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Tea consumption and oxidative stress: a cross-sectional analysis of 889 premenopausal women from the Sister Study.

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Abstract

In experimental and clinical studies, green or black tea consumption has been shown to reduce oxidative stress. However, these studies involved high levels of tea consumption and may not reflect patterns in the general population. Here we examined the association between black or green tea consumption and oxidative stress in a cross-sectional study of 889 premenopausal U.S. women aged 35–54 years. Tea consumption was measured using the Block-98 food frequency questionnaire. Urinary 8-iso-prostaglandin $F_{2\alpha}$ (F_2-IsoP) and 2,3-dinor-5,6-dihydro-15-F_{2t}-isoprostane (15-F_{2t}-IsoP-M) were used as biomarkers of oxidative stress. These compounds were measured by mass spectrometry and normalized to creatinine. Linear regression was used to calculate geometric mean differences (GMD) and 95% confidence intervals (95% CI) for log-transformed urinary F_2-IsoP or 15-F_{2t}-IsoP-M in relation to black or green tea consumption. We further examined whether adjusting for caffeine impacted associations between tea and oxidative stress. Geometric means of urinary F_2-IsoP and 15-F_{2t}-IsoP-M were 1.44 (95% CI 1.39–1.49) and 0.71 (95% CI 0.69–0.73) ng/mg Cr, respectively. Overall, green tea consumption was not associated with urinary F_2-IsoP or 15-F_{2t}-IsoP-M. High-level black tea consumption (≥5 cups/week compared to 0) was associated with higher 15-F_{2t}-IsoP-M concentrations (aGMD=0.10, 95% CI 0.02–0.19) but not F_2-IsoP. Adjusting for caffeine nullified the association between black tea and 15-F_{2t}-IsoP-M. Our findings do not support the hypothesis that dietary tea consumption is inversely associated with oxidative stress.

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Keywords

Tea; Oxidative Stress; Epidemiology; Women's Health

Introduction

Oxidative stress describes an imbalance of oxidant/antioxidant networks that results in the disruption of redox signaling and/or molecular damage [1–3]. In humans, persistent oxidative stress can lead to oxidation of lipids, alteration of protein function, and mutation of DNA [4–7]. These disruptions may contribute to the pathogenesis of cancer, diabetes, and neurodegenerative disease [8–10]. To detect increases in oxidative stress, oxidation products of lipids are often used as biomarkers [11]. Urinary 8-iso-prostaglandin $F_{2\alpha}$ (F_2-IsoPs) and its primary metabolite, 2,3-dinor-5,6-dihydro-15-F_{2t}-isoprostane (15-F_{2t}-IsoP-M), are stable biomarkers of lipid peroxidation [12,13]. Several studies have reported higher levels of specific urinary F_2-IsoPs in medical conditions including cancer and cardiovascular disease [14–16].

Tea is a popular and accessible beverage worldwide [17] and may have beneficial health effects for diabetes, cardiovascular disease, and cancer [18–20]. Green tea and black tea contain polyphenols [21] that have potential antioxidant properties [22]. For example, the polyphenol epigallocatechin-3-gallate (EGCG) is a natural antioxidant found in green and black tea [23,24]. Experimental studies of the anti-oxidative effects of tea (green tea, black tea, and green tea extract)[25–28] assigned participants to high levels of tea consumption for a short period of time (e.g. 4 cups of green tea/day for 8 weeks or placebo beverage). Participants in the intervention group drinking green tea had lower levels of blood malondialdehyde (MDA), a biomarker of oxidative stress.[25] Participants assigned to receiving one capsule (379 mg) of green tea extract per day for 3 months had a higher total antioxidant status compared to placebo [26]. A third study reported that black tea consumption (4 cups/day for 6 months) reduced lipid peroxidation among 34 female former smokers.[28] These findings support a potential inverse association between tea consumption and oxidative stress.

However, in the general population, tea consumption patterns may reflect longer durations of lower consumption levels. It is unknown whether these patterns also translate to benefits for oxidative stress. Here we conducted a cross-sectional analysis of 889 premenopausal women to examine the association between tea consumption and oxidative stress.

Methods

Data for this analysis come from the National Institute of Environmental Health Sciences (NIEHS) Sister Study. Study participants (N=50,884) aged 35 to 74 years were enrolled between 2003 and 2009 across the United States and Puerto Rico [29]. To be eligible, participants had at least one sister who had been diagnosed with breast cancer, but no personal history of breast cancer. All participants provided written consent at enrollment. Study protocols were approved by the Institutional Review Board of the NIEHS, the National Institutes of Health, and the Copernicus Group.

Population for analysis

Within the Sister Study, 1,367 women were identified (456 cases, 911 controls) for a nested case-control study investigating oxidative stress and breast cancer risk among premenopausal women. To be eligible for the nested case-control study, participants had to meet the following criteria: aged 54 and younger, premenopausal status (at least one menstrual cycle in the previous 12 months or hysterectomy with ≥1 ovary conserved), and have an available blood and urine sample from enrollment. Controls were matched to cases with a ratio of 2:1 on the basis of age and enrollment year and were free of breast cancer at the time of their matched case's diagnosis. For this analysis, information from the 911 controls was used. We further excluded women missing data of black and green tea consumption levels (N=22), which yielded 889 participants for this study.

Oxidative stress measurement

At Sister Study enrollment, participants self-collected approximately 60 ml of first-morning void urine in a study-provided collection cup [29]. Participants refrigerated samples without preservative until they were picked up by study examiners who shipped the samples on ice to the study repository [30]. On receipt, urine samples were aliquoted and stored at −80℃. In 2012, samples were retrieved and urinary concentrations of F_2-IsoP and 15-F_{2t}-IsoP-M were measured using gas chromatography/negative ion chemical ionization mass spectrometry at the Eicosanoid Core Laboratory at Vanderbilt University Medical Center. The mean storage time of urinary samples was 8.3 years. Protocols for chemical analysis and procedures have been described in detail [31–34]. A total of 77 batches were run; each batch contained 18 samples from study subjects (12 controls and 6 cases) and two quality control (QC) samples. The coefficient of variation for QC duplicates was 16.0% and 12.5% for F_2-IsoP and 15-F_{2t}-IsoP-M, respectively [35]. Urinary levels of F_2-IsoP and 15-F_{2t}-IsoP-M were adjusted for creatinine (ng/mg Cr) to correct for urine diluteness.

Exposure and covariate measurement

During an enrollment home visit, trained examiners measured height and weight without shoes. These measurements were taken three times and values were rounded to the nearest quarter inch for height and whole pound for weight [36]. Body mass index (BMI) was calculated as weight (kg)/height $(m)^2$. Black and green tea consumption during the past 12 months was measured by the self-administered Block 98 food frequency questionnaire (FFQ) at study enrollment [37]. Within the FFQ, participants reported their frequency of tea consumption and the cups consumed each time [29]. Frequency was reported at 9 levels, ranging from "never" to "everyday". Participants reported how many cups of tea they consumed each time as "1 cup, 2 cups, 3–4 cups, or 5 or more cups." Regular (non-decaffeinated) coffee consumption was measured using the same methods described above. Healthy Eating Index, dietary fruit and vegetable intake, and dietary β-carotene, vitamin C, and vitamin E intake were obtained via information collected in self-administered FFQ. Total energy intake and caffeine from beverages (soda and black tea) and dietary sources was calculated from the FFQ by NutritionQuest [38]. We assigned caffeine levels to coffee (regular and decaffeinated) and green tea on the basis of data from USDA Food Composition Databases [39,40]. Each cup of regular coffee was assigned 95.2 mg caffeine, each cup of

decaffeinated coffee 2 mg caffeine, and each cup of green tea 24.8 mg caffeine. On average, one cup of black tea contains 47.2 mg caffeine [39].

A validated series of questions were used for measurement of physical activity.[41,42] Weekly energy expenditures at enrollment were calculated as metabolic equivalents (METs) and total physical activity was calculated by summing the MET-h/week of all sports, physical exercise, and daily activity self-reported at enrollment. Participants were also asked for information about the total annual income from all household members and the highest level of school they had completed as well as their age and race/ethnicity.

Statistical analysis—Tea consumption was categorized into 4 levels (0, <1, 1–<5, and ≥ 5 cups/week). The consumption value was obtained by multiplying frequency of consumption (times per week) and serving size (cups consumed each time) together. Cut-off points were determined based on the distribution of tea consumption among women who reported drinking black tea to approximate tertiles. Non-consumers were identified *a priori* as the reference group. The same cut-off points were used for green tea consumption for consistency. Tea consumers with missing serving size information (22 for black tea, 24 for green tea) were assigned a serving size of 1 cup per serving (the most common serving size for black (56.7%) and green (76.0%) tea consumption). For coffee consumption, 1 and 2 cups per serving were about equally common (37.0% and 38.5%, respectively), and coffee consumers with missing serving size information (N=13) were also assigned as drinking 1 cup per serving. Coffee consumption was categorized into 4 levels: 0, <10, 10–<15, and ≥15 cups/week. Caffeine intake was categorized based on approximate quartiles (<33.9, 33.9 –<111.2, 111.2 –<205.2, and≥205.2 mg/day). BMI categories were defined based on WHO guidelines as underweight/normal weight (<24.9 kg/m^2), pre-obesity (25.0–29.9 kg/m^2), obesity class I (30.0–34.9 kg/m^2), obesity class II (35.0–39.9 kg/m^2), and obesity class III (≥40 kg/m^2) [43]. The Healthy Eating Index, dietary fruit and vegetable intake, and dietary β-carotene, vitamin C, vitamin E, total energy intake, and physical activity were categorized to approximate quartiles.

Geometric means (GMs) and 95% confidence intervals (95% CI) of urinary F_2-IsoP and 15-F_{2t}-IsoP-M were calculated for each level of tea consumption and by other covariates. The distribution of urinary F_2-IsoP and 15-F_{2t}-IsoP-M concentrations was right-skewed, thus, a natural log-transformation was applied for these biomarkers to approximate normality. Univariate (uGMD) and adjusted (aGMD) geometric mean differences and 95% CI of urinary F_2-IsoP and 15-F_{2t}-IsoP-M were calculated using linear regression of the natural log-transformed values. To calculate aGMD of F_2-IsoP or 15-F_{2t}-IsoP-M across tea consumption levels, the linear regression model adjusted for age (35–<40, 40–<45, 45–<50, and ≥50 years), race (non-Hispanic white, non-Hispanic black, and other), body mass index (BMI, <25, 25–<30, 30–<35, 35–<40, and ≥40 kg/m^2), education (high school or less, some college or undergraduate, and graduate school), annual income (0–<$50,000, $50,000–<$100,000, and ≥$100,000), smoking status (never, former, current), Healthy Eating Index (<53, 53–<63, 63–<72, and ≥72), dietary fruit (<0.6, 0.6–<1.1, 1.1–<2, and ≥2 servings/day) and vegetable intake (<1.6, 1.6–<2.7, 2.7–<4.3, and ≥4.3 servings/day), dietary β-carotene (<2427.2, 2427.2–<4106.1, 4106.1–<6942.3, ≥6942.3 mcg/day), vitamin C (<55.3, 55.3–<84.1, 84.1–<121.9, ≥121.9 mg/day), and vitamin E intake (<5.6, 5.6–<7.6, 7.6–<10.1,

≥10.1 mg/day), total energy intake (<1,230.40, 1,230.40–<1,528.70, 1528.70–<1,974.90, and ≥1,974.90 kcal/day), and physical activity (<28.11, 28.11–<44.16, 44.16–<65.99, ≥65.99 MET-hours/week) as potential confounders [44]. We also evaluated the impact of additional adjustment for caffeine (<33.9, 33.9 –<111.2, 111.2 –<205.2, and≥205.2 mg/day) [45,46]. The assumptions of the linear regression (linearity, independence, multivariate normality, homoscedasticity) were examined by scatterplots of urinary F_2-IsoP or 15-F_{2t}-IsoP-M vs. tea consumption and plots of the residuals vs. fitted values of the regression model; results did not suggest that assumptions were violated.

Subgroup analyses were conducted to address potential effect modification of associations between tea and F_2-IsoP or 15-F_{2t}-IsoP-M according to overweight (BMI<25 kg/m^2 vs. BMI≥25 kg/m^2) and regular coffee consumption (drinker vs. non-drinker). Interaction terms between tea consumption and these covariates were included in multivariable linear regressions, and log-likelihood ratio tests were used to assess if the interaction terms were statistically significant.

We did not adjust for multiple comparisons as our analysis was hypothesis-driven.[47–49] Two-sided P values <0.05 were considered to be statistically significant. All statistical analyses were conducted with Sister Study Data Release 6.0 using Stata 13.0 (College Station, TX: StataCorp, LLP).

Results

Of the 889 participants in our analysis, the average age at baseline was 47.28 (SD 4.45) and the majority were non-Hispanic white (87.3%). The geometric means of urinary F_2-IsoP and 15-F2t-IsoP-M were 1.44 (95% CI 1.39–1.49) and 0.71 (95% CI 0.69–0.73) ng/mg Cr, respectively. Table 1 presents geometric means and mean differences of urinary F_2-IsoP and 15-F2t-IsoP-M according to participant characteristics. Both F2-IsoP and 15-F2t-IsoP-M decreased slightly as age increased, but differences were not statistically significant. Average F2-IsoP and 15-F2t-IsoP-M levels among non-Hispanic black women were lower compared to white women. Levels of both F_2-IsoP and 15-F_{2t}-IsoP-M were positively associated with BMI and inversely associated with higher income and physical activity. Current smokers had higher levels of both F_2-IsoP and 15-F_{2t}-IsoP-M compared to never smokers, but associations were statistically significant only for 15-F2t-IsoP-M. Inverse but non-significant associations with education were also observed for 15-F_{2t}-IsoP-M, but not F_2-IsoP. High-level coffee consumption (≥15 cups/week) was not associated with F_2-IsoP or 15-F_{2t}-IsoP-M. Total energy intake was positively associated with F_2-IsoP or 15-F_{2t}-IsoP-M. Associations with the Healthy Eating Index, vegetable intake, and vitamin C were not statistically significant for F_2-IsoP and 15-F2t-IsoP-M. Higher fruit intake and dietary β-carotene were inversely associated with F_2-IsoP and 15-F2t-IsoP-M, respectively, but not both markers. Dietary vitamin E appeared inversely associated with both biomarkers but only estimates of 15-F2t-IsoP-M were statistically significant.

Associations between black and green tea consumption and caffeine intake with urinary oxidative stress measures are shown in Table 2. Black tea consumption was more common than green tea consumption; 18.6% of women reported never drinking black tea, while

45.9% of women reported never drinking green tea. The highest level of consumption, ≥5 cups per week, was reported by 24.9% and 7.6% of women for black and green tea consumption, respectively. Overall, black and green tea consumption were not associated with F_2-IsoP levels (Table 2). However, mean concentrations of 15-F_{2t}-IsoP-M were higher for black tea consumption of 5 cups per week or more compared to 0 cups per week (aGMD=0.10, 95% CI 0.02–0.19). High-level green tea consumption (≥5 cups/week compared to 0) was not significantly associated with 15-F_{2t}-IsoP-M (aGMD=0.09, 95% CI −0.02, 0.20).

Caffeine intake was not associated with F_2-IsoP. As compared to the lowest quartile (<33.9 mg/day), higher levels of caffeine intake were positively associated with 15-F_{2t}-IsoP-M, but there was no consistent increase across quartiles. Additional adjustment for caffeine intake attenuated the association between black tea and 15-F_{2t}-IsoP-M towards the null (Table 2). Associations between tea consumption and urinary F_2-IsoP or 15-F_{2t}-IsoP-M were not modified by overweight (Supplementary Table 1) or regular coffee consumption (Supplementary Table 2).

Discussion

Our analysis did not provide support for an inverse association between dietary tea consumption and urinary F_2-IsoP or 15-F_{2t}-IsoP-M, high-quality biomarkers of oxidative stress. Green tea consumption was not associated with either F_2-IsoP or 15-F_{2t}-IsoP-M. Black tea consumption was not associated with F_2-IsoP; however, drinking at least 5 cups of black tea per week (compared to none) was associated with higher 15-F_{2t}-IsoP-M concentrations before adjustment for caffeine.

Clinical studies have found an inverse association between tea consumption and oxidative stress [25–27,50]. For example, by observing 19 people in a 5-day experimental study, Stote et al. [50] found that green tea consumption could lower plasma levels of F_2-IsoPs. However, subjects in this study consumed a higher level of tea (e.g. 2 servings of green tea/day for 5 days) than was commonly consumed in our population-based sample of the U.S. women. In addition, this study only enrolled 19 obese people at high risk of insulin resistance, which may have compromised the generalizability of their outcomes.

A cross-sectional epidemiologic study [12] of 845 Chinese women observed an almost null association between any tea drinking and urinary levels of F_2-IsoPs (geometric mean: never drinker: 1.62, ever drinker: 1.65, p=0.72) and 15-F_{2t}-IsoP-M (geometric mean: never drinker: 0.56, ever drinker: 0.61, p=0.06) after adjustment for age, education, occupation, smoking, BMI, multivitamin supplement use, fruit and vegetable intakes, plasma total carotenoids, tocopherols, and retinol, assay batch, and urinary tea polyphenols. However, the ever/never analysis did not consider level of consumption or potential difference between black and green tea [12]. Green and black tea differ in concentrations of polyphenols (e.g. EGCG) and caffeine [51,52]. For example, green tea has a higher level of EGCG compared to black tea [53], while black tea contains more caffeine [51]. Additionally, a previous study measuring total phenol levels and antioxidant capacity of tea products sold in the US found green tea had a higher antioxidant capacity than black tea of the same volume (436 mg vs.

239 mg vitamin C equivalents per serving).[54] These suggest analysis pooling all types of tea in to one category may obscure meaningful variation.

15-F_{2t}-IsoP-M is the metabolite of F_2-IsoP under beta-oxidation [12]. Both black and green tea contain EGCG and caffeine which have been found to facilitate beta-oxidation on the basis of laboratory evidence [55,56]. The suggested positive associations between black tea and caffeine with 15-F_{2t}-IsoP-M, but not F_2-IsoP, may be due, in part, to related increases in beta-oxidation pathways. We did not observe an association between green tea and 15-F_{2t}-IsoP-M; however, there were few high-level green tea consumers in our analysis.

Our results regarding the association between caffeine and 15-F_{2t}-IsoP-M were similar to an experimental study [57] that assigned 20 participants caffeine (5 mg/kg) or placebo before physical exercise and observed a positive association between caffeine and plasma MDA using blood samples collected immediately after exercise. However, other experimental studies have reported inverse associations between caffeine intake and biomarkers of oxidative stress using other caffeine dosages or different biomarkers of antioxidant activity (e.g. plasma glutathione) or oxidative stress (e.g. 8-hydroxydeoxyguanosine).[58,59] Due to the different study design, biomarkers used for analysis, and divergent findings to date, the association between caffeine and oxidative stress deserves further investigation.

Strengths of our study included the use of a general population sample, the clear categorization of tea type, and detailed information on sociodemographic and lifestyle factors for statistical adjustment. Particularly, using a population-based sample can better reflect real-world tea consumption pattern as compared to high-level tea assignment in experimental studies. The use of urinary F_2-IsoPs provided a stable biomarker of lipid peroxidation. A previous biochemical study has shown that plasma stored appropriately for at least 10 years has F_2-IsoP levels similar to freshly prepared samples [13]. Given that artefactual generation of F_2-IsoP through autoxidation of lipids only occurs in plasma and not in urine [12,13], our samples were likely to be equally or more stable. In some previous studies, MDA was used as the biomarker of oxidative stress [25,27]; however, MDA is more affected by dietary lipid consumption [60] and can be generated from non-lipid sources such as bile pigments [61], which may cause measurement error. 8-OHdG is another biomarker of oxidative stress which is an end product of non-enzymatic DNA oxidation [62]. However, levels of 8-OHdG can be influenced by DNA repair capacity which makes 8-OHdG an indicator of the combined effects of oxidative stress-associated damage and DNA repair capability. Furthermore, a previous study of 10 healthy volunteer suggests that there is not a significant diurnal variation of urinary F_2-IsoP [63], whereas many studies suggest that diurnal variation of urinary 8-OHdG is substantial [62,64,65]. These characteristics make urinary F_2-IsoP a more desirable biomarker of oxidative stress.

Our study also has some limitations. Our sample included only premenopausal women, which may compromise the external validity for men, older women, or individuals with specific medical conditions. Also, tea consumption was measured by retrospective self-report and non-differential measurement error could be introduced. Duration of tea consumption was not available for analysis and the antioxidant potential of green and black tea sources was not directly measured. Finally, our study is a cross-sectional analysis with

one-time urinary sampling and two biomarkers of oxidative, which makes it inappropriate for casual interpretation.

Our study contributes real-world data regarding associations between tea consumption and oxidative stress. In our study, we did not observe an inverse association between green or black tea consumption and urinary F_2-IsoPs. Additional studies with detailed information on the timing and duration of tea consumption, and additional measures of oxidative stress, may be warranted to inform use of antioxidant products.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix:

Supplementary files can be found online.

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Table 1.

Characteristics of study participants and estimates of urinary F2-IsoP or 15-F2t-IsoP-M by covariates.

Characteristics	N=889	F_2-IsoP			15-F_{2t}-IsoP-M		
	n (%)	GM (95% CI) ∥	uGMD (95% CI) ∀	aGMD (95% CI) ¶	GM (95% CI) ∥	uGMD (95% CI) ∀	aGMD (95% CI) ¶
Age (year)							
35–<40	61 (6.9)	1.61 (1.41, 1.83)	Ref	Ref	0.75 (0.67, 0.83)	Ref	Ref
40–<45	177 (19.9)	1.43 (1.33, 1.53)	−0.13 (−0.28, 0.02)	−0.09 (−0.24, 0.05)	0.72 (0.67, 0.77)	−0.04 (−0.17, 0.09)	−0.01 (−0.13, 0.11)
45–<50	377 (42.4)	1.44 (1.36, 1.51)	−0.11 (−0.25, 0.03)	−0.07 (−0.20, 0.07)	0.73 (0.70, 0.76)	−0.03 (−0.15, 0.09)	0.00 (−0.11, 0.12)
≥50	274 (30.8)	1.41 (1.32, 1.51)	−0.13 (−0.28, 0.01)	−0.08 (−0.22, 0.06)	0.68 (0.65, 0.72)	−0.10 (−0.23, 0.02)	−0.06 (−0.18, 0.05)
Race							
Non-Hispanic white	776 (87.3)	1.45 (1.40, 1.51)	Ref	Ref	0.72 (0.69, 0.74)	Ref	Ref
Non-Hispanic black	56 (6.3)	1.25 (1.09, 1.44)	−0.14 (−0.28, 0.00)	−0.23 (−0.37, −0.09)	0.65 (0.58, 0.74)	−0.09 (−0.21, 0.03)	−0.18 (−0.29, −0.06)
Other	57 (6.4)	1.42 (1.27, 1.60)	−0.02 (−0.16, 0.12)	−0.01 (−0.15, 0.13)	0.73 (0.65, 0.81)	0.01 (−0.11, 0.13)	0.01 (−0.10, 0.12)
BMI (kg/m^2)							
<25	406 (45.7)	1.29 (1.23, 1.36)	Ref	Ref	0.63 (0.60, 0.65)	Ref	Ref
25–<30	246 (27.7)	1.46 (1.38, 1.55)	0.13 (0.04, 0.21)	0.11 (0.03, 0.20)	0.70 (0.67, 0.74)	0.12 (0.05, 0.19)	0.10 (0.03, 0.17)
30–<35	122 (13.7)	1.50 (1.37, 1.65)	0.15 (0.05, 0.26)	0.10 (−0.01, 0.20)	0.79 (0.74, 0.85)	0.24 (0.16, 0.33)	0.17 (0.08, 0.26)
35–<40	67 (7.5)	1.71 (1.49, 1.97)	0.27 (0.14, 0.40)	0.19 (0.05, 0.32)	0.94 (0.84, 1.05)	0.41 (0.30, 0.52)	0.36 (0.25, 0.47)
≥40	47 (5.3)	2.23 (1.90, 2.63)	0.54 (0.39, 0.69)	0.46 (0.30, 0.62)	1.17 (1.06, 1.30)	0.63 (0.51, 0.76)	0.57 (0.44, 0.70)
Missing	1 (0.1)	6.08 (−)			1.85 (−)		
Education level							
High school or less	107 (12.0)	1.57 (1.41, 1.76)	Ref	Ref	0.84 (0.77, 0.91)	Ref	Ref
Some college or undergraduate	543 (61.1)	1.42 (1.36, 1.48)	−0.09 (−0.20, 0.02)	0.02 (−0.09, 0.14)	0.72 (0.69, 0.75)	−0.14 (−0.24, −0.05)	−0.03 (−0.12, 0.06)
Graduate school	239 (26.9)	1.42 (1.33, 1.52)	−0.10 (−0.22, 0.03)	0.06 (−0.07, 0.18)	0.65 (0.62, 0.69)	−0.25 (−0.35, −0.14)	−0.09 (−0.19, 0.02)
Annual household income ($)							
<50,000	144 (16.2)	1.64 (1.50, 1.80)	Ref	Ref	0.83 (0.76, 0.90)	Ref	Ref
50,000–<100,000	364 (40.9)	1.54 (1.46, 1.63)	−0.05 (−0.15, 0.04)	0.00 (−0.10, 0.10)	0.76 (0.72, 0.79)	−0.08 (−0.17, 0.00)	0.00 (−0.08, 0.08)

Characteristics	N=889	F_2-IsoP			15-F_{2t}-IsoP-M		
	n (%)	GM (95% CI) //	uGMD (95% CI)♥	aGMD (95% CI)¶	GM (95% CI) //	uGMD (95% CI)♥	aGMD (95% CI)¶
≥100,000	360 (40.5)	1.29 (1.23, 1.35)	−0.24 (−0.34, −0.14)	−0.13 (−0.23, −0.02)	0.63 (0.60, 0.66)	−0.27 (−0.35, −0.18)	−0.09 (−0.18, −0.01)
Missing	21 (2.4)	1.11 (0.90, 1.38)			0.76 (0.63, 0.91)		
Smoking history							
Never	545 (61.3)	1.41 (1.36, 1.47)	Ref	Ref	0.70 (0.67, 0.72)	Ref	Ref
Former	267 (30.0)	1.42 (1.33, 1.52)	−0.01 (−0.09, 0.07)	−0.01 (−0.08, 0.07)	0.70 (0.67, 0.74)	0.01 (−0.06, 0.07)	0.00 (−0.07, 0.06)
Current	77 (8.7)	1.69 (1.50, 1.92)	0.16 (0.03, 0.29)	0.04 (−0.09, 0.17)	0.88 (0.79, 0.97)	0.24 (0.14, 0.35)	0.10 (0.00, 0.21)
Regular (not decaf) coffee consumption (cups/wk)							
0	279 (31.4)	1.53 (1.44, 1.63)	Ref	Ref	0.73 (0.69, 0.78)	Ref	Ref
<10	257 (28.9)	1.37 (1.28, 1.46)	−0.12 (−0.21, −0.03)	−0.07 (−0.15, 0.02)	0.69 (0.66, 0.73)	−0.06 (−0.13, 0.02)	0.00 (−0.07, 0.07)
10−<15	203 (22.8)	1.37 (1.28, 1.48)	−0.12 (−0.22, −0.03)	−0.09 (−0.19, 0.00)	0.69 (0.64, 0.73)	−0.06 (−0.15, 0.02)	−0.05 (−0.12, 0.03)
≥15	143 (16.1)	1.49 (1.36, 1.62)	−0.06 (−0.16, 0.05)	−0.04 (−0.14, 0.07)	0.76 (0.71, 0.81)	0.03 (−0.06, 0.12)	0.04 (−0.05, 0.12)
Missing	7 (0.8)	1.39 (0.97, 2.00)			0.63 (0.44, 0.92)		
Total energy intake (kcal/day)							
<1,230.40	222 (25.0)	1.41 (1.32, 1.51)	Ref	Ref	0.70 (0.66, 0.75)	Ref	Ref
1,230.40−<1,528.70	223 (25.1)	1.40 (1.31, 1.50)	−0.02 (−0.12, 0.08)	0.02 (−0.09, 0.13)	0.68 (0.64, 0.72)	−0.03 (−0.12, 0.05)	0.03 (−0.06, 0.12)
1,528.70–<1,974.90	221 (24.9)	1.46 (1.36, 1.56)	0.03 (−0.07, 0.12)	0.10 (−0.03, 0.22)	0.74 (0.69, 0.78)	0.05 (−0.04, 0.13)	0.12 (0.02, 0.22)
≥1974.90	223 (25.0)	1.48 (1.38, 1.58)	0.02 (−0.07, 0.12)	0.18 (0.03, 0.32)	0.73 (0.69, 0.78)	0.05 (−0.04, 0.13)	0.16 (0.04, 0.28)
Physical activity (MET-hour/week)							
<28.11	221 (24.9)	1.68 (1.57, 1.81)	Ref	Ref	0.82 (0.77, 0.87)	Ref	Ref
28.11–<44.16	221 (24.9)	1.40 (1.31, 1.49)	−0.18 (−0.27, −0.08)	−0.12 (−0.22, −0.03)	0.70 (0.66, 0.74)	−0.16 (−0.25, −0.08)	−0.10 (−0.18, −0.02)
44.16–<65.99	221 (24.9)	1.43 (1.34, 1.53)	−0.17 (−0.27, −0.07)	−0.09 (−0.18, 0.01)	0.70 (0.66, 0.74)	−0.17 (−0.25, −0.09)	−0.10 (−0.18, −0.02)
≥65.99	221 (24.9)	1.27 (1.19, 1.36)	−0.29 (−0.39, −0.20)	−0.16 (−0.25, −0.06)	0.65 (0.61, 0.69)	−0.24 (−0.33, −0.16)	−0.12 (−0.20, −0.04)
Missing	5 (0.4)	1.34 (0.86, 2.09)			0.76 (0.54, 1.07)		
Healthy Eating Index (HEI)							

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Characteristics	N=889	F_2-IsoP			15-F_{2t}-IsoP-M		
	n (%)	GM (95% CI) //	uGMD (95% CI)¥	aGMD (95% CI)¶	GM (95% CI) //	uGMD (95% CI)¥	aGMD (95% CI)¶
(0–100)<53	213 (24.0)	1.54 (1.42, 1.66)	Ref	Ref	0.77 (0.72, 0.82)	Ref	Ref
53–<63	230 (25.9)	1.54 (1.44, 1.64)	0.00 (−0.10, 0.09)	0.08 (−0.02, 0.18)	0.75 (0.71, 0.79)	−0.03 (−0.12, 0.05)	0.02 (−0.06, 0.11)
63–<72	223 (25.1)	1.35 (1.27, 1.44)	−0.12 (−0.22, −0.03)	0.06 (−0.06, 0.18)	0.68 (0.64, 0.72)	−0.14 (−0.22, −0.05)	0.00 (−0.10, 0.10)
≥72	223 (25.1)	1.34 (1.26, 1.44)	−0.14 (−0.23, −0.04)	0.13 (−0.01, 0.26)	0.66 (0.62, 0.70)	−0.17 (−0.25, −0.08)	0.03 (−0.09, 0.14)
Dietary fruit intake (serving/day)							
<0.6	210 (23.6)	1.62 (1.51, 1.73)	Ref	Ref	0.78 (0.73, 0.82)	Ref	Ref
0.6–<1.1	212 (23.9)	1.51 (1.40, 1.63)	−0.05 (−0.15, 0.05)	−0.04 (−0.15, 0.06)	0.73 (0.69, 0.78)	−0.07 (−0.16, 0.02)	−0.01 (−0.09, 0.08)
1.1–<2	203 (22.8)	1.40 (1.31, 1.48)	−0.13 (−0.23, −0.03)	−0.09 (−0.22, 0.04)	0.71 (0.67, 0.76)	−0.08 (−0.17, 0.01)	0.01 (−0.09, 0.12)
≥2	264 (29.7)	1.29 (1.21, 1.37)	−0.21 (−0.31, −0.12)	−0.13 (−0.27, 0.00)	0.65 (0.62, 0.69)	−0.19 (−0.27, −0.11)	−0.01 (−0.13, 0.10)
Dietary vegetable intake (serving/day)							
<1.6	202 (22.7)	1.63 (1.51, 1.75)	Ref	Ref	0.75 (0.71, 0.80)	Ref	Ref
1.6–<2.7	240 (27.0)	1.45 (1.36, 1.55)	−0.10 (−0.20, −0.01)	−0.09 (−0.20, 0.03)	0.76 (0.72, 0.80)	0.01 (−0.08, 0.09)	0.09 (0.00, 0.19)
2.7–<4.3	221 (24.9)	1.40 (1.31, 1.49)	−0.15 (−0.25, −0.05)	−0.09 (−0.24, 0.06)	0.67 (0.64, 0.71)	−0.11 (−0.20, −0.03)	0.05 (−0.07, 0.17)
≥4.3	226 (25.4)	1.31 (1.22, 1.40)	−0.22 (−0.32, −0.12)	−0.05 (−0.23, 0.13)	0.67 (0.63, 0.71)	−0.13 (−0.22, −0.04)	0.12 (−0.03, 0.26)
Dietary β-carotene intake (mcg/day)							
<2427.2	222 (25.0)	1.63 (1.52, 1.74)	Ref	Ref	0.80 (0.75, 0.84)	Ref	Ref
2427.2–<4106.1	222 (25.0)	1.49 (1.38, 1.60)	−0.07 (−0.17, 0.02)	0.01 (−0.11, 0.13)	0.75 (0.71, 0.80)	−0.06 (−0.15, 0.02)	−0.04 (−0.14, 0.06)
4106.1–<6942.3	222 (25.0)	1.42 (1.32, 1.52)	−0.13 (−0.23, −0.04)	−0.02 (−0.18, 0.13)	0.67 (0.64, 0.72)	−0.18 (−0.27, −0.10)	−0.13 (−0.26, −0.01)
≥6942.3	223 (25.1)	1.25 (1.17, 1.33)	−0.26 (−0.36, −0.16)	−0.13 (−0.31, 0.05)	0.64 (0.60, 0.68)	−0.22 (−0.31, −0.14)	−0.16 (−0.31, −0.01)
Dietary vitamin C intake (mg/day)							
<55.3	221 (24.9)	1.60 (1.48, 1.72)	Ref	Ref	0.77 (0.73, 0.82)	Ref	Ref
55.3–<84.1	223 (25.1)	1.48 (1.39, 1.58)	−0.06 (−0.16, 0.03)	0.00 (−0.11, 0.11)	0.75 (0.71, 0.79)	−0.04 (−0.13, 0.04)	0.02 (−0.07, 0.11)
84.1–<121.9	222 (25.0)	1.38 (1.29, 1.48)	−0.14 (−0.24, −0.04)	−0.01 (−0.14, 0.12)	0.67 (0.63, 0.71)	−0.15 (−0.23, −0.06)	−0.03 (−0.13, 0.08)
≥121.9	223 (25.1)	1.30 (1.22, 1.39)	−0.20 (−0.30, −0.11)	−0.04 (−0.20, 0.12)	0.67 (0.63, 0.72)	−0.14 (−0.22, −0.06)	−0.01 (−0.14, 0.12)

Characteristics	N=889	F_2-IsoP			15-F_{2t}-IsoP-M		
	n (%)	GM (95% CI) //	uGMD (95% CI)ψ	aGMD (95% CI)¶	GM (95% CI) //	uGMD (95% CI)ψ	aGMD (95% CI)¶
Dietary vitamin E intake (mg/day)							
<5.6	217 (24.4)	1.54 (1.43, 1.65)	Ref	Ref	0.77 (0.73, 0.82)	Ref	Ref
5.6–<7.6	225 (25.3)	1.44 (1.33, 1.55)	−0.07 (−0.17, 0.03)	−0.03 (−0.15, 0.08)	0.70 (0.66, 0.74)	−0.11 (−0.19, −0.02)	−0.09 (−0.18, 0.01)
7.6–<10.1	222 (25.0)	1.46 (1.37, 1.57)	−0.06 (−0.15, 0.04)	−0.04 (−0.17, 0.09)	0.71 (0.67, 0.76)	−0.08 (−0.17, 0.00)	−0.10 (−0.21, 0.01)
≥10.1	225 (25.3)	1.33 (1.25, 1.41)	−0.16 (−0.26, −0.06)	−0.13 (−0.29, 0.03)	0.67 (0.63, 0.72)	−0.14 (−0.22, −0.05)	−0.18 (−0.31, −0.05)

Abbreviations: BMI: body mass index, MET: metabolic equivalent of task, Cr: creatinine, F_2-IsoP: 8-iso-prostaglandin $F_{2\alpha}$, 15-F_{2t}-IsoP-M: 2,3-dinor-5,6-dihydro-15-F2t-isoprostane, GM: geometric mean, SD: standard deviation, uGMD: univariate geometric mean difference, aGMD: adjusted geometric mean difference, CI: confidence interval.

// Geometric mean was calculated using the whole sample (n=889).

ψ Univariate models were restricted to participants without missing values of the covariates and had the same size as adjusted models (n=856).

¶ aGMD was calculated in multivariable model adjusting for all variables in table 1.

Geometric mean difference and 95% CI were calculated on the basis of natural logarithm of F_2-IsoP and 15-F_{2t}-IsoP-M.

Table 2.

Association between tea consumption or caffeine intake and urinary F2-IsoP or 15-F2t-IsoP-M

Characteristics	N=889	F_2-IsoP			15-F_{2t}-IsoP-M		
	n (%)	GM (95% CI) //	uGMD (95% CI)¥	aGMD (95% CI)¶	GM (95% CI) //	uGMD (95% CI)¥	aGMD (95% CI)¶
Black tea (cups/wk)							
0	165 (18.6)	1.50 (1.38, 1.63)	Ref	Ref	0.71 (0.66, 0.75)	Ref	Ref
<1	311 (35.0)	1.39 (1.32, 1.47)	−0.07 (−0.17, 0.03)	−0.06 (−0.15, 0.04)	0.70 (0.67, 0.74)	0.00 (−0.09, 0.08)	0.04 (−0.04, 0.12)
1–<5	187 (21.0)	1.38 (1.28, 1.48)	−0.08 (−0.19, 0.03)	−0.09 (−0.20, 0.01)	0.68 (0.64, 0.73)	−0.04 (−0.13, 0.06)	−0.01 (−0.10, 0.08)
≥5	221 (24.9)	1.51 (1.40, 1.62)	0.01 (−0.09, 0.12)	0.01 (−0.10, 0.11)	0.76 (0.71, 0.81)	0.08 (−0.02, 0.17)	0.10 (0.02, 0.19)
Missing	5 (0.5)	1.62 (0.81, 3.24)			0.63 (0.34, 1.15)		
Green tea (cups/wk)							
0	408 (45.9)	1.47 (1.40, 1.55)	Ref	Ref	0.72 (0.69, 0.75)	Ref	Ref
<1	315 (35.4)	1.45 (1.37, 1.54)	0.00 (−0.08, 0.07)	0.03 (−0.05, 0.10)	0.72 (0.68, 0.76)	0.00 (−0.07, 0.06)	0.05 (−0.01, 0.12)
1–<5	96 (10.8)	1.29 (1.17, 1.43)	−0.12 (−0.24, −0.01)	−0.03 (−0.14, 0.08)	0.66 (0.61, 0.72)	−0.09 (−0.19, 0.01)	0.01 (−0.09, 0.10)
≥5	67 (7.6)	1.41 (1.24, 1.60)	−0.04 (−0.18, 0.09)	0.06 (−0.07, 0.19)	0.70 (0.64, 0.78)	−0.02 (−0.14, 0.10)	0.09 (−0.02, 0.20)
Missing	3 (0.3)	1.17 (0.24, 5.77)			0.67 (0.21, 2.16)		
Caffeine intake (mg/day)							
<33.9	222 (25.0)	1.42 (1.33, 1.52)	Ref	Ref	0.67 (0.64, 0.71)	Ref	Ref
33.9–<111.2	223 (25.1)	1.46 (1.36, 1.57)	0.03 (−0.07, 0.13)	0.03 (−0.07, 0.13)	0.74 (0.69, 0.79)	0.09 (0.00, 0.17)	0.09 (0.01, 0.17)
111.2–<205.2	221 (24.9)	1.38 (1.29, 1.48)	−0.03 (−0.13, 0.06)	−0.02 (−0.11, 0.08)	0.69 (0.65, 0.74)	0.03 (−0.06, 0.11)	0.05 (−0.03, 0.13)
≥205.2	223 (25.0)	1.49 (1.39, 1.59)	0.03 (−0.07, 0.12)	0.01 (−0.09, 0.11)	0.75 (0.71, 0.79)	0.10 (0.02, 0.18)	0.08 (0.00, 0.16)
Black tea (cups/wk)§							
0				Ref			Ref
<1				−0.05 (−0.15, 0.04)			0.03 (−0.05, 0.11)
1–<5				−0.09 (−0.20, 0.02)			−0.02 (−0.11, 0.07)
≥5				0.01 (−0.10, 0.12)			0.08 (−0.01, 0.17)
Green tea (cups/wk)§							

Characteristics	N=889	F_2-IsoP			15-F_{2t}-IsoP-M		
	n (%)	GM (95% CI) ∥	uGMD (95% CI) ψ	aGMD (95% CI) ¶	GM (95% CI) ∥	uGMD (95% CI) ψ	aGMD (95% CI) ¶
0				Ref			Ref
<1				0.03 (−0.05, 0.10)			0.05 (−0.02, 0.11)
1–<5				−0.03 (−0.15, 0.08)			−0.01 (−0.10, 0.09)
≥5				0.05 (−0.08, 0.19)			0.07 (−0.04, 0.18)

Abbreviations: F_2-IsoP: 8-iso-prostaglandin $F_{2\alpha}$, 15-F_{2t}-IsoP-M: 2,3-dinor-5,6-dihydro-15-F2t-isoprostane, uGMD: univariate geometric mean difference, aGMD: adjusted bgeometric mean difference, CI: confidence interval

∥ Geometric mean was calculated using the whole sample (n=889).

ψ Univariate models were restricted to participants without missing values of the covariates (black tea: n=858, green tea: n=861, caffeine: n=863).

¶ The multivariable model adjusted for age, race, smoking status, BMI, physical activity, household income, education level, energy intake, HEI, dietary fruit, vegetable, β-carotene, vitamin C, and vitamin E intake. (black tea: n=858, green tea: n=861, caffeine: n=863).

§ The multivariable model additionally adjusted for caffeine intake.

Geometric mean difference and 95% CI were calculated on the basis of natural logarithm of F_2-IsoP and 15-F_{2t}-IsoP-M.