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Original Research

Interaction between Habitual Green Tea and Coffee Consumption and *ACTN3* Genotype in Association with Skeletal Muscle Mass and Strength in Middle-Aged and Older Adults

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Abstract

BACKGROUND: Recent studies have suggested the potential benefits of habitual coffee and green tea consumption on skeletal muscle health. However, it remains unclear whether these benefits are modified by genetic factors, particularly the alpha-actinin-3 (*ACTN3*) genotype, which is associated with the skeletal muscle phenotype. This study aimed to investigate the interaction between habitual coffee or green tea consumption and the *ACTN3* genotype in association with skeletal muscle mass (SMM) and strength.

METHODS: This cross-sectional study was conducted on 1,023 Japanese middle-aged and older adults (619 females, aged 45–74 years) living in the community. SMM was gauged using a bioelectrical impedance spectroscopy device, and handgrip strength (HGS) was used to measure muscle strength. The *ACTN3* genotype (RR, RX, and XX) was determined from blood samples. Sex-specific linear regression models were used to analyze the interactions between coffee or green tea consumption and the *ACTN3* genotype in association with SMM and HGS.

RESULTS: In females, a significant interaction was observed between green tea consumption and the *ACTN3* genotype in association with HGS (P interaction < 0.05). Furthermore, stratified analysis revealed a positive association between green tea consumption and HGS, specifically in females with the *ACTN3* XX genotype (P trend < 0.05). In males, no significant interactions were observed between coffee or green tea consumption and the *ACTN3* genotype in association with SMM or HGS (P interaction > 0.05).

CONCLUSION: Our findings suggest that the skeletal muscle strength benefits associated with habitual green tea consumption may be contingent upon sex and the *ACTN3* genotype.

Key words: Coffee, tea, muscle strength, ACTN3 protein, human.

Abbreviations: ACTN3: alpha-actinin-3; SMM: skeletal muscle mass; HGS: handgrip strength; FFQ: food frequency questionnaire; FMI: fat mass index; PAL: physical activity level; SMI: skeletal muscle mass index.

Introduction

Frailty and sarcopenia, conditions frequently associated with an elevated risk of falls, hospitalization, and mortality, are becoming pressing health concerns in rapidly aging populations (1, 2). Skeletal muscle aging is a cardinal determinant of these conditions, emphasizing the importance of understanding the mechanisms and interventions to curb their onset and progression (3, 4). Additionally, the interaction between genetic predispositions and lifestyle choices may offer deeper insights into these mechanisms, underscoring the need to explore these interactions to develop targeted preventive strategies (5, 6).

Genetic factors accounting for muscle strength and skeletal muscle mass (SMM) variability have been reported to be 32–67% and 46–76%, respectively (5). The alpha-actinin-3 (*ACTN3*) genotype, which contributes to the skeletal muscle phenotype, encodes α-actinin-3, a protein expressed in fast-twitch muscle fibers (7). This gene polymorphism has been reported to affect lower SMM and its function. X-allele holders are characterized by lower muscle mass and strength than R-allele holders and are considered a potential genetic risk factor for the development of sarcopenia (7).

Emerging evidence has suggested the habitual consumption of green tea and coffee as a potential modifiable factor for the prevention of frailty and/or sarcopenia (8-13). Although the biological mechanisms by which habitual consumption of green tea and coffee affects SMM and skeletal muscle function have not been fully elucidated, it has been suggested that various antioxidant and anti-inflammatory pathways induce autophagy and differentiation of myogenic stem cells because of the active ingredients in green tea and coffee, polyphenols (tea catechins and chlorogenic acid) and caffeine, and may prevent age-related decline in SMM and muscle strength (13-16). However, how genetic factors modulate the associations between habitual green tea and coffee consumption and skeletal muscle has not yet been investigated.

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In this study, we examined the potential interaction between habitual coffee or green tea consumption and the *ACTN3* genotype in association with skeletal muscle strength and mass. We hypothesized that the benefits of green tea and coffee consumption vary depending on an individual's *ACTN3* genotype.

Methods

Study design and population

This cross-sectional study was conducted using secondary survey data from the Japan Multi-institutional Collaborative Cohort Study in the Saga Region (Saga J-MICC Study) (17, 18). Details of the Saga J-MICC study have been reported previously (17, 18). Briefly, the J-MICC study was initiated in 2005 by 10 research groups in Japan to investigate the interaction between genes and the environment in lifestyle-related diseases, such as cancer (19). The first survey in the Saga region included 12,078 participants; the second survey, conducted 5 years later, included 8,454 of the 12,078 participants. Skeletal muscle assessment, including handgrip strength (HGS) and SMM measurements, was newly added to the secondary survey (11, 20, 21). Genotype data were available for the analysis of a subset of secondary study participants (random selection) from the Saga region (22). Therefore, 1,350 participants in the secondary survey for whom genotype data were available for analysis were considered for this study. Out of 1,350 participants, 327 were excluded from the analysis for the following reasons: missing data on coffee consumption (n = 1), green tea consumption (n = 1), SMI (n = 15), HGS (n = 4), and covariates such as FMI (n = 15) and PAL (n = 44). Moreover, participants with a history of cancer (n = 107), cardiovascular disease (n = 87), diabetes (n = 118), liver disease (n = 18), and renal failure (n = 3) were excluded to reduce comorbid influences on the skeletal muscle phenotype since these conditions can independently affect muscle health. Consequently, the final analysis encompassed 1,023 individuals (619 females).

The research protocol was approved by the ethics committees of the Saga University Faculty of Medicine (approval no. 17-11) and Nagoya University Graduate School of Medicine (approval no. 253). The purpose, content, and conditions of the study were explained in writing and orally, and the participants provided written informed consent to participate in the study.

Assessment of habitual coffee and green tea consumption

The habitual consumption of coffee or green tea over the past year was assessed using a validated Japanese Food Frequency Questionnaire (FFQ) (23). This FFQ was validated against 3-day weighted dietary records for energy and 26 specific nutrients, yielding correlation coefficients primarily within the range of 0.4 to 0.6 (23). A subsequent validation study evaluated the accuracy of FFQ regarding food group intake, and the identified correlation coefficients ranged from 0.17 to 0.76 in males and 0.23 to 0.77 in females (24). Specifically for coffee and green tea, the correlation coefficients were 0.56 and 0.52, respectively, for males and 0.56 and 0.51, respectively, for females (24). The frequency of coffee and green tea consumption was evaluated as follows: almost none, 1–3 times/month, 1–2 times/week, 3–4 times/week, 5–6 times/week, 1 time/day, 2 times/day, and >3 times/day. The frequency of coffee and green tea consumption was classified into four categories (almost none, <1 cup/day, 1–2 cups/day, and >3 cups/day) based on previous studies (11, 25).

Assessment of SMM and HGS

The SMM was gauged using a multifrequency bioelectrical impedance spectroscopy device (MLT-30, SK Medical, Electronics Co., Ltd., Shiga, Japan) (11, 20, 21, 26). Individuals with artificial joints or cardiac pacemakers were excluded from measurements. SMM measurements were conducted by placing electrodes on the right dorsal hand and right dorsal foot, and whole-body SMM was determined using specialized software accompanying MLT-30. The software computed the SMM with reference to the values measured using magnetic resonance imaging (27). In alignment with prior research, the SMM index (SMI, kg/m^2) was derived by adjusting SMM against height squared (28).

To determine the HGS values of the left and right hands, a Smedley-type HGS dynamometer (Grip-D, T.K.K. 5401; Takei Scientific Instruments, Niigata, Japan) was used. The participants had their HGS gauged once for each hand while standing and with their elbows fully extended. For analytical purposes, a greater value, whether from the left or right hand, was chosen (29).

Determination of the ACTN3 genotype

Buffy coat fractions were prepared from blood samples and stored at –80 °C at the central office of the J-MICC Study. DNA was extracted from all buffy coat fractions using the BioRobot M48 Workstation (Qiagen Group) at the central office. Genotyping was conducted at the RIKEN Center for Integrative Medicine Sciences using the HumanOmniExpressExome-8 v1.2 BeadChip array (Illumina Inc.). After quality control (30), we extracted data from the *ACTN3* variant (rs1815739), which was directly genotyped. The C and T alleles for rs1815739 corresponded to arginine (R) and the stop codon (X), respectively (31). Accordingly, we used the following designations: homozygous fully functional RR genotype, heterozygous intermediate RX genotype, and homozygous low-functional XX genotype (32).

Other covariates

The covariates required for analysis were selected based on a previous study (11). Age was calculated from the date of birth and date of face-to-face measurements. Data on demographics

Table 1. Sex-based demographic characteristics of the participants

Characteristics	Overall, N = 1,023	Male, N = 404	Female, N = 619	P-value§
Age, y	61.0 (8.1)	61.3 (7.9)	60.8 (8.2)	0.346
Weight, kg	58.9 (10.2)	66.6 (8.8)	53.9 (7.5)	<0.001
Height, cm	158.6 (8.1)	166.0 (5.7)	153.7 (5.2)	<0.001
BMI, kg/m^2	22.9 (3.0)	23.7 (2.9)	22.5 (3.0)	<0.001
FMI, kg/m^2	8.3 (2.6)	7.9 (2.3)	8.6 (2.7)	<0.001
HGS, kg	29.2 (8.4)	37.7 (6.0)	23.6 (3.9)	<0.001
SMI, kg/m^2	6.9 (0.8)	7.1 (0.8)	6.7 (0.8)	<0.001
Coffee intake, n [%]				0.662
Almost none	111 [11%]	44 [11%]	67 [11%]	
<1 cup/day	323 [32%]	125 [31%]	198 [32%]	
1–2 cups/day	388 [38%]	148 [37%]	240 [39%]	
≥3 cups/day	201 [20%]	87 [22%]	114 [18%]	
Green tea intake, n [%]				<0.001
Almost none	61 [6.0%]	25 [6.2%]	36 [5.8%]	
<1 cup/day	127 [12%]	66 [16%]	61 [9.9%]	
1–2 cups/day	324 [32%]	158 [39%]	166 [27%]	
≥3 cups/day	511 [50%]	155 [38%]	356 [58%]	
Smoking status, n [%]				<0.001
Current	141 [14%]	119 [29%]	22 [3.6%]	
Former	214 [21%]	173 [43%]	41 [6.6%]	
Never	668 [65%]	112 [28%]	556 [90%]	
Alcohol consumption, n [%]				<0.001
Current	563 [55%]	325 [80%]	238 [38%]	
Former	13 [1.3%]	7 [1.7%]	6 [1.0%]	
Never	447 [44%]	72 [18%]	375 [61%]	
PAL	1.45 (0.09)	1.45 (0.10)	1.45 (0.08)	0.897
Energy intake, kcal/day	1,662 (337)	1,886 (352)	1,516 (231)	<0.001
Protein intake, g/day	52.7 (11.6)	56.0 (11.5)	50.5 (11.1)	<0.001
Postmenopausal status, n [%]	509 [50%]	0 [0%]	509 [82%]	<0.001
ACTN3 genotype, n [%]				0.137
RR	222 [22%]	75 [19%]	147 [24%]	
RX	528 [52%]	219 [54%]	309 [50%]	
XX	273 [27%]	110 [27%]	163 [26%]	

Continuous variable, mean (standard deviation); Categorical variable, number [percent-age]. BMI, body mass index; FMI, fat mass index; HGS, handgrip strength; SMI, skeletal muscle mass index; PAL, physical activity level; *ACTN3*, alpha-actinin-3; RR, homozy-gous fully functional genotype; RX, heterozygous intermediate genotype; XX, homozy-gous low functional genotype. § Compared by sex.

and lifestyle, including sex, smoking status, alcohol consumption, and menopausal status, were gathered using self-reported questionnaires. Data regarding smoking habits included current smoking presence/absence/quitting, when they quit, the number of cigarettes smoked per day, and the age at which they started smoking. Data regarding drinking habits (alcohol consumption) included whether they had a drinking habit (yes, if they consumed alcohol at least once a month)/never/stopped; when they stopped, the age at which they started consuming alcohol habitually, and the type and amount of alcohol that they consumed. Based on this information, smoking and alcohol consumption statuses were classified into three categories (never, former, and current). Fat mass was estimated using the same bioelectrical impedance spectroscopy device used to measure SMM, and the fat mass index (FMI, kg/m^2) was calculated by dividing the fat mass by the square of height. Based on the FFQ, total energy intake (kcal/day) and protein intake (g/day) were calculated. Physical activity level (PAL) was measured using a validated accelerometer (Lifecorder, Suzuken, Japan) (22). The individuals were directed to attach the accelerometer to their belt or waistband, aligned with the midline of either thigh, throughout their awake

Table 2. *ACTN3* genotype-based demographic characteristics of the participants

Characteristics	RR	RX	XX	P-value
Male, N = 404				
n	75	219	110	
Age, y	60.6 (8.0)	61.3 (7.8)	62.0 (8.0)	0.441
Weight, kg	66.7 (8.4)	66.5 (8.3)	66.5 (10.2)	0.937
Height, cm	166.5 (5.5)	165.7 (5.6)	166.3 (5.9)	0.549
BMI, kg/m^2	23.6 (2.7)	23.8 (2.8)	23.5 (3.3)	0.565
FMI, kg/m^2	7.7 (2.0)	8.0 (2.2)	7.9 (2.6)	0.551
HGS, kg	38.1 (6.7)	37.6 (5.9)	37.7 (5.8)	0.553
SMI, kg/m^2	7.1 (0.9)	7.1 (0.8)	7.0 (0.8)	0.393
Coffee intake, n [%]				0.677
Almost none	7 [9.3%]	22 [10%]	15 [14%]	
<1 cup/day	22 [29%]	65 [30%]	38 [35%]	
1–2 cups/day	32 [43%]	80 [37%]	36 [33%]	
≥3 cups/day	14 [19%]	52 [24%]	21 [19%]	
Green tea intake, n [%]				0.509§
Almost none	3 [4.0%]	18 [8.2%]	4 [3.6%]	
<1 cup/day	14 [19%]	32 [15%]	20 [18%]	
1–2 cups/day	31 [41%]	80 [37%]	47 [43%]	
≥3 cups/day	27 [36%]	89 [41%]	39 [35%]	
Smoking status, n [%]				0.135
Current	16 [21%]	76 [35%]	27 [25%]	
Former	37 [49%]	88 [40%]	48 [44%]	
Never	22 [29%]	55 [25%]	35 [32%]	
Alcohol consumption, n [%]				0.362
Current	60 [80%]	180 [82%]	85 [77%]	
Former	3 [4.0%]	2 [0.9%]	2 [1.8%]	
Never	12 [16%]	37 [17%]	23 [21%]	
PAL	1.46 (0.10)	1.46 (0.10)	1.44 (0.09)	0.131
Energy intake, kcal/day	1,882 (335)	1,912 (336)	1,836 (391)	0.030
Protein intake, g/day	55.3 (12.4)	56.3 (11.3)	55.7 (11.3)	0.425
Female, N = 619				
n	147	309	163	
Age, y	61.3 (8.3)	60.5 (8.2)	60.9 (8.2)	0.588
Weight, kg	53.0 (7.8)	54.4 (7.8)	53.7 (6.7)	0.296
Height, cm	153.2 (5.3)	154.1 (5.0)	153.5 (5.5)	0.121
BMI, kg/m^2	22.2 (3.1)	22.6 (3.1)	22.5 (2.8)	0.540
FMI, kg/m^2	8.4 (2.7)	8.8 (2.8)	8.6 (2.5)	0.400
HGS, kg	23.1 (3.9)	23.7 (3.8)	23.8 (4.0)	0.174
SMI, kg/m^2	6.7 (0.8)	6.7 (0.8)	6.7 (0.7)	0.734
Coffee intake, n [%]				0.007
Almost none	13 [8.8%]	27 [8.7%]	27 [17%]	
<1 cup/day	51 [35%]	103 [33%]	44 [27%]	
1–2 cups/day	53 [36%]	134 [43%]	53 [33%]	
≥3 cups/day	30 [20%]	45 [15%]	39 [24%]	

Table 2 (continued). *ACTN3* genotype-based demographic characteristics of the participants

Characteristics	RR	RX	XX	P-value
Green tea intake, n [%]				0.455
Almost none	5 [3.4%]	19 [6.1%]	12 [7.4%]	
<1 cup/day	13 [8.8%]	36 [12%]	12 [7.4%]	
1–2 cups/day	45 [31%]	80 [26%]	41 [25%]	
≥3 cups/day	84 [57%]	174 [56%]	98 [60%]	
Smoking status, n [%]				0.529
Current	5 [3.4%]	11 [3.6%]	6 [3.7%]	
Former	12 [8.2%]	15 [4.9%]	14 [8.6%]	
Never	130 [88%]	283 [92%]	143 [88%]	
Alcohol consumption, n [%]				0.454
Current	60 [41%]	121 [39%]	57 [35%]	
Former	0 [0%]	5 [1.6%]	1 [0.6%]	
Never	87 [59%]	183 [59%]	105 [64%]	
PAL	1.44 (0.08)	1.44 (0.07)	1.45 (0.08)	0.773
Energy intake, kcal/day	1,510 (253)	1,525 (233)	1,503 (203)	0.532
Protein intake, g/day	50.3 (13.8)	51.0 (10.2)	49.8 (10.3)	0.281
Postmenopausal status, n [%]	125 [85%]	249 [81%]	135 [83%]	0.496

Continuous variable, mean (standard deviation); Categorical variable, number [percentage]. BMI, body mass index; FMI, fat mass index; HGS, handgrip strength; SMI, skeletal muscle mass index; PAL, physical activity level; *ACTN3*, alpha-actinin-3; RR, homozygous fully functional genotype; RX, heterozygous intermediate genotype; XX, homozygous low functional genotype. § Fisher's exact test.

hours (excluding bathing or swimming times) over a span of 10 days (33). After the measurement period, the accelerometers were returned via post. To mitigate the impact of alterations in PALs due to the initial adaptation to the accelerometer, the data recorded during the initial 3 days were not included in the analysis. Only the data recorded over the subsequent 7 days, wherein the device was worn for a minimum of 8 h per day, were considered for analysis (33). If the number of effective days of 8-h wear was <3, the PAL data were considered as missing values. PAL was derived by dividing the total energy output, as captured by the accelerometer, by the basal metabolic rate (33).

Statistical analysis

Genotype distributions were tested for Hardy–Weinberg equilibrium using the chi-square test. The demographic characteristics of the participants were compared based on sex and the *ACTN3* genotype. Independent t-tests (continuous variables), chi-square tests (categorical variables), and Fisher's exact tests (categorical variables) were used for sex-based comparisons. One-way analysis of variance (continuous variables), chi-square test (categorical variables), and Fisher's exact test (categorical variables) were used for *ACTN3* genotype-based comparisons.

An interaction test based on a general linear model was performed using coffee/green tea consumption (almost none, <1 cup/day, 1–2 cups/day, and ≥3 cups/day; ordinal) × *ACTN3* genotype (RR, RX, and XX; ordinal) as the interaction term and skeletal muscle variables (i.e., SMI [continuous] and HGS [continuous]) as the outcome variables. Potential confounders included age (continuous), FMI (continuous), smoking status (never, former, and current; categorical), alcohol consumption status (never, former, and current; categorical), PAL (continuous), total energy intake (continuous), protein intake (continuous), postmenopausal status (females only; yes or no; categorical), and coffee/green tea consumption (almost none, <1 cup/day, 1–2 cups/day, and ≥3 cups/day; categorical; either one not an exposure variable), following previous studies (11).

Finally, a stratified analysis of the association between coffee/green tea consumption and skeletal muscle variables, stratified by the *ACTN3* genotype was performed. The covariates included the same variables as above, and least-squares means, and 95% confidence intervals were calculated. Trend P-values based on linear regression models were calculated with habitual coffee or green tea consumption as the ordinal variable. All statistical analyses were performed using R version 4.1.2 (The R Foundation for Statistical Computing, Vienna, Austria), with a significance level set at <5%.

Results

The *ACTN3* genotype frequencies were in Hardy–Weinberg equilibrium (P = 0.29). Table 1 presents the demographic characteristics stratified by the sex of the participants. Significant differences were observed in all variables, except for age, coffee intake, PAL, and the *ACTN3* genotype (P < 0.05).

Table 2 presents demographic characteristics stratified by *ACTN3* genotype. In males, there was a significant difference

Table 3. Association of *ACTN3* genotype-stratified SMI and HGS with coffee consumption: adjusted mean and 95% confidence intervals

Coffee	*ACTN3* genotype					
	RR		RX		XX	
	Adjusted means§	95% CIs§	Adjusted means§	95% CIs§	Adjusted means§	95% CIs§
Outcome, SMI						
Male, N = 404						
Almost none	7.18	6.82–7.54	7.16	6.99–7.33	6.91	6.70–7.11
<1 cup/day	7.21	7.03–7.40	7.00	6.91–7.10	6.94	6.82–7.07
1–2 cups/day	7.11	6.95–7.27	7.12	7.03–7.20	7.03	6.90–7.17
≥3 cups/day	7.08	6.82–7.33	7.20	7.08–7.31	7.07	6.89–7.24
P for trend	0.386		0.131		0.140	
Female, N = 619						
Almost none	6.67	6.53–6.82	6.72	6.63–6.81	6.66	6.56–6.75
<1 cup/day	6.62	6.55–6.70	6.78	6.73–6.82	6.73	6.65–6.80
1–2 cups/day	6.67	6.60–6.74	6.73	6.69–6.77	6.68	6.61–6.75
≥3 cups/day	6.70	6.60–6.80	6.74	6.67–6.81	6.78	6.70–6.86
P for trend	0.366		0.594		0.137	
Outcome, HGS						
Male, N = 404						
Almost none	40.5	35.7–45.3	39.5	37.0–42.1	37.2	34.4–40.0
<1 cup/day	37.1	34.7–39.6	36.9	35.4–38.3	36.9	35.1–38.7
1–2 cups/day	38.6	36.5–40.7	37.7	36.5–39.0	38.6	36.8–40.5
≥3 cups/day	37.3	33.9–40.7	37.4	35.8–39.1	37.8	35.4–40.3
P for trend	0.768		0.592		0.400	
Female, N = 619						
Almost none	22.7	20.7–24.8	22.4	21.0–23.7	22.9	21.4–24.4
<1 cup/day	22.4	21.4–23.4	24.0	23.3–24.7	24.3	23.2–25.5
1–2 cups/day	24.0	23.0–24.9	23.7	23.1–24.4	23.9	22.9–25.0
≥3 cups/day	22.7	21.3–24.1	23.7	22.6–24.8	23.7	22.5–24.9
P for trend	0.432		0.427		0.663	

SMI, skeletal muscle mass index; HGS, handgrip strength; *ACTN3*, alpha-actinin-3; RR, homozygous fully functional genotype; RX, heterozygous intermediate genotype; XX, homozygous low functional genotype; CI, confidence interval. § Adjusted means and 95% confidence intervals are adjusted for the following covariates: age, fat mass index, smoking status, alcohol consumption, total energy intake, protein intake, green tea consumption, physical activity level, and postmenopausal status (females only).

in energy intake ($P < 0.05$), while in females, a significant difference was observed in coffee consumption ($P < 0.05$).

Multivariate linear regression analyses showed no significant interactions between coffee consumption and the *ACTN3* genotype associated with SMI (males, P for interaction = 0.43; females, P for interaction = 0.44) and HGS (males, P for interaction = 0.64; females, P for interaction = 0.46) in males and females. Similarly, no significant interactions were observed between green tea intake and the *ACTN3* genotype associated with SMI in both males and females (males, P for interaction = 0.73; females, P for interaction = 0.49). However, a significant interaction was observed between green tea consumption and the *ACTN3* genotype associated with HGS, exclusively in females (males, P for interaction = 0.22; females, P for interaction = 0.02).

Table 3 presents the stratified analysis of the association between coffee consumption and SMI or HGS, stratified by the *ACTN3* genotype. Similarly, the stratified analysis for the association between green tea consumption and SMI or HGS, stratified by the *ACTN3* genotype, is presented in Table 4. The analysis revealed a significant positive association between green tea consumption and HGS, exclusively in females with the *ACTN3* XX genotype (Table 4, P for trend = 0.02). In contrast, no significant associations were observed between coffee consumption and SMI or HGS in females stratified by the *ACTN3* genotype (Table 3, P for trend > 0.05), and no significant associations were observed between coffee and green tea consumption and SMI or HGS in males stratified by the *ACTN3* genotype (Tables 3 and 4, P for trend > 0.05).

Table 4. Association of *ACTN3* genotype-stratified SMI and HGS with green tea consumption: adjusted mean and 95% confidence intervals

Green tea	*ACTN3* Genotype					
	RR		RX		XX	
	Adjusted means§	95% CIs§	Adjusted means§	95% CIs§	Adjusted means§	95% CIs§
Outcome, SMI						
Male, N = 404						
Almost none	7.24	6.73–7.75	7.12	6.93–7.31	6.91	6.49–7.32
<1 cup/day	7.07	6.84–7.30	7.12	6.98–7.26	6.98	6.80–7.15
1–2 cups/day	7.05	6.89–7.22	7.15	7.07–7.24	7.05	6.94–7.16
≥3 cups/day	7.27	7.09–7.44	7.06	6.97–7.14	6.94	6.81–7.06
P for trend	0.267		0.409		0.742	
Female, N = 619						
Almost none	6.51	6.27–6.75	6.70	6.59–6.81	6.71	6.57–6.86
<1 cup/day	6.70	6.55–6.84	6.81	6.73–6.89	6.68	6.53–6.83
1–2 cups/day	6.68	6.60–6.75	6.75	6.70–6.80	6.66	6.58–6.74
≥3 cups/day	6.66	6.60–6.71	6.74	6.70–6.78	6.74	6.69–6.79
P for trend	0.843		0.662		0.365	
Outcome, HGS						
Male, N = 404						
Almost none	35.1	28.3–41.9	39.0	36.3–41.8	37.5	31.7–43.2
<1 cup/day	37.7	34.6–40.8	38.5	36.5–40.6	38.2	35.8–40.6
1–2 cups/day	37.4	35.2–39.5	36.8	35.5–38.1	38.6	37.1–40.2
≥3 cups/day	39.5	37.2–41.8	37.6	36.4–38.9	36.3	34.6–38.0
P for trend	0.153		0.329		0.190	
Female, N = 619						
Almost none	26.9	23.5–30.3	22.6	20.9–24.3	20.9	18.7–23.2
<1 cup/day	22.5	20.5–24.5	23.9	22.7–25.1	22.8	20.5–25.1
1–2 cups/day	22.8	21.7–23.9	24.0	23.2–24.8	24.1	22.9–25.3
≥3 cups/day	23.1	22.3–23.9	23.7	23.1–24.2	24.1	23.4–24.9
P for trend	0.490		0.706		0.015	

SMI, skeletal muscle mass index; HGS, handgrip strength; *ACTN3*, alpha-actinin-3; RR, homozygous fully functional genotype; RX, heterozygous intermediate genotype; XX, homozygous low functional genotype; CI, confidence interval. § Adjusted means and 95% confidence intervals are adjusted for the following covariates: age, fat mass index, smoking status, alcohol consumption, total energy intake, protein intake, coffee consumption, physical activity level, and postmenopausal status (females only).

Discussion

We hypothesized that the efficacy of habitual coffee/green tea consumption on SMM and skeletal muscle strength would differ depending on the *ACTN3* genotype. Our results showed a significant interaction between habitual green tea consumption and *ACTN3* genotype in association with HGS in female participants. Stratified analysis showed that the positive association between habitual green tea consumption and HGS was observed only for the *ACTN3* XX genotype in females. The results of this study suggest that the benefits of habitual green tea consumption on skeletal muscle strength may vary depending on the *ACTN3* genotype.

In this study, we observed a significant interaction between green tea consumption and the *ACTN3* genotype associated with HGS in females only. This association is difficult to interpret but given the results that allowed for a sex-specific association, it may suggest the involvement of sex hormones. Significant components of green tea, such as catechins, exhibit estrogenic activity (34). The skeletal muscle is the predominant tissue in which estrogen receptors are located (35). Estrogen deficiency in females can induce myosin dysfunction and hinder muscle regeneration, consequently leading to muscle weakness (36). Moreover, a meta-analysis indicated that estrogen-based hormone therapy may confer benefits in terms of skeletal muscle strength in postmenopausal females (35). In this study, 82% of the female participants were postmenopausal, and we observed a significant positive association between green tea consumption and HGS only in the *ACTN3* XX genotype of postmenopausal females (Supplementary Table 1). Thus, it is conceivable that the regular consumption of green tea could trigger estrogen

activation and mitigate age-associated muscle weakness in postmenopausal females with declining estrogen levels. In addition, carriers of the X allele of the *ACTN3* gene are usually characterized by lower muscle strength, performance, and SMM than R allele carriers, indicating that they may be more susceptible to exercise-induced muscle damage (37). Repeated skeletal muscle damage and inadequate repair capacity contribute to muscle weakness in the older adults (36, 38). Given estrogen's role in muscle repair (36), it could be speculated that individuals with the *ACTN3* XX genotype, who may be predisposed to muscle damage, could potentially experience some muscle recovery benefits from habitual green tea consumption. Nonetheless, the current body of evidence remains preliminary. Comprehensive investigations are essential to unravel the potential advantages of green tea, particularly those concerning the *ACTN3* XX genotype.

Habitual coffee consumption showed no significant interaction with the *ACTN3* genotype associated with SMI or HGS in either sex. These results suggest that the association between habitual coffee consumption and both SMM and muscle strength is not modified by the *ACTN3* genotype. While previous observational studies have found a beneficial association between habitual coffee consumption and SMM or sarcopenia (11-13, 39), our analysis found no such association with any *ACTN3* genotype. This discrepancy may be attributed to factors not evaluated in this study, such as the addition of sugar or milk to coffee, or low power due to insufficient sample size. Therefore, further research is necessary to clarify the interplay between genetic factors, skeletal muscle phenotypes, and coffee consumption, including the addition of sugar and milk.

Our use of a FFQ in this study meant we couldn't quantify potentially beneficial compounds like caffeine, tea catechins, chlorogenic acid, and caffeic acid found in green tea and coffee for skeletal muscle. Caffeine is widely recognized for its ergogenic effects, enhancing endurance, power, and muscle strength (40). Catechins could prevent, mitigate, and treat muscle-related disorders (14). Similarly, chlorogenic acid, and its metabolite caffeic acid, through studies in animal models, have been shown to improve muscle strength and glucose uptake in skeletal muscles (41, 42), suggesting their potential as effective compounds for muscle health. However, our study's design limited our ability to directly investigate the interactions between these bioactive components and the *ACTN3* genotype. Therefore, we are unable to pinpoint which specific compounds, including tea catechins which we have considered as potentially impactful, might have contributed to the observed interaction between habitual green tea consumption and HGS in females in association to the *ACTN3* genotype. Future research that can quantify the intake of these compounds and explore their direct effects on muscle health and genetic interactions will be critical to deepening our understanding of these complex relationships.

In our study, we did not observe the general characteristics of low SMM, and low muscle strength compared to *ACTN3* X allele carriers and R allele carriers. Several factors may contribute to this discrepancy. SMM was estimated using bioelectrical impedance analysis, which, compared to gold-standard methods such as magnetic resonance imaging or computed tomography, may have limited ability to detect minor differences in SMM, potentially leading to prediction errors (43). Skeletal muscle strength assessment in our study was based solely on HGS. While HGS is commonly used as a proxy for global muscle strength (44), age-related declines in muscle strength are more pronounced in the lower extremities (45). Our study did not evaluate lower extremity muscle strength, which might have led to a failure in detecting differences in muscle strength between the *ACTN3* genotypes. Additionally, the age range of our study population (middle-aged to older adults) could have influenced the results. Age-related atrophy of fast-twitch muscle fibers (46) may have obscured differences in SMM and strength between *ACTN3* genotypes. These points highlight the need for methodological refinement in future studies, particularly with diverse age groups and more comprehensive strength assessments. Given these considerations, the results of our study should be interpreted cautiously, recognizing the inherent challenges and methodological constraints.

This study has several limitations. First, this study was cross-sectional; thus, causal relationships remain unclear. Second, coffee and green tea consumption was evaluated using FFQ and therefore was not classified based on the exact amount consumed. Differences in habitual means of drinking, such as cups, cans, and bottles, might have caused misclassification. Third, information on the use of sugar and milk in habitually consumed coffee was not collected and, therefore, was not analyzed. Fourth, the SMM estimated using the bioimpedance device might have had a prediction error compared with the SMM measured using the gold standard methods.

In conclusion, our study suggests a potential interaction between habitual green tea consumption and the *ACTN3* genotype in association with HGS in females. In particular, within the *ACTN3* XX genotype, habitual consumption of green tea was associated with higher HGS in females. However, the current data remain insufficient to elucidate the underlying mechanism associated with these observations; therefore, further studies are warranted to validate these findings and explore the potential mechanisms involved.

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