Effects of green tea catechin extract on serum lipids in postmenopausal women: a randomized, placebo-controlled clinical trial[1,2]

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ABSTRACT

Background: Green tea has been suggested to improve cardiovascular disease risk factors, including circulating lipid variables. However, current evidence is predominantly based on small, short-term randomized controlled trials conducted in diverse populations.

Objective: The aim of this study was to examine the efficacy and impact of green tea extract (GTE) supplementation high in epigallocatechin gallate (EGCG) on blood lipids in healthy postmenopausal women.

Design: This was an ancillary study of a double-blind, randomized, placebo-controlled, parallel-arm trial investigating the effects of a GTE supplement containing 1315 mg catechins (843 mg EGCG) on biomarkers of breast cancer risk. Participants were randomly assigned to receive GTE ($n = 538$) or placebo ($n = 537$) and were stratified by catechol-*O*-methyltransferase (*COMT*) genotype activity (high *COMT* compared with low or intermediate *COMT* genotype activity). They consumed either 4 GTE or identical placebo capsules daily for 12 mo. A total of 936 women completed this substudy. Circulating lipid panels including total cholesterol (TC), HDL cholesterol, and triglycerides were measured at baseline and at months 6 and 12.

Results: Compared with placebo, 1-y supplementation with GTE capsules resulted in a significant reduction in circulating TC (-2.1% compared with 0.7%; $P = 0.0004$), LDL cholesterol (-4.1% compared with 0.9%; $P < 0.0001$) and non-HDL cholesterol (-3.1% compared with 0.4%; $P = 0.0032$). There was no change in HDL-cholesterol concentration, but triglyceride concentrations increased by 3.6% in the GTE group, whereas they decreased by 2.5% in the placebo group ($P = 0.046$). A significant reduction in TC was observed only among women with high (i.e., $\geq$200 mg/dL) baseline TC concentrations (P-interaction = 0.01) who consumed GTE capsules. The effect of GTE on the increase in triglycerides was mainly observed among obese women and statin users (P-interaction = 0.06).

Conclusion: Supplementation with GTE significantly reduced circulating TC and LDL-cholesterol concentrations, especially in those with elevated baseline TC concentrations. This trial was registered at clinicaltrials.gov as NCT00917735. *Am J Clin Nutr* doi: 10.3945/ajcn.116.137075.

Keywords: green tea, EGCG, blood lipids, postmenopausal, cardiovascular, randomized controlled trial

INTRODUCTION

Cardiovascular disease (CVD)[7] remains the primary cause of death in the United States and worldwide (1, 2). Hyperlipidemia is considered to be a major risk factor for CVD, and currently a high percentage of US women have elevated concentrations of total cholesterol (TC) and LDL cholesterol ($\sim$45.0% and 32.0%, respectively) (3). Existing guidelines on cholesterol management mainly include LDL-lowering drugs, such as β-hydroxy-β-methylglutaryl coenzyme A reductase inhibitors (statins), and lifestyle changes such as weight loss, physical activity, or diet therapy (4). Due to side effects associated with statin use, there is great interest in dietary modifications to lower cholesterol.

Green tea as a dietary factor has been shown to lower the risk of a number of chronic diseases, including heart disease (5–8). Although not consistent, a number of small short-term human trials showed that green tea and its major bioactive constituent, epigallocatechin gallate (EGCG), exert hypocholesterolemic effects, particularly on lowering the concentrations of TC and LDL cholesterol. Current meta-analyses of green tea and lipid clinical trials, all with short durations (3–24 wk), showed that

green tea extract (GTE) or green tea beverage significantly decreased both TC (by 5–7 mg/dL) and LDL cholesterol (by 2–7 mg/dL) in various populations (9–12).

Catechol-*O*-methyltransferase (COMT) is one of the enzymes involved in the methylation metabolism of tea catechins. Polymorphisms in *COMT*, in particular a G-to-A transition at codon 158 of *COMT* (single nucleotide polymorphism rs4680), have been shown to influence the metabolism of tea polyphenols (13), such that individuals with low *COMT* genotype activity metabolize and excrete catechins more slowly. As a result, they may retain more tea catechins in their bodies and derive greater lipid-lowering benefit from tea consumption.

The present randomized controlled trial (RCT) was an ancillary study of a large RCT conducted to evaluate the effects of a GTE on breast cancer risk biomarkers in postmenopausal women who were at high risk of breast cancer due to high breast density. Blood lipid concentrations in postmenopausal women are of interest due to their increased risk and incidence of developing heart disease (14). We hypothesized that supplementation with a concentrated GTE that included ∼800 mg EGCG for 1 y would significantly reduce circulating concentrations of TC and LDL cholesterol and increase serum HDL-cholesterol concentrations. We also explored the potential modifying effects of the *COMT* genotype activity on GTE supplementation, speculating that those with the low-activity *COMT* genotype would show the greatest response to GTE supplementation. To our knowledge, this is the largest and longest RCT to evaluate the effects of green tea catechins on lipids in postmenopausal women. Significant findings may provide additional avenues of treatment or adjunct care for risk management in this and similar populations.

METHODS

Study population and recruitment

The current trial is a substudy of the Minnesota Green Tea Trial (MGTT), which was previously described in detail elsewhere (15). Briefly, the MGTT was a double-blind, placebo-controlled, randomized clinical trial (clinicaltrials.gov; NCT00917735). The purpose of the MGTT was to evaluate the effects of consumption of GTE on a number of breast cancer risk biomarkers, including mammographic density, circulating reproductive hormones, insulin-like growth factor axis proteins, urinary estrogens and estrogen metabolites, and markers of oxidative stress. Participants for this study were women with differing *COMT* genotypes at high risk of breast cancer due to having dense breast tissue.

Participants were recruited between 2009 and 2013 on the basis of age (50–70 y old) and breast density as recorded in routine mammogram reports (heterogeneously or extremely dense breasts). Exclusionary criteria included the following: current smoker; use of menopausal hormone therapy (within the past 6 mo); weight fluctuation of >10 pounds (4.5 kg) within the past year; had a menstrual period within the past 12 mo; diabetic; positive for hepatitis B or C; current user of >10 prescription medications; current user of methotrexate or etanercept; elevated liver enzymes >1.5 upper limit of normal; intake of >7 alcoholic drinks/wk; any history of breast cancer, ovarian cancer, or proliferative breast disease; history of any other cancer within the past 5 y; BMI (in kg/m^2) <18.5 or >40; and consumer of ≥1 cup green tea/wk.

After an initial phone screening, eligible participants attended an orientation session. All of the participants signed a consent form before proceeding with the study. Consented women attended a clinical screening to assess further eligibility. The clinical screening included measurement of anthropometric variables and a small nonfasting blood draw for *COMT* genotyping, hepatic function, and serologic markers of hepatitis B or C virus. If eligibility was confirmed at their clinical screening, the women were enrolled in the study. Randomization was performed by Investigational Drug Services at the University of Minnesota Medical Center, Fairview, by using a permuted block method in blocks of 8, stratified by *COMT* genotype. The randomization code was kept confidential from all participants and investigators throughout the study and during analysis, with the exception of the study biostatistician. The MGTT was conducted according to the guidelines described in the Declaration of Helsinki and was approved by the institutional review boards of the University of Minnesota, the Park Nicollet Institute, the University of Pittsburgh, and the University of Southern California.

Study protocol

Nutrient and calorie intakes were determined and analyzed for each participant by completion of a Diet History Questionnaire (developed by the National Cancer Institute) at baseline and month 12 visits. Height was measured at screening, baseline (month 0), and month 12 visits. Weight and vital signs, including systolic and diastolic blood pressure, heart rate, respiration, and temperature, were collected at screening, baseline, and then every 3 mo throughout the study. After randomization, participants attended their baseline visit for fasting blood draws, measurement of vital signs, return of their 24-h urine collections, and to receive their first 3-mo supply of the study supplements. Baseline, month 6, and month 12 were the most comprehensive visits and included a longer overnight fasting blood draw (between 0630 and 1000) for biochemical assays including a lipid panel, a 24-h urine collection, and completion of the Diet History Questionnaire. A comprehensive health history questionnaire was completed at the baseline visit, and a Menopause-Specific Quality of Life questionnaire was completed at baseline and months 6 and 12. A small volume of blood was drawn monthly through month 6 for monitoring of liver function enzymes. After month 6, participants returned to the clinic once every 3 mo for the remainder of the study (totaling 2 visits past the month 6 time point: months 9 and 12). To evaluate treatment compliance, participants were asked to return all unused capsules at each clinic visit. Accordingly, compliance was determined by dividing the number of consumed capsules by the number the participants were supposed to consume. As a secondary measure of compliance, spot urine samples were also collected at months 3 and 9 for all participants and urinary catechins, including epigallocatechin (EGC) and epicatechin (EC), were measured in a randomly selected 10% of participants.

Blood collection and processing

Serum collected at the clinic for analysis was separated from whole blood by centrifugation at 1500 × *g* for 25 min at 4°C, then separated into 1.5-mL aliquots and stored at −80°C until

analysis. Frozen samples were sent in batches to Quest Diagnostic laboratories for measurement of a standard lipid panel. Batches were prepared by arranging participants into GTE-placebo pairs, and all samples from each participant and pair in a batch were analyzed together in the same analysis batch, with all staff blinded to the assigned treatment code. Standard lipid panels including TC, HDL cholesterol, and triglycerides were measured in fasting serum samples. All biospecimen analyses were performed at Quest Diagnostics by using the spectrophotometry methodology with the Beckman Olympus AU5400 chemistry analyzer. Non-HDL cholesterol was calculated by subtracting HDL cholesterol from TC concentrations, and LDL cholesterol was calculated by using the Friedewald method for participants with triglycerides <400 mg/dL (16). The interassay CVs obtained from quality-control samples were 1.4% for TC, 2.6% for HDL cholesterol, and 2.1% for triglycerides. DNA was extracted from buffy coat fractions by using the Qiagen DNeasy Blood and Tissue Kit method (Qiagen, Inc.), and *COMT* genotyping (rs4680) was conducted by a TaqMan PCR Core Reagent kit (Applied Biosystems) according to the manufacturer's instructions.

Study supplement

The study supplement, Green Tea Extract Catechin Complex (Corban Complex GTB; abbreviated as "GTE" in this article), was manufactured and provided by Corban Laboratories/Eniva Nutraceutics. The GTE was made from green tea leaves grown by Youshan Tea Farm in China and supplied by Taiyo Green Power Co. Ltd. in China. Corban provided 8 batches of green tea supplement over the course of the trial. Samples were randomly drawn from each new batch for catechin composition analysis by 2 independent laboratories: Covance Laboratories and the laboratory of CS Yang (Rutgers University). Results for catechin compositions of capsules were similar between the 2 laboratories. A detailed description of catechin and caffeine composition of the treatment and placebo capsules was presented previously (15). GTE capsules were decaffeinated with <4 mg caffeine/capsule and, on average, provided 1315 mg catechins/d, including 843 mg EGCG, 202 mg epicatechin gallate, 107 mg EGC, and 107 mg EC. Placebo capsules were identical in appearance to the GTE and mainly composed of maltodextrin and cellulose (50.0% and 49.5% of each capsule's weight, respectively) with no caffeine included. Supplements were dispensed by the Investigational Drug Services' pharmacy at the University of Minnesota, and both participants and investigators were blinded to individual participant assignment throughout the entirety of the study. All of the capsules were stored and dispensed on the basis of individual patient schedules and were stored in a temperature-controlled, locked cabinet until given to participants by professional clinic staff at regular clinic visits. Participants were provided a 3-mo supply of supplement at the baseline, month 3, month 6, and month 9 visits (135 capsules of GTE or placebo were provided for each month). Each participant was instructed to take 2 capsules (either GTE or placebo) in the morning after breakfast and 2 capsules in the evening after dinner.

Statistical analyses

Statistical analyses were performed after both intention-to-treat (ITT) and per-protocol paradigms, but the results presented in this article are based on the ITT principle (**Figure 1**). The differences in the distributions of baseline demographic characteristics and dietary intakes between GTE and placebo participants were examined by Pearson's chi-square test (categorical or nominal variables) or by Student's *t* test (continuous variables).

All serum lipids are expressed in milligrams per deciliter. The differences in the distributions of serum lipid concentrations at baseline between GTE and placebo participants were examined by using ANOVA, with adjustment for age and BMI. To assess the effect of GTE on lipid concentration, we first calculated the absolute change in concentration of a given serum lipid from baseline to months 6 and 12, respectively. We then used mixed-effects repeated-measures ANOVA to assess the magnitude of these changes in circulating lipid concentrations among participants in the GTE group compared with those in the placebo group. This model simultaneously examined the effect of treatment (i.e., GTE compared with placebo) on lipid concentration change overall as well as at months 6 and 12. We used the same ANOVA for stratified analysis to investigate the potential impact of certain participants' characteristics at baseline, such as TC, BMI, regular statin use, triglycerides, *COMT* genotype, and time since menopause, on the effect of GTE on serum lipid concentrations. In all subgroup analyses, age and BMI at baseline were also adjusted for. The potential interaction effect of baseline characteristics and GTE on the change in lipid concentrations was examined by including a product term in the ANOVA. If the interaction was significant, we included the product term in the final model; otherwise, we dropped it from the final model that produced the results presented.

The MGTT sample size was based on a power calculation conducted for the primary endpoint of the MGTT (i.e., change in mammographic density). We further performed post hoc power calculations for the changes in blood lipids as primary outcome measures of this substudy. Assuming a 2-sided significance level of 0.05 and a total sample size of 936 women (468 in the GTE and 468 in the placebo group), we would have an 80% statistical power to detect a 6.1-mg/dL reduction in TC and a 5.1-mg/dL decrease in LDL-cholesterol concentrations in the GTE group compared with the placebo group. However, we did not have sufficient statistical power to examine the modifying effects of *COMT* genotype activity on GTE supplementation, which, in fact, was part of the exploratory nature of this substudy.

Statistical analyses were carried out by using SAS software version 9.3 (SAS Institute). Reported *P* values were 2-sided, and $P < 0.05$ was considered significant for lifestyle and dietary intake (**Tables 1** and **2**). Given the exploratory nature of the present analysis on the effect of GTE on blood lipid concentrations, Bonferroni correction was used to adjust for multiple comparisons, and $P < 0.05$ was considered significant (**Tables 3–6**, **Supplemental Tables 1** and **2**).

RESULTS

Of 1075 participants randomly assigned into either the GTE ($n = 538$) or placebo ($n = 537$) groups, 937 women (or 87.2% of the randomly assigned participants) completed the intervention (Figure 1). One participant was excluded from all analyses for this substudy due to missing data on all lipids at baseline. Therefore, the final sample size for this substudy was 936 (GTE: $n = 463$; placebo: $n = 473$).
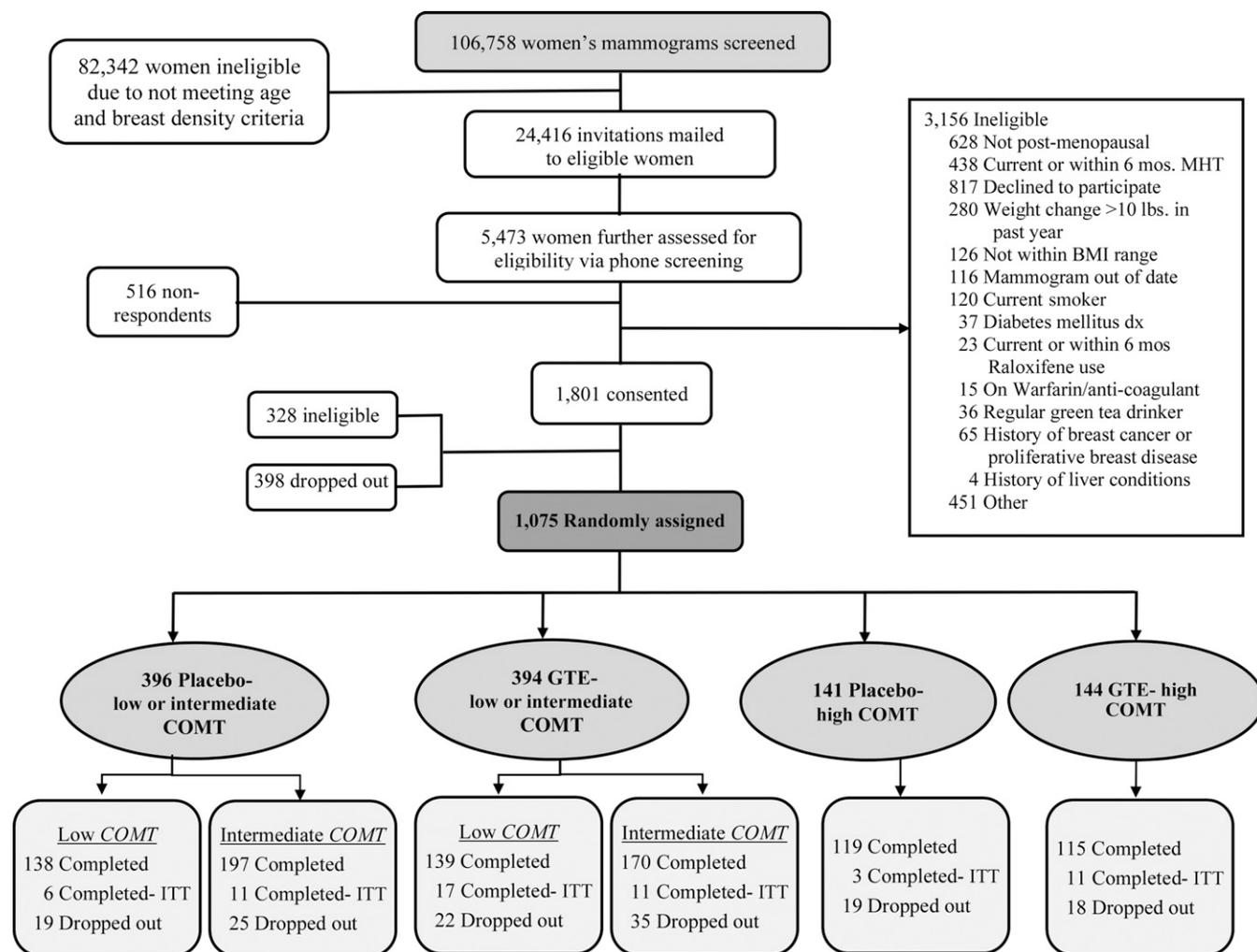
FIGURE 1 Study participant diagram of recruitment, screening, randomization, and follow-up of the Minnesota Green Tea Trial. COMT, catechol-*O*-methyltransferase; dx, diagnosis; GTE, green tea extract; ITT, intention-to-treat; MHT, menopausal hormone therapy. Adapted from reference 17 with permission.

An analysis of baseline characteristics showed no significant differences between treatment groups, with the exception of the GTE group, who reported greater regular intakes of vitamin and/or mineral supplements at baseline than the placebo group ($P = 0.02$) (Table 1). Intakes of energy, nutrients, and select food groups were also compared both at baseline and after 1 y in the study (Table 2). Only vegetable intake at month 12 showed a significant difference between treatment groups, with a slightly higher intake in the GTE group ($P = 0.03$). Changes from baseline in energy and nutrient intakes were not different between the 2 groups (data not shown).

Baseline concentrations of TC, HDL cholesterol, LDL cholesterol, and non-HDL cholesterol were not different between the GTE and placebo groups (Table 3). However, triglycerides and the TC-to-HDL-cholesterol ratio were significantly lower in the GTE group than in the placebo group at baseline ($P = 0.001$ and 0.03, respectively). After 1 y of supplementation, compared with placebo, participants in the GTE group experienced significant reductions in TC (-2.1% compared with 0.7%; $P = 0.0004$), LDL cholesterol (-4.1% compared with 0.9%; $P < 0.0001$), and non-HDL cholesterol (-3.1% compared with 0.4%; $P = 0.0032$). At the same time,

participants in the GTE group experienced a significant increase in triglycerides (3.6% compared with -2.5%; $P = 0.046$), whereas concentrations of HDL cholesterol and the TC-to-HDL-cholesterol ratio did not change significantly between the 2 groups. There were no significant interactions between treatment and time.

Table 4 shows changes in serum lipids when stratifying participants by baseline TC into 1 of 3 clinical subcategories of TC as established by the National Cholesterol Education Program of the NIH (4): <200 mg/dL ("desirable"), 200–239 mg/dL ("borderline high"), and ≥240 mg/dL ("high"). There were significant or borderline significant interactions between treatment and baseline category for TC ($P = 0.01$), LDL cholesterol ($P = 0.06$), and non-HDL cholesterol ($P = 0.05$), suggesting that the lipid-lowering effects of the GTE occurred only in the "borderline high" and "high" cholesterol groups. At 12 mo, for TC, changes in the GTE compared with the placebo groups in the "borderline high" category were -3.6% compared with 0.20%, whereas the changes in the "high" cholesterol group were -8.3% compared with -2.8% ($P < 0.0001$ and $P = 0.0004$ for overall treatment effect, respectively). For LDL cholesterol, changes in the GTE compared with placebo groups in the

TABLE 1
Baseline demographic and other selected characteristics of study participants[1]

Variables	GTE (n = 463)	Placebo (n = 473)	P
Age at baseline, y	60.02 ± 4.89	59.65 ± 5.04	0.26
Weight, kg	67.34 ± 10.66	67.40 ± 10.33	0.93
BMI, kg/m^{2}	25.16 ± 3.72	25.01 ± 3.73	0.53
Waist-to-hip ratio[2]	0.84 ± 0.07	0.83 ± 0.07	0.22
Race,[3] n (%)			
White	453 (98.05)	457 (97.03)	0.31
Nonwhite	9 (1.95)	14 (2.97)	
Ethnicity,[4] n (%)			
Hispanic	5 (1.09)	4 (0.86)	0.72
Non-Hispanic	453 (98.91)	463 (99.14)	
Smoking status,[5] n (%)			
Never	316 (68.55)	324 (68.64)	0.97
Former	145 (31.45)	148 (31.36)	
Educational level (degree),[6] n (%)			
High school or less	27 (5.86)	31 (6.61)	0.08
Some college	313 (67.90)	286 (60.98)	
Postgraduate or professional	121 (26.25)	152 (32.41)	
Regular use of vitamin and/or mineral supplements,[7,8] n (%)			
No	42 (9.09)	66 (13.95)	0.02
Yes	420 (90.91)	407 (86.05)	
Regular use of aspirin,[8,9] n (%)			
No	339 (73.22)	341 (72.25)	0.74
Yes	124 (26.78)	131 (27.75)	
Regular use of statins,[8,10] n (%)			
No	360 (78.43)	378 (80.60)	0.41
Yes	99 (21.57)	91 (19.40)	
Consumption of soy,[8,11] n (%)			
No	327 (71.40)	307 (66.16)	0.09
Yes	131 (28.60)	157 (33.84)	
Times/wk[12]	2.39 ± 2.68	1.98 ± 2.48	0.21
Regular consumption of black and/or green tea,[8] n (%)			
No	187 (40.39)	179 (37.84)	0.21
Yes	275 (59.40)	289 (61.10)	
Unknown	1 (0.22)	5 (1.06)	
Years since menopause[13]	11.07 ± 7.63	10.32 ± 7.24	0.13
Self-reported physical activity,[9] MET-h/wk	45.71 ± 53.97	51.07 ± 106.95	0.33

[1] Values are means ± SDs for continuous variables or frequencies (percentages) for categorical variables. P values were derived from Student's t test for continuous variables and Pearson's chi-square test for categorical variables. GTE, green tea extract; MET-h, metabolic equivalent hours.

[2–6] Participant numbers for the GTE and placebo groups, respectively, are as follows: [2] n = 461 and 473, [3] 462 and 471, [4] 458 and 467, [5] 461 and 472, and [6] 461 and 469.

[7] n = 462 for the GTE group.

[8] Self-reported on the baseline health history questionnaire.

[9] n = 472 for the placebo group.

[10–13] Participant numbers for the GTE and placebo groups, respectively, are as follows: [10] n = 459 and 469, [11] 458 and 464, [12] 119 and 143, and [13] 440 and 453.

"borderline high" cholesterol group were −5.5% compared with 0.50%, whereas the changes in the "high" cholesterol group were −12.2% compared with −4.4% (P < 0.0001 and P = 0.006 for overall treatment effect, respectively). For non-HDL cholesterol, changes in the GTE compared with placebo groups in the "borderline high" cholesterol group were −4.3% compared with 0.001%, whereas the changes in the "high" cholesterol group were −11.1% compared with −4.4% (P = 0.004 and 0.01 for overall treatment effect, respectively). Results were not markedly affected after excluding statin users among those in the high-baseline-TC category (data not shown).

Table 5 shows findings stratified into 1 of 3 subcategories of baseline BMI: BMI <25 (normal or healthy), 25–29.9 (overweight), and ≥30.0 (obese). There was a borderline significant interaction between treatment and baseline BMI category only for triglycerides (P = 0.06). GTE supplementation resulted in a significant increase in triglyceride concentrations compared with placebo only in obese participants (P-overall treatment = 0.031). When the analysis was limited to obese statin users, GTE had no effect on triglycerides or any other lipids (data not shown).

Supplementation with GTE did not enhance the lipid-lowering effectiveness of statins in our substudy (Table 6). We observed a borderline significant interaction between treatment and statin-use category for triglycerides (P-interaction = 0.06). Surprisingly, serum triglyceride concentrations increased at both 6 and 12 mo only in the GTE statin users, whereas their placebo counterparts experienced reductions at both time points (P-overall

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TABLE 2
Daily nutrient intake at month 0 (baseline) and month 12 (endpoint) by treatment group[1]

Nutrient	GTE[2]	Placebo[3]	P
Total energy, kcal			
Baseline	1438.26 ± 537.50	1447.83 ± 525.18	0.78
Month 12	1370.91 ± 523.00	1365.66 ± 468.77	0.87
Carbohydrate, % of energy			
Baseline	50.40 ± 7.49	50.36 ± 7.28	0.93
Month 12	49.72 ± 7.61	49.33 ± 7.41	0.42
Protein, % of energy			
Baseline	16.33 ± 2.75	15.99 ± 2.67	0.06
Month 12	16.36 ± 2.79	16.08 ± 2.61	0.11
Total fat, % of energy			
Baseline	32.89 ± 6.76	33.15 ± 6.48	0.54
Month 12	33.85 ± 6.75	34.02 ± 6.50	0.70
Saturated fat, % of energy			
Baseline	10.13 ± 2.29	10.14 ± 2.23	0.93
Month 12	10.49 ± 2.35	10.38 ± 2.33	0.47
Monounsaturated fat, % of energy			
Baseline	12.75 ± 3.22	12.87 ± 3.12	0.56
Month 12	13.13 ± 3.19	13.33 ± 3.25	0.33
Polyunsaturated fat, % of energy			
Baseline	7.56 ± 2.28	7.70 ± 2.25	0.33
Month 12	7.74 ± 2.33	7.82 ± 2.28	0.59
Omega-3 FAs, g			
EPA (20:5)			
Baseline	0.02 ± 0.03	0.02 ± 0.02	0.52
Month 12	0.02 ± 0.03	0.02 ± 0.02	0.54
DHA (22:6)			
Baseline	0.05 ± 0.04	0.05 ± 0.04	0.44
Month 12	0.05 ± 0.05	0.05 ± 0.04	0.57
ALA (18:3)			
Baseline	1.03 ± 0.51	1.04 ± 0.53	0.60
Month 12	0.99 ± 0.52	0.98 ± 0.45	0.82
trans FAs, g			
Baseline	2.68 ± 1.38	2.66 ± 1.33	0.79
Month 12	2.62 ± 1.39	2.53 ± 1.26	0.32
Cholesterol, mg			
Baseline	145.96 ± 72.35	142.65 ± 72.36	0.47
Month 12	141.94 ± 73.35	140.30 ± 68.84	0.73
Total dietary fiber, g			
Baseline	17.53 ± 8.21	17.72 ± 7.96	0.72
Month 12	16.83 ± 7.95	16.47 ± 6.81	0.46
Soluble fiber, g			
Baseline	5.78 ± 2.78	5.86 ± 2.63	0.62
Month 12	5.56 ± 2.69	5.45 ± 2.26	0.50
Caffeine,[4] mg			
Baseline	353.59 ± 312.11	378.62 ± 322.85	0.23
Month 12	336.59 ± 296.57	361.02 ± 306.99	0.22
Alcohol, g			
Baseline	6.89 ± 15.35	6.63 ± 8.57	0.75
Month 12	5.76 ± 8.00	6.36 ± 8.88	0.27
Total red meat intake, ounces			
Baseline	1.18 ± 0.85	1.12 ± 0.81	0.26
Month 12	1.11 ± 0.80	1.05 ± 0.71	0.22
Total vegetable intake, servings			
Baseline	3.51 ± 2.28	3.38 ± 2.14	0.39
Month 12	3.41 ± 2.23	3.13 ± 1.78	0.03

[1] Values are means ± SDs. There were no significant interactions between treatment and time for any of the nutrients. P values for differences in mean nutrients between the GTE and placebo groups were derived from Student's t test. ALA, α-linolenic acid; FA, fatty acid; GTE, green tea extract.

[2] $n = 463$ and $n = 461$ for baseline and month 12 data, respectively.

[3] $n = 473$ and $n = 469$ for baseline and month 12 data, respectively.

[4] Excluding the small amount of caffeine from the supplement.

TABLE 3
Means (95% CIs) and changes from baseline concentrations of blood lipids by treatment group[1]

Lipid and time point	GTE ($n = 463$)	Placebo ($n = 473$)	P[2]	P-overall treatment[3]
TC, mg/dL				
Baseline	206 (204, 209)	209 (206, 212)	0.17	
Δ Month 6	−6.64 (−8.52, −4.76)	−0.53 (−2.39, 1.33)	<0.001	0.002
Δ Month 12	−4.35 (−6.35, −2.35)	1.43 (−0.54, 3.41)	0.0004	
HDL cholesterol, mg/dL				
Baseline	70 (69, 72)	69 (68, 71)	0.39	
Δ Month 6	−1.29 (−2.04, −0.53)	0.55 (−0.20, 1.30)	0.0045	0.003
Δ Month 12	−0.12 (−0.88, 0.65)	0.83 (0.08, 1.59)	0.50	
LDL cholesterol,[4] mg/dL				
Baseline	118 (115, 120)	120 (117, 122)	0.32	
Δ Month 6	−5.66 (−7.31, −4.01)	−0.54 (−2.17, 1.10)	0.0001	<0.001
Δ Month 12	−4.81 (−6.58, −3.04)	1.05 (−0.70, 2.80)	<0.0001	
Triglycerides, mg/dL				
Baseline	93 (89, 97)	102 (98, 106)	0.001	
Δ Month 6	1.57 (−1.17, 4.31)	−2.09 (−4.80, 0.63)	0.38	0.004
Δ Month 12	3.31 (0.23, 6.39)	−2.60 (−5.64, 0.45)	0.046	
TC:HDL-cholesterol ratio				
Baseline	3.10 (3.02, 3.18)	3.22 (3.15, 3.30)	0.03	
Δ Month 6	−0.06 (−0.10, −0.02)	−0.03 (−0.07, 0.004)	1.00	0.24
Δ Month 12	−0.07 (−0.12, −0.02)	−0.03 (−0.08, 0.01)	1.00	
Non-HDL cholesterol, mg/dL				
Baseline	136 (133, 139)	140 (137, 143)	0.06	
Δ Month 6	−5.35 (−7.10, −3.60)	−1.08 (−2.82, 0.65)	0.0042	<0.001
Δ Month 12	−4.23 (−6.16, −2.29)	0.60 (−1.31, 2.51)	0.0032	

[1] Values are least-squares means (95% CIs). Values were Bonferroni-corrected and adjusted for age and BMI at baseline. There were no significant interactions between treatment and time for any blood lipids by using the linear mixed models. GTE, green tea extract; TC, total cholesterol; Δ, change.

[2] P values comparing baseline concentrations of lipids between GTE and placebo groups were derived from ANOVA with adjustment for age and BMI. P values for the assessment of changes in lipids from baseline to months 6 and 12 separately between GTE and placebo groups were derived from a mixed-effects repeated-measures ANOVA with adjustment for age and BMI at baseline.

[3] P values for the overall treatment effect between GTE and placebo groups were derived from a mixed-effects repeated-measures ANOVA with adjustment for age and BMI at baseline.

[4] $n = 472$ for the placebo group.

treatment = 0.018). Findings with regard to changes in triglyceride concentrations were in accord with the main results in Table 3, regardless of statin use.

There was no interaction between treatment and baseline triglyceride category for any of the lipids, suggesting that women with different concentrations of baseline triglycerides responded similarly to GTE supplementation (Supplemental Table 1). Likewise, stratifying data by *COMT* genotype activity yielded inconsistent patterns of changes in lipid concentrations, with no evidence of interaction between GTE intake and *COMT* genotype activity (Supplemental Table 2).

The main findings from the per-protocol analysis were very similar to those in the ITT analysis in which GTE supplementation for 1 y resulted in a 2.2% reduction in TC and a 3.2% decrease in non–HDL cholesterol concentrations (compared with a 0.8% and 0.6% increase in the placebo group; $P = 0.0002$ and 0.002, respectively).

DISCUSSION

This double-blind, randomized clinical trial assessed the longer-term effects of supplementation with a high dose of GTE on lipid profiles in healthy postmenopausal women. Daily supplementation of ∼1315 mg green tea catechins (843 mg EGCG)

significantly reduced concentrations of TC, LDL cholesterol, and non-HDL cholesterol over the course of 12 mo. These findings are in agreement with the results of most epidemiologic studies (18–21) and currently published meta-analyses (9–12) that indicate that the consumption of green tea significantly lowers serum concentrations of TC and LDL cholesterol.

We observed no change in the concentrations of HDL cholesterol after 1 y of GTE supplementation, which is consistent with the data from meta-analysis studies (9–12) and most of the RCTs (22–43) conducted to date. A few intervention studies (44–46) found increased concentrations of HDL cholesterol after the ingestion of a green tea beverage or extract. However, participants in the latter studies were overweight or obese, with chronic complications such as hypertension or metabolic syndrome. In addition, these studies had very small sample sizes ($n < 60$) with a shorter duration than our trial and used catechin doses less than half of the dosage that we administered in the MGTT.

Surprisingly, the GTE group had significantly lower triglyceride concentrations than the placebo group at baseline; this difference was unanticipated, given the randomized design and large sample size of the MGTT. Although the GTE group experienced an increase in triglycerides over the course of 12-mo trial, the placebo group experienced a slight decline, providing no

TABLE 4
Treatment effect: changes in blood lipids in the GTE or placebo groups by TC category at baseline[1]

Lipid and time point	TC, mg/dL						
	<200 (n = 388)[2]		200–239 (n = 408)		≥240 (n = 140)		
	GTE (n = 199)	Placebo (n = 189)	GTE (n = 200)	Placebo (n = 208)	GTE (n = 64)	Placebo (n = 76)	P-interaction[3]
TC, mg/dL							0.01
Baseline	180	180	216	218	259	260	
Δ Month 6	0.44	4.18	−9.43	−1.54	−19.88	−9.46	
Δ Month 12	4.65	6.06	−7.75	0.41	−21.57	−7.31	
P[4]		1.00		<0.0001		0.0004	
HDL cholesterol, mg/dL							0.19
Baseline	65	64	74	72	75	75	
Δ Month 6	0.24	1.70	−2.22	−0.35	−3.09	0.17	
Δ Month 12	1.72	1.27	−1.59	0.41	−1.20	0.89	
P[4]		1.00		0.083		0.37	
LDL cholesterol,[5] mg/dL							0.06
Baseline	98	96	124	125	161	163	
Δ Month 6	−0.40	2.99	−7.82	−0.71	−15.23	−8.93	
Δ Month 12	1.92	4.81	−6.80	0.58	−19.58	−7.20	
P[4]		0.70		<0.0001		0.006	
Triglycerides, mg/dL							0.43
Baseline	89	99	90	101	116	115	
Δ Month 6	3.14	−2.39	3.07	−2.26	−7.99	−0.86	
Δ Month 12	5.21	0.01	3.10	−3.03	−1.89	−7.89	
P[4]		0.59		0.36		1.00	
TC:HDL-cholesterol ratio							0.90
Baseline	2.94	2.97	3.09	3.25	3.65	3.76	
Δ Month 6	−0.02	0.005	−0.07	−0.03	−0.16	−0.14	
Δ Month 12	−0.02	0.05	−0.06	−0.06	−0.26	−0.19	
P[4]		1.00		1.00		1.00	
Non-HDL cholesterol, mg/dL							0.05
Baseline	115	116	142	146	184	185	
Δ Month 6	0.20	2.48	−7.21	−1.18	−16.79	−9.63	
Δ Month 12	2.94	4.79	−6.16	−0.001	−20.37	−8.20	
P[4]		1.00		0.004		0.01	

[1] Values are least-squares means, Bonferroni-corrected, and adjusted for age and BMI at baseline. GTE, green tea extract; TC, total cholesterol; Δ, change.

[2] n = 198 and 189 in the GTE and placebo groups, respectively, for the 12-mo time point.

[3] P values for the interaction between treatment and baseline TC category were derived from a mixed-effects repeated-measures ANOVA with adjustment for age and BMI.

[4] P values for the overall change in lipids from baseline to months 6 and 12 between the GTE and placebo groups were derived from a mixed-effects repeated-measures ANOVA with adjustment for age and BMI at baseline within each category of TC.

[5] One subject was excluded due to missing values at baseline.

evidence of improvement in triglycerides associated with GTE in this study. This is consistent with data from meta-analyses (10–12), but 3 randomized, double-blind, controlled trials reported lowered concentrations of triglycerides after the consumption of GTE or beverage (30, 35, 44). These studies, however, were shorter in length (3 mo each) than our trial, study participants were obese, the treatment dose was much lower (EGCG doses varying from 208 to 214 mg/d), comparisons were mostly made within treatment groups, and/or the green tea supplementation was added to an exercise-induced weight-loss intervention.

Subgroup analyses showed that significant reductions in TC and borderline significant reductions in LDL and non-HDL cholesterol occurred only among those with the "borderline high" and "high" baseline TC categories. The greatest effects were seen in the baseline "high" cholesterol group (−8.3% in TC, −12.2% in LDL cholesterol, and −11.1% in non-HDL cholesterol for those in the GTE group). These results are consistent with an RCT that provided 250 mg GTE/d for 8 wk (22), but are inconsistent with 2 RCTs (37, 40) in which hypercholesterolemic participants drank green tea beverages (3 g tea leaves in 500–600 mL water) daily for 2–3 mo.

Higher triglyceride and cholesterol concentrations have been associated with increasing age and BMI and postmenopausal status (47). To control for this, the subgroup analyses in our study adjusted for baseline age and BMI, and all of the women in our study were postmenopausal. In addition, average years since menopause was taken into consideration in the statistical analysis, but results were not different between the 2 groups (data not shown). To the best of our knowledge, only 2 RCTs (27, 36) have so far examined the effects of green tea catechins on lipids in postmenopausal women. Hill et al. (27) did not observe any changes in lipids after the ingestion of 150 mg

TABLE 5
Treatment effect: changes in blood lipids by baseline BMI category[1]

| | BMI, kg/m^2 | | | | | | |
| | <25 (n = 520)[2] | | 25–29.9 (n = 313) | | ≥30 (n = 103) | | |
Lipid and time point	GTE (n = 256)	Placebo (n = 264)	GTE (n = 147)	Placebo (n = 166)	GTE (n = 60)	Placebo (n = 43)	P-interaction[3]
TC, mg/dL							0.28
Baseline	207	209	208	210	199	210	
Δ Month 6	−5.46	−0.76	−7.87	0.55	−8.79	−3.11	
Δ Month 12	−2.67	1.99	−7.19	1.6	−4.67	−2.39	
P[4]		0.058		0.0006		1.00	
HDL cholesterol, mg/dL							0.96
Baseline	75	75	66	64	56	59	
Δ Month 6	−1.30	0.57	−1.10	0.55	−1.68	0.50	
Δ Month 12	0.39	1.08	−0.97	0.53	−0.23	0.50	
P[4]		0.61		0.76		1.00	
LDL cholesterol,[5] mg/dL							0.35
Baseline	116	116	120	123	118	126	
Δ Month 6	−4.41	−0.60	−6.50	0.26	−9.07	−3.05	
Δ Month 12	−3.49	1.05	−6.62	1.74	−6.16	−1.40	
P[4]		0.055		0.0007		1.00	
Triglycerides, mg/dL							0.06
Baseline	79	90	108	115	119	127	
Δ Month 6	1.25	−3.54	−1.29	0.24	10.09	−2.42	
Δ Month 12	2.05	−0.98	2.04	−4.04	11.92	−7.19	
P[4]		1.00		1.00		0.031	
TC:HDL-cholesterol ratio							0.65
Baseline	2.87	2.93	3.28	3.52	3.7	3.78	
Δ Month 6	−0.04	−0.04	−0.08	−0.01	−0.1	−0.09	
Δ Month 12	−0.07	−0.01	−0.07	−0.04	−0.08	−0.15	
P[4]		1.00		1.00		1.00	
Non-HDL cholesterol, mg/dL							0.30
Baseline	132	134	142	146	142	151	
Δ Month 6	−4.17	−1.33	−6.76	0.01	−7.08	−3.58	
Δ Month 12	−3.06	0.89	−6.22	1.07	−4.41	−2.86	
P[4]		0.42		0.0066		1.00	

[1] Values are least-squares means, Bonferroni-corrected, and adjusted for age and BMI at baseline. GTE, green tea extract; TC, total cholesterol; Δ, change.

[2] n = 255 and 264 in the GTE and placebo groups, respectively, for the 12-mo time point.

[3] P values for the interaction between treatment and baseline BMI category were derived from a mixed-effects repeated-measures ANOVA with adjustment for age and BMI.

[4] P values for the overall changes in lipids from baseline to months 6 and 12 between the GTE and placebo groups were derived from a mixed-effects repeated-measures ANOVA with adjustment for age and BMI at baseline within each BMI category.

[5] One subject was excluded due to missing values at baseline.

EGCG along with moderate-intensity exercise for 12 wk in overweight or obese postmenopausal women. In a second RCT by Wu et al. (36), 103 postmenopausal women were supplemented with either 400 or 800 mg EGCG as Polyphenon E daily for 2 mo. Only the reduction in LDL cholesterol was significant compared with the placebo group (percentage changes were 0.5% with placebo, −7.9% with 400 mg EGCG, and −6.6% with 800 mg EGCG; P = 0.02).

Among the bioactive green tea catechins, EGCG is of great interest because it is the most abundant and purported to be the main bioactive catechin responsible for the hypolipidemic effects of green tea. The exact mechanisms by which EGCG and green tea exert their lipid-lowering effects remain largely unknown. The hypothesized mechanisms are through the suppression of cholesterol biosynthesis (48–50), the interference of lipid absorption (51, 52), and the increase in fecal excretion of cholesterol (53, 54).

Most of the studies on the effects of green tea on cardiometabolic risk factors were conducted in overweight and obese populations, with conflicting findings. We did not observe significant interactions between green tea supplementation and baseline BMI for either TC or LDL cholestserol in our study, which is consistent with most studies conducted in overweight participants (25, 26, 37, 46). At the same time, 2 studies (30, 44) reported lower concentrations of TC and/or LDL cholesterol after the ingestion of GTE in overweight men and/or women. This discrepancy may be due to different dosages or composition of GTE or green tea beverages. GTE supplementation in our study resulted in an increase in triglycerides exclusively in obese participants. We are not aware of any study that reported higher concentrations of triglycerides in obese subjects by taking GTE, so we cannot rule out the possibility of this result by chance.

The use of statins to reduce serum cholesterol and triglycerides is a common clinical practice in the United States. The effects of

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TABLE 6
Treatment effect: mean changes in blood lipids by statin users and nonusers[1]

Lipid and time point	Statin users ($n = 190$)		Nonusers of statins ($n = 738$)		P-interaction[2]
	GTE ($n = 99$)	Placebo ($n = 91$)	GTE ($n = 360$)	Placebo ($n = 378$)	
TC, mg/dL					0.35
Baseline	194	190.0	210.0	214.0	
Δ Month 6	−1.67	3.58	−7.93	−1.76	
Δ Month 12	1.30	3.26	−5.89	0.66	
P[3]		1.00		<0.0001	
HDL cholesterol, mg/dL					0.44
Baseline	63.0	65.0	72.0	71.0	
Δ Month 6	−0.001	1.24	−1.60	0.38	
Δ Month 12	0.15	0.26	−0.21	0.96	
P[3]		1.00		0.016	
LDL cholesterol,[4] mg/dL					0.91
Baseline	108.0	103.0	120.0	124.0	
Δ Month 6	−2.69	3.27	−6.41	−1.64	
Δ Month 12	−0.61	3.68	−5.94	0.12	
P[3]		0.17		<0.0001	
Triglycerides, mg/dL					0.06
Baseline	112.0	112.0	88.0	100.0	
Δ Month 6	5.11	−4.58	0.42	−1.67	
Δ Month 12	9.02	−3.42	1.75	−2.57	
P[3]		0.018		0.53	
TC:HDL-cholesterol ratio					0.80
Baseline	3.20	3.09	3.07	3.23	
Δ Month 6	0.01	0.02	−0.08	−0.05	
Δ Month 12	0.03	0.05	−0.1	−0.06	
P[3]		1.00		1.00	
Non-HDL cholesterol, mg/dL					0.51
Baseline	130.0	125.0	138.0	144.0	
Δ Month 6	−1.67	2.33	−6.33	−2.13	
Δ Month 12	1.15	3.00	−5.68	−0.3	
P[3]		1.00		0.0011	

[1] Values are least-squares means, Bonferroni-corrected, and adjusted for age and BMI at baseline. $n = 4$ in both the GTE and placebo groups had unknown statin use or nonuse. GTE, green tea extract; TC, total cholesterol; Δ, change.

[2] P values for the interaction between treatment and baseline statin use were derived from a mixed-effects repeated-measures ANOVA with adjustment for age and BMI.

[3] P values for the overall changes in lipids from baseline to months 6 and 12 between GTE and placebo groups were derived from a mixed-effects repeated-measures ANOVA with adjustment for age and BMI at baseline within users or nonusers of statin.

[4] One subject was excluded due to missing values at baseline.

GTEs on lipids were not modified by statin use, except for a greater increase in triglycerides in the GTE–statin user group than in the GTE—non-statin user group. This modifying effect was observed after a borderline significant interaction between GTE intake and statin use category. Possible contributing factors to these null results may include the following: *1*) GTE does not enhance the effects of statin therapy; *2*) different statins work through different mechanisms, thus GTE may enhance the function of some statins and not others; and *3*) other factors, not monitored in our study, may be important, such as consistency and duration of use. This subgroup analysis was exploratory in nature and took advantage of the unique opportunity to test the potential of a green tea–medication interaction in a large study population. To our knowledge, no previous intervention or observational study has examined the effects of green tea intake on lipid concentrations stratified by statin use; these findings should be further investigated in future studies.

It was expected that women with low *COMT* genotype activity would show the greatest response to GTE intake because they may retain more tea polyphenols in their bodies. However, in our study, we did not observe an interaction between treatment and *COMT* genotype, which may be due to the fact that we were not statistically powered to detect this effect. To the best of our knowledge, no other green tea intervention study has evaluated the role of *COMT* genotype on lipids.

There are some limitations to our study that should be considered. Our study population was predominantly non-Hispanic white and educated. Blood lipid analysis was based on a single measure and samples had been stored for 1–3 y; thus, the effects of daily variations in lipid concentrations (55) and long-term storage of serum (56) on our results cannot be entirely ruled out, although randomization should have helped to minimize this effect.

This study also has some notable strengths. It was a well-designed, comprehensive, double-blind RCT of the effects of

daily supplementation of ∼1315 mg green tea catechins (843 mg as EGCG) on components of the lipid profile in postmenopausal women. Although assessing the effectiveness of green tea catechin supplementation on serum lipid concentrations was not the primary outcome of the MGTT, this RCT had statistically adequate power and is the largest study with the longest treatment duration to date. Participants showed excellent compliance, taking, on average, 96.5% of their prescribed supplements. This was confirmed by analysis of urinary catechin content in a random subsample of participants (15), by which participants in the GTE group showed a >10-fold increase in the urinary concentrations of EGC and EC compared with the placebo group.

Taken together, supplementation with GTE for 12 mo was shown to significantly reduce TC, LDL cholesterol, and non-HDL cholesterol in postmenopausal women. GTE appears to generally exert stronger cholesterol-lowering effects in participants with baseline TC >200 mg/dL; in particular, GTE resulted in an 8.5% reduction in TC and a 12.4% decrease in LDL-cholesterol concentrations in hypercholesterolemic participants. GTE did not enhance the lipid-lowering effect of statin therapy in our study, possibly due to the small number of participants that used statins ($n = 190$). This should be pursued further in other large intervention studies. Current evidence from this trial suggests that GTE may be recommended for cholesterol lowering, in particular in those with borderline or high cholesterol concentrations. Green tea is an inexpensive, easily accessible, and popular drink and may indirectly lead to lower morbidity and mortality rates due to CVD through improving hyperlipidemia outcomes.

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