Quercetin with Vitamin C and Niacin does not affect body Mass or Composition

Authors
Amy M. Knab, **R. Andrew Shanely**, Fuxia Jin, Melanie D. Austin, Wei Sha, and David C.Nieman

Abstract

In vitro and animal data suggest that quercetin affects adipogenesis and basal metabolism; however, whether this metabolic effect translates to reductions in body mass or improvement in body composition in humans is unknown. This study investigated 12-week supplementation of 2 different doses of quercetin, combined with vitamin C and niacin, on body mass and composition in a large, heterogeneous group of adults (n = 941; 60% female, 40% male; 18–85 years of age; 45%normal body mass index, 30% overweight, 25% obese). Subjects were randomized into 3 groups, with supplements adminis-tered in double-blind fashion: Q500 = 500 mg quercetin·day–1, Q1000 = 1000 mg quercetin·day–1, and placebo. Quercetin supplements were consumed twice daily over a 12-week period, and pre- and poststudy body mass and composition meas-urements were taken in an overnight fasted state. A general linear model was used to predict change in body mass and com-position across groups with adjustment for demographic and lifestyle factors. Plasma quercetin increased in a dose-responsive manner in both Q500 and Q1000 groups relative to placebo. After adjustment for confounders, no significant dif-ferences in body mass (males interaction p value = 0.721, females p = 0.366) or body composition (males p = 0.650, fe-males p = 0.639) were found between Q500 or Q1000 groups compared with placebo. No group differences in body mass or body composition were found in a subgroup of overweight and obese subjects. High-dose quercetin supplementation (500 and 1000 mg·day–1) for 12 weeks in a large, heterogeneous group of adults did not affect body mass or composition.

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Quercetin with vitamin C and niacin does not affect body mass or composition

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Abstract: In vitro and animal data suggest that quercetin affects adipogenesis and basal metabolism; however, whether this metabolic effect translates to reductions in body mass or improvement in body composition in humans is unknown. This study investigated 12-week supplementation of 2 different doses of quercetin, combined with vitamin C and niacin, on body mass and composition in a large, heterogeneous group of adults (n = 941; 60% female, 40% male; 18–85 years of age; 45% normal body mass index, 30% overweight, 25% obese). Subjects were randomized into 3 groups, with supplements administered in double-blind fashion: Q500 = 500 mg quercetin·day^{-1}, Q1000 = 1000 mg quercetin·day^{-1}, and placebo. Quercetin supplements were consumed twice daily over a 12-week period, and pre- and poststudy body mass and composition measurements were taken in an overnight fasted state. A general linear model was used to predict change in body mass and composition across groups with adjustment for demographic and lifestyle factors. Plasma quercetin increased in a dose-responsive manner in both Q500 and Q1000 groups relative to placebo. After adjustment for confounders, no significant differences in body mass (males interaction p value = 0.721, females p = 0.366) or body composition (males p = 0.650, females p = 0.639) were found between Q500 or Q1000 groups compared with placebo. No group differences in body mass or body composition were found in a subgroup of overweight and obese subjects. High-dose quercetin supplementation (500 and 1000 mg·day^{-1}) for 12 weeks in a large, heterogeneous group of adults did not affect body mass or composition.

Key words: body fat, BMI, body mass, flavonoid.

Résumé : Il semble d'après des observations in vitro et sur des animaux que la quercétine modifie l'adipogenèse et le métabolisme de base; néanmoins, on ne sait pas si cet effet entraîne chez les humains une perte de masse ou une amélioration de la composition corporelle. Dans cette étude, on analyse sur une période de 12 semaines l'effet d'une supplémentation (2 doses différentes) en quercétine combinée à de la vitamine C et à de la niacine sur la masse et la composition corporelles d'un groupe hétérogène d'adultes formant un imposant effectif (n = 941, 60 % de femmes 40 % d'hommes, de 18 à 85 ans, 45 % présentant un IMC normal, 30 % un surpoids et 25 %, de l'obésité). On répartit aléatoirement les sujets en trois groupes recevant en double insu l'une des 3 supplémentations suivantes : 500 mg de quercétine·jour^{-1} (Q500), 1000 mg de quercétine·jour^{-1} (Q1000) ou un placebo. Les sujets prennent les suppléments à raison de 2 fois par jour sur une période de 12 semaines; au début et à la fin de cette période, on évalue la masse et la composition corporelles après un jeûne de toute une nuit. On applique un modèle linéaire général pour prédire les variations de la masse et de la composition corporelles des trois groupes tout en prenant en compte des variables démographiques et des facteurs du mode de vie. La concentration plasmatique de quercétine augmente selon une relation dose/effet chez les deux groupes recevant de la quercétine comparativement au groupe recevant le placebo. Après correction pour les variables parasites, on n'observe aucune différence significative de masse corporelle (interaction: hommes, p = 0,721; femmes, p = 0,366) ou de composition corporelle (hommes, p = 0,650; femmes, p = 0,639) entre les groupes Q500 et Q1000 comparativement au groupe placebo. En outre, on n'observe aucune différence de masse ou de composition corporelle dans un sous-groupe de sujets obèses et présentant un surpoids. De fortes doses de supplémentation en quercétine (500 et 1000 mg·jour^{-1}) durant 12 semaines chez un important groupe hétérogène d'adultes ne modifient ni la masse corporelle ni la composition corporelle.

Mots-clés : gras corporel, BMI, masse corporelle, flavonoïde.

[Traduit par la Rédaction]

Introduction

The obesity pandemic has accelerated cell, animal, and human research on the anti-obesity effects of flavonoids (Borchardt and Huber 1975; Melzig 1996; Hase et al. 2001; Nagao et al. 2001, 2005, 2007; Singh et al. 2003; Alexander 2006; Greenberg et al. 2006; Harwood et al. 2007; Bose et al. 2008; Egert et al. 2008; Ito et al. 2008; Stewart et al. 2008; Liu et al. 2009; Faria et al. 2010; Grove and Lambert 2010; Zhu et al. 2010). For example, several animal studies indicate that 3–15 weeks of supplementation with green tea extract and epigallocatechin gallate (EGCG) reduce body mass and fat mass (Bose et al. 2008; Ito et al. 2008). The catechins in green tea may increase thermogenesis and fat oxidation by inhibiting catechol-*O*-methyltransferase, leading to increased expression of norepinephrine and heightened sympathetic nervous system activity (Borchardt and Huber 1975). Epidemiological research supports the anti-obesity influence of green tea intake (Grove and Lambert 2010), and controlled human trials indicate a small but significant decrease in body mass, waist circumference, and body fat in subjects randomized to green tea extract supplementation (Hase et al. 2001; Nagao et al. 2001, 2005, 2007). Other polyphenols such as soy isoflavones demonstrate positive effects on weight loss in humans. For example, 6 months of supplementation with 15 g soy protein and 100 mg isoflavones significantly reduced body mass and body fat percentage in postmenopausal Chinese women (Liu et al. 2009).

Aside from tea catechins, quercetin is the most widely consumed flavonoid and is found in foods such as onions, berries, and apples (Harwood et al. 2007). Quercetin crosses the blood–brain barrier (Faria et al. 2010), inhibits adenosine receptor activity (Melzig 1996; Alexander 2006), and inhibits catechol-*O*-methyltransferase by acting as a competing substrate (Singh et al. 2003; Zhu et al. 2010). Studies also indicate that quercetin affects adipogenesis and causes apoptosis of adipocytes through the adenosine monophosphate-activated protein kinase (AMPK) pathway (Ahn et al. 2008). This mode of action is similar to that of caffeine, which has been related to small but significant decreases in body mass (Greenberg et al. 2006). Animal and human data on the anti-obesity influences of quercetin are limited. In one study, mice fed a high-fat diet with quercetin supplements exhibited transiently increased energy expenditure after 3 weeks and decreased inflammatory markers, but without measurable effects on body mass or fat mass (Stewart et al. 2008). One small-scale human study reported no effects of 2-week, low-dose quercetin supplementation (50, 100, or 150 mg·day^{-1}) on body mass or body composition in healthy subjects (Egert et al. 2008).

EGCG and quercetin have similar mechanisms of action, and we hypothesized that long-term supplementation of high doses of quercetin would cause small but biologically significant decreases in body mass and fat in male and female subjects. Specifically, this study measured the influence of 2 quercetin doses (500 or 1000 mg·day^{-1}) over a 12-week period on body mass and composition in a large group (n = 933) of male and female adults. The quercetin in this investigation was combined with vitamin C and niacin to improve quercetin bioavailability, as explained in the Methods. The quercetin dose is based on animal studies showing increased mitochondrial biogenesis beginning at 12.5 mg quercetin·(kg body mass)$^{-1}$ (Davis et al. 2009).

Materials and methods

Subjects

Male and female noninstitutionalized subjects (n = 941), 18–85 years of age, were recruited from the community via mass advertising. Approximately half the subjects were studied during a 12-week period from January to April 2008, and the second half from August to November 2008. Women who were pregnant or lactating were excluded from the study, but no other exclusion criteria were employed. Both diseased and nondiseased subjects were allowed to participate, and during recruitment, subjects were stratified by sex (~40% male, 60% female), age (40% young adult, 18–40 years of age; 40% middle-aged, 41–65; and 20% elderly, 65 and over), and body mass index (BMI) (45% normal, or 18.5–24.9 kg·m^{-2}; 30% overweight, or 25–29.9 kg·m^{-2}; and 25% obese, or ≥30 kg·m^{-2}) to ensure representation of these various subgroups. Thirty-seven percent of subjects reported past or current history for one or more chronic diseases: hypertension (19%), arthritis (16%), cancer (6%), cardiovascular disease (4%), and (or) diabetes (4%). During the study, subjects agreed to avoid any other supplements containing quercetin; no other restrictions were placed on diet, supplement usage, or medications. Several papers have recently been published from this large study, with a focus on quercetin supplementation effects on inflammation, oxidative stress, plasma quercetin response, immune function, and upper respiratory tract infections (Heinz et al. 2010*a*, 2010*b*; Jin et al. 2010; Shanely et al. 2010). All experimental procedures were approved by the Appalachian State University Institutional Review Board, and written informed consent was obtained from each subject.

Research design

Subjects were randomized to 1 of 3 groups: Q500 (500 mg quercetin·day^{-1}), Q1000 (1000 mg quercetin·day^{-1}), or placebo (PL). Supplements were administered utilizing double-blind procedures. Subjects ingested 2 soft chew supplements twice daily (upon awakening, and between 1400 hours and the last meal of the day) during the 12-week study period. Supplements were prepared by Nutravail Technologies (Chantilly, Va., USA) with Quercegen Pharmaceuticals (Newton, Mass., USA), and were soft, individually wrapped chews (5.3 g·piece^{-1}) that contained either 125 or 250 mg quercetin, 125 or 250 mg vitamin C (ascorbic acid and sodium ascorbate), 5 or 10 mg niacin, and 20 kcal of sugars in a carnauba wax, soy lecithin, corn starch, glycerine, and palm oil base colored with FD&C yellows 5 and 6. Vitamin C and niacin were added to the supplements based on unpublished animal data indicating that these compounds increase the bioavailability of quercetin. Placebo supplements were prepared exactly the same way minus the quercetin, ascorbic acid, sodium ascorbate, and niacin. Subjects ingested the soft chew supplements for 12 weeks. The following information was also reported via monthly logs by each subject: adherence to the supplementation regimen, physical activity and diet status, change in disease status and medication use, as well as gastrointestinal (constipation, heartburn, bloating,

diarrhea, nausea, vomiting), skin (rash, dryness, flushing), allergy, and mental (energy, headache, stress, focus and concentration) symptoms.

Outcome measures: body composition, body mass, and lifestyle risk factors

Subjects were required to come to the laboratory in an overnight fasted state (no food within 9 h of the test), in normal hydration status, with no alcohol or caffeine within 9 h of the test, no vigorous exercise within 24 h of the test, and routine urination upon waking up. Height was measured using a stadiometer, while body mass and body composition were measured using a Tanita (model TBF 305) bioelectrical impedance (BIA) scale (Tanita Corporation of America Inc., Arlington Heights, Ill., USA). The Tanita BIA scale has been validated as an accurate testing device for body composition (Brock et al. 2001). Similarly, Utter et al. showed no differences between underwater weighing and BIA measurement using the Tanita scale in obese and nonobese women (Utter et al. 1999). In a separate study, between-day instrument precision was measured to be between 1% and 3.5% (Nunez et al. 1997). Testing took place between 0700 and 0930 hours. Subjects were measured while standing erect, wearing light clothing, with bare feet on the analyzer's foot pads. Measurements were taken pre- and poststudy.

Subjects completed a lifestyle habit survey 2 weeks prior to the first laboratory visit of the study. The survey was a comprehensive questionnaire and posted on http://www.SurveyMonkey.com (Portland, Ore., USA). For subjects without Internet access, hard copies of the survey were completed. Semiquantitative food frequency questionnaires were used to assess intake of fruits, vegetables, cereals, meat, dairy, and fat. Subjects were asked to check a box indicating "on average, how many servings of… do you eat per day", and serving size information was provided in accordance with MyPyramid Food Guide (US Department of Health and Human Services and US Department of Agriculture 2005). Similarly, exercise frequency was assessed using a questionnaire, where subjects answered the following question: "Outside of your normal work or daily responsibilities, how often do you engage in exercise that at least moderately increases your breathing and heart rate, and makes you sweat, for at least 20 minutes." Responses were limited to seldom or never, less than 1, 1–2, 3–4, or 5 or more times per week. Based on the subject's response, they were classified into aerobic frequency tertiles of $\leq$1, 1–4, or $\geq$5. Other lifestyle factors such as chronic disease status, smoking, weight loss history, fatty food intake, and cigarette habits were assess in a similar manner.

Plasma quercetin measurement

Plasma quercetin was measured as previously described (Jin et al. 2010). Blood samples were drawn into heparin tubes after an overnight fast in the morning (0700–0900 hours) before and after the 12-week supplementation period. A subgroup of 170 subjects had their blood drawn monthly following the starting point of supplementation. Blood was immediately centrifuged at 4000*g* at 4 °C, and aliquots of plasma samples were snap-frozen to store at –80 °C.

Quercetin and its conjugates were measured as previously described (Nieman et al. 2007*a*, 2007*b*, 2007*c*, 2009). To each 500 μL human plasma, 10% DL-dithiothreitol solution (10 μL) was added prior to the addition of 50 μL of 0.58 mol·L^{-1} acetic acid. The mixture was then spiked with 10 μL of 0.356 μmol·L^{-1} fisetin internal standard. To this, a mixture of 50 μL enzyme β-glucuronidase–arylsulfatase and crude extract from Helix pomatia (Roche Diagnostics Corp., Indianapolis, Ind., USA) was added. The mixture was incubated for 2 h at 37 °C. Then 500 μL of 0.01 mol·L^{-1} oxalic acid was added to stop the enzymatic reactions. The microplate was vortexed for 1 min before centrifugation at 3000 r·min^{-1} (1109*g*) for 17 min (Allegra X-22R centrifuge; Beckman Coulter, Fullerton, Calif., USA).

Waters (Milford, Mass., USA) Oasis HLB 96-well sample extraction plates (30 mg, 30 μm) were conditioned with 1.0 mL methanol, 0.5 mL 0.01 mol·L^{-1} oxalic acid, and 1.0 mL distilled water sequentially. The waste was pulled through at a speed of less than 0.2 mL·min^{-1}. The supernatant of the enzyme hydrolysis mixture was then loaded in the extraction plate, and the samples were washed with 1.0 mL of 5% methanol in 0.5 mol·L^{-1} phosphoric acid and 1.0 mL of 50% methanol in 0.5 mol·L^{-1} phosphoric acid solution, respectively. Finally, samples were eluted with 2 volumes of 0.5 mL methanol, and the eluents were combined into a clean microplate with elution flow rate kept at less than 0.2 mL·min^{-1}. A 10% DL-dithiothreitol solution (10 μL) was added prior to solvent evaporation at 30 °C with N_2 blowing through. The dried samples were reconstituted into 50–50 methanol–water for high-performance liquid chromatography analysis.

Chromatographic analysis was performed using the Ultimate 3000 HPLC-PDA system (Dionex Corporation, Sunnyvale, Calif., USA) using a Gemini C18 column (150 mm × 4.6 mm, 100 A, 5 μm) with Gemini C18 4 mm × 3.0 mm SecurityGuard cartridges (Phenomenex, Torrance, Calif., USA). The column was kept at 30 °C, and the flow rate was 1.0 mL·min^{-1}. Separation was carried out using a 15-min gradient of acetonitrile containing 0.1% formic acid and water containing 0.1% formic acid. The PDA detector was set to monitor at 375 nm as well as scanning from 250 to 700 nm, and the injection volume was kept at 50 μL.

Statistics

Data are expressed as mean values with their standard deviations. Subject characteristics were contrasted between groups using 1-way ANOVA (Table 1). Data were analyzed using a 3 (group) × 2 (time) repeated-measures ANOVA, between-groups design, with post hoc analysis using independent Student's *t* tests that contrasted pre- to postsupplementation changes of Q500 and Q1000 with placebo for each sex (Tables 2 and 3). Change in body mass was correlated with change in plasma quercetin using Pearson correlations (Fig. 1). χ-square analysis was used to determine whether lifestyle factors (categorical data) differed across groups (Table 4).

In addition, to study whether there is a significant quercetin effect on the change of body mass or percent body fat, we used a general linear model (GLM) to predict change in body mass or percent body fat (response variable) with quercetin intake (placebo, Q500, and Q1000 groups) after adjusting for confounding variables. Stepwise selection in the GLMSELECT procedure in SAS (version 9.1.3; SAS Institute

Table 1. Subject characteristics.

	Placebo	Q500	Q1000	Group difference
Total sample size (*n*)	322	310	309	
Male	115	130	125	
Female	207	180	184	
Age (years)				
Male	44.2±17.2	45.3±17.6	46.2±16.8	0.655
Female	47.4±16.2	47.6±15.4	45.8±15.1	0.455
Height (m)				
Male	1.78±0.07	1.78±0.07	1.77±0.08	0.359
Female	1.64±0.06	1.65±0.08	1.64±0.06	0.142
BMI ($kg \cdot m^{-2}$)				
Male	27.1±4.6	26.9±5.4	27.9±4.7	0.246
Female	26.4±5.7	26.3±5.7	26.3±6.2	0.98
Marital status (%)	S, M, O	S, M, O	S, M, O	
Male	33.0, 53.9, 13.0	27.7, 64.6, 7.7	24.8, 68.8, 6.4	0.136
Female	30.0, 54.1, 15.9	24.4, 58.3, 17.2	31.0, 50.5, 18.5	0.563
Current smoker (%)	5.6	7.8	8.1	0.414
Exercise frequency				
No. days per week	>5, 1–4, <1	>5, 1–4, <1	>5, 1–4, <1	
% of group	20.2, 61.8, 18.0	23.8, 55.6, 20.6	21.4, 53.1, 25.6	0.109
Race (% Caucasian)	93.8	95.8	93.5	0.397
Education (years)	15.5±2.7	15.7±2.9	15.6±2.7	0.871

Note: BMI, body mass index; S, single; M, married; O, other.

Table 2. Body mass and composition of study subjects (values are means ± SD).

Variable	Placebo	Q500	Q1000	*p* values for interaction, time
Body mass (kg)				
Males	$n = 115$	$n = 130$	$n = 125$	
Pre	85.0±15.0	85.2±17.7	87.2±16.6	0.627, <0.001
Post	85.7±14.6	86.1±18.2	87.8±16.3	
Females	$n = 207$	$n = 180$	$n = 184$	
Pre	71.0±15.4	71.7±16.5	70.8±17.4	0.142, <0.001
Post	71.4±15.6	72.4±16.5	71.2±17.5	
Body composition (%)				
Males				
Pre	21.9±9.5	21.8±9.4	24.4±9.2	0.644, <0.001
Post	22.2±9.3	22.4±9.5	25.0±9.2	
Females				
Pre	34.8±9.6	34.7±9.6	33.9±9.9	0.112, 0.325
Post	34.6±9.7	35.0±9.6	34.1±9.8	

Note: Pre, prestudy body mass; Post, poststudy body mass.

Inc., Cary, N.C., USA) was used to determine confounding variables. The potential confounders that GLMSELECT selected from were sex (male, female), age, exercise frequency, cigarette smoking habit, self-reported diet intake by food groups (tertiles of fruit, vegetable, red meat food groups, and fatty food frequency), weight loss history, chronic disease status, and interaction between each confounding variable and quercetin. Stepwise selection removes nonsignificant terms from the model based on Akaike's information corrected criterion. Change in body mass (or percent body fat) was calculated by subtracting presupplementation from postsupplementation levels. A contrast was constructed to estimate whether there was a quercetin-related trend in change of body mass or percent body fat. Outliers with studentized residual >3.5 or <–3.5 were excluded from the analysis to meet the normality assumption of the general linear model. This analysis was applied to all subjects first, and was then applied to subjects who were overweight (BMI 25–29.9) or obese (BMI ≥ 30).

Results

Subject characteristics are reported in Table 1. For all demographic factors listed in Table 1, no prestudy differences were found between groups. No significant interaction *p* values were found for change in body mass or body composition for each sex, as summarized in Table 2. There was a slight increase in body mass within groups in both males and females over the 12-week treatment period ($p < 0.001$). GLM analysis, after adjustment for confounding variables, showed that quercetin was not found to have a significant effect on

Table 3. Body mass and composition in overweight and obese individuals (values are means ± SD).

Variable	Placebo	Q500	Q1000	*p* values for interaction, time
Body mass (kg)				
Males	$n = 69$	$n = 76$	$n = 89$	
Pre	92.7±13.6	94.5±16.9	93.0±15.8	0.357, <0.001
Post	93.4±13.0	95.5±17.5	93.5±15.6	
Females	$n = 105$	$n = 88$	$n = 89$	
Pre	82.2±13.1	83.7±14.7	83.6±16.2	0.737, <0.001
Post	82.8±13.5	84.4±14.7	84.0±16.3	
Body composition (%)				
Males				
Pre	27.6±6.7	27.2±7.7	28.3±7.1	0.637, 0.011
Post	27.8±6.7	27.7±7.8	28.8±7.0	
Females				
Pre	41.6±5.7	42.0±5.3	41.5±5.8	0.506, 0.151
Post	41.6±5.8	42.2±5.2	41.7±5.8	

Note: Pre, prestudy body mass; Post, poststudy body mass.

Fig. 1. Change in body mass vs. change in plasma quercetin after 12 weeks of supplementation ($r = 0.016$, $p = 0.628$).

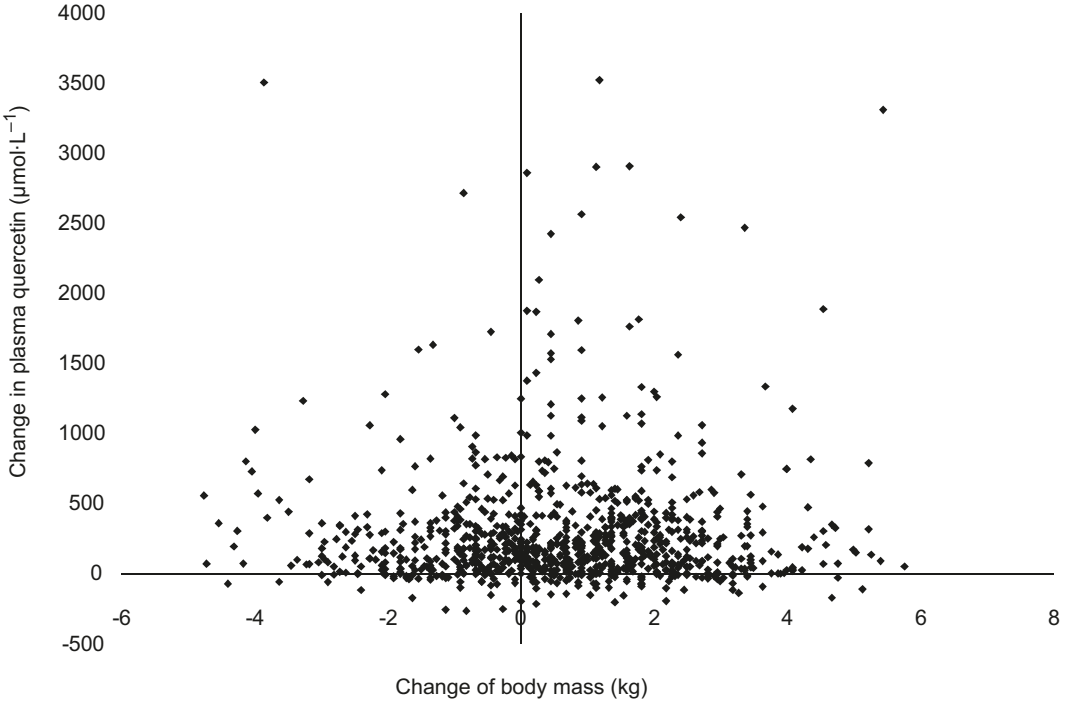

Table 4. χ-square analysis of selected categorical factors across groups.

Confounder	χ^2	*p*
Exercise frequency	7.57	0.109
Fruit intake	2.19	0.70
Vegetable intake	2.97	0.563
Red meat intake	1.10	0.894
Chronic disease status	0.238	0.888
Smoker vs. nonsmoker	1.76	0.414
Weight loss history	4.96	0.549
Fatty food frequency	0.675	0.714

the change of body mass ($p = 0.0599$; $p_{trend} = 0.6782$) or percent body fat ($p = 0.1457$; $p_{trend} = 0.1016$).

Table 3 summarizes data for all subjects with a BMI of 25 or higher and shows that there were no significant interaction *p* values for change in body mass or body composition in male or female overweight and obese subjects. GLM analysis with adjustment for potential confounders within these overweight and obese subjects revealed no group differences for body mass ($p = 0.0718$; $p_{trend} = 0.7206$) or percent body fat ($p = 0.4682$; $p_{trend} = 0.2793$).

The 8 factors that were related to body mass and percent body fat included exercise frequency, fruit intake, vegetable intake, red meat intake, chronic disease status, smoking, weight loss history, and visible fat intake. χ-square analysis

for these categorical variables showed no significant differences between groups (Table 4). For percent body fat models, no confounding variables were selected by the model selection procedure. For the body mass models, red meat was the only variable that was selected by the model selection procedure and was found to have a significant effect ($p < 0.0001$) on change in body mass in the 12-week study period. Subjects who had high red meat intake had a significantly higher increase in body mass than subjects with medium or low red meat intake. In addition, change in body mass after quercetin concentration was not related to plasma quercetin response, as shown in Fig. 1.

Discussion

Supplementation with 500 or 1000 mg·day^{-1} of quercetin with vitamin C and niacin did not significantly affect body mass or percent body fat in a large, heterogeneous group of males and females, or in overweight and obese subjects analyzed separately. This finding was strengthened by GLM analysis of group data with 10 demographic and lifestyle characteristics. Changes in body mass and composition and plasma quercetin were not related in correlational analysis.

This finding is in concert with animal studies that show no differences in body mass after quercetin supplementation. Stewart et al. (2008) found that feeding quercetin to mice on high-fat diets caused an initial increase in energy expenditure (after 3 weeks), but this increase in energy expenditure was not detected after long-term supplementation (8 weeks). Regardless of the energy expenditure differences, there were no differences in body mass or body composition between mice fed quercetin versus placebo at any time point (Stewart et al. 2008). In separate studies, no differences in body mass were detected after supplementation with quercetin in rats fed either high-fat or high-fat–high-sucrose chow (Barrenetxe et al. 2006; Yamamoto and Oue 2006).

Similar to our findings, Egert et al. (2008) showed that low doses of quercetin supplements (50, 100, and 150 mg·day^{-1}) for 2 weeks did not alter body mass or percent body fat in healthy human subjects. In addition, in a subset of subjects, quercetin failed to alter resting energy expenditure (Egert et al. 2008). Thus, quercetin supplements tested over a wide range of doses (50–1000 mg·day^{-1}) have not been linked to changes in body mass or composition.

Quercetin is hypothesized to have similar but slightly different mechanisms of action from that of caffeine or green tea by increasing catacholamines in the brain and circulation, as well as suppressing adipogenesis. The green tea catechin EGCG has produced positive effects on body mass and composition in animals (Bose et al. 2008; Ito et al. 2008). Although quercetin had no effect on body mass or composition in the current study, small effects on body mass have been observed with tea catechins (Hase et al. 2001; Nagao et al. 2001, 2005, 2007; Harada et al. 2005) and other polyphenols such as soy flavonoids (Jenkins et al. 2002; Liu et al. 2009). However, Park et al. (2008) found that a combination of genistein, quercetin, and resveratrol was more effective at inhibiting adipogenesis and inducing apoptosis in human adipocytes than any individual compound alone.

Thus, although a multitude of individual natural compounds have been identified to have beneficial effects on adipocytes in vitro, "targeted monotherapy" in animals and humans has exhibited little success (Relume et al. 2008). Andersen et al. (2010) also highlighted that the pharmacological doses used successfully in vitro often fail to affect adipogenesis in animal or human models; however, combinations of photochemical, as opposed to isolated compounds, may be more beneficial in eliciting desired weight loss effects. For example, Nakazato et al. (2006) found that supplementing rats with 5% apple polyphenols in the diet resulted in significantly reduced adipose tissue masses and reduced adipogenesis compared to that in control animals. Also, Nieman et al. (2009) found that 2 weeks of supplementation with quercetin combined with EGCG resulted in a significant reduction in inflammation following heavy exertion in cyclists. Thus, combining several natural compounds to target multiple signal transduction pathways may be more efficacious in the treatment of obesity than treatment with single compounds in isolation (Relume et al. 2008). Quercetin, combined with vitamin C and niacin for improved bioavailability of quercetin, did not elicit any benefit on body mass or composition in the current human study; however, the next step in this line of research will be to combine quercetin with other natural compounds that will target multiple signaling pathways involved in thermogenesis, fat oxidation, and adipogenesis to effectively alter obesity-related risk factors.

The current study confirms, on a large scale, that even high doses of quercetin, combined with vitamin C and niacin, do not affect body mass or composition in the general human population. Although quercetin does not effectively reduce body mass in a large population of subjects, including overweight and obese individuals, additional research is warranted focusing on a cocktail approach in combining multiple bioactive polyphenols that may together induce a small but significant decrease in body fat.

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