Does Caffeine Increase Fat Metabolism? A Systematic Review and Meta-Analysis

Scott A. Conger,¹ Lara M. Tuthill,¹ and Mindy L. Millard-Stafford²

¹Department of Kinesiology, Boise State University, Boise, ID, USA; ²School of Biological Sciences, Georgia Institute of Technology, Atlanta, GA, USA

Whether caffeine (CAF) increases fat metabolism remains debatable. Using systematic review coupled with meta-analysis, our aim was to determine effects of CAF on fat metabolism and the relevant factors moderating this effect. Electronic databases PubMed, SPORTDiscus, and Web of Science were searched using the following string: CAF AND (fat OR lipid) AND (metabolism OR oxidation). A meta-analytic approach aggregated data from 94 studies examining CAF’s effect on fat metabolism assessed by different biomarkers. The overall effect size (ES) was 0.39 (95% confidence interval [CI] [0.30, 0.47], p < .001), indicating a small effect of CAF to increase fat metabolism: however, ES was significantly higher (p < .001) based on blood biomarkers (e.g., free fatty acids, glycerol) (ES = 0.55, 95% CI [0.43, 0.67]) versus expired gas analysis (respiratory exchange ratio, calculated fat oxidation) (ES = 0.26, 95% CI [0.16, 0.37]), although both were greater than zero. Fat metabolism increased to a greater extent (p = .02) during rest (ES = 0.51, 95% CI [0.41, 0.62]) versus exercise (ES = 0.35, 95% CI [0.26, 0.44]) across all studies, although ES was not different for studies reporting both conditions (ES = 0.49 and 0.44, respectively). There were no subgroup differences based on participants’ fitness level, sex, or CAF dosage. CAF ingestion increases fat metabolism but is more consistent with blood biomarkers versus whole-body gas exchange measures. CAF has a small effect during rest across all studies, although similar to exercise when compared within the same study. CAF dosage did not moderate this effect.

**Keywords:** lipid, RER, fat oxidation

Caffeine (CAF) is a well-documented performance aid ingested by athletes either before or during exercise. The acute performance benefits have been reviewed previously across a range of activities including muscular strength/power (Warren et al., 2010), anaerobic power (Grigic, 2018), and endurance (Conger et al., 2011; Doherty & Smith, 2004; Graham, 2001). In general, the mechanism by which CAF appears to reduce fatigue has been ascribed to influence metabolism of substrate (e.g., fat) and/or the central nervous system via adenosine antagonism. Other purported potential neuromuscular effects include direct effects on muscle via intracellular calcium (Herrmann-Frank et al., 1999), increased motor unit recruitment (Warren et al., 2010), and/or central nervous system activation (Kalmar & Cafarelli, 2004; Warren et al., 2010). However, from the historical perspective, the metabolic theory was initially advanced with classic studies (Costill et al., 1978; Ivy et al., 1979), indicating endurance performance improvements appeared linked to greater fat oxidation and/or increased lipolysis which, in turn, might delay fatigue by sparing endogenous stores of carbohydrate. The latter assumption has been disassociated as the basis of ergogenic benefits during exercise (Jeukendrup & Randell, 2011).

The metabolic theory of increased fat oxidation with CAF during exercise persisted for decades (Graham, 2001; LeBlanc et al., 1985) until more recent studies suggested that, in fact, the opposite might occur (i.e., increased carbohydrate metabolism; Graham et al., 2008; Yeo et al., 2005) following CAF administration. Furthermore, it was suggested (Graham et al., 2008) the ergogenic benefits of CAF may not be the result of shifts in either carbohydrate or fat metabolism; although, this does not rule out the possibility that fat metabolism is augmented with CAF. A recent meta-analysis on 19 studies (Collado-Mateo et al., 2020) indicated CAF increased fat metabolism during exercise based on whole-body gas exchange variables (e.g., respiratory exchange ratio [RER] and calculated fat oxidation rates) but that fitness level modulated this effect (i.e., CAF had less effect in trained individuals who may have higher fat oxidative capacity during exercise). However, these findings contrast an earlier meta-analysis that found no effect of CAF on RER during exercise while increasing blood glucose and lactate (Glaister & Gissane, 2018). Thus, despite two meta-analyses on the topic, the fat metabolic theory as a physiological effect of CAF during exercise remains debatable. Several studies have also reported enhanced fat metabolism after consuming CAF under resting conditions (Acheson et al., 2004; Bellet et al., 1965, 1968; Jo et al., 2016), suggesting the metabolic equivalent of tasks level (from rest to low-intensity exercise) may be an important mediating factor. Moreover, the methods used to assess fat metabolism vary, with some studies reporting blood biomarkers of lipolysis and others relying exclusively on whole-body gas exchange data. Other factors related to the research design may also impact the degree of CAF’s effect on fat metabolism. These include the CAF dose administered and individual variability in the response to CAF, specifically when comparing men to women who may rely on fat metabolism to a greater degree (Cano et al., 2022).

Although previous reviews (Guest et al., 2021) and meta-analyses (Grigic et al., 2020; Pickering & Kiely, 2019) have reported effects of CAF on exercise performance, few (Collado-Mateo et al., 2020; Glaister & Gissane, 2018) have quantified the effect of CAF on fat metabolism during exercise. Inexplicably, those two aforementioned studies do not agree, despite basing conclusions solely on gas exchange data. No meta-analysis to our
knowledge has determined CAF’s impact based upon the metabolic equivalent of tasks level (inclusive of rest upwards to higher exercise intensity) or utilized additional biomarkers of fat metabolism (i.e., blood parameters). Therefore, our purpose was to determine effects of CAF ingestion on fat metabolism using a comprehensive systematic review of the published literature and meta-analysis. We also sought to quantify the influence of factors moderating this effect such as the biomarkers assessed, rest compared with exercise, CAF dosage, and participant characteristics.

**Methods**

**Systematic Literature Review**

For this study, the preferred reporting items for systematic reviews and meta-analyses guidelines were followed (Moher et al., 2015). The electronic databases PubMed, SPORTDiscus, and Web of Science were searched through December 31, 2021 using the search terms: CAF AND (fat OR lipid) AND (metabolism OR oxidation). In addition, reference lists from each relevant study and review articles were examined for inclusion of additional studies in the analysis.

**Inclusion/Exclusion Criteria**

Studies meeting the following criteria were included in the analysis: (a) published in a peer-reviewed journal, (b) human participants free from any medical condition known to alter metabolic rate, (c) crossover study design that included both a CAF and placebo condition, and (d) reported some method of fat metabolism providing means and variances. Studies that included additional substances during CAF conditions were included if the investigational and placebo conditions were identical with the exception of CAF. Studies reporting either resting, exercise conditions, or both in the same study were included in the systematic review. Data were excluded if: (a) exercise was not primarily aerobic, (b) CAF/placebo were consumed <30 min prior to data collection, or (c) CAF/placebo were not ingested/swallowed (i.e., mouth rinse or chewing gum). We defined aerobic exercise as ≥5 consecutive min of activity since >80% of energy is supplied by the aerobic energy system (Gastin, 2001).

A total of 149 articles were identified for potential analysis. The review and selection process for identification of the included articles are summarized in Figure 1. After full-text review, 94 studies were retained and 55 studies excluded based on: did not report fat metabolism data, not a within-subjects study design, and missing placebo condition. Preferred reporting items for systematic reviews and meta-analyses guidelines, study quality assessment, and study methods are available in the Supplementary Material S1 (available online) and the Supplementary Table S1 (available online).

**Statistical Analysis**

Study data were extracted from text or relevant tables. If data were not reported elsewhere, figures were used for data extraction. Figures were enlarged, and the mean and variance data presented were measured to the nearest millimeters using the appropriate scale of the figure. Data from each study were converted into the same format by calculating the effect size (ES) as the standardized difference in means. The standardized difference in means was calculated as:

$$\frac{(M_{CAF} - M_{Pla})}{SD_{Pooled}}.$$
where $M$ is the mean, and $SD_{\text{pooled}}$ is the pooled $SD$ (Borenstein et al., 2009) and calculated as:

$$\left(\frac{SD^2_{\text{CAF}} + SD^2_{\text{Pla}} - 2 \times r_{\text{CAF,Pla}} \times SD_{\text{CAF}} \times SD_{\text{Pla}}}{2 \times (1 - r_{\text{CAF,Pla}})}\right)^{0.5},$$

where $r_{\text{CAF,Pla}}$ was the intertrial correlation between CAF and placebo conditions (Borenstein et al., 2009). In three study populations, we calculated $r_{\text{CAF,Pla}}$ from the reported data (Bellet et al., 1965; Wiles et al., 1992). For studies in which the correlations were not available, the mean of the reported correlations was used ($r = 0.474$ for exercise and $r = 0.580$ for resting studies). Hedges correction (Hedges’ $g$) was used to account for potential bias resulting from small sample sizes. Standardized difference in means and $SE$ were multiplied by the correction factor (Borenstein et al., 2009):

$$1 - \left\{\frac{3}{4 \times (r_{\text{CAF,Pla}} - 1)}\right\}.$$

Other data extracted from each study included: authors; publication year; participant demographic information (sex, age, height, body mass); maximal oxygen uptake ($VO_2\text{max}$); fasting state; CAF dose; fat metabolism biomarker; timing of data measurements; exercise intensity; exercise testing protocol; habitual CAF use; timing of CAF administration; and dietary control methods.

In studies that reported more than one fat metabolism outcome from the same population of participants, the mean study ES and their associated variances were used to calculate the meta-analyses’ overall ESs for each study. When a study reported data for more than one independent group, an ES was calculated for each group. Each independent group was then treated as an independent study (Borenstein et al., 2009). In the meta-analysis by fat assessment method, multiple methods were often utilized within the same study. In these cases, each method was analyzed independently. For steady state, submaximal exercise protocols, mean data were used in the calculation of the ES. In studies that reported data during different intensities, the ES was calculated for each intensity. In both cases, the average ES across all data points was used to calculate the overall ES for a given study.

Overall ESs were calculated using a random-effects model that accounts for true variation in effects occurring from study to study as well as random error within a given study. Heterogeneity was assessed using $Q$ and $I^2$ statistics. To assess whether moderator variables could explain variation in ES among studies, subgroup meta-analyses and meta-regressions (method of moments model) were conducted. Subgroup meta-analyses examined effects of categorical data: rest versus exercise, fat metabolism assessment method (blood vs. gas exchange based upon RER; Zuntz, 1901), CAF dosage (small, moderate, and large; Pickering & Kiely, 2019), exercise intensity, participants’ sex, habitual CAF use (yes or no without threshold levels), or fasted state ($\geq 3$ hr; Jeukendrup et al., 1998). Gas exchange data were reported as RER (ratio of carbon dioxide production to oxygen consumption) or by calculating fat oxidation in grams per minute based on oxygen consumption from standardized formulas (Zuntz, 1901). Meta-regressions also assessed the association between CAF ES for fat metabolism relative to continuous data (CAF dosage, body mass index [BMI], fitness level based on $VO_2\text{max}$, age, and exercise intensity).

Most studies reported approximate values for exercise intensity, typically using percentage of $VO_2\text{max}$ (%$VO_2\text{max}$). For studies that did not report exercise intensity, we based our estimate from the exercise description provided by the authors (see Supplementary Table S1 [available online]). To determine the intensity during resting conditions, if oxygen consumption data were not available, one metabolic equivalent of tasks (i.e., $3.5 \text{ ml-kg}^{-1}\text{-min}^{-1}$) was used as the estimated metabolic rate. If $VO_2\text{max}$ data were available, the intensity was then calculated (e.g., resting value of $3.5 \text{ ml-kg}^{-1}\text{-min}^{-1}$ + maximal value of $45 \text{ ml-kg}^{-1}\text{-min}^{-1} = 8\%$).

The effect of publication bias was addressed by combining a funnel plot assessment with the Duval and Tweedie (2000) trim and fill correction. Orwin’s Fail-Safe $N$ test determined the number of missing studies that would have been needed to bring the overall ES down to a level favoring the placebo condition for fat metabolism (Borenstein et al., 2009).

All data were presented as mean ± 95% confidence interval (CI). ES thresholds of $0.2$, $0.5$, and $0.8$ were considered small, medium, and large, respectively (Cohen, 1988). An $\alpha$ level of .05 was used to indicate statistical significance. All calculations were completed using comprehensive meta-analysis (version 2.2.064, Biostat).

**Results**

**Study Characteristics**

Ninety-four studies published between 1965 and 2021 were included. In 11 studies, data from two independent populations were presented, for a total of 105 independent study populations and 435 separate ESs. Data from five different measures assessing fat metabolism were presented: plasma free fatty acids (FFAs), plasma glycerol, triglycerides, RER, and fat oxidation calculated from RER (gas exchange data). Fifty-five percent of studies presented data using more than one method to assess fat metabolism. Most studies (63%) reported participants in a fasted state ($\geq 3$ hr from last meal (mean duration: 7.1 hr, median: 8 hr). CAF dosage used in the studies varied considerably, averaging 5.7 mg/kg (median: 5.0 mg/kg, range: 1.0–15.0 mg/kg).

**Participant Characteristics**

Data from 984 participants were included (828 males/146 females). Most studies utilized relatively small sample sizes (mean $n = 9.4$, median: 9, range: 5–24). In 72% of studies, all participants were males, 9% of studies consisted of only females, and 18% of studies included both males and females presented combined. In studies that combined males and females, ~70% of participants were males. One study did not identify sex (Wiles et al., 1992). In general, the average participant was young adult (mean age: 26.1 years), lean (mean BMI: 23.7 kg/m²), and fit (mean $VO_2\text{max}$: 54.1 ml·kg⁻¹·min⁻¹). However, there was variation across a range (age: 15.6–71 years, BMI: 18.3 to 29.6 kg/m², $VO_2\text{max}$: 27.6 to 75.5 ml·kg⁻¹·min⁻¹).

**Fat Metabolism With CAF Consumption**

Of the 105 study populations that reported fat metabolism after ingesting CAF, overall ESs ranged from ~2.36 (greater fat metabolism with placebo) to 3.87 (greater fat metabolism with CAF; see Supplementary Figure S1 (a–c) [available online]). Overall, the ES was $0.39$ (95% CI [0.30, 0.47], $p < .001$), reflecting a small effect of CAF on fat metabolism (Figure 2A). There was significant
heterogeneity across studies, $Q(104) = 315.22, p < .001$. The within-study heterogeneity was moderate ($I^2 = 67.0\%$), while the between-study heterogeneity was low ($\tau^2 = .12$).

### Subgroup Meta-Analyses

Subgroup meta-analyses were used to assess effects of moderator variables as potential underlying explanation for the heterogeneity.

### Resting Versus Exercise Conditions

Of the 105 independent study populations, data during resting conditions were reported in 13 studies, data during exercise conditions in 34 studies, and during both resting and exercise conditions in 58 studies. A total of 71 and 92 independent ESs were reported for rest and exercise, respectively. Across all studies, ES for fat metabolism during both rest ($ES = 0.51, 95\% CI [0.41, 0.62], p < .001$) and exercise ($ES = 0.35, 95\% CI [0.26, 0.44], p < .001$) conditions were significantly increased with CAF; however, the ES for rest was greater versus exercise, $Q(1) = 5.33, p = .02$, (Figure 2B). ES for fat metabolism reporting both rest ($ES = 0.49, 95\% CI [0.37, 0.60], p < .001$) and exercise ($ES = 0.44, 95\% CI [0.33, 0.56], p < .001$) in the same study were increased with CAF, but not different between rest and exercise, $Q(1) = 0.26, p = .61$.

Meta-regression was also completed for CAF ES on fat metabolism relative to exercise intensity (%VO2max) for combined rest and exercise data. This inverse relationship was significant with a slope of $-0.003 (95\% CI [-0.004, -0.001], p < .001$), indicating a slight decrease in fat metabolism as exercise-intensity increases above rest. Meta-regression completed on only the exercise studies found an inverse relationship but it was not statistically significant (slope = $-0.002, 95\% CI [-0.006, 0.002], p = .32$).

### Fat Metabolism Assessment Method

Five different fat metabolism biomarkers were reported across studies. The most common method reported was RER ($n = 77$), and least common was triglycerides ($n = 9$). CAF significantly increased fat metabolism based upon FFA, glycerol, RER, and calculated fat oxidation with ESs ranging from 0.19 (RER) to 0.56 (glycerol, FFA; $p < .001$) but not based on triglycerides ($ES = 0.30, 95\% CI [0.29, 0.62], p = .07$; Figure 3A). The ESs based on RER were small and significantly lower compared with the ES using FFA and glycerol, $Q(4) = 23.54, p < .05$. There were no other significant differences between fat metabolism assessment methods.

Biomarkers used to assess fat metabolism were then categorized by lipolytic blood measures (at least one of either FFA, glycerol, or triglycerides across 64 studies) versus gas analysis (RER and/or fat oxidation in 84 studies). ESs using blood biomarkers ($ES = 0.55, 95\% CI [0.43, 0.67], p < .001$) and gas analysis ($ES = 0.26, 95\% CI [0.16, 0.37], p < .001$) were significantly greater than zero (Figure 3B), although blood biomarkers ESs were greater, $Q(1) = 12.61, p < .001$. In 43 studies including both blood and gas analysis measures, ES for blood measures ($ES = 0.58$) remained significantly larger than gas exchange ($ES = 0.28$, $Q(1) = 7.07, p = .01$).

### Other Potential Modifier Variables

Figure 4 summarizes the impact of other factors on CAF ES on fat metabolism. When assessed by sex, CAF naive or regular user, CAF dosage, or fasted status prior to testing, all subgroup ESs were significantly different from zero (favoring increased fat metabolism with CAF). Studies with men ($ES = 0.40, 95\% CI [0.30, 0.50]$), men and women combined ($ES = 0.37, 95\% CI [0.17, 0.56]$), and only women ($ES = 0.34, 95\% CI [0.03, 0.65]$) had significant ES with CAF ($p < .05$; Figure 4A) with no differences between subgroups ($p = .90$). There were also no differences within moderator variables: habitual CAF use (Figure 4B), CAF dosage (Figure 4C), or fasting condition (Figure 4D). Meta-regression evaluated these variables as continuous data relative to ES: BMI (slope = 0.020, 95\% CI [0.011, 0.029], $p = .001$), VO2max (slope = 0.005, 95\% CI [-0.008, 0.012], $p = .11$), and CAF dosage (slope = 0.002, 95\% CI [-0.024, 0.027], $p = .90$), which were also not statistically significant.

### Publication Bias

Publication bias was assessed by examining a funnel plot of $SE$ versus ES. Minor asymmetry was noted in the plot; thus, a Duval and Tweedie’s (2000) trim and fill correction to the overall ES was calculated. This correction shifted the overall ES from 0.39 (95\% CI [0.30, 0.47], $p < .001$) to 0.25 (95\% CI [0.16, 0.35], $p < .001$; Figure 5), which did not change interpretation of results (small ES with CAF). Using the Orwin’s Fail-Safe N test to reduce the overall...
ES down to a trivial negative overall ES (i.e., ES = −0.10), we assumed that the missing studies had a mean ES of −0.20. Given these criteria, the ES of 474 independent groups (compared with 105 retrieved) would have theoretically been needed to be omitted from our search to conclude fat metabolism is not increased with CAF versus placebo.

Discussion

Our aim was to determine whether CAF increases fat oxidation. In our analysis of 94 studies with 105 independent groups (984 participants), CAF ingestion significantly increased fat metabolism with a small effect (ES = 0.39) based upon gas exchange and blood parameters. The increase in fat metabolism tended to be greater when consumed during rest compared with exercise, although both conditions significantly elevated fat metabolism. Unlike a previous meta-analysis (Collado-Mateo et al., 2020) which only included 19 exercise studies, we found this effect to be independent of various individual factors including fitness level, sex, and CAF dosage.

In the present study, our subgroup analysis comparing rest to exercise conditions (Figure 2B) suggests that the impact of CAF on fat metabolism may be more definitive under resting conditions. It is well known that fat oxidation decreases as exercise intensity increases, consistent with a greater reliance on carbohydrate (Glaister & Gissane, 2018). For the studies under resting conditions included in our analysis, most (63%) were reported under fasting conditions. These conditions might optimize fat metabolism.
regardless of participants’ fitness level or sex as these factors may contribute to greater variability among individuals’ metabolic response during exercise (particularly as intensity increases). Because of energy requirements at rest and low-intensity exercise, >90% of the energy are supplied from fat sources as compared with the shift to carbohydrate oxidation (>90% of energy) during high-intensity exercise (Romijn et al., 1993). Maximal fat oxidation rates are considered to be between 59% and 64% of VO2max in trained individuals but lower (47%-52% of VO2max) in the general population (Achten & Jeukendrup, 2004). Our results suggest the original metabolic theory with CAF ingestion is valid while under both rest and exercise, but prescribing an “optimal” intensity for enhancing fat metabolism may be less definitive across the exercise spectrum with different populations.

Fat metabolism has historically been measured using biomarkers related to lipolysis in the blood (i.e., FFA, glycerol) or indicators of whole-body substrate oxidation using gas exchange at steady state conditions (RER and calculations of fat oxidation). Breakdown of triglyceride occurs in many tissues of the body providing FFA which can be utilized endogenously for energy production except in adipose tissue which releases FFA and glycerol to supply nonadipose tissues (Schweiger et al., 2014). Since fat may be oxidized within skeletal muscle during exercise, the most optimal and sensitive methods to assess blood markers of lipid oxidation continue to evolve (Schweiger et al., 2014). In the present study, all methods reportedly linked to fat oxidation (with the exception of blood triglycerides) increased after consuming CAF. Blood triglycerides were also the least commonly reported measure (9% of studies) and may be less physiologically relevant. However, expressing fat metabolism using blood biomarkers (including triglycerides) yielded a significantly higher ES than gas exchange measures (RER and calculated fat oxidation) (Figure 3B). The ES based on blood biomarkers across all studies was moderate (ES = 0.55). In studies reporting gas exchange data, a majority of the studies demonstrated a positive ES. In those studies reporting both measures, this difference between lipolytic blood markers and gas exchange was further confirmed (Figure 3C). Therefore, while fat metabolism increased after consuming CAF based upon either blood biomarkers or gas exchange data, blood lipolytic biomarkers elicited more consistent changes. We can only speculate a reason for this discrepancy but perhaps is linked to concomitant increases in glycogenolysis (simultaneously influencing carbohydrate oxidation) with CAF.

Numerous studies have reached the opposite conclusion regarding metabolic effects of CAF when assessed based upon gas exchange variables: either no change or significant decreases in fat metabolism after ingesting CAF. While CAF likely mobilizes fatty acids from adipose tissue, RER measures do not consistently indicate increased fat oxidation during exercise (Glaister & Gissane, 2018). Furthermore, there is little evidence to support the hypothesis that CAF exerts its ergogenic effect due to enhanced fat oxidation (Graham et al., 2008). In contrast, a recent meta-analysis (Collado-Mateo et al., 2020) found a significant but small ES for RER during exercise (ES = −0.33), a magnitude remarkably similar to our gas exchange data in the present meta-analysis (ES = 0.26). Our values were expressed in the positive direction as increased fat oxidation unlike the former (Collado-Mateo et al., 2020), which report ES for RER as negative values (indicative of decreased RER). Both meta-analyses contradict a previous one (Glaister & Gissane, 2018) indicating RER during exercise was not significantly impacted by CAF. Exercise studies in that meta-analysis (Glaister & Gissane, 2018) were delimited to 5–30 min
bouts of 60%–85% VO2max and also reported higher blood glucose and lactate with CAF dosages between 3 and 6 mg/kg. Inclusion criteria for the previous two meta-analyses of RER data resulted in two very different sets of studies, which may account for the differential findings between them. Of the combined 33 studies included between the two meta-analyses, only three studies were common to both (Collado-Mateo et al., 2020; Glaister & Gissane, 2018). In the present meta-analysis, 77 of 94 studies reported RER data. All but two of the studies included in these earlier meta-analyses were included in our analysis.

The metric used to assess fat metabolism after consuming CAF could be critical in the interpretation of results, particularly when measures do not align within studies. One study (Yeo et al., 2005) found CHO metabolism significantly increased (and fat oxidation decreased) during exercise at 64% VO2max after CAF. Increased CHO metabolism was based on RER data; however, FFA and glycerol suggested a nonsignificant increase in fat metabolism. These seemingly contradictory findings of decreased fat metabolism reported by gas analysis data while blood biomarkers suggest increased lipolysis were reported by others (Casal & Leon, 1985; Lee et al., 2012; Spriet et al., 1992; Wells et al., 1985) with authors’ interpretation varying. While not mechanistic, our findings suggest the method used can yield differential results regarding fat metabolism after ingesting CAF and should be considered when interpreting CAF’s effect.

Unlike the recent meta-analysis (Collado-Mateo et al., 2020), we did not find a CAF dose–response effect on fat metabolism. Those authors reported the ES for fat metabolism was significantly higher for “threshold” CAF doses above 3 mg/kg, although not a true dose–response since >6.0 mg/kg did not exhibit a greater ES. However, a high degree of variability (F = 92%) was reported specifically in their subgroups comparing the high CAF dose (6 mg/kg). The number of studies in their low dose (<3 mg/kg) was also more limited (n = 5) than in our present meta-analysis (n = 18). In contrast, we found no dose–response effect of CAF on fat metabolism or a minimum 3 mg/kg “threshold level effect.” All CAF doses demonstrated increased fat metabolism over placebo (p < .05) with no apparent benefit from consuming larger CAF doses (Figure 4c). When two or more CAF doses were investigated in the same study (see Supplementary Table S1 [available online]), there was no clear dose–response effect with CAF dosage ranging from 1.0 to 15.0 mg/kg. Dose–response studies did not appear in the literature until 1995 (Spriet, 2014), and doses of –3 mg/kg were commonly considered “low” dose. Seven of the 12 studies included doses of 3.0 mg/kg or less, and six studies included doses of 6.0 mg/kg or greater. We speculate that by including resting studies, the impact of CAF on fat metabolism may be less influenced by other potential factors at play during exercise (intensity, participant fitness level) and enhance the possibility to elicit more consistent metabolic effects at “lower” CAF dosages (~3 mg/kg). To that end, a CAF dosage of only 100 mg has been shown to increase resting energy expenditure by 3%–4% although fat oxidation was not measured (Dulloo et al., 1989). The lack of a clear CAF dose–response effect has also been previously demonstrated related to endurance performance (Conger et al., 2011) and ratings of perceived exertion (Doherty & Smith, 2005), although (Spriet, 2014) suggests higher CAF doses, while not needed for central nervous system antagonism of adenosine (i.e., influencing performance and perceived exertion), might be necessary for metabolic actions (e.g., lipolysis). Additional investigations with multiple CAF dosages (particularly at the low end) may prove beneficial in our understanding and alter the present findings.

Strengths and Limitations

With 105 different participant populations and nearly 1,000 participants included in the analysis, this large sample size allowed for a number of important subgroup analyses to address several key moderator variables considered important for assessing the impact of CAF. However, there are inherent limitations related to risk of bias. Our search did not include unpublished or non-English studies, thus making it likely we did not capture every relevant study on fat metabolism after CAF ingestion within the gray literature. While omission of relevant studies may have altered the individual ESs, we do not believe that it would have significantly impacted our overall conclusions based on the Orwin’s Fail-Safe N and Duval–Tweedie tests (Figure 5).

Another limitation of our approach is that the ergogenicity of CAF for exercise performance cannot be tied to fat oxidation as the underlying mechanism. Of interest, however, is emerging evidence that low doses (< 3 mg/kg) may be ergogenic and our results found that fat oxidation occurs similarly with low versus moderate doses. The exercise protocols used in each study also varied considerably. Since mean values were utilized to compute ES, this approach may limit the ability to interpret results during specific exercise conditions. Increases in lipolytic biomarkers do not always align with increased fat oxidation as referenced earlier. A strength of our analysis was for studies that measured both gas exchange and lipolytic markers (Figure 3C), results suggest lipolysis occurs to a moderate degree while RER decrease may be tempered. Whether this differential effect is potentially due to concomitant increases glycolysis with CAF (and reports of increased carbohydrate metabolism) which offset the relative contribution of fat substrate being oxidized is unclear since we did not systematically extract measures of carbohydrate oxidation.

Practical Applications

Understanding factors that increase fat oxidation are important not only for optimizing exercise performance but also for clinically relevant conditions such as reducing obesity and metabolic syndrome (Achten & Jeukendrup, 2004). That CAF increased fat oxidation in women (similar to men) and was not dependent on fitness level would suggest metabolic advantages in weight control for sedentary populations, especially since the rest effect was equal to or greater than exercise of varying intensities. Exercise intensity and duration both impact fat oxidation, but the optimal intensity remains obscure (Achten & Jeukendrup, 2004). Our results suggest exercise coupled with CAF (even at low dosages) may enhance fat oxidation, potentially providing metabolic advantages. This statement concurs with significant ES observed with CAF on weight control variables (lowered body mass, fat mass, and BMI) with CAF (Tabrizi et al., 2019). However, we acknowledge generalizations are challenging due to the large interindividual variability in substrate utilization (Achten & Jeukendrup, 2004). Despite the backdrop of individual variability related to several factors, our meta-analysis finds CAF increases fat oxidation across a range of CAF dosages and individual characteristics.

Conclusions

Based upon 94 studies with variable findings regarding fat metabolism after ingesting CAF under both resting and exercise conditions, we report a highly significant but small effect (ES = 0.39) of CAF to increase fat metabolism. The ES of CAF was at least equal

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