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TEA CONSUMPTION REDUCES THE INCIDENCE OF NEUROCOGNITIVE DISORDERS: FINDINGS FROM THE SINGAPORE LONGITUDINAL AGING STUDY

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Abstract: *Objectives:* To examine the relationships between tea consumption habits and incident neurocognitive disorders (NCD) and explore potential effect modification by gender and the apolipoprotein E (APOE) genotype. *Design:* Population-based longitudinal study. *Setting:* The Singapore Longitudinal Aging Study (SLAS). *Participants:* 957 community-living Chinese elderly who were cognitively intact at baseline. *Measurements:* We collected tea consumption information at baseline from 2003 to 2005 and ascertained incident cases of neurocognitive disorders (NCD) from 2006 to 2010. Odds ratio (OR) of association were calculated in logistic regression models that adjusted for potential confounders. *Results:* A total of 72 incident NCD cases were identified from the cohort. Tea intake was associated with lower risk of incident NCD, independent of other risk factors. Reduced NCD risk was observed for both green tea (OR=0.43) and black/oolong tea (OR=0.53) and appeared to be influenced by the changing of tea consumption habit at follow-up. Using consistent non-tea consumers as the reference, only consistent tea consumers had reduced risk of NCD (OR=0.39). Stratified analyses indicated that tea consumption was associated with reduced risk of NCD among females (OR=0.32) and APOE ε4 carriers (OR=0.14) but not males and non APOE ε4 carriers. *Conclusion:* Regular tea consumption was associated with lower risk of neurocognitive disorders among Chinese elderly. Gender and genetic factors could possibly modulate this association.

Key words: Tea, aging, neurocognitive disorders, Chinese, cohort study.

Introduction

Tea is one of the most widely consumed beverages in the world. It is generally believed that tea drinking is good for health but scientific evidence are available only in recent decades (1-6). Because tea is easily available, cheap and has no side effects at normal consumption level, drinking tea is potentially a good preventive measure for chronic diseases and may help to reduce healthcare cost at population level. This is especially relevant in the context of an growing and fast aging world population (7). It is well established that advancing age increases the risk of many chronic conditions, including major and mild neurocognitive disorders, which correspond to previously widely used diagnostic categories of dementia [based on earlier versions of the Diagnostic and Statistical Manual of Mental Disorders (DSM)] and mild cognitive impairment (MCI) (8).

Tea is traditionally viewed as a natural 'cognitive enhancer' and drinking strong tea to maintain alertness and concentration is a common practice in Chinese culture. This short-term effect of tea drinking on attention is supported by data from experimental studies (9). In addition to the well-known short-term cognitive effects of tea drinking, it is theoretically plausible that regular tea drinking may also benefit cognitive health in the long term. Tea contains various bioactive compounds such as the catechins, L-theanine, and caffeine. These compounds exert a neuroprotective effect via different mechanisms, namely antioxidant and anti-inflammatory actions, modification of Alzheimer's disease (AD) and its pathology (10-12), as well as the regulation of various biological mechanisms such as the secretion of stress hormones and the production of catecholamines; the cAMP-response element binding protein signaling cascade; inhibition of acetylcholinesterase activity; and the regulatory role of L-theanine in brain neurotransmitter systems (10, 13).

The first study on long term benefit of tea consumption on cognitive function was published by Kuriyama and colleagues in 2006 based on data from the Tsurugaya Project 1 (14). Our previous work based on the Singapore Longitudinal Aging Study (SLAS) cohort showed that tea consumption was associated with better cognitive performance (15), lowered risk of cognitive impairment (16), and reduced risk of future cognitive decline (16). Consistent findings were reported from the Hordaland Health Study (Norway) (17), the Chinese Longitudinal Healthy Longevity Survey (China) (18), and the Cardiovascular Health Study (United States) (19). Since cognitive decline from a previous level of performance is the first symptom of NCD, it is reasonable to postulate that tea consumption would be associated with lowered risk of incident NCD. However, data from the Cardiovascular Risk

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Factors, Aging and Dementia (CAIDE) study did not support an association between mid life tea drinking and reduced incidence of dementia or Alzheimer disease in late life (20) while analysis from the Nakajima Project support a protective role of green tea but not black tea (21). The causal association between tea consumption and incident NCD therefore remains uncertain.

In this study, we aim to test the longitudinal association between tea consumption and incident NCD and examine potential effect modification by gender and apolipoprotein E (APOE) genotype. We hypothesize that tea consumers have reduced odds of developing NCD during follow-up period as compared with non-tea consumers and that there is an inverse dose-dependent relationship between baseline level of tea consumption and incident NCD risk.

Methods

Subjects

The Singapore Longitudinal Aging Study (SLAS) is a community-based epidemiological study of aging and health of Singaporeans. Residents aged 55 years or above in a whole community in South East urban region of Singapore were identified from door-to-door census to participate in the study. A total of 2,808 participated. The study was approved by the National University of Singapore Institutional Review Board, and written informed consent was obtained from all participants. In the SLAS cohort, baseline data were collected from September 2003 to December 2005. The follow-up assessments for the ascertainment of incident cases of mild NCD were conducted from June 2006 to December 2010. The current study involved 957 SLAS participants who had a baseline MMSE total score of 26 or above and with information on cognitive status (normal cognitive function or neurocognitive disorder) at the second follow-up assessment.

Operational definition of neurocognitive outcomes

In the SLAS cohort, cognitive function was assessed by a modified version of the Mini-Mental State Examination (MMSE) (22) at baseline and follow-up assessments. Based on results from our validation study (22), a MMSE score of 26 and above was considered as normal. At follow-up assessments, subjects who had a MMSE score of <26 or a MMSE decline rate >= 1 point per year underwent further assessment by trained research staffs using the Clinical Dementia Rating (CDR) scale (23). All cases were reviewed by a panel consisting of two geriatricians (MSC, WSL), one psychiatrist (TSL), one psychiatric epidemiologist (LF) and the clinical assessment team (QG, MSZN). Global CDR scores were assigned based on scoring algorithm from the Washington University website (http://www.biostat.wustl.edu/~adrc/cdrpgm/).

In this analysis, we defined incident neurocognitive disorder as a CDR global score of 0.5 or above. We defined normal cognitive function as a MMSE score of 26 or above at the second follow-up. Based on the above definitions, there were 72 incident cases of neurocognitive disorders out of 957 subjects who had normal cognitive function at baseline; yielding a cumulative incident rate of 7.5% in this sub-cohort of SLAS participants.

There were 24 subjects who were lost to follow-up after MMSE but before CDR could be completed. They were not included in the current analysis.

Tea consumption

Detailed information on tea consumption habit was collected during baseline. Items on the tea questionnaire were designed according to the habitual intake of common tea types among local elderly using indigenous references and terms such as: 'Ceylon/English' tea, 'Chinese' tea', and 'Green" tea. Coding of the frequency of tea consumption was as follow: 0=Never or rarely; 1=Less than 1cup/wk; 2=More than 1 cup/wk but less than 1 cup/day; 3=1-2 cups/day; 4≥3 cups/day. A participant was classified as a non-tea consumer if the sum of the three scores equal to zero. A participant was classified as a tea consumer if the sum of the three scores is equal or greater than one. The level of tea consumption was also divided into four groups based on total tea consumption scores: 0=none, 1-2=low, 3-4=medium, >=5 =high. Because of the small number of pure green tea drinker (only one), we classified types of tea consumption as follows: green tea consumption= drink green tea with or without black/oolong tea; black/oolong tea consumption= drink black tea or oolong tea, but not green tea. We collected tea consumption information at the second follow-up assessment and divided study subjects into four subgroups based on tea consumption information at both baseline and follow-up: (1) Consistent non-tea consumers; (2) Tea consumption at follow-up but not at baseline; (3) Tea consumption at baseline but not at follow-up; (4) consistent tea consumers.

Baseline covariates

Related data collected at SLAS baseline included socio-demographic variables (age, gender, and education), substance use (cigarette smoking, alcohol consumption), coffee consumption, vegetable and fruits consumption, fish consumption, medical conditions, weight, height, blood pressure, and fasting blood glucose. The Geriatric Depression Scale (GDS) (24), which has been validated locally (25), was administered as a measure of depression. APOE genotyping was identified by PCR amplification followed by restriction endonuclease digestion of the PCR product. Physical activities were measured by the frequency (0=never, 1=sometimes, 2=often) with which the respondents engaged in fitness activities such as physical exercise routines, walking, active sports or swimming, and taiji. Social and productive activities were measured by the frequency (0=never, 1=sometimes, 2=often) with which the respondents engaged in social activities and productive activities.

Table 1
Descriptions of the study sample by tea consumption at baseline

Baseline characteristics	Tea drinkers (N=660)	Non-tea drinkers (N=297)	P
MMSE[1] total score at baseline, mean (SD)	28.5 (1.32)	28.3 (1.31)	0.012
MMSE total score at 5 year follow-up	28.8 (1.63)	28.4 (2.04)	0.007
Age, mean (SD)	64.5 (6.79)	64.6 (6.77)	0.78
Female (%)	371 (56.2)	219 (73.7)	<0.001
Education: Primary and below (%)	250 (38.0)	160 (54.1)	<0.001
Current and ex-smoker (%)	100 (15.2)	41 (13.9)	0.59
Current alcohol drinker (%)	96 (14.6)	20 (6.7)	0.001
Body Mass Index[2]	23.6 (3.29)	23.3 (3.77)	0.21
Hypertension[3] (%)	332 (50.3)	152 (51.2)	0.80
Diabetes mellitus[4] (%)	93 (14.1)	38 (12.8)	0.60
Heart disease (%)	31 (4.7)	14 (4.7)	0.99
History of stroke (%)	21 (3.2)	7 (2.4)	0.48
APOE ε4 carrier (%)	128 (20.6)	49 (17.7)	0.31
Depression[5] (%)	65 (9.8)	35 (11.8)	0.37
Physical activities score, mean (SD)	2.84 (1.94)	2.43 (2.06)	0.003
Social and productive activities score, mean (SD) (SD)	7.61 (3.55)	7.32 (3.32)	0.23
Eat a lot of vegetable and fruits[6] (%)	620 (94.2)	277 (93.9)	0.84
Eat a lot of fish (%)[7]	582 (90.7)	251 (86.3)	0.044
Coffee daily (%)	418(63.4)	196 (66.0)	0.44

1. Mini-Mental State Examination; 2. Weight (kg) / height $(m)^2$; 3. Defined as systolic blood pressure of >140 mm Hg or diastolic blood pressure of >90 mm Hg or a history of treatment for hypertension; 4. Defined as a fasting blood glucose concentration of ≥7.0 mmol/L or a history of treatment for diabetes mellitus; 5. Defined as Geriatric Depression Scale total score ≥5; 6. At least one serving everyday; 7. At least 3 times a week; P values were calculated using student t test for continuous variables and chi-squared test for categorical variables.

Statistical Analysis

Differences in characteristics between tea consumers and non-consumers or between incident NCD cases and subjects who maintained normal cognition at follow-up were evaluated using Chi-square test for categorical variables and student t test for continuous variables. We then conducted logistic regression analysis to examine the relationship between baseline tea consumption status and incident NCD. In the first set of analysis, tea consumption was treated as a simple binary variable (tea consumer versus non-tea consumer); in the second set of analysis, tea consumption was treated as polychotomous variable (none, low, medium, high). Non-tea consumers served as the reference group for both sets of analyses. We constructed two regression models: the unadjusted model included tea consumption as the sole variable. The adjusted model included the following baseline covariates: age, gender, education, smoking, alcohol consumption, Body Mass Index (BMI, as continuous variable), hypertension, diabetes, heart diseases, stroke, depression, APOE ε4, physical activities (as categorical variable), social and productive activities (as categorical variable), vegetables and fruits consumption (at least one serving everyday), fish consumption (at leas three times a week), daily coffee consumption. Hypertension was defined as systolic blood pressure of > 140 mm Hg or diastolic blood pressure of > 90 mm Hg or a history of treatment for hypertension. Diabetes mellitus was defined as a fasting blood glucose concentration of ≥ 7.0 mmol/L or a history of treatment for diabetes mellitus. Depression was defined as Geriatric Depression Scale total score ≥ 5.

To examine potential role of tea types, we repeated the above logistic regression analyses using tea type (no tea, black/oolong tea, green tea) as the predictor of interest. To examine the influence from the changing of tea consumption habit, we repeated the above analyses using the categorical variable on tea consumption status at baseline and at follow-up as the predictor of interest. To examine the effect modification by gender or APOE genotype, we performed stratified analyses for the subgroups of males and females, APOE ε4 carriers and APOE ε4 non-carriers, and then tested the interactions tea*gender and tea*APOE through the addition of cross-product terms to the regression model for the entire study sample.

All the statistical tests were two-sided, and a P value of < 0.05 was regarded as statistically significant. All data analysis

Table 2
Descriptions of the study sample by cognitive status 5 years after baseline

Characteristics	Normal cognition (N=885)	Neurocognitive disorder (N=72)	P
MMSE[1] total score at baseline, mean (SD)	28.5 (1.31)	28.1 (1.42)	0.02
MMSE total score at 5 year follow-up	28.8 (1.43)	25.7 (3.57)	<0.001
Age, mean (SD)	64.2 (6.50)	69.0 (8.47)	<0.001
Female (%)	550 (62.1)	40 (55.6)	0.27
Education: Primary and below (%)	369 (41.8)	41 (56.9)	0.013
Current and ex-smoker (%)	127 (14.4)	14 (19.4)	0.24
Current alcohol drinker (%)	111 (12.6)	5 (6.9)	0.16
Body Mass Index[2]	23.5 (3.50)	23.6 (2.86)	0.84
Hypertension[3] (%)	445 (50.3)	39 (54.2)	0.53
Diabetes mellitus[4] (%)	112 (13.8)	9 (12.5)	0.76
Heart disease (%)	37 (4.2)	8 (11.4)	0.006
History of stroke (%)	27 (3.1)	1 (1.4)	0.43
APOE ε4 carrier (%)	166 (19.9)	11 (16.7)	0.52
Depression[5] (%)	86 (9.7)	14 (19.4)	0.009
Physical activities score, mean (SD)	2.73 (1.99)	2.50 (1.96)	0.35
Social and productive activities score, mean (SD)	7.61 (3.50)	6.40 (3.19)	0.004
Eat a lot of vegetable and fruits[6] (%)	829 (94.1)	68 (94.4)	0.9
Eat a lot of fish (%)[7]	768 (89.1)	61 (91.5)	0.52
Coffee daily (%)	562 (63.6)	52 (72.7)	0.14
Tea consumption (%)	621 (70.2)	39 (54.2)	0.005
No tea intake	264 (29.8)	33 (45.8)	0.015
Low tea intake	161 (18.2)	15 (20.8)	
Medium tea intake	249 (28.1)	12 (16.7)	
High Tea intake	211 (23.8)	12 (16.7)	

1. Mini-Mental State Examination; 2. Weight (kg) / height (m) 2; 3. Defined as systolic blood pressure of >140 mm Hg or diastolic blood pressure of >90 mm Hg or a history of treatment for hypertension; 4. Defined as a fasting blood glucose concentration of ≥7.0 mmol/L or a history of treatment for diabetes mellitus; 5. Defined as Geriatric Depression Scale total score ≥5; 6. At least one serving everyday; 7. At least 3 times a week; P values were calculated using student t test for continuous variables and chi-squared test for categorical variables.

was conducted by IBM SPSS version 22 (SPSS Inc. Chicago, Illinois, US).

Results

The majority (69%) of the 957 study participants were tea consumers at baseline; 297 participants (31.0%) reported that they never or rarely consumed any tea and were classified as non-tea consumers. In univariable analysis, tea consumption was significantly associated with higher MMSE total scores, lower female proportion, higher education level, higher proportion of alcohol drinker, higher levels of physical activities, and higher fish consumption. (Table1) Compared with subjects who maintained normal cognition through out the follow-up period, the incident NCD cases had older age, lower education level, higher proportions of heart diseases and depression, lower level of social and productive activates, and lower proportion of tea consumers at baseline. They also had lower scores of MMSE and a clear decline on performance during the follow-up period (from 28.1 to 25.7). (Table 2)

Table 3 shows the associations between tea consumption and incident NCD. There were 39 incident cases (5.9%) from the 660 tea consumers, compared with 33 (11.1%) out of 297 non-tea consumers. The OR of incident NCD for tea consumption was 0.50 in the unadjusted model. The result remained unchanged (OR=0.50) when we controlled for potential confounders in the adjusted model. The results were further supported by regression analysis based on 4 levels of tea consumption (none, low, medium, high): the ORs with reference to none-tea consumer for low, medium and high level of tea intake were 0.75, 0.39 and 0.46 respectively in the unadjusted model (P for linear trend=0.004). With adjustment for potential confounders, the ORs were modified but the liner

Table 3
Risk of neurocognitive disorder according to tea consumption status at baseline

Tea consumption	No. (%)		OR (95% CI)	
	Total	Neurocognitive disorder	Unadjusted	Adjusted
No	297	33 (11.1)	1 [reference]	1 [reference]
Yes	660	39 (5.9)	0.50 (0.31 – 0.82)	0.50 (0.28 – 0.87)
Level of tea intake				
Low	176	15 (8.5)	0.75 (0.39 – 1.42)	0.65 (0.31 – 1.36)
Medium	261	12 (4.6)	0.39 (0.19 – 0.76)	0.36 (0.16 – 0.78)
High	223	12 (5.4)	0.46 (0.23 – 0.90)	0.54 (0.25 – 1.20)
Type of tea				
Black/Oolong tea Green tea1	390	26 (6.7)	0.57 (0.33 – 0.98)	0.53 (0.29 – 0.98)
Green Tea	270	13 (4.8)	0.41 (0.21 – 0.78)	0.43 (0.20 – 0.95)

For level of tea intake: unadjusted model, P for linear trend=0.004; Adjusted model, P for linear trend=0.025; Odds Ratios and 95% confidence intervals were calculated using multiple logistic regression; Variables that were adjusted for in the model are: age, gender, education, smoking, Alcohol consumption, BMI (continuous), Hypertension, Diabetes, Heart disease, Stroke, Depression (GDS ≥5), APOE ε4, Physical activities, social and productive activities, vegetables and fruits consumption, fish consumption, coffee consumption.

Table 4
Risk of neurocognitive disorder according to tea consumption status at baseline and follow-up assessment (N=908)

Tea Consumption		No. (%)		OR (95% CI)	
Baseline	Follow-up	Total	Neurocognitive disorder	Unadjusted	Adjusted
No	No	179	17 (8.7)	1 [reference]	1 [reference]
	Yes	77	5 (6.5)	0.73 (0.26 – 2.01)	0.65 (0.21 – 1.98)
Yes	No	200	11 (5.5)	0.61 (0.28 – 1.34)	0.44 (0.17 – 1.10)
	Yes	435	16 (3.7)	0.40 (0.20 – 0.81)	0.39 (0.18 – 0.88)

Odds Ratios and 95% confidence intervals were calculated using multiple logistic regression; Variables that were adjusted for in the model are: age, gender, education, smoking, Alcohol consumption, BMI (continuous), Hypertension, Diabetes, Heart disease, Stroke, Depression (GDS ≥5), APOE ε4, Physical activities, social and productive activities, vegetables and fruits consumption, fish consumption, coffee consumption.

Table 5
Lowered odds of having incident neurocognitive disorder among tea drinkers as compared with non-tea drinkers: stratified analyses based on gender and APOE ε4 status at baseline

Subgroup	Subgroup N	Tea consumption N		NCD N (%)	Adjusted OR (95% CI)
Men	367	Yes	289	23 (8.0)	0.91 (0.34 – 2.49)
		No	78	9 (11.5)	
Women	590	Yes	371	16 (4.3)	0.32 (0.15 – 0.69)
		No	219	24 (11)	
APOE ε4 carriers	177	Yes	128	5 (3.9)	0.14 (0.02 – 0.93)
		No	49	6 (12.2)	
Non APOE ε4 carriers	722	Yes	494	31 (6.3)	0.56 (0.30 – 1.04)
		No	228	24 (10.5)	

Odds Ratios and 95% confidence intervals of incident NCD for tea drinkers, calculated using multiple logistic regression; Variables that were adjusted for in the model are: age, gender, education, smoking, Alcohol consumption, BMI (continuous), Hypertension, Diabetes, Heart disease, Stroke, Depression (GDS ≥5), APOE ε4, Physical activities, social and productive activities, vegetables and fruits consumption, fish consumption, coffee consumption; The two interaction terms were tested in the logistic regression model for the entire study sample, both interactions were not significant at alpha=0.05 level. P value for the interaction term tea*gender was 0.089; P value for the interaction term tea*APOE ε4 was 0.431.

trend and the OR for medium tea intake remained statistically significant (adjusted ORs: 0.65, 0.36, 0.54, P for linear trend =0.025). Both green tea and black/oolong tea were associated with lowered odds of having NCD, the adjusted OR was 0.43 and 0.53 respectively. The results remained essentially the same when we further included interval to follow-up as a covariate in the regression models.

Analysis results based on 908 study subjects who had information on both baseline and follow-up tea consumption are shown in Table 4. Using subjects who were non tea consumers at both baseline and follow-up as the reference group, only subjects who reported tea consumption at both time points had reduced odds of developing NCD, the adjusted odds ratio was 0.39. Further analyses stratified by gender and APOE genotype are shown in Table 5. Tea consumption was associated with reduced risk of NCD among females (OR=0.32) and APOE ε4 carriers (OR=0.14) but not males (OR=0.91) and non APOE 4 carriers(OR=0.56) . However, the interaction terms were not statistically significant when tested in the entire study sample.

Discussion

Using longitudinal data from 957 participants of the Singapore Longitudinal Aging Study, we demonstrated that baseline tea consumption reduced the risk of developing neurocognitive disorder (NCD) at follow-up. The association between tea consumption and reduced risk of NCD was independent of known risk factors and appeared to be dose and duration dependent. The protective effect of tea consumption on incident NCD was evident for both green tea and black/oolong tea, and was much stronger among females and APOE ε4 carriers. Our data suggest that drinking tea reduces the risk of NCD, and certain subgroups in the population may benefit more than others.

Our findings are consistent with the results from our earlier study (16) that used MMSE as the primary outcome. In the current study, clinical outcome of incident NCD was used as the dependent variable in all analyses. This is critical and important as a decline on cognitive test score happens in normal aging and can be the consequence of many factors other than dementia. With a clinically relevant study outcome, our current study firmly established the relationship between tea consumption and pathological cognitive decline. Further more, we reported new finding on gender and APOE genotype as potential effect modifier; the findings are important in view of growing interests in personalized medicine and disease prevention.

Our findings have important implications for dementia prevention. Despite high quality drug trials, effective pharmacological therapy for dementia (major neurocognitive disorders) still remains elusive and prevention strategies are far from satisfactory. Our data suggest that a simple lifestyle measure such as tea drinking can reduce a person's risk of developing neurocogntive disorders in late life. Together with earlier reports on cognitive benefits of tea drinking (13), our study supports the promotion of tea drinking as a simple, culturally acceptable and cheap preventive measure among other known protective interventions such as participating in physical, social and cognitive activities.

Only two previous studies have rigorously examined the association between tea consumption and incident NCD (dementia or MCI). The CAIDE Study identified 61 (4.3%) incident dementia cases (48 with Alzheimer disease, AD) during a follow-up period of 21 years. In adjusted logistic regression analysis, the OR of dementia and AD for tea drinkers was 1.04 (95% CI 0.59–1.84) and 0.91 (95% CI 0.48–1.71) using non consumer as the reference group (20). We argue that the negative findings from the CAIDE study can be largely explained by the small number of tea consumers in their study sample, hence their findings from a Caucasian population may not be directly translated into other populations with more prevalent tea-drinking habits. Indeed, the researchers from the CAIDE team conceded that the statistical power in their analysis was low because tea drinking was not common in their sample (20). However, one-time baseline classification of tea drinking in mid-life may be subject to misclassification bias towards the null finding if tea consumptions changed over a long follow up interval. The second report was based on analysis of longitudinal data from 490 participants in the Nakajima Project, Japan (21). The participants were assessed as cognitively normal in 2007-2008 (baseline); 26 incident dementia cases and 64 MCI cases were ascertained at the follow-up survey in 2011-2013. The odds ratio for combined incidence of dementia and MCI was 0.32 for daily green tea consumers and 0.47 for participants who consumed green tea 1-6 days per week compared with participants who did not consume green tea at baseline (21). There was no association between black tea and the incidence of dementia and MCI but the number of black tea consumers was very small: only 86 (17.6%) of the participants consumed black tea at least 1 day per week, and the number of daily black tea consumers was only 6 (in contrast, the number of daily green tea consumer was 157) (21).

We have demonstrated in earlier analysis that the protective effect of tea consumption on cognitive function was not limited to a particular type of tea (15, 16), and any findings on tea types may be peculiar to the tea drinking habits of the study population under examination. Our findings are therefore consistent with findings from the Nakajima Project in showing that tea consumption does reduce the incidence of NCD. Given that the homogeneity of tea consumption habits as seen in the Japanese study population may not be widely applicable to most populations, the observed null finding on black tea from the Nakajima Project should be viewed with circumspection. Due to extremely small number of pure green tea consumers in our study sample, we have defined green tea consumer as individuals who drank green tea with

or without the consumption of black/oolong tea and revealed that both green tea and black/oolong tea consumers (those who drank black/oolong tea only) had reduced odds of developing NCD at follow-up. The findings suggest that the protection of tea consumption against incident NCD is not limited to any specific type of tea.

Our findings support a dose-dependent association between tea consumption and NCD risk. In regression analysis based on the levels of baseline tea intake, the liner trend between tea consumption (never, low, medium, high) was statistically significant (P for linear trend=0.025) despite the observations that the OR for high tea consumption subgroup was greater than that of the medium tea consumption subgroup (adjusted value: 0.54 vs. 0.39) and was statistically non-significant (95% CI: 0.25, 1.20). Somewhat errant OR values can be explained by the insufficient statistical power caused by small numbers of NCD cases in each of the subgroups. Refined analysis could be conducted using data from cohorts that have larger sample sizes. Our analysis based on information of baseline and follow-up tea consumption supports the importance of consumption duration. Compared with subjects who did not report tea intake at both baseline and follow-up, only subjects who were tea drinkers at both time points had reduced odds of developing NCD (OR=0.39). It is reasonable to postulate that those subjects had longer total duration of tea consumption than those who reported tea consumption at one time point (baseline or follow-up) only. However, since no details on lifetime consumption duration were collected, the conclusion is preliminary and should be replicated by further studies.

We conducted statistical analysis using binary logistic regression because NCD status was ascertained one time only for each subject that was eligible for further clinical assessment. The outcome of interest in our analysis is indeed cumulative incident NCD cases. In longitudinal study, the best design is to conduct follow-up assessments for the ascertainment of disease status at multiple clearly separated time points to produce survival time data that are suitable for analysis techniques such as the Cox proportional hazards regression. Because binary logistic regression was used in our analysis in view of the data structure, cautions should be exercised in the interpretation of effect size as odds ratio is not equivalent to relative risk.

We conducted stratified analysis based on gender and found that the protective effect of tea drinking against incidence NCD was only statistically significant for females. This finding was consistent with an earlier finding from the Cardiovascular Health Stud (CHS) in the United States: in this longitudinal analysis of 7.9 years cognitive data from 4,809 participants aged 65 years and above, there was attenuated rate of cognitive decline among tea consumers compared to non-consumers in women but not men. Our data suggest an effect modification role of gender but since the interaction was not statistically significant in the whole study sample, firm conclusions can not be drawn. Furthermore, the biological basis underlying this potential effect modification remains unclear at this juncture.

We also conducted stratified analysis based on APOE genotype. This is motivated by the fact that APOE is the single most important risk gene for Alzheimer disease, our earlier finding of the interaction between APOE and other nutritional factors (26), and a recent report on the interaction of tea drinking and the FOXO genotypes in determining cognitive status among the oldest old (27). While the huge difference in ORs for APOE ε4 carriers (0.14) and non APOE ε4 carriers (0.56) may be suggestive, the interaction term APOE*Tea on incident NCD was not statistically significantly. Thus, our findings that the neuroprotective benefits of tea drinking may, in part, depend upon individual genetic profiles need to be replicated in further studies.

The neuroprotective role of tea consumption is biologically plausible; the postulated mechanisms have been reviewed by Feng and colleagues recently (10). However, the neural mechanisms lacked support from human data. Recently, Schmidt and colleagues provided the first human evidence for the putative beneficial effect of tea consumption on cognitive functioning. They demonstrated that green tea extract enhanced parieto-frontal connectivity during working memory, and the magnitude of increased connectivity positively correlated with improvement in task performance (28). It is possible that long term repeated consumption may result in lasting structural and functional changes in the brain of tea consumers, which confer protection against the development of NCD. Based on current knowledge, this long term benefit is largely due to catechins and L-theanine in tea leaves but other compounds such as caffeine may also play an important role. Caffeine is the best known psychoactive stimulant, and both caffeine consumption and plasma caffeine levels have been associated with mild cognitive impairment and its progression to dementia (29).

In summary, we found that tea drinking reduced the incidence of neurocognitive disorders among community living older adults. The neuroprotective effects of tea drinking as a preventive measure at the population level clearly deserves further research. Of note, objective biomarkers of tea intake (30-32) are now available and can be used in future studies. Clinical trials on tea extracts or bioactive compounds in tea should be undertaken to delineate the contribution of various bioactive compounds in tea in preventing cognitive decline and incident NCD.

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Author Contributions: Lei Feng formulated the hypothesis, performed literature review and statistical analysis, drafted and revised the manuscript. Mei Sian Chong, Wee-Shiong Lim, Tih-Shih Lee, Ee-Heok Kua reviewed statistical analysis, interpreted the results, reviewed and revised the manuscript. Tze Pin Ng conceptualized and designed the SLAS project, reviewed statistical analysis, interpreted the results, and revised the manuscript. Qi Gao, Ma Shwe Zin Nyunt, Tih-Shih Lee, Simon Lowes Collinson, Tung Tsoi and Ee-Heok Kua reviewed and revised the manuscript.

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