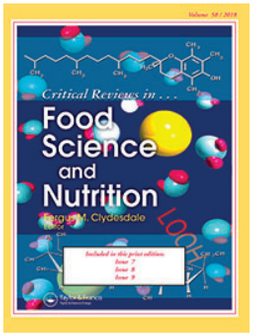

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Capsaicin and capsiate could be appropriate agents for treatment of obesity: A meta-analysis of human studies

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ABSTRACT

Consumption of capsaicin or its nonpungent analogues, capsinoids has been reported to affect energy expenditure and fat oxidation, although available data are still controversial. The aim of the present study was to conduct a meta-analysis regarding the effects of these substances on energy expenditure and respiratory quotient, with special emphasis on the role of body mass index (BMI) of the participants. Medical databases were systematically searched for papers. Of the 627 trials identified, 9 provided results suitable to be included in analysis. Data analysis showed that after ingestion of capsaicin or capsinoids the energy expenditure increased (245 kJ/day, 58.56 kcal/day, $p = 0.030$) and the respiratory quotient decreased (by 0.216; $p = 0.031$) indicating a rise in fat oxidation. Studies with mean BMI of the participants below 25 kg/m^2 failed to report any effect of capsaicin or capsinoids on the energy expenditure ($p = 0.718$) or on the respiratory quotient ($p = 0.444$), but studies with mean BMI exceeding 25 kg/m^2 demonstrated an increase in energy expenditure (292 kJ/day, 69.79 kcal/day, $p = 0.023$) and a marked decrease in respiratory quotient (−0.257, $p = 0.036$). Our data clearly suggest that capsaicin or capsiate could be a new therapeutic approach in obesity promoting a negative energy balance and increased fat oxidation.

KEYWORDS

Capsaicinoid; energy expenditure; metabolic rate; obesity management; fat oxidation

Introduction

Obesity is one of the major worldwide unresolved health challenges: it is a major risk factor for a number of common, potentially lethal diseases, such as hypertension, stroke, coronary heart disease, noninsulin-dependent diabetes mellitus, liver failure, or osteoarthritis (Noppa, 1980; Hubert et al., 1983; Kromhout, 1983; Haslam and James, 2005; Flegal et al., 2010). Although many strategies are available to reduce body weight via reduction of caloric intake and/or enhancement of the metabolic rate, prevalence of obesity is still increasing (Ogden et al., 2015). A potential new target for anti-obesity therapy is capsaicin (Leung, 2014), the pungent principal constituent of red pepper, that is able to influence both energy intake and energy expenditure and is a very popular spice.

Spicy foods and especially hot chili pepper are consumed worldwide in high amounts; therefore the evaluation of metabolic effects of capsaicin and similar molecules is highly important. Controversial findings regarding the metabolic effects of capsaicin and those of similar molecules have been reported in the literature. According to some studies, capsaicin, increases energy expenditure (EE) (Yoshioka et al., 1995; Matsumoto et al., 2000; Chaiyata et al., 2003; Smeets et al., 2013). However, other studies reported no effect on EE (Ahuja et al., 2007; Lejeune et al., 2003; Janssens et al., 2013; Schwarz et al., 2013) and there are also conflicting reports regarding the effect on substrate oxidation. Some studies found no change in respiratory quotient (RQ) after capsaicin ingestion (Lejeune et al., 2003; Ahuja et al., 2007; Smeets and Westerterp-Plantenga, 2009; Janssens et al., 2013; Schwarz et al., 2013), while in other studies there was a significant decrease in RQ (Yoshioka et al., 1998; Smeets et al., 2013) and one study even reported an increase (Lim et al., 1997). On the one hand, it would be important to confirm hypermetabolic effects of capsaicin convincingly, because then, this compound could serve as a research target for safe anti-obesity therapy. On the other hand, these metabolic effects would also be important from the point of view of people with normal or even low BMI, who also consume hot, chili pepper on a regular basis. In their case, hypermetabolism or excessive fat utilization could prove to be harmful.

Mechanisms of capsaicin effects have been widely investigated. The chemical structure of this compound is 8-methyl-N-vanillyl-6-nonenamide (Nelson, 1919). It selectively binds to transient receptor vanilloid subtype 1 (TRPV1). TRPV1 is an ion channel activated under physiological conditions by low (extracellular) and high (intracellular) pH, positive voltages,

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pungent chemicals including capsaicin and by noxious high temperatures (>42°C) (Caterina et al., 1997; Dhaka et al., 2009). This nonselective cation (K^+, Ca^{++}) channel is present in various sites of the body (different brain regions, keratinocytes, smooth muscles of the bladder, urothelium, glial cells, liver, granulocytes, macrophages, etc.), most of the TRPV1 ion channels are expressed in polymodal nociceptive afferent nerve fibers (Vennekens et al., 2008).

Capsinoids, including capsiate, dihydrocapsiate, and nordihydrocapsiate are a group of substances with a molecular structure similar to capsaicin. These capsaicin-like ingredients can be found in "CH-19 Sweet" (*Capsicum annuum* L.), that is a nonpungent cultivar of red pepper (Yazawa et al., 1989, Kobata et al., 1998). Capsiate is the main compound of "CH-19 Sweet" pepper (Iwai et al., 2003). The chemical structure of capsaicin and capsiate differ from each other only in the central linkage (Iwai et al., 2003). Capsiate like capsaicin can bind to TRPV1 receptor with high affinity in the gut but not in the oral cavity or on the skin surface or in the eye (Iwai et al., 2003; Lida et al., 2003). This nonpungent characteristic of capsiate may be explained by its rapid hydrolysation under aqueous conditions, leading to decreased accessibility to nociceptors (e.g., in the oral cavity) (Lida et al., 2003). However, capsiate induces nociceptive responses in mice when injected subcutaneously with a similar dose dependency as capsaicin (Lida et al., 2003).

Several human trials investigated the effect of capsinoids on EE and RQ with contradictory results. Capsiate ingestion has been reported to increase EE (Ohnuki et al., 2001; Inoue et al., 2007; Josse et al., 2010; Galgani and Ravussin, 2010a; Lee et al., 2010) or to evoke no change in EE (Snitker et al., 2009; Galgani et al., 2010) and also to decrease RQ (Inoue et al., 2007; Snitker et al., 2009; Josse et al., 2010; Lee et al., 2010) or cause no change in RQ (Galgani et al., 2010).

Exact mechanism regarding metabolic effects of orally administered capsaicin or capsinoids remain largely unknown. It has been shown, that both capsaicin and its analogues are passively absorbed in the gastrointestinal tract, they are transported to the portal vein after being absorbed in the stomach and in the upper portion of the small intestine (Kawada et al., 1984). Metabolic effects of capsaicin may be at least partially explained by increased thermogenesis caused by activation of TRPV1 receptors accompanied by pain sensation (Szallasi and Blumberg, 1999). Capsaicin was also shown to increase catecholamine secretion and to activate the sympathetic nervous system (Kawada et al, 1986; Watanabe et al., 1987). While capsiate does not evoke burning sensation in the oral cavity, thermoregulatory effect may be caused by sympathetic nerve activation (Ono et al., 2011). A role of brown adipose tissue in the thermic effect of capsaicin and capsinoids is suggested in mice (Kawabata et al., 2009) and in humans (Yoneshiro et al., 2012). Oral sensing appears to be nonessential for the anti-obese actions of capsiate or other capsinoids (Ahern, 2013).

Attempts have been made to summarize available human data concerning effects of this group of substances on body weight and energy homeostasis. It has been demonstrated by a meta-analysis that capsaicinoid ingestion slightly reduces energy intake (Whiting et al., 2014). However, high heterogeneity of the study suggests the role of other determining factors in the background. According to another comprehensive meta-analysis both capsaicin and capsiate increase EE somewhat and enhance fat oxidation at a high dose (Ludy et al., 2012), but the question remains, whether these effects would be maintained upon repeated use of these substances, as well. However, no meta-analysis, as yet, focused on the BMI of the participants or on the length of intervention concerning the metabolic efficacy of capsaicin and capsiate.

Therefore, the aim of the present study was to conduct a meta-analysis investigating the effects of these substances on EE and RQ in humans, with special interest regarding the role of BMI of the participants and the length of the supplementation.

Materials and methods

Search strategy for identification of studies

Meta-analysis was performed using the PICO format: whether an intervention with capsaicin or capsiate supplementation (I) compared with placebo (C) will have any effect on EE and RQ (O) in human participants with normal or higher than normal BMI (P). Trials were identified by searching PubMed, EMBASE and Cochrane Library databases in January to February 2016. In general, the following search terms were used in all databases: ("capsaicin" or "capsaicinoid" or "capsiate") and ("energy expenditure" or "metabolic rate" or "heat production" or "oxygen consumption"). On 28th of January, in Pubmed we searched the following terms: (("capsaicin" [MeSH Terms] OR "capsaicin" [All Fields]) OR "capsaicinoid" [All Fields] OR ("capsiate" [Supplementary Concept] OR "capsiate" [All Fields])) AND ("energy expenditure" [All Fields] OR "metabolic rate" [All Fields] OR "oxygen consumption" [All Fields] OR "heat loss" [All Fields]). On 26th of January, in EMBASE we searched for: 'capsaicin'/exp OR 'capsaicin' OR 'capsaicinoid' OR 'capsiate' AND ('energy expenditure'/exp OR 'energy expenditure' OR 'oxygen consumption'/exp OR 'oxygen consumption' OR 'metabolic rate'/exp OR 'metabolic rate' OR 'heat loss'/exp OR 'heat loss'). In 9th of February, in the Cochrane Library we used the following search terms: ("capsaicin" or "capsaicinoid" or "capsiate,,) and ("energy expenditure" or "metabolic rate" or "heat production" or " oxygen consumption,,) in Trials'. We included human trials without any restriction to language or year of publication. Two reviewers independently extracted data from all the studies fulfilling the inclusion criteria and any disagreement was resolved by consensus. A total of 627 trials were identified from the database searches. 514 trials were immediately excluded based on their title and abstract. In case of the remaining 113 articles full contents were reviewed. Duplicate results were removed, along with studies that did not investigate EE or RQ, or papers with animal studies, and those in which the trial was performed in warm or cold environment. We also excluded trials in which the intervention included other bioactive ingredients (such as green tea and caffeine) leaving a total of 21 trials. 12 papers were then excluded because of insufficient data presentation, leaving a final total of 9 studies (with 255 participants) which were included in the meta-analysis (Fig. 1). Data extracted from the papers included: number of participants, BMI, study type, dosage, the intervention used and study duration. The

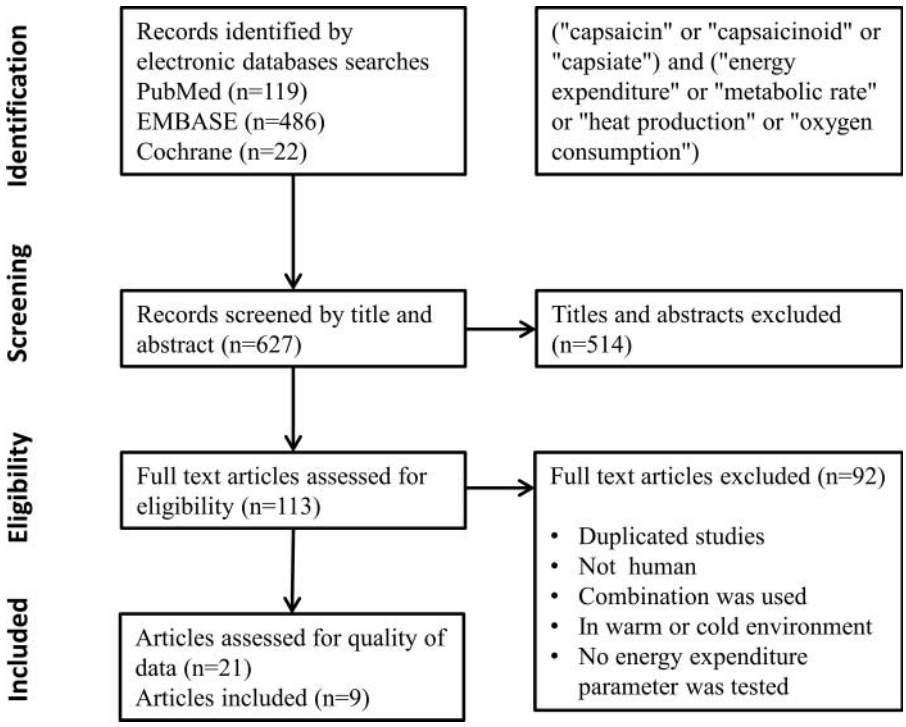

Figure 1. A flow diagram detailing process of study selection for the meta-analysis.

studies' authors and year of publication were also recorded. Effect sizes were then extracted for analysis, including mean daily EE and RQ values for control and intervention groups, along with standard deviations. Among the studies included into our analyses, two used respiratory exchange ratio (respiratory VCO_2/VO_2) and the others described the measured values as RQ. That is why, the term RQ has been used in our analysis. Respiratory exchange ratio is equivalent to the RQ in most cases, except e.g. during some phases of physical exercise (Albouaini et al., 2007). Energy expenditure values published originally as values/minute were converted to daily values in one case (Josse et al., 2010).

Statistical analysis

We have used standardized mean differences with 95% confidence intervals (CI) as effect size data. Studies were grouped by BMI as low (up to 25 kg/m^2) and high (above 25 kg/m^2) and by length of intervention as short (effect of a single meal) and long (when supplementation lasted at least 24 hours). Forest plots were used to describe differences. Means were compared by investigating the presence or absence of overlaps in CIs in both cases. Between-study heterogeneity was tested with a) Q homogeneity test statistic (p values of less than 0.05 were considered as indicators of significant heterogeneity) and b) I^2 statistics, where I^2 is the proportion of total variation attributable to between-study variability (an I^2 value of more than 50% was considered as indicating considerable heterogeneity). These two values were used to model selection purposes as well (fixed vs. random). The tests revealed low heterogeneity in the overall EE group ($Q = 8.589$; $p = 0.378$; $I^2 = 6.86\%$) and also in the overall RQ group ($Q = 2.209$; $p = 0.988$; $I^2 = 0.00\%$). Therefore, we applied the fix effect model in all our forest plot analyses. Publication biases were tested by inspecting the funnel plot. All analyses were performed with the software Comprehensive Metaanalysis (Biostat, Inc., Engelwood, NJ, USA).

Results

A total of 9 studies (with 255 participants) were included in the meta-analysis. Characteristics of the included studies are shown in Table 1. In six studies participants had a BMI higher than 25 kg/m^2 (25+), and four studies presented data about participants with BMI below 25 kg/m^2 (25−). Seven studies included raw data about energy expenditure and seven studies about RQ. Four studies contained more than one treated and control groups (Matsumoto et al., 2000; Inoue et al., 2007; Janssens et al., 2013; Smeets et al., 2013), a second comparison group from the same study were indicated in our forest plots by a number 1 after the study name. Four studies used single meal interventions, in five studies capsaicin or capsiate was administered at least for 1 day. The majority of the included studies showed no significant difference between the treated and control groups, however a tendency for increased EE or decreased RQ was often observable in the treated groups.

The effect of capsaicin or capsiate to EE and RQ were compared in our analyses. Forest plot for overall effects on EE is shown in Fig. 2. Data analysis of EE showed that after ingestion of capsaicin or capsiate there is a significant increase (245 kJ/day, 58.56 kcal/day, $p = 0.030$). To explore the effect of BMI on the results, the studies were subdivided to low and high BMI groups (Fig. 2). If we combined studies with BMI of participants below 25 kg/m^2 there was no significant effect of capsaicin or capsiate to the EE ($p = 0.718$), however, combined analysis of studies with participants exceeding BMI 25 kg/m^2 a significant increase was observed in EE (292 kJ/day, 69.79 kcal/day, $p = 0.023$).

Table 1. Characteristics and findings of the studies included in the analysis.

Author (year)	n	Study type	Dose	BMI	Length	Groups	EE	RQ	Key findings
Matsumoto et al. (2000)	16	Randomized, crossover	3 mg capsaicin	25− and 25+	single meal	Lean group Obese group	✓		In lean group EE was increased after capsaicin, no difference in obese group
Lejeune et al. (2003)	91	Randomized, placebo- controlled	135 mg capsaicin/day	25+	13 weeks	Capsaicin Control	✓	✓	No difference in EE or RQ between groups
Kawabata et al. (2006)	12	Parallel-arm	0.4 g/kg capsinoid/day	25−	2 weeks	Capsinoid Control	✓	✓	Neither parameter changed after 2 weeks vs. control
Inoue et al. (2007)	44	Randomized	3 mg or 10 mg capsinoid/ day	25+	4 weeks	Low dose High dose Control		✓	Neither parameter changed after 4 weeks vs. control
Smeets et al. (2009)	30	Randomized, crossover, single blind	1.03 g red pepper	25−	single meal	Capsaicin Control		✓	No change was detected
Josse et al. (2010)	12	Placebo-controlled, repeated measures study design	10 mg capsinoid	25+	single meal	Capsaicin Control	✓		Metabolic rate increased and RQ decreased
Janssens et al. (2013)	15	Randomized crossover	2.56 mg capsaicin/meal	25−	36 hours	Capsaicin Control 75%Capsaicin 75%Control	✓	✓	No change in EE or RQ vs. control
Schwarz et al. (2013)	11	Randomized, uniform-balanced, crossover	1.25 mg capsaicin	25+	single meal	Capsaicin Control	✓	✓	No difference in EE or RQ between the groups
Smeets et al. (2013)	24	Randomized controlled, crossover	1.03 g red pepper/meal	25+	1 day	Capsaicin Control 80%Capsaicin 80%Control	✓	✓	EE increased and RQ decreased in the capsaicin treated groups vs. control in both conditions

n, number of participants; EE, energy expenditure; RQ, respiratory quotient; BMI, body mass index; 25+, mean BMI above 25 kg/m^2; 25−, mean BMI below 25 kg/m^2; 75%Capsaicin or control, 25% energy intake restriction; 80%Capsaicin or control, 20% energy intake restriction; ✓, absolute data could be included in the analysis.

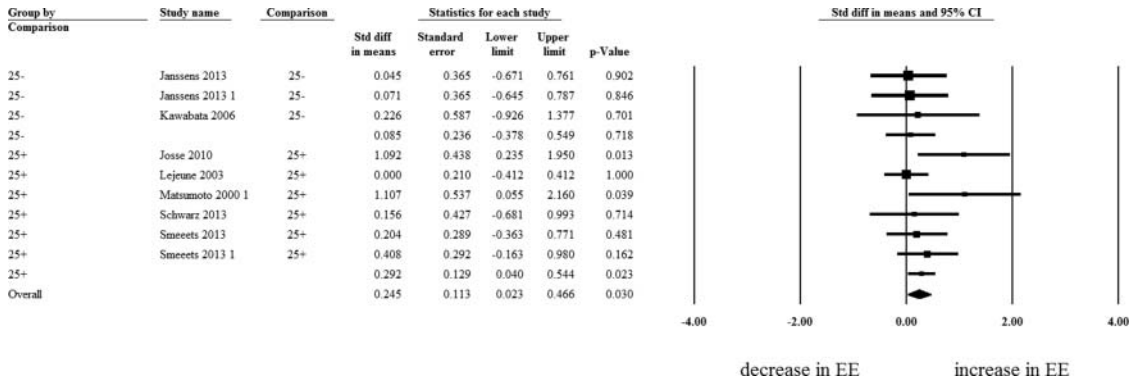

Figure 2. Forest plot of standard difference in mean (with 95% confidence intervals [CIs]) change in energy expenditure (EE) in participants treated with capsaicin or capsinoid compared with controls. The figure shows the summary of studies subdivided by BMI. 25+ indicates studies with mean BMI above 25 kg/m^2, whereas 25− indicates studies with mean BMI below 25 kg/m^2.

Forest plot for overall effects on RQ is shown in Fig. 3. Capsaicin or capsiate supplementation reduced RQ significantly by 0.216, $p = 0.031$. BMI of the participants had a strong impact on the efficacy of the substances to RQ. In the studies where BMI of the participants was below 25 kg/m^2 no significant effect of capsaicin or capsiate to RQ ($p = 0.444$) was detected, while in studies where participants had a BMI higher than 25 kg/m^2 a significant decrease in RQ (-0.257, $p = 0.036$) was observed.

Studies were than subdivided to short (single exposure) and long term intervention (lasting at least for 1 day) groups. Forest plot analysis for effects of length of intervention on EE is shown in Fig. 4. In combined studies of long term intervention, there was no significant change in EE ($p = 0.274$), while combination of short term interventions led to a significant increase of EE (734 kJ/day, 175.43 kcal/day, $p = 0.006$). The short intervention group this time contained studies only with 25+ participants. To reveal the impact of the length of intervention, we performed another forest plot analysis without the 25− studies (Fig. 5) to exclude the effect of BMI. Capsaicin or capsiate supplementation had no significant effect on EE in the long intervention subgroup ($p = 0.288$), whereas there was a significant

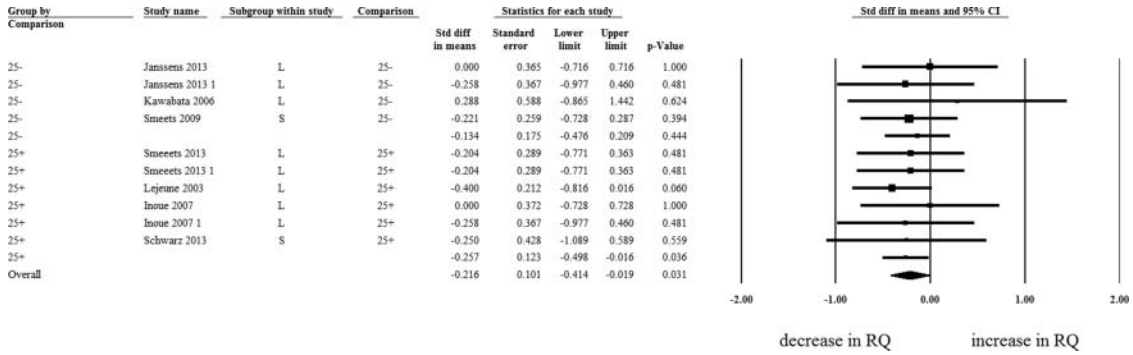

Figure 3. Forest plot of standard difference in mean (with 95% confidence intervals [CIs]) change in respiratory quotient (RQ) in participants treated with capsaicin or capsinoid compared with controls. The figure shows the summary of studies subdivided by BMI. 25+ indicates studies with mean BMI above 25 kg/m^2, whereas 25− indicates studies with mean BMI below 25 kg/m^2. S indicates short intervention (single meal), whereas L indicates longer intervention (at least 24 hours).

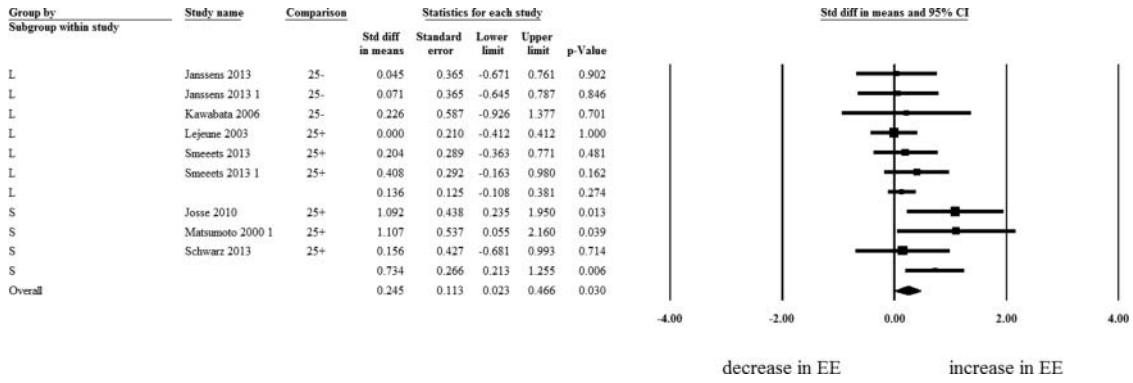

Figure 4. Forest plot of standard difference in mean (with 95% confidence intervals [CIs]) change in energy expenditure (EE) in participants treated with capsaicin or capsinoid compared with controls. The figure shows the summary of studies subdivided by the length of intervention. 25+ indicates studies with mean BMI above 25 kg/m^2, whereas 25− indicates studies with mean BMI below 25 kg/m^2. S indicates short intervention (single meal), whereas L indicates longer intervention (at least 24 hours).

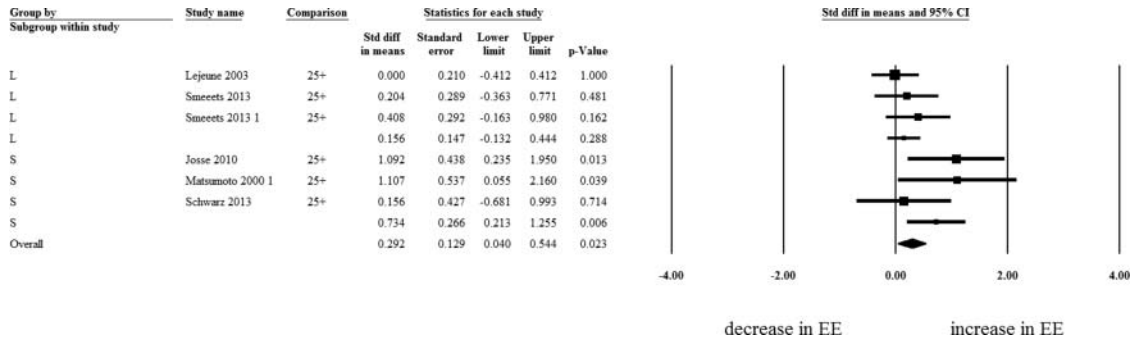

Figure 5. Forest plot of standard difference in mean (with 95% confidence intervals [CIs]) change in energy expenditure (EE) in participants treated with capsaicin or capsinoid compared with controls. The figure shows the summary of studies with mean BMI above 25 subdivided by the length of intervention. 25+ indicates studies with mean BMI above 25 kg/m^2, whereas 25− indicates studies with mean BMI below 25 kg/m^2. S indicates short intervention (single meal), whereas L indicates longer intervention (at least 24 hours).

increase in EE in the short intervention subgroup (0.734 MJ/day, $p = 0.006$).

With regard to the effect of intervention length on changes of RQ a forest plot of RQ data is shown in Fig. 6. Neither combined studies of long term ($p = 0.059$) or short term ($p = 0.302$) intervention was able to change RQ significantly. Limitation of this analysis is that only two observations belong to the short term intervention group, which means there is not enough data to clearly see the effect of length of intervention on this parameter.

Discussion

In the present meta-analysis, we aimed to evaluate the effects of capsaicin and capsiate ingestion on EE and RQ in humans, with special interest regarding the role of BMI of the participants and the length of the supplementation. Such an evaluation is of high potential importance as pharmacological methods of obesity treatment are limited. A large number of anti-obesity drugs have been withdrawn from the market (e.g., fenfluramine, dexfenfluramine, and sibutramin), because of their potentially lethal side effects (McGavigan et al., 2012). Capsaicin and capsinoids provide a potential innovative approach to help in body weight management. In addition, safety considerations for people with normal or low body weight consuming traditional hot foods, would also need to be addressed.

Controversial findings of individual studies investigating the effect of capsaicin or capsiate on metabolic parameters raise the possibility that some determining factors have not been considered yet. The possible impact of BMI on the metabolic efficacy of these substances was raised in the study of Inoue and coworkers (Inoue et al., 2007). In that study they found that increase in oxygen consumption, EE and fat oxidation was significant in subjects with a BMI higher than 25 kg/m^2. In the present meta-analysis, we had similar results, capsaicin or capsiate administration was effective only in subjects with abnormally high BMI values. According to our analysis, in people with normal BMI (lower than 25 kg/m^2) consumption of chili or CH-19 sweet pepper does not seem to raise the risk of unnecessary weight loss or cachexia, because these people do not seem to react with hypermetabolism or increased fat oxidation to capsaicin or capsiate consumption. Thus, these substances are safe in this sense.

Accordingly, the results of the current meta-analysis strongly suggest that capsaicin and capsiate would be appropriate agents for treatment of obesity promoting a negative energy balance and increased fat oxidation.

The question would still arise, whether these components have any serious side effects. One severe limitation of consumption of capsaicin or capsinoids is a possible mutagenic or carcinogenic long term effect. Two studies confirmed a carcinogenic effect of long term use of red pepper (Notani and Jayant, 1987; Lopez-Carillo et al., 1994), while in another population study there was no carcinogenic effect (Buiatti et al., 1989).

Another limitation of the long-term use of these substances is a possible negative effect on the cardiovascular system. An

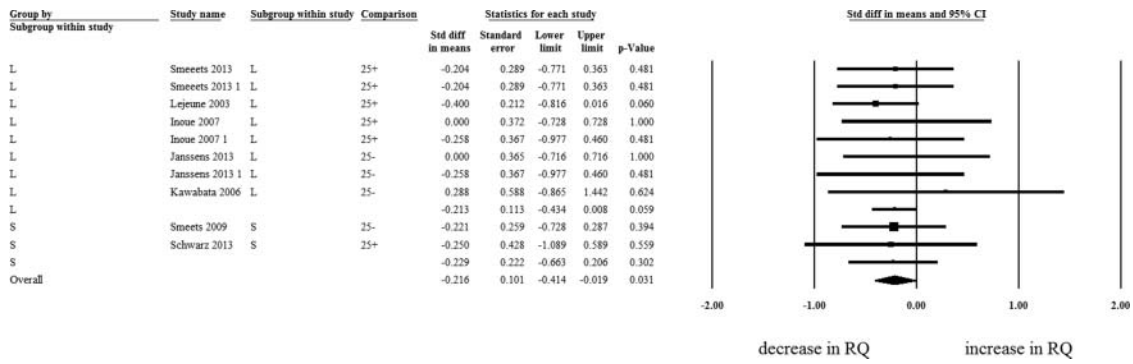

Figure 6. Forest plot of standard difference in mean (with 95% confidence intervals [CIs]) change in respiratory quotient (RQ) in participants treated with capsaicin or capsinoid compared with controls. The figure shows the summary of studies subdivided by the length of the intervention. 25+ indicates studies with mean BMI above 25 kg/m^2, whereas 25− indicates studies with mean BMI below 25 kg/m^2. S indicates short intervention (single meal), whereas L indicates longer intervention (at least 24 hours).

increase in the sympathetic tone and the subsequently released catecholamines after capsaicin or capsiate ingestion was already described in rats (Watanabe et al., 1994) and in humans (Kawabata et al., 2006). Weight loss due to repeated intake of capsiate was correlated with an increased sympathetic nervous response after ingestion (Kawabata et al., 2006). However, in a Japanese study of Matsumoto in obese woman reduced sympathetic responsiveness to capsaicin was measured compared to the lean control group (Matsumoto et al., 2000). Increased sympathetic activation upon capsaicin or capsiate intake raises the possibility of increasing blood pressure if capsaicinoids are used regularly as an anti-obesity agent. This may lead to a negative circulatory effect especially in heart failure patient. However, in human studies no such negative effect of capsaicin or capsiate consumption was observed so far. In healthy subjects, acute capsinoid administration had no influence on blood pressure (Galgani et al., 2010). In another study, after 4 weeks of consumption of chili the parameters of vascular function were not altered: according to this study regular consumption of chili has no beneficial or harmful effects on the cardiovascular risk factors (Ahuja et al., 2007). No significant changes in either diastolic or systolic blood pressure were apparent during 4 weeks of capsinoid consumption in a different study (Inoue et al., 2007). According to these findings capsaicin and capsinoid supplementation seems to have no harmful effect on blood pressure.

In contrast to the abovementioned possible harmful effects of capsaicin, some studies demonstrated medical benefits of capsaicin consumption. Gastroprotective effect of capsaicin consumption was described (Mozsik et al., 2005) and other study revealed its role in prevention of gastric ulcers (Yeoh et al., 1995). Several studies demonstrated antitumor activity of capsaicin, e.g., among others, capsaicin directly inhibits the growth of leukemic cells (Ito et al., 2004) of human esophagus carcinoma cells (Wu et al., 2006) or in prostate cancer cells (Mori et al., 2006).

Another limitation of our study lies in the fact that mechanisms in the background of the analyzed metabolic effects of capsaicinoids are not fully understood. On the one hand, administration of these substances has been described to induce vasodilation and transient hypothermia followed by hyperthermia in animal studies (for review, see Romanovsky et al., 2009). On the other hand, other studies emphasized the hypermetabolic effects of these agonists (for review, see Ahern, 2013). It may serve as an explanation of hypermetabolic effects that Watanabe and coworkers (1987) described capsaicin-induced catecholamine secretion from the adrenal medulla of rats. In addition, capsaicin and capsiate were shown to activate the brown adipose tissue and upregulate uncoupling protein production (Masuda et al., 2003, Kawabata et al., 2009, Yoneshiro et al., 2012, Kida et al., 2016). Moreover, the lower doses of capsaicinused in human studies may be more effective at causing skin vasodilation than at suppressing metabolism, so the secondary (indirect) increase in metabolic rate that compensates for the increased heat loss may result in an overall hypermetabolism.

Prolonged or repeated application of TRPV1 agonists induces desensitization leading to insensitivity of the receptor to subsequent stimuli (Szallasi and Blumberg, 1999). Repeated application of capsaicin on the human tongue decreased the perceived burning sensation because of desensitization of the area to capsaicin (Karrer and Bartoshuk, 1991). This desensitization to perceived burn may develop parallel with the decrease of the observed metabolic effects of capsaicinoids. This may limit the long-term effects of capsaicin or capsiate therapy on energy expenditure. However, several studies demonstrated upregulation in uncoupling proteins by capsaicin and its analogs in rodents (Cui and Himms-Hagen, 1992, Masuda et al., 2003). Based on these findings Ahern (2013) concluded that the metabolic effects of chronic daily TRPV1 agonist administration may influence long-term body weight and adiposity. Nevertheless, future long-term longitudinal studies would be needed, in order to address this problem.

In summary, the main conclusion of our meta-analysis is that the metabolic effects of capsaicin and capsinoids are significant in individuals having abnormally high BMI. Capsaicin or capsiate supplementation may be a natural new method for weight-loss in participants with an abnormally high BMI, furthermore, these substances appear to be safe for people with normal BMI.

Conflict of interest

No potential conflicts of interest associated with this article were reported and there has been no significant financial support for this work that could have influenced its outcome.

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References

Ahern, G. P. (2013). Transient receptor potential channels and energy homeostasis. *Trends Endocrinol. Metab.* **24**:554–560.

Ahuja, K. D. K., Robertson, I. K., Geraghty, D. P. and Ball, M. J. (2007). The effect of 4-week chilli supplementation on metabolic and arterial function in humans. *Eur. J. Clin. Nutr.* **61**:326–333.

Albouaini, K., Egred, M., Alahmar, A. and Wright, D. J. (2007). Cardiopulmonary exercise testing and its application. *Heart* **93**:1285–1292.

Buiatti, E., Palli, D., Decarli, A., Amadori, D., Avellini, C., Bianchi, S., Biserini, R., Cipriani, F., Cocco, P. and Giacosa, A. (1989). A case-control study of gastric cancer and diet in Italy. *Int. J. Cancer* **44**:611–616.

Caterina, M. J., Schumacher, M. A., Tominaga, M., Rosen, T. A., Levine, J. D. and Julius, D. (1997). The capsaicin receptor: A heat-activated ion channel in the pain pathway. *Nature* **389**:816–824.

Chaiyata, P., Puttadechakum, S. and Komindr, S. (2003). Effect of chili pepper (*Capsicum frutescens*) ingestion on plasma glucose response and metabolic rate in Thai women. *J. Med. Assoc. Thai* **86**:854–860.

Cui, J. and Himms-Hagen, J. (1992). Long-term decrease in body fat and in brown adipose tissue in capsaicin-desensitized rats. *Am. J. Physiol.* **262**:568–573.

Dhaka, A., Uzzell, V., Dubin, A. E, Mathur, J., Petrus, M., Bandell, M. and Patapoutian, A. (2009). TRPV1 is activated by both acidic and basic pH. *J. Neurosci.* **29**:153–158.

Flegal, K. M., Carroll, M. D., Ogden, C. L. and Curtin, L. R. (2010). Prevalence and trends in obesity among US adults, 1999–2008. *J. Am. Med. Assoc.* **303**:235–241.

Galgani, J. E. and Ravussin, E. (2010a). Effect of dihydrocapsiate on resting metabolic rate in humans. *Am. J. Clin. Nutr.* **92**:1089–1093.

Galgani, J. E., Ryan, D. H. and Ravussin, E. (2010). Effect of Capsinoids on Energy Metabolism in Humans. *Br. J. Nutr.* **103**:38–42.

Haslam, D. W. and James, W. P. (2005). Obesity. *Lancet* **366**:1197–1209.

Hubert, H. B., Feinleib, M., McNamara, P. M. and Castelli, W. P. (1983). Obesity as an independent risk factor for cardiovascular disease: A 26-year follow-up of participants in the Framingham Heart Study. *Circulation* **67**:968–977.

Inoue, N., Matsunaga, Y., Satoh, H. and Takahashi, M. (2007). Enhanced energy expenditure and fat oxidation in humans with high BMI scores by the ingestion of novel and non-pungent capsaicin analogues (capsinoids). *Biosci. Biotechnol. Biochem.* **71**:380–389.

Ito, K., Nakazato, T., Yamato, K., Miyakawa, Y., Yamada, T., Hozumi, N., Segawa, K., Ikeda, Y. and Kizaki, M. (2004). Induction of apoptosis in leukemic cells by homovanillic acid derivative, capsaicin, through oxidative stress implication of phosphorylation of p53 at Ser-15 residue by reactive oxygen species. *Cancer Res.* **64**:1071–1078.

Iwai, K., Yazawa, A. and Watanabe, T. (2003). Roles as metabolic regulators of the non-nutrients, capsacicin and capsiate, supplemented to diets. *Proc. Jpn. Acad. Ser. B.* **79**:207–212.

Janssens, P. L., Hursel, R., Martens, E. A. and Westerterp-Plantenga, M. S. (2013). Acute effects of capsaicin on energy expenditure and fat oxidation in negative energy balance. *PLoS One* **8**:e67786.

Josse, A. R., Sherriffs, S. S., Holwerda, A. M., Andrews, R., Staples, A. W. and Phillips, S. M. (2010). Effects of capsinoid ingestion on energy expenditure and lipid oxidation at rest and during exercise. *Nutr. Metab.* **7**:65.

Karrer, T. and Bartoshuk, L. (1991). Capsaicin desensitization and recovery on the human tongue. *Physiol. Behav.* **49**:757–764.

Kawabata, F., Inoue, N., Masamoto, Y., Matsumura, S., Kimura, W., Kadowaki, M. and Fushiki, T. (2009). Non-pungent capsaicin analogs (capsinoids) increase metabolic rate and enhance thermogenesis via gastrointestinal TRPV1 in mice. *Biosci. Biotechnol. Biochem.* **73**:2690–2697.

Kawabata, F., Inoue, N., Yazawa, S., Kawada, T., Inoue, K. and Fushiki, T. (2006). Effects of CH-19 sweet, a non-pungent cultivar of red pepper, in decreasing the body weight and suppressing body fat accumulation by sympathetic nerve activation in humans. *Biosci. Biotechnol. Biochem.* **70**:2824–2835.

Kawada, T., Suzuki, T., Takahashi, M. and Iwai, K. (1984). Gastrointestinal absorption and metabolism of capsaicin and dihydrocapsaicin in rats. *Toxicol. Appl. Pharmacol.* **72**:449–456.

Kawada, T., Watanabe, T., Takaishi, T., Tanaka, T. and Iwai, K. (1986). Capsaicin-induced β-adrenergic action on energy metabolism in rats: Influence of capsaicin on oxygen consumption, the respiratory quotient, and substrate utilization. *Exp. Biol. Med.* **183**:250–256.

Kida, R., Yoshida, H., Murakami, M., Shirai, M., Hashimoto, O., Kawada, T., Matsui, T. and Funaba, M. (2016). Direct action of capsaicin in brown adipogenesis and activation of brown adipocytes. *Cell Biochem. Funct.* **34**:34–41.

Kobata, K., Todo, T., Yazawa, S., Iwai, K. and Watanabe, T. (1998). Novel capsaicinoid-like substances, capsiate and dihydrocapsiate, form the fruits of a nonpungent cultivar, CH-19 Sweet, of pepper (*Capsicum annuum* L.). *J. Agric. Food Chem.* **46**:1695–1697.

Kromhout, D. (1983). Body weight, diet, and serum cholesterol in 871 middle-aged men during 10 years of follow-up (the Zutphen Study). *Am. J. Clin. Nutr.* **38**:591–598.

Lee, T. A, Li, Z., Zerlin, A. and Heber, D. (2010). Effects of dihydrocapsiate on adaptive and diet-induced thermogenesis with a high protein very low calorie diet: A randomized control trial. *Nutr. Metab. (Lond).* **7**:78.

Lejeune, M. P., Kovacs, E. M. and Westerterp-Plantenga, M. S. (2003). Effect of capsaicin on substrate oxidation and weight maintenance after modest body-weight loss in human subjects. *Br. J. Nutr.* **90**:651–659.

Leung, F. W. (2014). Capsaicin as an anti-obesity drug. *Prog. Drug. Res.* **68**:171–179.

Lida, T., Moriyama, T., Kobata, K., Morita, A., Murayama, N., Hashizume, S. and Tominaga, M. (2003). TRPV1 activation and induction of nociceptive response by a non-pungent capsaicin-like compound, capsiate. *Neuropharmacology* **44**:958–967.

Lim, K., Yoshioka, M., Kikuzato, S., Kiyonaga, A., Tanaka, H., Shindo, M. and Suzuki, M. (1997). Dietary red pepper ingestion increases carbohydrate oxidation at rest and during exercise in runners. *Med. Sci. Sport. Exer.* **29**:355–361.

Lopez-Carillo, L., Hernandez Avila, M. and Dubrow, R. (1994). Chili pepper consumption and gastric cancer in Mexico: A case-control study. *Am. J. Epidemiol.* **139**:263–271.

Ludy, M. J., Moore, G. E. and Mattes, R. D. (2012). The effects of capsaicin and capsiate on energy balance: Critical review and meta-analyses of studies in humans. *Chem. Senses* **37**:103–121.

Masuda, Y., Haramizu, S., Oki, K., Ohnuki, K., Watanabe, T., Yazawa, S., Kawada, T., Hashizume, S. and Fushiki, T. (2003). Upregulation of uncoupling proteins by oral administration of capsiate, a nonpungent capsaicin analog. *J. Appl. Physiol.* **95**:2408–2415.

Matsumoto, T., Miyawaki, C., Ue, H., Yuasa, T., Miyatsuji, A. and Moritani, T. (2000). Effects of capsaicin-containing yellow curry sauce on sympathetic nervous system activity and diet-induced thermogenesis in lean and obese young women. *J. Nutr. Sci. Vitaminol.* **46**:309–315.

McGavigan, A. K. and Murphy, K. G. Gut hormones. (2012). The future of obesity treatment? *Br. J. Clin. Pharmacol.* **74**:911–919.

Mori, A., Lehmann, S., O'Kelly, J., Kumagai, T., Desmond, J. C., Pervan, M., McBride, W. H., Kizaki, M. and Koeffler, H. P. (2006). Capsaicin, a component of red peppers, inhibits the growth of androgen-independent, p53 mutant prostate cancer cells. *Cancer Res.* **66**:3222–3229.

Mozsik, Gy., Szolcsanyi, J. and Racz, I. (2005). Gastroprotection induced by capsaicin in healthy human subjects. *World J. Gastroenterol.* **11**:5180.

Nelson, E. K. (1919). The constitution of capsaicin, the pungent principal capsicum. *J. Am. Chem. Soc.* **41**:1115–1121.

Noppa, H. (1980). Body weight change in relation to incidence of ischemic heart disease and change in risk factors for ischemic heart disease. *Am. J. Epidemiol.* **111**:693–704.

Notani, P. N. and Jayant, K. (1987). Role of diet in upper aerodigestive tract cancers. *Nutr. Cancer* **10**:103–113.

Ogden, C. L., Carroll, M. D., Fryar, C. D. and Flegal, K. M. (2015). Prevalence of obesity among adults and youth: United States, 2011–2014. *NCHS Data Brief* **219**:1–8.

Ohnuki, K., Niwa, S., Maeda, S., Inoue, N., Yazawa, S. and Fushiki, T. (2001). CH-19 sweet, a non-pungent cultivar of red pepper, increased body temperature and oxygen consumption in humans. *Biosci. Biotechnol. Biochem.* **65**:2033–2036.

Ono, K., Tsukamoto-Yasui, M., Hara-Kimura, Y., Inoue, N., Nogusa, Y., Okabe, Y., Nagashima, K. and Kato, F. (2011). Intragastric administration of capsiate, a transient receptor potential channel agonist, triggers thermogenic sympathetic responses. *J. Appl. Physiol.* **110**:789–798.

Romanovsky, A. A., Almeida, M. C., Garami, A., Steiner, A. A., Norman, M. H., Morrison, S. F., Nakamura, K., Burmeister, J. J. and Nucci, T. B. (2009). The transient receptor potential vanilloid-1 channel in thermoregulation: A thermosensor it is not. *Pharmacol. Rev.* **61**:228–261.

Schwarz, N. A., Spillane, M., La Bounty, P., Grandjean, P. W., Leutholtz, B. and Willoughby, D. S. (2013). Capsaicin and evodiamine ingestion does not augment energy expenditure and fat oxidation at rest or after moderately-intense exercise. *Nutr. Res.* **33**:1034–1042.

Smeets, A. and Westerterp-Plantenga, M. (2009). The acute effects of a lunch containing capsaicin on energy and substrate utilisation, hormones, and satiety. *Eur. J. Clin. Nutr.* **48**:229–234.

Smeets, A. J., Janssens, P. L. and Westerp-Plantenga, M. S. (2013). Addition of capsaicin and exchange of carbohydrate with protein counteract energy intake restriction effects on fullness and energy expenditure. *J. Nutr.* **143**:442–447.

Snitker, S., Fujishima, Y., Shen, H., Ott, S., Pi-Sunyer, X., Furuhata, Y., Sato, H. and Takahashi, M. (2009). Effects of novel capsinoid treatment

on fatness and energy metabolism in humans: Possible pharmacogenetic implications. *Am. J. Clin. Nutr.* **89**:45–50.

Szallasi, A. and Blumberg, P. M. (1999). Vanilloid (Capsaicin) receptors and mechanisms. *Pharmacol. Rev.* **51**:159–212.

Vennekens, R., Owsianik, G. and Nilius, B. (2008). Vanilloid transient receptor potential cation channels: An overview. *Curr. Pharm. Des.* **14**:18–31.

Watanabe, T., Kawada, T., Kato, T., Harada, T. and Iwai, K. (1994). Effects of capsaicin analogs on adrenal catecholamine secretion in rats. *Life Sci.* **54**:369–374.

Watanabe, T., Kawada, T., Yamamoto, M. and Iwai, K. (1987). Capsaicin, a pungent principle of hot red pepper, evokes catecholamine secretion from the adrenal medulla of anesthetized rats. *Biochem. Biophys. Res. Commun.* **142**:259–264.

Whiting, S., Derbyshire, E. J. and Tiwari, B. (2014). Could capsaicinoids help to support weight management? A systematic review and meta-analysis of energy intake data. *Appetite* **73**:183–188.

Wu, C. C., Lin, J. P., Yang, J. S., Chou, S. T., Chen, S. C., Lin, Y. T., Lin, H. L. and Chung, J. G. (2006). Capsaicin induced cell cycle arrest and apoptosis in human esophagus epidermoid carcinoma CE 81T/VGH cells through the elevation of intracellular reactive oxygen species and Ca 2+ productions and caspase-3 activation. *Mutat. Res. Fund. Mol. M.* **601**:71–82.

Yazawa, S., Suetome, N., Okamoto, K. and Namiki, T. (1989). Content of capsaicinoids and capsaicinoid-like substances in fruit of pepper (Capsicum annuum L.) hybrids made with "CH-19 Sweet" as a parent. *J. Jpn. Soc. Hort. Sci.* **58**:601–607.

Yeoh, K. G., Kang, J. Y., Yap, I., Guan, R., Tan, C. C., Wee, A. and Teng, C. H. (1995). Chili protects against aspirin-induced gastroduodenal mucosal injury in humans. *Dig. Dis. Sci.* **40**:580–583.

Yoneshiro, T., Aita, S., Kawai, Y., Iwanaga, T. and Saito, M. (2012). Non-pungent capsaicin analogs (capsinoids) increase energy expenditure through the activation of brown adipose tissue in humans. *Am. J. Clin. Nutr.* **95**:845–850.

Yoshioka, M., Lim, K., Kikuzato, S., Kiyonaga, A., Tanaka, H., Shindo, M. and Suzuki, M. (1995). Effects of red-pepper diet on the energy metabolism in men. *J. Nutr. Sci. Vitaminol. (Tokyo)* **41**:647–656.

Yoshioka, M., St-Pierre, S., Suzuki, M. and Tremblay, A. (1998). Effects of red pepper added to high-fat and high-carbohydrate meals on energy metabolism and substrate utilization in Japanese women. *Br. J. Nutr.* **80**:503–510.