0001
Time * Daily drinker	-0.14	0.01	-0.13	0.01
Time * Occasional drinker	-0.002	0.98	-0.01	0.87

In the adjusted model, the following variables were controlled for: age, gender, years of schooling, exercise, activities score.

Figure 2
The Decline in verbal fluency scores during follow-up period according to tea drinking frequency in year 1998



Discussion

This longitudinal analysis of data from a group of oldest-old Chinese found that tea drinking was associated with better cognitive function measured by verbal fluency test during a 7-year follow-up period. The association was consistently significant for daily tea drinking regardless of whether the participants reported tea drinking frequency at age 60 or at study baseline year 1998 (when their mean age was 91.4 years). Although their performance was consistently higher than non-drinkers at all time points, we also found that daily tea drinkers had a steeper slope of decline (faster decline) in verbal fluency score from a higher baseline level.

The main results of our study are in line with several recent reports from population based studies (3, 5-7) that linked tea consumption to better cognitive function in older persons. To our knowledge, the present study examined for the first time this link in oldest-old, and the analysis was performed on a far larger sample, longer follow-up periods, and larger number of follow-up assessments. We adjusted for a number of potential

confounding factors in linear mixed effects models, and the results proved to be remarkably robust and consistent.

Because the baseline of cognitive function was imbalanced between tea drinking and non-tea drinking groups, we conducted further analysis by including baseline verbal fluency score in addition to the original predictor variables in all models considered in this paper. The effects of baseline cognitive function (measured by verbal fluency test) are significant in all these models ($P<0.001$). It was noticed from our analysis that the regression coefficients in these models were not much different from what we reported in tables.

A sizeable body of biological research data suggests that various phytochemicals including catechines, L-theanine and caffeine play major roles in explaining the underlying biological mechanisms for the favorable neurocognitive effects of tea drinking. Catechins, especially EGCG, are strong antioxidants and iron chelators and are involved in the modulation of signal transduction pathways, cell survival/death genes, and mitochondrial function (10). EGCG reduce β-amyloid generation by promoting α-secretase cleavage of amyloid precursor protein (11) and efficiently inhibits the fibrillogenesis of amyloid-beta by directly binding to the natively unfolded polypeptides and preventing their conversion into toxic, on-pathway aggregation intermediates (12). L-theanine, a free amino acid naturally found in tea, also possesses neuroprotective effect (13, 14). In addition, caffenine, another important component of tea leaf, is well known for its effect on attention and there are evidence that the combination of L-theanine and caffeine are beneficial for improving performance on cognitively demanding tasks (15, 16). There is evidence from a Finnish cohort study to suggest that midlife coffee consumption was related to reduced dementia risk (17).

In the linear mixed effects model, we observed that the slope for daily tea drinkers was steeper than non drinkers, suggesting a faster decline in verbal fluency scores. The result is unexpected at first glance and appear to contradict our previous findings that total tea consumptions was significantly associated with lower risk of cognitive decline (defined as drop in Mini-Mental Examination (18, 19). Score of > or =1 point during a median of 18 months period) in a cohort of Chinese older adults in the Singapore Longitudinal Ageing Study (SLAS) Cohort (7). However, it is important to note that the cohort participants in the current analysis were oldest-old. Although we excluded subjects who performed very poorly on verbal fluency test at baseline (score <3), a considerable number of subjects with dementia may be expected to arise in this oldest-old cohort from 7 years of follow up. Given this, this observation could be explained with cognitive reserve theory (20). Tea drinking helps to build up cognitive reserve which can compress the expression of brain damage. As the result of extra reserve, tea drinkers would have delayed manifestation of pathological processes in the brain but once it begins, the progression rate will be faster. This argument is supported by a number of recent studies (21-23). For example, based on data from 1157 participants who were free of dementia at study enrollment, it was reported that a modifiable factor for dementia risk, namely the frequency of cognitive activity predicts slower cognitive decline before dementia onset and faster decline thereafter (24).

The hypothesis that tea drinking can help to build up cognitive reserve is supported by recent data from population based studies. Among non-demented Chinese older adults, tea consumption was associated with better performance on global cognitive function, memory, executive function, and information processing speed (5). Tea consumption also reduced the risk of cognitive decline among community living older adults who had no evident cognitive impairment at baseline (7). However, there is no direct experimental data that support the hypothesized tea drinking and cognitive reserve association, and hence the explanation is still tentative.

Our study has several limitations: (1) We did not make detailed measurements of lifelong tea intake (frequency × duration), types of tea and blood concentrations of tea compounds (e.g. catechins and L-theanine) (25). (2) Although we have controlled for major factors that are known to be strongly associated with cognitive performance, it remains possible that residual confounding may still exist owing to imperfect measurement of these factors or lack of control of other potential confounders (3). Because we did not performed clinical diagnosis of Alzheimer's disease and other dementias, we cannot differentiate the effect of tea drinking on pathological cognitive decline associated with dementia and cognitive decline associated with normal ageing. We are also unable to determine the specific relationship between tea drinking and dementia risk. Given the rising tide of elderly persons with dementia in the coming decades (26) and the promising potential of tea drinking as a simple and cheap preventive measure, future cohort study with dementia incidence as the primary outcome is urgently needed.

Conclusion

In summary, our findings support a positive association between tea drinking and cognitive function in old people. The association should be investigated in more details in future studies.

Contributors: YZ is the principal investigator of the CLHLS project. LF proposed the analysis. JL and LF did the analysis. LF wrote the article. JL, TPN, TSL, EHK, YZ participated in revising the article. All authors read and commented on the final manuscript.

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