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GxE Interactions between FOXO Genotypes and Tea Drinking Are Significantly Associated with Cognitive Disability at Advanced Ages in China

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Logistic regression analysis based on data from 822 Han Chinese oldest old aged 92+ demonstrated that interactions between carrying FOXO1A-266 or FOXO3-310 or FOXO3-292 and tea drinking at around age 60 or at present time were significantly associated with lower risk of cognitive disability at advanced ages. Associations between tea drinking and reduced cognitive disability were much stronger among carriers of the genotypes of FOXO1A-266 or FOXO3-310 or FOXO3-292 compared with noncarriers, and it was reconfirmed by analysis of three-way interactions across FOXO genotypes, tea drinking at around age 60, and at present time. Based on prior findings from animal and human cell models, we postulate that intake of tea compounds may activate FOXO gene expression, which in turn may positively affect cognitive function in the oldest old population. Our empirical findings imply that the health benefits of particular nutritional interventions, including tea drinking, may, in part, depend upon individual genetic profiles.

Key Words: FOXO genotypes—Tea drinking—GxE interactions—Cognitive disability—Oldest old.

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PREVIOUS studies have found that FOXO3A is associated with human longevity in Japanese-Americans from Hawaii (1), Italians (2), Ashkenazi Jews, Americans in California and New England (3), and Germans (4); and FOXO1A and FOXO3A have been associated with longevity in Han Chinese (5,6). It is well known that in the mammalian brain, FOXO is involved in the regulation of many processes associated with cognitive functioning (7,8).

Accumulating data from various studies indicate that tea drinking improves health and reduces the risk of age-associated chronic diseases, such as stroke (9) and depression (10), and effectively shut down high mobility group box-1 (HMGB1)-induced inflammation in a life-saving fashion (11). Tea drinking also elicits improvements in cognitive function in both human and animal studies (12–16). Recent publications showed that tea drinking was significantly associated with cognitive disability (14) and mortality (17) among Chinese oldest old aged 80+.

Various studies have shown that interactions between genotypes and social/behavioral factors (GxE) play a crucial role in health (18), and the effects of tea consumption on diseases vary by genotypes (19–23). Belguise and coworkers showed that intake of green tea polyphenol epigallocatechin-3-gallate activated FOXO3A gene expressions, which in turn induced estrogen receptor-α expression and reversed invasive phenotype of breast cancer cells in mouse (24). Several other studies using animal and human cell models demonstrated that intake of tea compounds activate FOXO gene expression and modulate its biological functions (25–30).

Given the important roles of FOXO genes and tea polyphenols in the health of humans and the FOXO-by-tea interaction effects in animal and human cell models reported in the literature, we posed the following research question: Are the GxE interactions between carrying the FOXO genotypes and tea drinking significantly associated with cognitive disability in human populations at advanced ages?

Previous studies indicated that, in general, genetic (including GxE) impacts on health and longevity are more profound at advanced ages (31). Also, the oldest old population, which is more likely to need care assistance, has been increasing much more rapidly than any younger age groups in many countries including China (32). These facts imply that focusing on the oldest old is a useful way to investigate the GxE effects on healthy aging. However, almost all previous studies in this field have focused on young–old and middle-aged adults and few had large enough numbers of oldest old subjects. Moreover, our in depth review of the literature did not reveal any previous publications of the effects of GxE interactions between FOXO genotypes and tea drinking on healthy aging in human populations.

Data Sources, Measurements, and Methods

Data Sources

Our analyses are mainly based on genotypic and phenotypic data from 822 oldest old aged 92+ in the 1998 initial baseline interview of the Chinese Longitudinal Healthy Longevity Survey (CLHLS). The CLHLS was conducted in 1998, 2000, 2002, 2005, 2008–2009, and 2011–2012 in a randomly selected half of the counties and cities in 22 out of 31 provinces in China (33). Extensive data were collected using internationally standardized questionnaires adapted to Chinese cultural and social context. Careful evaluations, including reliability coefficients, factor analysis, and age reporting at oldest old ages, have shown that the data quality of CLHLS surveys is of reasonably high quality (34,35). All of the genotypic and phenotypic data used in this study are from participants who belong to the same ethnic group of Han Chinese in China. The single SNP association analysis, genotype association analysis, linkage disequilibrium, and haplotype association analysis, based on these data, were presented in Li and coworkers (5), and thus there is no need to repeat them here. We abbreviate in this article the SNP rs17630266 of FOXO1A gene as FOXO1A-266, the two SNPsrs2253310 and rs2802292 of FOXO3A gene as FOXO3A-310 and FOXO3A-292, respectively.

We briefly discuss the dependent variable, main independent variables, and covariates below. The statistical frequency distributions of these variables are presented in Table 1, which are straightforward and self-explanatory, and thus will not be discussed in detail here due to space limitation.

Table 1. Statistical Description of the Basic Variables

Variables	% or Average	Variables	% or Average
Dependent variable		Main independent variables (continue)	
Average MMSE score	18.8	FOXO1A-266 (dominant)	62.0%
Cognitive disability	37.8%	FOXO1A-266 (recessive)	16.2%
		FOXO3A-310 (dominant)	53.8%
Main independent variables		FOXO3A-292 (dominant)	53.8%
Drank tea around age 60			
Almost everyday	17.6%	Covariates	
Sometimes	18.5%	Males	23.6%
Rarely or never	63.8%	Average age	100.4
		Urban residents	28.0%
Drank tea at present time		1+ year of schooling	17.4%
Almost everyday	20.7%	Regular exercise	23.8%
Sometimes	15.6%	Smoking in recent 5 years	12.4%
Rarely or never	63.7%	Currently drink alcohol	22.7%

Dependent Variables: Cognitive Disability

In CLHLS, cognitive function was measured by Mini-Mental State Examination (MMSE), which is an internationally standardized assessment tool (36), and adapted to the Chinese cultural context and carefully tested in the pilot survey (37). The questionnaire includes 24 items regarding orientation, registration, attention, calculation, recall, and language, with a total score ranging from 0 to 30. No proxy was allowed in answering the MMSE questions. Following the practice adopted in the literature concerning cognitive function among Chinese elderly (38), we use the following MMSE score cutoffs to define cognitive disability: less than or equal to 17 for those without schooling, less than or equal to 20 for those with 1–6 years of education, and less than or equal to 24 for those with more than 6 years of education. We also use the continuous MMSE score to compare with the results using categorized cognitive disability.

Main Independent Variables

The FOXO genotypes.—FOXO genotypes may be defined following the dominant, recessive, or additive models. In a dominant model, any genotype that contains one or two copies of the minor allele is coded as 1, namely, carrier; otherwise the genotype that does not contain any copy of the minor allele is coded as 0, namely, noncarrier (ie, mm, Mm = 1; MM = 0, here, M: major allele, m: minor allele). In a recessive model, only the homozygous mm genotype is coded as 1 (ie, mm = 1; Mm, MM = 0). In an additive model, genotype MM is coded as 0, Mm, 1, mm, 2. We mainly use dominant and recessive models (rather than additive model) to define the genotypes in this study, as they clearly distinguish the genotype carriers and noncarriers statuses, but the additive model does not. Also, further grouping the samples in the additive model results in much more GxE interaction terms in the regressions and would in turn negatively affect the estimates and complicate the discussions.

Tea drinking at present time (in the baseline survey conducted in 1998) and tea drinking at around age 60.—Respondents were asked questions: (i) "Do you drink tea regularly at present time?" and (ii) "Did you drink tea regularly at around 60 years old?" Response categories were "almost everyday"; "sometimes"; and "rarely or never." The variable "tea drinking" is coded as 1 if the answer is "almost everyday" or "sometimes" and coded as 0 otherwise. We also tried to code "tea drinking" as 1 if the answer is "almost everyday," and as 0 if the answer is "sometimes" or "rare or never," but the results were less meaningful compared to coding "almost everyday" or "sometimes" as 1. The tea drinking at around age 60 and at present time are highly correlated with a correlation coefficient of 0.70; 81.1% of those who were a tea drinker at around age 60 continued doing so until they reached oldest old age category, and 88.8% of those who were not a tea drinker at around age 60 remained as non-tea drinkers at advanced ages.

Other Controlled Covariates

Other covariates controlled for in all of our multivariate statistical models include gender, age, residence (rural vs urban), education (<1 year of schooling vs ≥ 1 year of schooling), marital status (currently married vs unmarried including never-married, divorced, or widowed), regular exercise (yes vs no), smoking (yes vs no), and alcohol drinking (yes vs no).

Statistical Analysis

We employ the multiple logistic regression model with categorized cognitive disability as the dependent variable. Following the standard Aiken and West procedure (39), we conducted blocked multiple regressions and Chi-square tests to examine whether the difference in likelihood ratios between the full models including the interaction block (Models I-2, II-2, III-2, and IV-2 in Table 2) and the models without the interaction block (the Models I-1, II-1, III-1, and IV-1 in Table 2) are statistically significant. Such tests also inform whether the interaction terms included in the regressions are statistically significant. The results of these additional tests are listed in the last three rows of Tables 2, and they are all consistent with the p value estimates of the interaction terms. The significant results of these additional tests also imply that the likelihood of a Type I error in our estimates of the interaction terms may be small (40).

The logistic regression analyses were performed using STATA/SE 12.0.

Results

The Estimates of the GxE Interaction Terms Between Carrying FOXO Minor Allele and Tea Drinking

The results presented in Table 2 indicate that GxE interaction terms between carrying FOXO1A-266 minor allele (recessive model) and drinking tea at the present are significantly associated with lower risk of cognitive disability at advanced ages (odds ratio = 0.32; p = .04). The estimates also indicate that GxE interaction terms between carrying the FOXO1A-266 or FOXO3A-310 or FOXO3A-292 minor allele (dominant model) and tea drinking at around age 60 are significantly associated with lower risk of cognitive disability at advanced ages (odds ratios = 0.45–0.46; p = .02). Similar significant results of the effects of FOXO-by-tea-drinking interactions on reduced cognitive disability were also found if we define the genotypes of carrying the FOXO1A-266 or FOXO3A-310 or FOXO3A-292 minor allele by the additive model, with somewhat lower significance level due to further grouping the samples and much more GxE interaction

Table 2. Odds Ratios Estimates of the Main and GxE Interactive Effects on Cognitive Disability at Advanced Ages

	I-1	I-2	II-1	II-2	III-1	III-2	IV-1	IV-2
Drank tea at around age 60 (no)	0.87	1.41			0.87	1.33	0.87	1.32
Drank tea at present time (no)			0.62‡	0.72*				
			(0.45, 0.87)	(0.51, 1.04)				
FOXO1A-266 dominant = 1 (0)	0.84	1.11						
FOXO1A-266 recessive = 1 (0)			0.77	1.04				
FOXO3A-310 dominant = 1 (0)					0.90	1.19		
FOXO3A-292 dominant = 1 (0)							0.88	1.16
GxE interactions								
(FOXO1A-266 dominant = 1) ×		0.46†						
(Drank tea around age 60)		(0.23, 0.89)						
(FOXO3A-310 dominant = 1) ×						0.45†		
(Drank tea around age 60)						(0.23, 0.87)		
(FOXO3A-292 dominant = 1) ×								0.46†
(Drank tea around age 60)								(0.24, 0.88)
(FOXO1A-266 recessive = 1) ×				0.32†				
(Drink tea at present time)				(0.11, 0.92)				
Covariates								
Male (female)	0.51‡	0.51‡	0.51‡	0.50‡	0.53†	0.54†	0.52‡	0.53†
Age	1.06‡	1.06‡	1.06†	1.06†	1.06‡	1.06†	1.06‡	1.06†
Urban (Rural)	1.04	1.04	1.01	1.01	1.06	1.08	1.05	1.07
1+ year of schooling (0)	1.29	1.29	1.29	1.30	1.25	1.24	1.27	1.25
Regular exercise (no)	0.39‡	0.39‡	0.41‡	0.41‡	0.39‡	0.38‡	0.39‡	0.38‡
Smoking in recent 5 years (no)	0.88	0.90	0.92	0.91	0.88	0.87	0.89	0.87
Currently drink alcohol (no)	0.87	0.84	0.88	0.89	0.87	0.88	0.86	0.87
−2 LL (-2 log likelihood)	908.2	903.0	904	899.1	909.8	904.2	910.4	904.9
Likelihood ratio χ^2		5.2		4.9		5.6		5.5
Probability > χ^2 (p)		.031		.04		.021		.023

Notes: The categories "no" and "0" in the parentheses after the variables in the first column are reference groups. The figures in parentheses below the significant estimates are 95% confidence intervals.

*$p < .1$, †$p < .05$, ‡$p < .01$.

terms in the regressions. Note that, as discussed in section Dependent Variables: Cognitive Disability, we use MMSE score cutoffs (following the practice in the literature) to define cognitive disability in the logistic regressions presented in Table 2. We also used the continuous MMSE score as the dependent variable to measure the cognitive capacity in the linear regression model; the results are basically the same as the findings based on the categorized MMSE score, with slightly reduced significance level.

Testing the Potential Confounding Effects of rGE Correlation Between Carrying the FOXO Minor Alleles and Tea Drinking

Note that the significant estimates of the GxE interaction terms in the regressions represent synergistic associations but may not exactly reflect the true effects of GxE interaction on the health outcome because the estimates may be confounded by correlations between genotype and social/behavioral factors (abbreviated as rGE) (41). Therefore, we use Chi-square tests to explore whether the rGE exists, or more specifically, whether the differences in tea drinking between the carriers and noncarriers of the FOXO genotype are statistically significant, for all synergistic significant FOXO-by-tea-drinking interaction terms discovered in Table 2. If rGE is not statistically significant, the estimates of the interaction terms represent the true GxE interaction effects. Otherwise, we need to further conduct path analysis employing structural equation models, adjusted for various confounders, to further explore the direct, indirect, and interactive associations of the genetic and social/behavioral factor with the health outcome indicator (42).

The Chi-square tests were all not significant, ruling out the rGE correlation between carrying the FOXO minor alleles and tea drinking (see Table 3). Thus, the estimates of the GxE interaction terms between carrying the FOXO1A or FOXO3A minor alleles and tea drinking presented in Table 2 and discussed in the section The Estimates of the GxE Interaction Terms Between Carrying FOXO Minor Allele and Tea Drinking above represent true associations between the GxE interactions and cognitive disability and they are not confounded by rGE correlation.

Differences of Effects of Tea Drinking on Cognitive Disability Between the FOXO Genotype Carriers and Noncarriers: A More Intuitive Way to Assess the GxE Interactions

An interaction between a social/behavioral factor and a genotype is present if the association between the social/

behavioral factor and a health outcome indicator differs among individuals with different genotypes, or if the association between the genotype and a health outcome indicator differs among individuals with different social/behavioral factors (18). Consequently, in addition to looking at the odds ratios of the GxE interaction terms presented in Table 2, another more intuitive way to assess the effects of the FOXO-by-tea-drinking interactions is to assess the differences in the odds ratio of cognitive disability between those who drink tea and those who do not drink tea by the FOXO genotype carrier status (see the Supplementary Appendix for the technical note).

The estimates presented in Figure 1a show that for both carriers and noncarriers of FOXO1A-266 minor alleles (recessive model), drinking tea at present time was substantially associated with reduced odds ratio of cognitive disability; but the reduction effects among the FOXO1A-266 carriers was −76.9%, much larger than that among the noncarriers, that is, −27.5%. As shown in Figures 1b and Figures 2a and b, the effects of tea drinking at around age 60 (compared with non–tea-drinking round age 60) on reducing cognitive disability were −35.9% to −40.1% among carriers of FOXO3A-310, FOX3A-292, or FOXO1A-266 minor alleles (all with dominant models). However, in contrast to the carriers of these genotypes, the effects of tea drinking at around age 60 (compared with non–tea-drinking round age 60) on cognitive disability among the noncarriers were in the opposite direction and all of the estimates were not statistically significant (see Figures 1b and 2a and b, and see Supplementary Tables A1 and A2 in the Supplementary Appendix for estimates of the odds ratios and their significance levels).

Effects of Three-Way Interactions Across the FOXO Genotypes, Tea Drinking at Around Age 60, and Tea Drinking at Present Time

To explore the impacts of consistency or inconsistency of tea consumption at around age 60 and at present time, we further conducted analysis of effects of three-way interactions across carrier or noncarrier status of the FOXO genotypes, tea drinking at around age 60, and/or tea drinking at present time on cognitive disability, adjusted for various covariates. As shown in Table 4, three interesting points and a note are observed, although most of the estimates of the odds ratios of three-way interactions are not statistically significant, due to largely reduced subsample sizes by further divisions of the sample, and the number of interaction terms in one regression increased from one in the two-way interaction (see Table 2) to seven in the three-way interaction analysis (see Table 4). First, among the very oldest old carriers of the FOXO genotypes, tea drinking either at around age 60 or at present time was substantially helpful to reduce cognitive disability, especially for those who were tea drinkers both at around age 60 and at present time (see last three lines, especially the last line, of Table 4). Second, however, among the noncarriers of the FOXO genotypes, tea drinking seems to be much less

Table 3. Chi-Square Tests to Assess rGE Correlation Between the FOXO Genotypes and Tea Drinking for all Synergistic Significant FOXO-by-Tea-Drinking Interaction Terms Discovered in Table 2

	Drink tea	Do not drink tea	*p* Value
Drink tea at present time			
% Carrying FOXO1A-266 (recessive mode)	14.7	17.0	.408
Drank tea at around age 60			
% Carrying FOXO1A-266 (dominant model)	63.5	62.1	.690
% Carrying FOXO3A-310 (dominant model)	55.1	53.4	.646
% Carrying FOXO3A-292 (dominant model)	54.4	53.9	.891

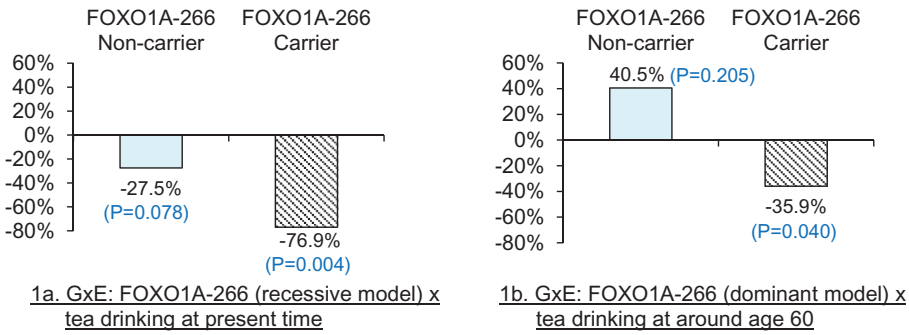

Figure 1. Effects of tea drinking (compared with non-tea drinking) at present time or at around age 60 on cognitive disability, among the *FOXO1A* minor allele carriers vs noncarriers.

Notes: The percentages in the figure are the relative differences in the odds ratios of cognitive disability between those who drink tea and those who do not drink tea, among the FOXO carriers or noncarriers. These percentages represent the effects of tea drinking (compared with non-tea-drinking) on cognitive disability, among the FOXO genotypes carriers vs non-carriers. See Supplementary Tables A1 and A2 for detailed numerical estimates including the odds ratios and their statistical significant levels for tea-drinkers and non-tea drinkers among the carriers vs noncarriers.

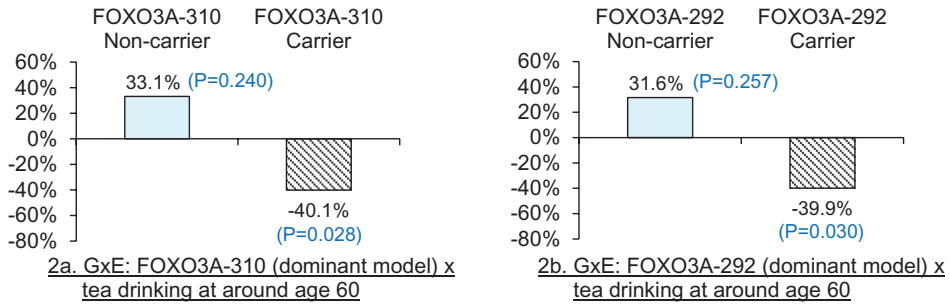

Figure 2. Effects of tea drinking (compared with non-tea drinking) at around age 60 on cognitive disability, among the FOXO3A minor allele carriers vs non-carriers.

Notes: The percentages in the figure are the relative differences in the odds ratios of cognitive disability between those who drink tea and those who do not drink tea, among the FOXO carriers or noncarriers. These percentages represent the effects of tea drinking (compared with non-tea-drinking) on cognitive disability, among the FOXO genotypes carriers vs non-carriers. See Supplementary Tables A1 and A2 for detailed numerical estimates including the odds ratios and their statistical significant levels for tea-drinkers and non-tea drinkers among the carriers vs noncarriers.

connected to the phenotype of reduced cognitive disability compared with the carriers. For example, the odds ratios of cognitive disability for those noncarriers who were tea drinkers both at around age 60 and at advanced ages were 0.82–1.09 and all of the four estimates were not significant. Third, the odds ratios of cognitive disability of those oldest old noncarriers of the FOXO genotypes who were tea drinkers at around age 60 but did not drink tea at present time were 1.47–2.94, and among the four estimates for this group, three were significant (p = .03–.05), and one was not (p = .26). These estimates indicate that discontinuation of the tea drinking among the noncarriers of the FOXO genotypes might increase the risk of cognitive disability at advanced ages. These estimates may also provide explanation on why the average odds ratios of cognitive disability at advanced ages associated with tea drinking at around age 60 were considerably greater than one (although not significant) among noncarriers of FOXO3A-310, FOX3A-292, or FOXO1A-266 minor alleles (all with dominant models); more specifically, nearly 20% of those noncarriers who drank tea at around age 60 discontinued tea drinking at advanced ages 92+, and they substantially contributed to the larger-than-one average odds ratios of cognitive disability among all of the oldest old noncarriers who were tea drinkers at around age 60. Note that among the noncarriers of the FOXO genotypes, the odds ratios of cognitive disability for those who were not tea drinkers at around age 60 but tea drinkers at advanced ages (7.6% of the noncarriers) were 0.43–0.62, which were much lower than the odds ratios for those noncarriers who were tea drinkers both at around age 60 and at advanced ages, but none of the estimates were significant. We are not sure whether this is due to the possibility that these small number of noncarriers who were not tea drinkers at around age 60 had good cognitive function induced by other causes and thus could manage to prepare and drink tea at advanced ages, or due to stochastic fluctuation caused by the small size of this special group, or due to other unknown mechanisms.

Summing up the three interesting points discussed above, our additional three-way interaction analysis has reconfirmed findings of the two-way interactions and indicate that the association of tea drinking with reduced cognitive disability was much stronger among very oldest old carriers of the FOXO genotypes than that among the noncarriers.

Discussion

For the first time (to our knowledge), we discovered that GxE interactions between carrying the minor alleles of FOXO1A-266 or FOXO3A-310 or FOXO3A-292 and tea drinking at around age 60 or at present time were significantly associated with lower risk of cognitive disability at advanced ages in a human population, and the potential confounding effects of correlations between carrying the FOXO minor alleles and tea drinking were ruled out. Based upon pioneer studies using animal or human cell models (24,30), we postulate that results in our present study indicate that intake of tea compounds could be activating FOXO gene expression that offer protection against cognitive decline at oldest old ages.

Our empirical findings imply that health benefits of certain nutritional interventions, including tea drinking, may, in part, depend upon individual genetic profiles. This suggests that, if the exploratory findings in this study are further replicated by the other studies in humans in other populations in the future, geriatric psychiatrists or other health care professionals may advise elders who carry the FOXO genotypes to drink tea frequently and continuously to prevent or reduce cognitive disability. At the same time, such advice on tea drinking may not be as applicable to noncarriers of the FOXO genotype, and it may be more beneficial to suggest them to frequently drink other beverages which have been shown to be more appropriate for their genotype.

We must be aware that our statistical association study did not investigate the causal effects of biological mechanisms. Because the genotype data were available for 822 oldest old aged 92+ only, we restricted our present study

Table 4. Odds Ratio Estimates of Risk of Cognitive Disability at Advanced Ages by the Three-Way Interactions Across Carrier/Noncarrier Status of the FOXO Genotypes, Tea Drinking at Around Age 60, and Tea Drinking at Present Time, Adjusted for the Covariates

Composition of the Three-Way Interactions	FOXO1A-266 (dominant model)		FOXO1A-266 (recessive model)		FOXO3A-310 (dominant model)		FOXO3A-292 (dominant model)	
	OR	#	OR	#	OR	#	OR	#
G = 0, tea age 60 = 0, tea present = 0	1.00	172	1.00	367	1.00	201	1.00	201
G = 0, tea age 60 = 0, tea present = 1	0.46	17	0.62	48	0.43* (0.16, 1.12)	32	0.45	30
G = 0, tea age 60 = 1, tea present = 0	2.72† (1.01, 7.31)	23	1.47	47	2.76† (1.03, 7.38)	22	2.94† (1.11, 7.79)	23
G = 0, tea age 60 = 1, tea present = 1	1.09	79	0.82	192	1.00	105	0.97	106
G = 1, tea age 60 = 0, tea present = 0	1.17	272	1.13	77	1.15	243	1.13	244
G = 1, tea age 60 = 0, tea present = 1	0.61	38	—	7	0.70	24	0.65	26
G = 1, tea age 60 = 1, tea present = 0	0.94	32	0.91	8	0.91	33	0.82	32
G = 1, tea age 60 = 1, tea present = 1	0.64* (0.38, 1.07)	147	0.32† (0.13, 0.83)	34	0.59† (0.35, 1.00)	121	0.59* (0.35, 1.01)	120

Notes: G = 1 or 0: carrier or noncarrier of the genotype. Tea age 60 = 1 or 0: tea drinking or not tea drinking at around age 60. Tea present = 1 or 0: tea drinking or not tea drinking at present time. "—" means the number of the observations is too small to produce any meaningful estimate. The figures in parentheses below the significant estimates are 95% confidence intervals. OR = odds ratio; # = number of the observations in the corresponding category.
*$p < .1$, †$p < .05$.

to advanced ages. We categorized tea drinking as "yes" or "no" without classification of frequency to avoid complications in exploring too many GxE interaction terms given the sample size limitation. Furthermore, we are not able to distinguish what type of teas the participants used to drink, as no such information was collected in CLHLS. As there were only 194 male oldest old in our sample, the potential confounding effects of gender were controlled for by including sex as a covariate in the regression models, but we were not able to conduct more detailed analysis for males in the oldest old category. These limitations will need to be addressed in the future when the new genotypic/phenotypic datasets covering all elderly age groups with much larger sample size are available.

Finally, we would like to emphasize that we must be cautious in interpreting our results and treat them as exploratory findings and look forward to further replication studies.

Supplementary Material

Supplementary material can be found at: http://biomedgerontology.oxfordjournals.org/

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