Influence of Age on the Thermic Response to Caffeine in Women

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The purpose of this study was to examine age-related differences in the magnitude of caffeine-induced thermogenesis and the relationship of aerobic fitness, body composition, and hormone and substrate concentrations to the thermic effect of caffeine in younger and older women. Using a placebo-controlled, double-blind study design, 10 older (50 to 67 years) and 10 younger (21 to 31 years) healthy women who were moderate consumers of caffeine (self-reported intake: younger, 139 ± 152 mg/d; older, 204 ± 101 mg/d, NS, mean ± SD) were characterized for fasting plasma glucose, insulin, free fatty acid (FFA), and caffeine levels, energy expenditure, body composition, anthropometry, aerobic fitness, physical activity, and energy intake. Before and after placebo and caffeine ingestion (5 mg/kg fat-free mass [FFM]), the following variables were measured: fasting plasma glucose, insulin, FFA, and energy expenditure, plasma glucose, insulin, and FFA, and energy expenditure in response to placebo and caffeine ingestion. Caffeine ingestion resulted in similar increases in younger and older women for plasma caffeine (younger, 80 ± 34 to 5,604 ± 528 ng/mL, $P < .01$; older, 154 ± 134 to 5,971 ± 867 ng/mL, $P < .01$) and fatty acids (younger, 294 ± 118 to 798 ± 248 μmol/L, $P < .01$; older, 360 ± 180 to 727 ± 310 μmol/L, $P < .01$), whereas plasma insulin and glucose levels remained unchanged from baseline. Energy expenditure increased following caffeine ingestion in both groups (younger, 15.4%, 1.09 ± 0.14 to 1.24 ± 0.13 kcal/min, $P < .05$; older, 7.8%, 0.98 ± 0.14 to 1.06 ± 0.12 kcal/min, $P < .05$), although there was a blunted thermic response in the older versus younger women (older, 6.9 ± 5 kcal/90 min; younger, 15.5 ± 7 kcal/90 min, $P < .05$). In younger women, the thermic response to caffeine was positively correlated with the waist circumference ($r = .70$, $P < .05$) and body weight ($r = .91$; $P < .01$), whereas aerobic fitness ($r = .77$; $P < .05$) was the only significant correlate in older women. In conclusion, older and younger women increase energy expenditure significantly following caffeine ingestion, but older women have a blunted thermic response compared with younger women. Second, the thermic response to caffeine is positively associated with the body weight and waist circumference in younger women, whereas a positive association with aerobic fitness was observed in older women. Thus, the physiologic determinants of the thermic response to caffeine differ among women of different age groups.

THE DECLINE in total daily energy expenditure and its components and an increase in total body fatness are hallmarks of the aging process. For example, the elderly have a lower resting metabolic rate (RMR)[1,2] and thermic response to food[3,4] compared with younger individuals. Additionally, the ability to mobilize lipid stores in response to β-adrenergic stimulation, including an acute exercise bout[5] and fasting,[6] is blunted in older individuals, suggesting that energy and lipid conservation may be factors contributing to the increase in body fat accumulation with advanced age. The age-related increase in fatness, especially in the central region, increases the risk for numerous health conditions, including atherosclerosis, hypertension, hypercholesterolemia, and insulin resistance.[7,8]

Despite a general lack of data regarding women's health issues, there is a growing body of literature to suggest that women may be at an increased risk of body fat accumulation with advancing age compared with men. Specifically, previous investigations found resting and physical activity–related energy expenditure to be lower in women versus men.[9-11] Moreover, a recent study examining the increase in total and central body fatness in men and women across a broad age range found that the age-related increase in fat mass and waist circumference is greater in women than in men.[12] Taken together, these findings prompted us to systematically examine whether differences exist between women of different ages in the response to caffeine, a noncaloric pharmacological agent known for its metabolic stimulatory effects.[13-15]

Recently, we found that older and younger men exhibit a similar thermogenic response to caffeine, although older men showed a smaller increase in fatty acid appearance after the same relative caffeine challenge compared with younger men.[13] To our knowledge, no studies have considered age-related changes in the thermic response to caffeine in women, as well as body composition, hormone and substrate status, and lifestyle factors that may be associated with the thermogenic response.

Using a double-blind placebo-controlled study design, our first objective was to determine whether older and younger women demonstrate a similar thermic response to caffeine as previously observed in older and younger men.[13] Thereafter, we considered the relationships between aerobic fitness, body composition, and hormone and substrate concentrations as factors associated with the age-related thermic effect of caffeine.

SUBJECTS AND METHODS

Subjects

Ten younger (18 to 22 years) and 10 older (50 to 66 years) healthy women who regularly consumed moderate amounts of caffeinated substances (self-reported mean intake for younger *v* older, 139 ± 152 *v* 204 ± 101 mg/d, NS) were recruited from the surrounding community for this study. Excessive caffeine consumers (>4 cups of coffee per day) were not included in the study because heavy caffeine intake induces tolerance to some of the metabolic and cardiovascular effects of caffeine.[16] All subjects met the following criteria for participation in the

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study: (1) no history of cardiovascular disease, (2) normal electrocardiogram at rest and during an exercise test, (3) normal blood pressure (supine blood pressure <140/90 mm Hg), (4) no history of diabetes mellitus, renal failure, or liver disease, (5) no medication that could influence cardiovascular function or metabolic rate, (6) nonsmoker and free of nicotine use within the previous year, and (7) weight stability (±2 kg) during the past year. All older women were postmenopausal and were not on estrogen replacement therapy or hormone-regulating contraceptives at the time of testing. All premenopausal women were tested during the follicular phase (days 5 to 12) of the menstrual cycle to standardize the measurements and were not presently taking oral contraceptives for 1 month prior to testing. The nature, purpose, and possible risks were explained to each subject before they provided written consent to participate. The experimental protocol was approved by the Human Subjects Review Committee at Skidmore College.

Experimental Design and Procedures

The experiment was designed as a placebo-controlled double-blind test of caffeine ingestion (5 mg/kg fat-free mass [FFM]) and placebo (lactose) conducted in 2 separate treatment blocks sequenced in randomized order and performed within a 1-month period. Each subject participated in both blocks, consisting of placebo and caffeine ingestion in pill form.

Order of testing. Before the first test day, all subjects had their FFM and fat mass determined by skinfold analysis and performed either a submaximal (older) or maximal (younger) oxygen consumption ($VO_{2peak}/VO_{2estimated peak}$) test on a motor-driven treadmill. Within 1 month after the initial visit, subjects returned to the laboratory between 5:30 and 6:00 AM for the first test day, and were instructed to abstain from exercise and alcohol for 24 hours and from caffeine for 48 hours prior to testing to remove tolerance effects to caffeine.[17] Subjects were also instructed to fast for 12 hours before each test day and to standardize the meal each night before the 2 test days, ie, to use the meal the evening before the first test day as the standard meal for the second test day. For the second test day, subjects underwent the same procedures but received the treatment that was not administered during the first visit.

Testing procedures. At the initial visit, each subject was familiarized with the procedures and equipment used in testing during the 2 test days. On the morning of each test day following a 12-hour overnight fast, subjects were instructed to wake slowly, minimize movement, and promptly drive or be driven to the Human Performance Laboratory at Skidmore College, expending as little energy as possible and arriving at about 5:30 AM. Starting at 6:00 AM, body weight was measured after the subjects voided, and a polyethylene catheter was inserted into an antecubital vein for blood sampling. The subject was instructed to lie quietly for 30 minutes before testing began. Resting baseline blood samples were collected for the next 30 minutes to determine fasting plasma glucose, insulin, free fatty acids (FFAs), and caffeine (30 minutes), and RMR was measured (0 to 30 minutes). After each blood sampling, the catheter was flushed with 1.5 mL saline. Between 6:30 and 6:45 AM, each subject received either placebo (lactose) or caffeine (5 mg/kg FFM) in pill form with 50 mL tepid water, followed by 90 minutes of serial measurements (every 30 minutes) of glucose, insulin, FFA, and caffeine levels and 3 15-minute interval measurements of RMR.

Body composition and circumferences. Body density was calculated from skinfold thicknesses obtained with a Lange caliper at the triceps, suprailiac, and thigh using the Jackson-Pollock equation.[18] The body fat percentage was calculated according to the Siri equation.[19] Waist and hip circumferences were measured using standardized procedures.[20] All skinfold and circumference measurements were obtained by the same investigator (P.J.A.).

VO_{2peak}, estimation of VO_{2peak}, and leisure time physical activity. In the younger women, VO_{2peak} was determined by a progressive and continuous test to exhaustion on a motorized treadmill. Subjects self-selected their running speed while the grade was increased by 2.5% every 2 minutes from an initial level of 0% until volitional fatigue. All younger women reached their age-predicted maximal heart rate (198 ± 1 bpm) and maximal respiratory exchange ratio (RER) higher than 1.10 ± 0.01 during the exercise test. Due to personnel constraints, VO_{2peak} was estimated during level walking or running on the treadmill in the older women using the procedures recommended by the American College of Sports Medicine.[20] Briefly, a continuous exercise protocol consisting of 2-minute stages was performed, and tests were terminated when subjects reached 85% of their estimated heart rate reserve $[(((HR_{max} - HR_{rest}) \times 85\%) + HR_{rest})]$. Expired gases were collected throughout the test and O_2 and CO_2 levels were determined on electrochemical O_2 (Ametek, Pittsburgh, PA) and infrared CO_2 (Ametek) analyzers, respectively. As recommended,[20] VO_{2peak} was predicted from heart rate, and VO_2 data were extrapolated to the age-predicted maximal heart rate (220 − age). The energy expended in leisure time physical activity during the past year was assessed by a structured interview using the Minnesota Leisure Time Physical Activity Questionnaire.[21]

Estimated daily energy intake. Energy intake and caffeine consumption were determined from a 3-day food diary. Briefly, each subject was asked to weigh and record all foods and beverages ingested for 2 weekdays and 1 weekend day. Particular emphasis was placed on the importance of maintaining typical eating habits and describing foods and methods of preparation in accurate detail. The Nutritionist III computer program (N-Squared Computing, version 4.0, San Bruno, CA) was used to analyze all diets for energy and caffeine intake and relative and absolute quantities of macronutrients.

Time Course of Plasma Sampling During Treatment Visits

Hormone and substrate concentrations. The treatment visit testing procedures were identical in nature except that subjects received either placebo or caffeine. Baseline, placebo, and caffeine-stimulated levels of plasma glucose were determined using a YSI glucose analyzer (Yellow Springs Instrument, Yellow Springs, OH). Plasma immunoreactive insulin was determined by a modification of the radioimmunoassay technique of Starr et al.[22] Serum concentrations of fatty acids were measured with a modification of an enzymatic technique (Wako Chemicals, Richmond, VA). Plasma caffeine levels were measured by gas chromatography.[23]

RMR and thermic effect of caffeine. RMR and RER were measured between 6:00 and 7:30 AM for 30 to 45 minutes, and thereafter, energy expenditure (thermic effect of placebo and caffeine) was measured at 15-minute intervals for the next 90 minutes with a computerized open-circuit indirect calorimeter (VacuMed, Ventura, CA). Briefly, subjects were positioned supine and fitted with a facemask (model 7900; Hans-Rudolph, Kansas City, MO) connected to corrugated tubing that was in turn attached to the metabolic cart. A constant fraction of expired air was withdrawn, dried, and delivered to a zirconium-cell oxygen analyzer (Ametek, Pittsburgh, PA) and an infrared carbon dioxide analyzer (Ametek). Energy expenditure (kilocalories per minute) was calculated from the equation of Weir.[24] The intraclass correlation for test-retest measurement of RMR between tests 1 and 2 in the total group of 20 female subjects averaged .90.

Statistical Analysis

A 3 × 2 repeated-measures ANOVA was used to test for the effects of caffeine ingestion, age group, and time course of insulin, glucose, and FFA levels during the 2 treatment test days. Since younger and older women differed in RMR values, an analysis of covariance, with the initial baseline RMR serving as the covariate, was used to test for the effects of caffeine ingestion on energy expenditure. A Pearson product-moment correlation coefficient was used to estimate associations between variables. All data are expressed as the mean ± SD unless otherwise noted. Tukey's post hoc comparisons were performed to locate mean differences whenever an interaction was found.[25] Statistical significance was set at a P level less than .05.

RESULTS

Physical Characteristics

The physical characteristics of the younger and older women are shown in Table 1. Older women had a greater body weight, waist circumference, and body fat percent ($P < .05$) but similar levels of FFM. Thus, both groups received similar quantities of caffeine. Older women reported lower ($P < .05$) levels of energy expended in physical activity and were less ($P < .05$) aerobically fit than the younger women. There were no differences between younger and older women for sodium intake and fasting plasma levels of caffeine, glucose, insulin, and FFAs.

Plasma Caffeine

Caffeine ingestion (5 mg/kg FFM) significantly increased ($P < .01$) plasma caffeine levels in both groups at all time points (Table 2). There were no differences in plasma caffeine levels between the two groups either at rest (0 minutes) or following caffeine ingestion, concurring with our finding of similar quantities of FFM between the two groups. Plasma caffeine levels remained unchanged from baseline values after placebo ingestion (data not shown).

Plasma Hormones and Substrates

Caffeine ingestion significantly increased plasma FFAs at all time points in the younger women and at 60, 75, and 90 minutes in the older women (Fig 1). There was no difference between baseline and placebo test-day FFA concentrations in both groups (data not shown). Plasma concentrations of glucose (younger: baseline 4.41 ± 0.3; placebo-stimulated 4.37 ± 0.2, and caffeine-stimulated 4.4 ± 0.2 mg/dl; older: baseline 4.57 ± 0.3, placebo-stimulated 4.74 ± 0.4, and caffeine-stimulated 4.5 ± 0.3 mg/dL) and insulin (younger: baseline 6.76 ± 1.9, placebo-stimulated 7.48 ± 1.7, and caffeine-stimulated 6.67 ± 1.6 μU/mL; older: baseline 7.12 ± 0.9, placebo-stimulated 6.03 ± 0.9, and caffeine-stimulated 7.65 ± 1.5 μU/mL) were not significantly different within or between groups during any period.

RMR and Thermic Effect of Caffeine

Mean values for the RMR and thermic effect of caffeine are presented in Table 3. The baseline RMR was higher (11%, $P < .05$) in younger versus older women. Caffeine ingestion significantly increased ($P < .05$) energy expenditure in both age groups; however, older women exhibited a blunted thermic response compared with younger women when expressed as an absolute change in metabolic rate (mean change over 0 to 90 minutes following caffeine ingestion), total thermic response to caffeine, or percent increase above RMR (Table 3 and Fig 2).

The RER showed a tendency to decrease slightly from resting values following caffeine and placebo in the younger (rest, 0.77 ± 0.07; caffeine, 0.74 ± 0.05; and placebo, 0.75 ± 0.05) and older (rest, 0.80 ± 0.07; caffeine, 0.78 ± 0.07; and placebo, 0.75 ± 0.05) women; however, there were no significant differences in the integrated response between the caffeine and placebo trials within or between groups (data not shown). Thus, the increase in energy expenditure above baseline following caffeine compared with placebo was due to an equally increased carbohydrate and lipid oxidation.

Correlates of the Thermic Effect of Caffeine

Pearson product correlation analysis using all single factors tested separately against the integrated thermic response to caffeine produced the following significant relations in younger and older women, respectively: younger, waist circumference ($r = .70$, $P < .05$) and body weight ($r = .91$; $P < .01$; Fig 3); and older, $VO_{2peak\text{-}estimated}$ ($r = .77$, $P < .05$).

DISCUSSION

Our first objective was to examine age-related differences in the thermic and metabolic response to caffeine in women. Our

Table 1. Physical Characteristics of the Younger and Older Women

	Younger (n = 10)		Older (n = 10)	
Variable	Mean ± SD	Range	Mean ± SD	Range
Age (yr)	19.0 ± 1.5*	18-22	55.0 ± 5	50-67
Height (cm)	168.5 ± 6.7	159-184	166.4 ± 3.8	159-171
Weight (kg)	62.5 ± 7.3*	50-74	72.1 ± 9.4	58-86
Waist circumference (cm)	69.1 ± 5.0*	62.5-77	82.3 ± 10.4	67-100
Sum of skinfolds (mm)	62 ± 15*	46.3-96.5	81 ± 19	57.5-109.9
Body fat (%)	23.5 ± 5.1*	15.8-34.1	31.9 ± 5.8	24.5-40.1
FFM (kg)	46.7 ± 4.8	39.9-55.2	48.8 ± 5.2	37.2-55.6
LTA (kcal/d)	754.4 ± 386.5*	165.7-1,367.7	435.5 ± 165.9	178-700
Younger VO_{2peak} (mL/kg/min)				
Older esimated VO_{2peak} (mL/kg/min)	45.9 ± 8.74	34.7-59.9	27.8 ± 5.14	21.33-36.3
Self-reported food intake (kcal/d)	2,354.8 ± 843.7	1,253-3,734	2,020.3 ± 455.2	1,534-2,941
Sodium intake (mg/d)	3,894.5 ± 1,489.7	2,073-7,374	3,358.1 ± 692.9	2,450-4,421
Fasting caffeine (ng/mL)	80 ± 34	0-133	154 ± 134	0-550.1
Fasting glucose (mmol/L)	4.41 ± 0.3*	4.1-5.4	4.57 ± 0.3	4.6-4.9
Fasting insulin (μU/mL)	6.76 ± 1.9	4.03-9.4	7.12 ± 0.9	6.49-7.74
Fasting FFA (μmol/L)	293.9 ± 115.2	42-367	360.3 ± 134.9	222-484

Abbreviation: LTA, leisure time physical activity.
*$P < .05$ *v* older.

Table 2. Plasma Caffeine Levels (ng/mL) at Rest and Following Caffeine Ingestion

Group	0 min	Post-Caffeine Ingestion 30 min	45 min	60 min	75 min	90 min
Younger (n = 10)	80 ± 34	3,033 ± 2,244*	4,659 ± 1,724*	5,163 ± 1,349*	5,486 ± 765*	5,604 ± 528*
Older (n = 10)	154 ± 134	4,827 ± 2,604*	5,523 ± 1,452*	5,932 ± 1,133*	5,971 ± 902*	5,959 ± 867*

NOTE. Values are the mean ± SD.
*$P < .01$ *v* baseline.

second objective was to determine the association of lifestyle, physiologic, and metabolic variables with the thermic response to caffeine in women of different age groups. The major findings of this study are as follows: (1) younger and older healthy women exhibit a significant thermogenic response to caffeine ingestion, but older women appear to have a blunted response compared with younger (~15%) women (Table 2 and Fig 3); (2) body weight and waist circumference in younger women and aerobic fitness level in older women are significant correlates of the thermogenic response to caffeine; and (3) in response to caffeine ingestion, younger and older women show similar increases in FFAs and no significant change in insulin and glucose concentrations. These findings imply that age is an important parameter to consider when comparing the thermogenic response to caffeine, as it is associated with different physiological factors in younger and older women.

Thermic Effect of Caffeine

The present study examined the thermogenic response to a dose of caffeine (5 mg/kg FFM) that results in blood levels commonly found in younger and older women who regularly drink coffee. We found that the magnitude of increase in energy expenditure was 7.8% and 15.4% over baseline in older and younger women, respectively. Interestingly, we have previously shown a similar trend in the thermogenic response to caffeine ingestion in older (9.5%) and younger (11%) men.[13] These results also corroborate previous findings using similar doses of caffeine in younger female subjects.[14,26-28]

The RMR is the largest component of daily energy expenditure,[29] and accordingly, it has a significant impact on body weight regulation. It is well accepted that the quantity of FFM is the largest predictor of RMR, thus explaining why men, who possess a greater quantity, generally display a higher absolute RMR than women.[9] We have recently shown that women of different age groups have a lower RMR than men of similar age even after accounting for gender differences in body composition, as well as other physiological, endocrine, and lifestyle factors,[9,12] although these findings are not unanimous.[30,31] Moreover, Poehlman et al[12] recently found that as women age, they exhibit a faster rate of increase in fat mass and waist circumference compared with men. Although the physiological mechanisms underlying this phenomenon are unclear, the data suggest that the accelerated fat accumulation in women may be due to lifestyle and cultural differences that promote a more inactive lifestyle. For example, recent investigations have shown that energy expenditure in leisure time activities is lower in women than in men,[32,33] and women have an accelerated age-related decline in leisure time activity.[10,11] Collectively, these findings highlight the importance of considering gender as an independent factor influencing energy metabolism.

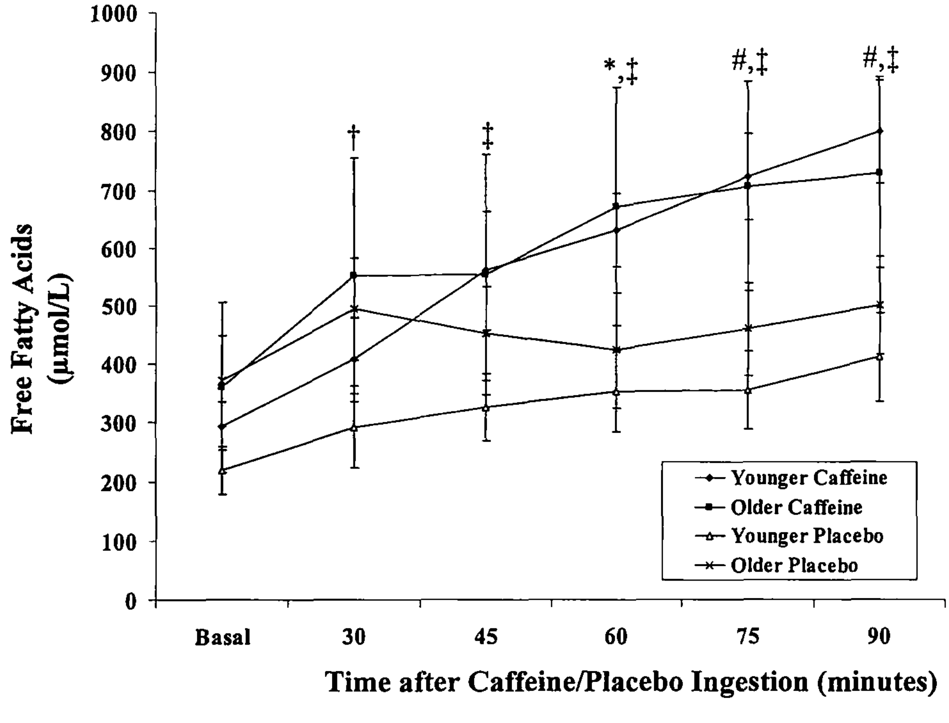

Fig 1. Plasma concentrations of free fatty acids before and after caffeine ingestion (5 mg/kg FFM) in younger and older women. Values are the mean ± SE. †Significantly different *v* baseline value in younger women, $P < .05$; *significantly different *v* baseline value in older women, $P < .05$; ‡significantly different *v* baseline value in younger women, $P < .01$; #significantly different *v* baseline value in older women, $P < .01$.

Table 3. RMR and Thermic Effect of Caffeine in Younger and Older Women

Group	Baseline RMR (kcal/min)	Change in RMR (0-90 min (kcal/min)	Total Thermic Response to Caffeine (kcal/90 min)	% Increase Above RMR
Younger	1.09 ± 0.14*	0.173 ± 0.06†	15.5 ± 7.0†	15.4 ± 7.0†
Older	0.98 ± 0.14	0.076 ± 0.05†	6.9 ± 5.0†	7.80 ± 6.0†

NOTE. Values are the mean ± SD; n = 10 per group.
*$P < .05$ v older.
†$P < .05$ v placebo.

Consistent with our original hypotheses, the thermic response to caffeine was significantly lower in the older (7 kcal/90 min) versus younger (16 kcal/90 min) women of the present study. In support of our findings, previous investigations using a meal challenge to examine age-related differences in thermogenesis generally observe a lower postprandial thermogenic response in older versus younger individuals, indicating an energy-sparing mechanism in older individuals.[3,4] Moreover, it is important to highlight that in the present study, the thermic response to caffeine was still significantly elevated in the younger women and not in the older women at the termination of the 90 minute test period (Fig 2). Thus, it is likely that the present study underestimated the total thermic response to caffeine in the younger women and thus may not have detected actual age-related differences in the thermic response to caffeine. A likely mechanism for the blunted age-related increase in the thermogenic response to caffeine may be the body composition and aerobic fitness differences. Previous investigations have found that obese individuals have a smaller thermic effect of caffeine (4 mg/kg) than lean individuals.[26,28,34] Although they were not specifically classified as obese, our older women were significantly fatter than the younger women, possibly explaining the tendency for the lower thermic effect of caffeine in our older female subjects. The long-term physiological significance of this blunted thermic response to caffeine for body weight control remains to be elucidated.

The exact mechanisms responsible for caffeine's thermogenic effect in humans are poorly understood, but may include adenosine inhibition, Na/K adenosine triphosphatase activity, sympathetic stimulation, and/or calcium release from the endoplasmic reticulum in heart and skeletal muscle.[35] In human subjects, the inhibition of the antilipolytic adenosine–adenylate cyclase complex,[35] causing increased fat mobilization, is one plausible explanation for the thermic effect of caffeine. Caffeine ingestion increases the stimulatory actions of adenosine 3′,5′-cyclic monophosphate on lipolysis, resulting in an increase in the release of FFAs, which, interestingly, has been suggested as a mechanism for the increase in metabolic rate.[28,34] In the present study, the significant increase in plasma FFA concentrations in both groups following caffeine ingestion is suggestive of adenosine inhibition and increased lipolysis and thus energy metabolism. Although it was not measured in the present study, epinephrine release, a proxy measure of sympathetic nervous system activity, increases following caffeine ingestion[36] and has a well-known thermogenic effect in humans. Thus, part of the caffeine-mediated thermogenic response may be attributed to an increase in plasma epinephrine.

Correlates of the Thermic Effect of Caffeine

Previous studies,[8,14,15,27,28,34] including our own,[13] have investigated changes in the RMR following caffeine ingestion; however, these studies were limited by including only male subjects,[13,15,37] combining lean and obese female and male subjects in the same data analysis,[14,27,34] or including only females all under the age of 50 years.[26,28] Although these studies document an increase in energy expenditure following caffeine ingestion, none have attempted to identify differences in the thermic effect of caffeine in women of different age groups, using a double-blind, placebo-controlled study design, as well

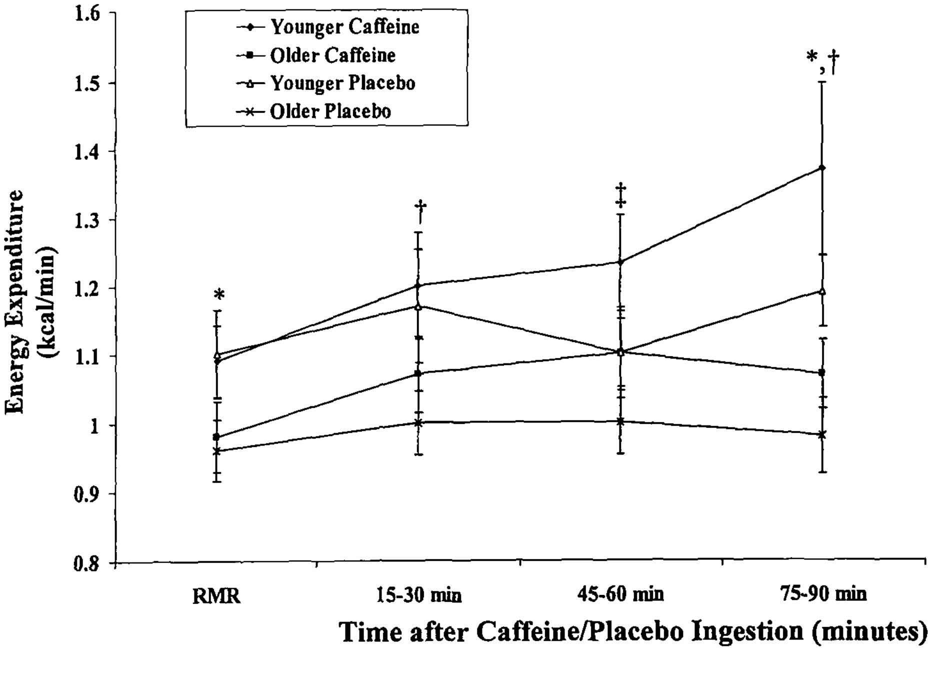

Fig 2. Energy expenditure before and after caffeine ingestion. Values are the mean ± SE. †Significantly different v RMR, $P < .05$; ‡significantly different v RMR, $P < .01$; *significantly different v older women, $P < .05$.

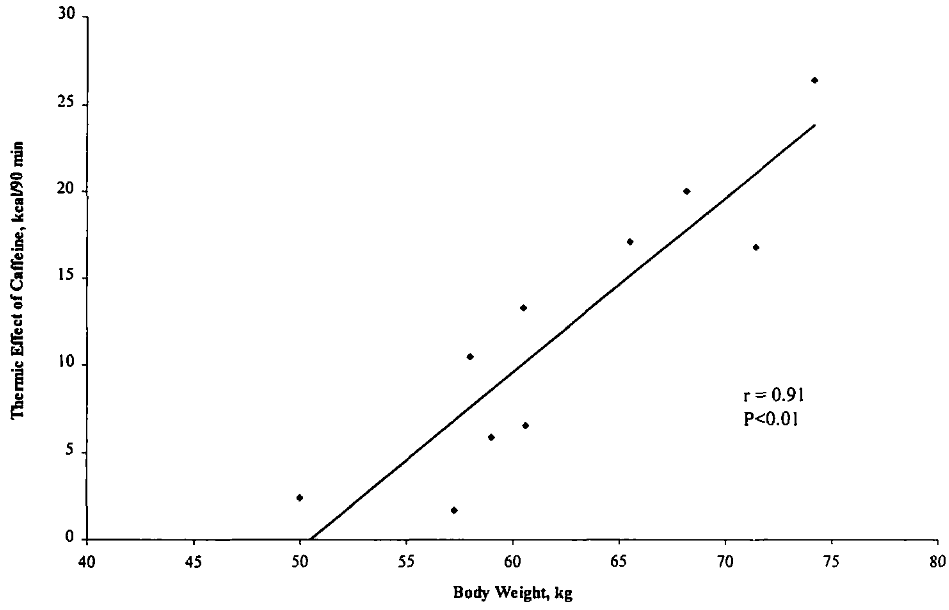

Fig 3. Correlation analysis between body weight and the thermic effect of caffeine in younger women.

as possible physiological correlates of the thermogenic response in the 2 groups. Poehlman et al[33] have previously shown no significant decline in the RMR in women aged 18 to 50 years, whereas a significant decline in the RMR was found in women over the age of 50 years. Taken together, these findings stress the importance of examining lifestyle and/or environmental stressors (ie, caffeine) that influence the RMR in younger and older women. Moreover, they emphasize the importance of identifying potential correlates of the thermic response to these stressors in an attempt to address the increase in body weight and fat mass that occurs with aging.[12]

Age-related variations among women in the thermogenic response to β-adrenergic stimulation may have significant long-term implications on total daily energy expenditure and thus body weight and composition. To our knowledge, no previous studies have systematically examined the age-related differences in caffeine-induced thermogenesis and possible correlates of the thermic response to caffeine in healthy female subjects. The results of the present study show that the thermic response to caffeine was related to different physiologic factors in younger and older women, suggesting that different factors are associated with the thermogenic response to caffeine in women of different age groups. In younger women, the thermic response to caffeine was significantly related to waist circumference and body weight, whereas in older women, only a measure of aerobic fitness correlated with the thermic response.

Our finding of body weight as a major correlate of the thermic effect of caffeine is not surprising, since body weight is highly correlated with the active protoplasmic tissue mass such as fat-free weight ($r = .74$, $P < .01$). Moreover, caffeine enters organs and tissues of the body in direct proportion to their water content.[38] Thus, most of the ingested caffeine exerts its effect on the portion of the body mass consisting of the metabolically active tissue mass (ie, FFM), since this comprises the largest depot of body water. It is unlikely that body weight and composition differences between the older and younger women are responsible for the thermogenic differences, as the older women were significantly heavier and both groups received identical relative doses of caffeine, and thus some other factor(s) are likely responsible.

Our finding that aerobic fitness, albeit an estimation, was the only significant and positive correlate for the thermic response to caffeine in older women further supports the relationship between aerobic fitness and caffeine-induced thermogenesis.[39] Moreover, it is interesting to note that fitness exerts its influence in an inverse manner in older women. Specifically, this association may imply that the more aerobically fit an older women, the greater the thermic response.

It is important to highlight several methodological aspects of the present study that support the validity of our findings. These include (1) precise control for individual differences among subjects by using a repeated-measures design with placebo and caffeine administered in a double-blind fashion, (2) standardization of all measurement procedures during the follicular phase of the menstrual cycle under identical testing conditions, (3) habituation of all subjects to the indirect calorimetry equipment prior to their first RMR test day, (4) measurements performed 36 to 48 hours after the last exercise session to avoid the residual effects of exercise on the dependent variables, and (5) high reproducibility of the RMR and plasma concentration of substrates and hormones in the younger and older women in this study. There are several caveats associated with our study. Our results should not be generalized to individuals beyond the age ranges included here (ie, 31 to 49 and >67 years) or to caffeine-naïve and excessive caffeine consumers. In addition, cause and effect cannot be inferred from this study, as it was cross-sectional in nature.

In summary, our findings suggest that (1) older and younger women exhibit a significant thermogenic response to caffeine, but older women have a blunted thermic response compared with younger women, and (2) body weight and waist circumference in younger women and aerobic fitness in older women are significantly related to the thermogenic response to caffeine.

The relative significance of the age-related influence of these variables on the thermogenic response to caffeine and subsequent impact on body weight and fat stores remain to be determined.

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