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IMPACTO DAS CARACTERÍSTICAS BIOLÓGICAS DOS INDVÍDUOS E NUTRICIONAIS DAS REFEIÇÕES NO EFEITO TÉRMICO DOS ALIMENTOS EM HUMANOS: METAREGRESSÃO DE ENSAIOS CLÍNICOS

KARINE MARIA MOREIRA ALMEIDA

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Dissertação apresentada à Faculdade de Nutrição da Universidade Federal de Alagoas como requisito à obtenção do título de Mestre em Nutrição.

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por

Karine Maria Moreira Almeida

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RESUMO

ALMEIDA, K. M. M. **Impacto das características biológicas indivíduos e nutricionais das refeições no efeito térmico dos alimentos em humanos: metaregressão de ensaios clínicos.** 82f. Dissertação (Mestrado em Nutrição) – Faculdade de Nutrição, Universidade Federal de Alagoas, Maceió, 2024.

O efeito térmico do alimento (ETA) tem sido objeto de investigação como alvo terapêutico para o excesso de peso e obesidade, porém ainda existem divergências na literatura sobre os possíveis fatores influenciadores, além de escassas revisões sistemáticas que abordem sobre o real impacto desses elementos sobre a resposta termogênica da dieta. Assim, esta dissertação objetivou contribuir com esta lacuna ao analisar o impacto de diferentes características biológicas e nutricionais no ETA em humanos por meio de uma revisão sistemática, com metanálise e metarregressão, de ensaios clínicos. Foi realizada uma busca de estudos publicados até novembro de 2023, nas seguintes bases de dados e plataformas MEDLINE/PubMed, Embase, CENTRAL, Web of Science e LILACS, de ensaios clínicos com indivíduos adultos e idosos, em estado de jejum, que ofertassem uma refeição-teste por via oral e realizassem mensuração do ETA por calorimetria. Esta revisão foi registrada no PROSPERO e seguiu recomendações do PRISMA. Os estudos foram analisados quanto ao risco de viés usando as ferramentas Cochrane RoB 2 para ensaios randomizados e ROBINS-I para ensaios não randomizados. O ETA médio foi o principal desfecho de busca e o impacto da idade, sexo, IMC, dos indivíduos e conteúdo energético, percentual de macronutrientes e grau de processamento alimentar das refeições sobre o ETA foi avaliado por meio de metanálise e metarregressão. Um total 3094 registros foram identificados, sendo 2951 excluídos, totalizando 143 publicações incluídas a partir de 133 estudos. A análise do risco de viés revelou que dos 89 estudos randomizados. 19 apresentaram baixo risco, 52 algumas preocupações e 18 alto risco. Todos os 44 estudos não randomizados foram considerados de risco moderado. Foi observado que o ETA foi maior no tempo entre 60 e 120min após uma refeição-teste, bem como no sexo masculino, estado de eutrofia e refeição com misto graus de processamento. O percentual de carboidratos não apresentou relação com o ETA, enquanto apenas a proporção de lipídios apresentou relação negativa com o ETA na análise principal. O percentual de proteínas se relacionou positivamente com o ETA apenas no subgrupo de refeições com até 1000 kcal. Esses resultados ressaltam a relevância do ETA como um potencial alvo terapêutico. No entanto, devido à alta heterogeneidade dos estudos, destaca-se a necessidade de pesquisas futuras com alto rigor metodológico.

Palavras-chave: Metabolismo energético; Ingestão de alimentos; Ingestão energética; Termogênese; Revisão Sistemática.

ABSTRACT

ALMEIDA, K. M. M. **Impact of individuals' biological and meals' nutritional characteristics on the thermic effect of food in humans: meta-regression of clinical trials.** 82f. Dissertação (Mestrado em Nutrição) – Faculdade de Nutrição, Universidade Federal de Alagoas, Maceió, 2024.

The thermal effect of food (TEF) has been the subject of investigation as a therapeutic target for overweight and obesity, however, there are still divergences in the literature regarding the possible influencing factors, in addition to few systematic reviews that address the real impact of these elements on the thermogenic response. Thus, this dissertation aimed to contribute to this gap by analyzing the impact of different biological and nutritional characteristics on TEF in humans through a systematic review, with meta-analysis and meta-regression, of clinical trials. A search was carried out for studies published up to November 2023 was carried out, in the databases and platforms used were MEDLINE/PubMed, Embase, CENTRAL, Web of Science and LILACS, in trials with adult and elderly individuals, in a fasting state, that offered a test meal orally and TEF by calorimetry. This review was registered in PROSPERO and followed PRISMA recommendations. The included studies were analyzed for risk of bias using the Cochrane RoB 2 tools for randomized trials and ROBINS-I for non-randomized trials. The average TEF was the main search outcome and the impact of age, sex, BMI of individuals and energy content, percentage of macronutrients and degree of food processing of meals on TEF was evaluated through meta-analysis and meta-regression. A total of 3094 records were identified, 2951 of which were excluded, totaling 143 publications included from 133 studies. The risk of bias analysis revealed that of the 89 randomized studies, 19 presented low risk, 52 some concerns and 18 high risk. All 44 non-randomized studies were considered moderate risk. It was observed that the ETA was higher between 60 and 120 minutes after a test meal, as well as in males, eutrophic states and meals with multiple degrees of processing. The percentage of carbohydrates showed no relationship with TEF, while only the proportion of lipids showed a negative relationship with TEF in the main analysis. The proportion of proteins was positively related to TEF only in the subgroup of meals with up to 1000 kcal. These results highlight the relevance of TEF as a potential therapeutic target. However, due to the high heterogeneity of studies, the need for future research with high methodological rigor.

Keywords: Energy metabolism; Eating; Energy intake; Thermogenesis; Systematic review.

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LISTA DE ABREVIATURAS

ADE – Ação Dinâmica Específica

ATP - *Adenosine Tri-Phosphate*

AUP – Alimentos Ultraprocessados

CD – Calorimetria Direta

CI – Calorimetria Indireta

ETA- Efeito Térmico do Alimento

GE – Gasto Energético

GEA – Gasto Energético de Atividade

GEPP – Gasto Energético Pós-Prandial

GER – Gasto Energético de Repouso

GET – Gasto Energético Total

IMC – Índice de Massa Corporal

TID – Termogênese Induzida pela Dieta

SUMÁRIO

INTRODUÇÃO

1. INTRODUÇÃO

A compreensão do papel do gasto energético (GE) no metabolismo humano é essencial para entender a regulação homeostática em várias condições clínicas, incluindo a obesidade, condição que vem crescendo de forma exponencial a nível mundial. As diferentes subdivisões do GE, como gasto energético de repouso (GER), gasto energético de atividade (GEA) e gasto pós-prandial (GEPP), desempenham papéis distintos e têm proporções variadas na manutenção do equilíbrio orgânico. Nesse sentido, o GEPP, também conhecido como efeito térmico dos alimentos (ETA), é o responsável por toda energia despendida após a ingestão de uma refeição, correspondendo ao processo de digestão, metabolização e transporte dos nutrientes e representando aproximadamente 10 a 15% do gasto energético total (GET) diário (Loffler et al., 2021; Ho, 2018; Hall; Guo, 2017).

Alguns fatores externos e internos aos indivíduos podem contribuir para aumentar ou reduzir o impacto no ETA, o que, por sua vez, pode afetar a resposta ao excesso de peso. No entanto, apesar do conhecimento existente sobre o ETA, esses fatores ainda são lacunas a serem exploradas na literatura. Portanto, a compreensão desses fatores se faz essenciais para estabelecer o ETA como um alvo terapêutico no controle dessa comorbidade (Du et al., 2014; Calcagno et al.; 2019). Revisões sistemáticas, em especial as metanálises e metarregressões, são capazes de fornecer evidências mais consistentes e concisas sobre determinado problema a ser investigado. Neste sentido, as atuais e elegantes revisões sistemáticas existentes na literatura, perpassam o tempo e deixam algumas destas lacunas fora de seus escopos (Quatela *et al.*, 2016; Park *et al.,* 2020).

Desta maneira, o presente estudo auxiliará nas respostas que tais fatores podem exercer no efeito termogênico do gasto energético após ingestão de uma refeição e permitirá obter conclusões efetivas sobre o ETA como estratégia de prevenção e tratamento do excesso de peso.

Assim, esta dissertação encontra-se dividida em duas seções: 1) revisão da literatura, abordando sobre o metabolismo energético, o efeito térmico do alimento e suas formas de mensuração; 2) artigo original que teve como objetivo de analisar o impacto de diferentes características biológicas dos indivíduos e nutricionais das refeições no ETA em humanos por meio de uma revisão sistemática com metaregressão de ensaios clínicos.

REVISÃO DA LITERATURA

2. REVISÃO DA LITERATURA

2.1 METABOLISMO ENERGÉTICO

A energia necessária para funcionalidade do organismo vivo chama-se adenosina trifosfato (ATP), molécula que fornece energia, denominada energia química, e utilizada após conversão por meio de cascatas bioquímicas (Ho, 2018). A produção de energia é obtida através da combustão de nutrientes, como carboidratos, proteínas, gorduras e/ou álcool. Durante esta dinâmica ocorre a troca dos gases oxigênio e gás carbônico, gerando gasto energético e produção de calor. A este processo, chamamos de metabolismo energético (Westerterp; Schols, 2008).

Organismos vivos obedecem, ou deveriam obedecer, a lei da conservação da energia, primeira lei da termodinâmica. Um balanço energético adequado deve-se ao equilíbrio entre entrada e saída de energia, isto é, uma equação subtraída entre ingestão de energia (por meio da alimentação) e o gasto energético (por meio dos processos bioquímicos). No entanto, esta "obediência" tem entrado em questionamento na literatura, principalmente em investigações que estudam a regulação do peso corporal em humanos (Galgani; Ravussin, 2008; Piaggi *et al.*, 2017).

O gasto energético total diário (GET) de um indivíduo corresponde a toda energia despendida em um dia para se manter em repouso (GER), para todo o trabalho realizado durante atividades físicas (GEA), espontânea ou sem exercícios, e em todo o processo de metabolização dos alimentos, o gasto energético pós-prandial (GEPP) (Hall; Guo, 2017).

O gasto energético de repouso é a energia necessária para manter as funções biológicas vitais enquanto um individuo está em descanso, em jejum e à temperatura ambiente e, comumente, pode englobar o gasto durante o sono e excitação e pode corresponder a aproximadamente 50-70% do GET. Este componente pode ter como principais determinantes a idade, o sexo, a composição corporal, hormonal e ação do sistema nervoso simpático

(Westerterp, 2022; Soares; Müller, 2018; Swinburn; Ravussin, 1994). Comparado ao GER, o segundo maior contribuinte para o GET é o relacionado às atividades (GEA). Embora seja o mais variável, este componente pode colaborar com 20 a 40% no gasto diário, a depender do nível de atividade física – comportamento sedentário, estilo de vida leve, moderada, ativa ou extremamente ativa –, ao tamanho e peso corporal, porém, não aumenta de forma linear com o aumento da atividade física (Westertep, 2022; Wolrd Health Organization, 2000).

2.2 EFEITO TÉRMICO DO ALIMENTO

O efeito térmico do alimento (ETA), também conhecido por GEPP, pode ser chamado por ação dinâmica específica (ADE) ou termogênese induzida pela dieta (TID). O ETA é o incremento de energia despendida sobre o GER e pode contribuir com 10 a 15% do GET, com um pico máximo entre 1 e 2 horas após ingestão (Figura 1). Este componente é comumente dividido em dois segmentos: 1) obrigatório - relacionado a todo o processo de digestão, transporte, absorção e armazenamento dos nutrientes, e 2) facultativo – pertinente à temperatura corporal relacionada à energia térmica (Ho, 2018; Hall; Guo, 2017).

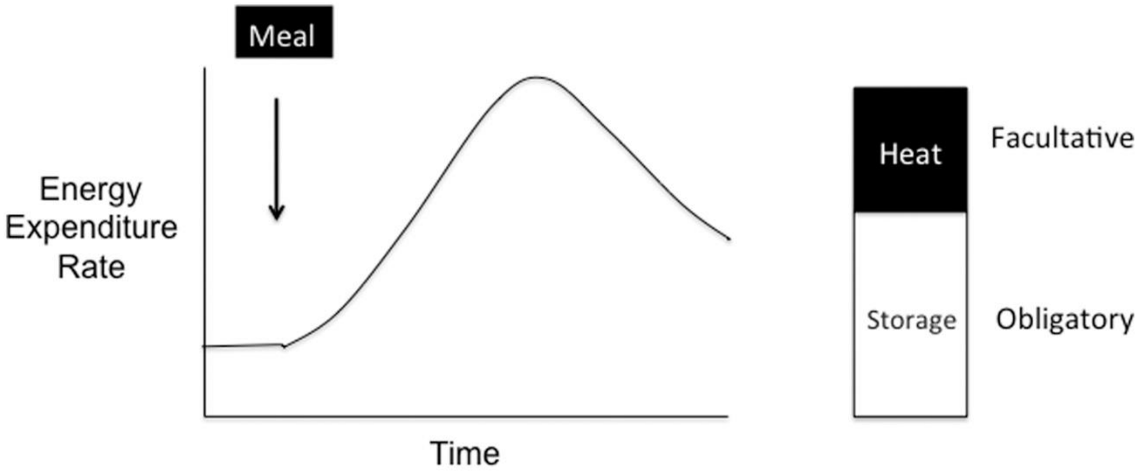

Figura 1. Representação do Efeito Térmico do Alimento após ingestão de uma refeição.

Fonte: Ho (2018).

Alguns elementos são tidos como influenciadores da variação desse efeito termogênico, porém, ainda existem divergências na literatura acerca do real impacto sobre o ETA. As características referentes aos alimentos/refeições são os principais fatores estudados, embora ainda com lacunas, como o conteúdo energético, composição nutricional e tipo de refeição (Westerterp, 2004; Quatela *et al.*, 2016; Park *et al.*, 2020). Apesar da resposta termogênica parecer estar mais associada a esses componentes, outros aspectos, como os biológicos, também são relatados como potenciais atores na resposta pós-prandial, são eles: idade, sexo e estado nutricional (De-Jonge; Bray, 1997; Calcagno *et al.*, 2019; Isacco; Miles-Chan, 2018).

2.2.1 Conteúdo energético e macronutrientes

As características das refeições também é um ponto de investigação. Já é bem estabelecido que o conteúdo energético pode influenciar no aumento do ETA, isto é, quanto maior a ingestão energética advinda da dieta, maior será a resposta no GEPP (Kinabo; Durnin, 1990; Ritcher *et al.*, 2020). Uma revisão sistemática, que analisou 35 estudos para comparar o ETA em diferentes ingestões energéticas, revelou que maiores ingestões são capazes de impactar positivamente no GEPP, mesmo como um aumento de pequena magnitude (Quatela *et al.*, 2016).

A distribuição dos macronutrientes parecem exercer alguma implicação na termogênese alimentar. Dentre esses macronutrientes, as proteínas parecem contribuir com maiores aumentos no ETA quando comparado aos carboidratos e lipídios (Johnston; Day; Swan, 2002; Sutton *et al.*, 2016). Os carboidratos, por sua vez, se sobressaem em relação aos lipídios (Kinabo; Durnin, 1990), e estes últimos tendem a diminuir os efeitos da termogênese pós-prandial (Nagai; Sakane; Moritani, 2005). No entanto, o estudo de Raben *et al.* (2003) mostrou que não houve diferença no ETA entre as refeições com carboidratos e lipídios e com densidades energéticas semelhantes. Diante do exposto, percebe-se que esses nutrientes tendem a induzir resposta térmica, porém ainda há divergências sobre o quanto e como estes nutrientes podem sensibilizar o ETA.

2.2.2 Grau de processamento

O tipo de refeição também é mencionado como potencial descritor da TID. A discussão entre graus de processamentos tem sido pautada entre autores como possível ponto crítico para respostas mais ou menos abrandados na TID, devido ao processo de refinamento da fabricação. Barr e Wright (2010) encontraram uma menor resposta termogênica após intervenção com alimentos ultraprocessados (AUP) quando comparadas às refeições integrais. Embora Mohr *et al.* (2020) encontraram resultados contrários. Outro estudo revelou que não houve diferença no ETA ao comparar refeições com e sem ultraprocessamento (Dioneda *et al.,* 2020). Esse conflito ainda é ponto de questionamento e, devido ao crescente consumo desses AUP e sua associação com o excesso de peso, merece ser mais explorado.

2.2.3 Idade

A literatura é controversa em relação à influência do envelhecimento no ETA. Algumas pesquisas indicam que o avançar da idade é capaz de levar a uma redução da resposta termogênica (Morgan; York, 1983; Du *et al.,* 2014), enquanto outros estudos não identificaram qualquer impacto significativo da idade (Das, 2001; Roberts *et al.,* 1996). Diversas hipóteses foram propostas para explicar essa possível diminuição no efeito térmico associado ao envelhecimento, destacando-se a atuação do sistema nervoso simpático e a menor atividade do tecido adiposo marrom, com menor quantidade de massa magra, conforme apontado em estudos anteriores (Jones *et al.,* 2004; Yoneshiro *et al.,* 2012).

2.2.4 Sexo

O fator sexo parece exercer influência sobre o ETA, com o sexo feminino demonstrando certa desvantagem em comparação ao masculino. Supõe-se que esses efeitos estejam associados a questões hormonais ou a uma resposta reduzida do sistema nervoso simpático às refeições. No entanto, a literatura ainda apresenta algumas inconsistências nesses achados, o que requerem uma investigação mais aprofundada (Gougeon *et al.*, 2005; Wu; O'Sullivan, 2011; Isacco; Miles-Chan, 2018).

2.2.5 Índice de massa corporal

O índice de massa corporal (IMC) também é alvo de controvérsia quando se questiona qual o estado nutricional estaria associado aos maiores aumentos no ETA. A obesidade parece apresentar valores inferiores de efeito termogênico após o consumo de uma refeição (De-Jonge; Bray, 1997). No entanto, um estudo com homens obesos e não obesos não observou diferenças significativas entre os grupos após a ingestão de uma dieta rica em gordura (Imbeault *et al.*, 2001), assim como em mulheres magras ou obesas após a ingestão de uma dieta rica em proteínas ou gorduras (Tentouloris *et al.*, 2008). Acredita-se que, se essas diferenças existirem, elas estão possivelmente relacionadas ao tempo de mensuração do ETA, bem como à composição corporal e ao percentual de massa magra (De-Jonge; Bray, 1997; Carneiro *et al.*, 2016).

A importância do conhecimento sobre este componente cresceu em detrimento do avanço da prevalência da obesidade, tendo em vista que esta condição vem, ao longo das décadas, se tornando um problema de saúde pública mundial. Tendo em vista o desequilíbrio energético propagado na obesidade – aumento da ingesta e redução do gasto energético – este é o componente intrinsecamente associado às questões alimentares, e por isso se tornou alvo de investigações na literatura (Granata; Brandon, 2002; Quatela *et al.*, 2016; Dioneda *et al.*, 2020)

2.3 FORMAS DE MENSURAÇÃO

O gasto energético (GE) pode ser mensurado por meio da produção e perda de calor, (calorimetria direta - CD) ou do consumo de oxigênio e produção de gás carbônico, (calorimetria indireta - CI) (Westerterp; Schols, 2008). Além disso, existem outras técnicas que podem ser empregadas, como água duplamente marcada, medições por meio da frequência cardíaca, eletromiografia e ventilação pulmonar. No entanto, essas últimas são menos utilizadas e não se aplicam para a mensuração do efeito térmico do alimento (ETA), devido à baixa acurácia e confiabilidade (Calcagno *et al.*, 2019; Levine, 2005).

Os métodos calorimétricos são mais empregados, a CD é considerada padrão-ouro para mensuração do GE e ETA, porém menos acessível devido ao alto custo. Consiste na quantificação de calor de todo o corpo, de forma não invasiva, utilizando uma câmera metabólica. Já o método indireto, bastante difundido em pesquisas científicas, corresponde a um procedimento não invasivo baseado na mensuração do consumo e produção de gases utilizando circuitos abertos ou fechados, além da aplicação de equações preditivas, e, assim, estimar o valor do objeto em questão. Estes métodos podem ser empregados em diversas condições clínicas ou investigativas, permitindo medir a produção de energia pelo metabolismo, bem como o gasto advindo de todos os processos fisiológicos (Delsoglio *et al.*, 2019; Kenny; Notley; Gagnon, 2017; Achamrah *et al.*, 2021; Lam; Ravussin, 2016).

3. ARTIGO ORIGINAL

ALMEIDA, KMM; GALDINO-SILVA, MB; PAULA, DTC; CARVALHO, GCO; BARROS, MR; REIS, TCG; MACENA, ML; BUENO, NB. **Impact of individuals' biological and meals' nutritional characteristics on the thermic effect of food in humans: meta-regression of clinical trials.** Artigo submetido à revista Metabolism: Clinical and Experimental (Classificação A1 segundo critérios do Sistema Qualis da CAPES / Área de Nutrição).

Title: Impact of individuals' biological and meals' nutritional characteristics on the thermic effect of food in humans: meta-regression of clinical trials.

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ABSTRACT

The thermic effect of food (TEF) is subject of intense research as a possible therapeutic target for the prevention and treatment of excess weight. This systematic review sought to analyze the impact of different biological and nutritional characteristics on TEF in humans. MEDLINE/PubMed, Embase, CENTRAL, Web of Science and LILACS databases and platforms were searched until November 2023, without language restrictions. Clinical trials, with adult and elderly individuals, in a fasting state, offering a test meal orally and investigating TEF by calorimetry were included. The mean TEF of each group was the outcome and the impact of age, sex, BMI, of the individuals and energy content, percentage of macronutrients and degree of food processing of the meals on the TEF was assessed using metaregression analysis. A total of 133 studies were included, with 4139 individuals and 321 groups. TEF was higher between 60 and 120 minutes after a test meal (262.48 kcal/day; 95%CI: 242.40; 282.56 kcal/day; n = 133; 1636 individuals), as well as in males, individuals in normal BMI range, and meals with mixed degrees of food processing. The energy content of meals was the variable more strongly associated with TEF. The percentage of carbohydrates in the meals showed no relationship with TEF, while only the proportion of lipids showed a negative relationship with TEF in the main analysis, including all groups. The proportion of proteins was positively related to TEF only in the subgroup of meals with < 1000 kcal. TEF peaks between one and two hours after a meal and is strongly influenced by energy content of the meal and sex. BMI showed an inconsistent association while age was not associated with TEF. Food processing degree of the meal seems to play a role on TEF. Lipids appear to be the macronutrients most consistently related to TEF, whereas protein content of the meal showed association only in meals <1000kcal.

Keywords: Energy metabolism; Eating; Energy intake; Thermogenesis; Systematic review.

1. Introduction

Energy metabolism is the subject of intense research in the scientific field, mainly in discussions about the prevention and treatment of excess weight [1]. Increased energy intake at the expense of reduced energy expenditure favors the development of adiposity and, in the long term, obesity. Energy homeostasis requires a balance between energy intake and expenditure for better body weight control. A disharmony in this balance, however, leading to a negative state, is the only way to reduce excess weight [2].

The energy expended by an individual to carry out all activities during a day is defined as total energy expenditure (TEE). This metabolic component encompasses three elements, in order of contribution: resting energy expenditure (REE), physical activity expenditure (PAEE) and postprandial expenditure (PPEE) or thermic effect of food (TEF) [3].

Considering that food, like oxygen, is a vehicle of energy, fundamental for maintaining the metabolic vitality of the organism [4], understanding TEF is extremely important. The specific dynamic action of food, as TEF is also known, corresponds to the energy dissipated for the entire process of digestion, metabolization, transport and storage of nutrients after consumption of a food or meal. Its contribution to energy expenditure can vary between 10 and 15% of TEE, with a peak 1-2 hours after ingestion, and being influenced by internal and external factors to the individual [5,6].

The magnitude of TEF seems to undergo positive and negative influence of 1) the energy quantity of the meals; 2) nutritional composition – intake of carbohydrates and proteins resulting in a higher PPEE to the detriment of fats, as well as the presence of dietary fiber; 3) nutritional status – individuals with obesity seem to express a reduced TEF, especially when associated with insulin resistance; 4) age 5) sex and 6) level of food processing [6-8]. Although the relevant reviews by Quatela et al. (2016) [9] and Park et al. (2020) [10] have investigated some of these elements, the amount of time elapsed since the former study, and the lack of meta-analysis in the latter study, lead to the need for a deeper and more systematic analyzes in order to explore the impact of such variables on TEF.

Therefore, aiming for a broader explanation of such divergences, the absence of systematic reviews that allow effective conclusions, and the need to establish TEF as a possible therapeutic target for the prevention and treatment of excess weight, the present study aims to assess the impact of different biological characteristics of individuals and nutritional characteristics of meals on TEF in humans, through a systematic review with meta-regression of clinical trials.

2. Methods

This review is registered in the International Prospective Register of Systematic Reviews (PROSPERO) under number CRD42023432504 and follows the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [11].

2.1. Search strategy

The databases and platforms searched were: MEDLINE/PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science (WoS) and Latin American and Caribbean Health Sciences Literature (LILACS). Articles published up to November 2023 were identified. The search strategy used terms indexed in MeSH (Medical Subject Headings) and DeCS (Health Sciences Descriptors): thermic effect of food, thermic effect of feeding, thermogenic effect of food, specific dynamic action, dietary induced thermogenesis, diet* induced thermogenesis, meal-induced thermogenesis, using the Boolean operator “OR”. The term “humans” was used as a filter to include studies only in humans. There were no time or language restrictions.

2.2. Eligibility Criteria

Only clinical trials were included, including adult and/or elderly individuals, in a fasting state (≥ 8h, “overnight fast” or the term “fasting”), and offering only one oral meal, as well as measurements carried out using direct or indirect calorimetry. Studies with a liquid consistency meal, measurements over ≥24 hours, more than one meal, and with physical activity or exercise in conjunction with the meal, were not included. Athletes, pregnant women, breastfeeding women, hospitalized individuals, and those with chronic diseases (except systemic arterial hypertension, diabetes mellitus, metabolic syndrome, asthma and glycemic and lipid changes) were also not included.

2.3. Data extraction

The data was extracted and reviewed by six authors, so that each article was read by two researchers; in case of disagreement, a third author was used to break the tie. The Rayyan Qatar Computing Research Institute (Rayyan QCRI) software was used to manage references and extract data of interest. An electronic spreadsheet was created to organize the collected data (outcome and complementary variables). The thermic effect of food (TEF) was the outcome sought, expressed as a delta (Δ), that is, the result of postprandial energy expenditure subtracted from resting energy expenditure (REE), in kcal/min.

Other variables were extracted as complementary data to characterize the studies: country, year of publication, type of clinical trial, washout period (crossovers), fasting time, sample size, sex, age, body mass index (BMI), body weight, participant characteristics (allocation group and intervention offered), presence of comorbidities, and meal offered (name, consistency, energy content and distribution, component foods and consumption time). The name of the meal could be obtained from either the term used in the study or estimated from the time at which the meal was offered. When the distribution of macronutrients in the test meals was not stated, a conversion was performed using 4, 4, 9 kcal/gram of the macronutrient to discover the percentages of carbohydrates, proteins and lipids, respectively, and when presented in a range, it was used the percentage average.

Furthermore, we also extracted the REE, presented in kcal/min, the moment of measurement, calorimetry time and the method used to measure/quantify the REE (direct or indirect calorimetry). The factor 4.196 was used as a conversion factor from kilojoule (kJ) to kcal and 1440 to extrapolate TEF from min to 24 hours (kcal/min to kcal/day). The TEF results when presented in graphs were taken by estimation using the GetData Graph Digitizer program (v. 2.26, S. Fedorov).

The types of interventions used in the studies were identified, aiming to evaluate the most predominant characteristics. The analysis of meal processing degree followed the NOVA classification [12] and for the categorization of "processed" and "unprocessed" we used the complete presence or absence, respectively, of processed and/or ultra-processed foods, and "mixed" when there was the presence of both categories. Furthermore, we stratified the energy content of the test meals offered by the studies into 3 ranges: ≤500, 501-1000 and >1000 kcal, to check whether there were changes in the impact of macronutrient composition on the TEF. Studies that did not present TEF results were excluded from the quantitative analysis.

2.4. Risk of bias analysis

The included studies were analyzed for risk of bias by two evaluators, independently, using the Cochrane RoB 2 (Risk of Bias in randomized trials) [13] tools for randomized trials and ROBINS-I (Risk Of Bias in Non-randomized Studies - of Interventions) for non-randomized trials[14]. Disagreements were resolved by consensus between the evaluators and, if needed, a third evaluator was contacted. These instruments are composed of domains, related to the type of study, conduction and results, expressed in the form of questions. Domains are judged as "low" or "high" risk of bias, or "some concerns", for RoB2, and "low", "moderate", "severe" or "critical" risk, for ROBINS-I.

2.5. Statistical analysis

We grouped the results using a random effects meta-analysis based on the Der-Simonian and Laird method, assigning weight to studies according to the inverse variance model, using Stata v.12 software (StataCorp, College Station, TX, USA). Heterogeneity was assessed using relevant statistical measures, such as the inconsistency index (I^2) and tau^2. Meta-regression analyzes were used to investigate the relationship between age (years), BMI (kg/m^2), meal energy content (kcal), and percentage of macronutrients in the test meal with TEF. All analyzes were grouped according to the measurement time reported in the studies (60 min, 61-120 min, 121-180min and 181-240min). We adopted an alpha value of 5% for all analyses.

3. Results

A total of 3094 occurrences were identified through database searches and of these, 1351 were excluded because they were duplicates. After screening by titles and abstracts, 617 occurrences had their full texts acquired for complete reading, and of these, 474 did not meet the eligibility criteria (type of publication, study design, population, consistency of the test meal, measurement in 24 hours, time fasting, different methods and lack of TEF data). Thus, 143 articles from 133 studies were included in this review, with 321 research groups in total (Figure 1).

3.1. Characteristics of the included studies

Regarding the general characteristics of the studies, 89 studies were randomized trials, 44 were non-randomized trials. A total of 4139 participants were evaluated and the average REE was 1555.78 with a standard deviation of 315.45 kcal/day. It was observed that fasting time between 8 and 12 hours, breakfast as a test meal, indirect calorimetry, TEF carried out between 181 and 240 minutes after ingestion of the meal and the period $\geq$ 30 minutes for measurement on the calorimeter were the most used methods. In relation to the researched groups, there was a predominance of adult individuals, males, without comorbidities, body mass index <25kg/m2, test meal consumption time ≥ 15 minutes, with presentation between 500 and 1000 kcal per meal, percentage of carbohydrates ≥ 45%, proteins ≥ 15% and lipids < 35% and mixed meals, regarding the degree of food processing (Table 1 and 2).

3.2 Risk of Bias Analysis

A total of 89 randomized studies were analyzed, of which 19 presented low risk, 52 some concerns and 18 high risk of bias. In the evaluation of non-randomized studies, all 44 were considered to be at moderate risk. The domains related to the lack of outcome data, measurement and selection bias were the main reasons why the studies presented moderate/high risk. Factors such as a lack of clarity in details related to outcome assessors, incomplete data, and a scarcity of pre-established research protocols were the most evident limitations (Appendix A and B).

3.3. Meta-analysis

For measurements of up to 60 minutes, 129 studies were included, with 1707 individuals and the TEF found was 261.75 kcal/day (95%CI 235.98; 287.51 kcal/day; $I^2 = 98.5\%$; $p < 0.001$); between 61-120 min, the average TEF was 262.48 kcal/day (95%CI 242.40; 282.56 kcal/day; n = 133; 1636 individuals; $I^2 = 96.8\%$, $p<0.001$). In the period between 121 and 180 min, the average was 244.45 kcal/day (95%CI 225.02; 263.87 kcal/day; n = 146; 1918 participants; $I^2 = 96.2\%$; $p<0.001$) and from 181-240 minutes it was 217.61 kcal/day (95%CI 191.06; 244.16 kcal/day; n = 111; 1347 participants; $I^2 = 98.9\%$; $p<0.001$) (Table 3).

3.4. Subgroup meta-analyses

Regarding sex and BMI, the meta-analysis showed that males have a higher TEF in the first two hours after eating a meal and the normal BMI classification has a greater expenditure, regardless of the measurement time ($p<0.01$). Mixed meals, regarding the degree of food processing, had a significantly higher TEF in the first 60 minutes of measurement ($p=0.03$). There were no significant differences between the adult and elderly subgroups (Table 3).

3.5. Meta-regression

The results of the meta-regression showed no significance of the mean BMI and age at TEF, at any of the measurement moments. However, the relationship between TEF and the average content of the meals offered was significant ($p<0.001$) in all periods analyzed. Regarding the macronutrient composition of the meals, considering the analysis with all meals, there was also no statistical significance of the average percentage of carbohydrates (%CHO) and proteins (%PTN) on the TEF, at any of the moments. However, the percentage of lipids (%LIP) showed a negative statistical association with TEF during the first two hours after a meal ($p<0.05$) (Table 4).

When analyzing meals according to energy ranges (≤500, 501-1000 and >1000 kcal), it was observed that %CHO did not show a statistical relationship with TEF in any of the three ranges. In the range of meals up to 500 kcal, %PTN showed a positive relationship with TEF only between 181 and 240 min ($p=0.002$), while %LIP showed a significant negative association consistently with TEF, except in the moment between 61 and 120 min. In the 501-1000 kcal category, %PTN was positively associated with TEF in the first three hours and %LIP negatively up to 120 min and from 180 to 240 min. No macronutrient was associated with TEF in the category of meals with energy content >1000 kcal (Table 5).

4. Discussion

This review identified 133 studies, with 321 different groups, that analyzed TEF as a result of test meal interventions. After the meta-analysis, we found that TEF was higher in the time between 60 and 120min after a meal (262.48 kcal/day), corroborating the literature [5], as well as showing a greater magnitude among men, individuals with normal weight and in mixed meals in terms of degree of food processing, but without age effects. However, the findings showed high heterogeneity (I2 > 90%). With the meta-regression it was possible to observe the striking positive relationship between TEF and the energy content of the meals offered, as already demonstrated in the literature. Furthermore, our results showed that %CHO was not related to TEF under any condition of moment or energy content of the meal, while %PTN and %LIP were positively and negatively related to TEF, but only in meals with up to 1000 kcal. Surprisingly, the association between %PTN and TEF was not as established as expected, having been consistently present only in the subgroup of meals between 500-1000 kcal of energy content, showing no relationship with TEF in the analysis involving all meals. On the other hand, %LIP showed a consistent negative relationship with TEF in the analysis involving all meals in moments up to 60 minutes and up to 120 minutes, as well as showing a negative association in all measurement moments in meals between 500 and 1000kcal. The analysis of the risk of bias of the randomized studies revealed that 21.35% were considered low risk, however this classification was not noticeable in any of the non-randomized studies, all of which were assessed as moderate risk.

4.1. Biological characteristics of the individuals

4.1.1 Body mass index

After the meta-analysis of subgroups, this review found that TEF differed between BMI classifications, showing greater energy expenditure in individuals with normal BMI, however, at the end of the meta-regression analysis, no significant relationship was evidenced when using the average BMI in its continuous form. Several studies provide conflicting results. The review by De-Jonge and Bray (1997) [15] analyzed 29 studies between individuals with and without obesity and demonstrated a reduced TEF in those with obesity, however it was seen that this significance could be related to the presence of insulin resistance and changes in sympathetic nervous system. Carneiro et al. (2016) [16] reported that methodological differences between studies can result in divergences found in the literature, and consequently in the lack of consistency of findings. According to the authors, the duration of TEF measurement, for example, may be an influencing factor, since individuals with obesity have a prolonged absorptive state. There are arguments that body composition and the amount of fat-free mass can also clarify these divergences, however, more studies are needed [16,17], and body composition was outside the scope of our study.

4.1.2 Age

Age is supposedly among the factors that can influence the degree of TEF, in which the aging process can contribute to greater impairment in thermogenesis [6]. This hypothesis contradicts the results of our meta-analysis since the age variable was not statistically related to TEF. It is important to highlight that the proportion of studies included in this review was notably different involving the two age groups, being more predominant in adults. The recent review by Miles-Chan and Harper (2023) [18] reported that this factor is still controversial. Studies with elderly individuals are warranted.

4.1.3 Sex

The disparity between sexes is still inconsistent, but a trend towards a lower TEF is found in females, which was similar to the results of our meta-analysis. Still conflicting in the literature, hormonal issues linked to sex have been the main hypothesis of this differentiation, focusing on the process of oxidation and fat storage [19]. Female individuals seem to have greater efficiency in this storage, even with a lower energy intake, due to estrogenic action [20]. Perhaps for this reason, males have a greater TEF.

4.2 Nutritional characteristics of the meals

4.2.1 Degree of food processing

Regarding the food processing degree in the test meals, after the meta-analysis, higher values were observed, in general, in meals composed of processed foods (mixed or exclusive type), however, with a significant result only in the first hour of measurement. A systematic review with meta-analysis and meta-regression, conducted by Quatela et al. (2016) [9], reported only one study that evaluated the effects of the degree of processing. Individuals who consumed the whole meal showed a significant increase in TEF. The effects of the degree of processing on TEF are still controversial, as it is believed that this procedure contributes to the simplification of the food structure, as it results in the loss of dietary fiber, requiring less metabolization work and favoring a reduction in TEF [21,22]. However, this possible mechanism requires further investigation.

4.2.2. Energy content and macronutrients

The energy content of the meal was directly related, significantly, to the TEF results, that is, the greater the amount of kcal ingested, the greater the thermogenic response. Furthermore, protein and lipid fractions were directly and inversely associated, respectively, with TEF, but not in all scenarios investigated.

Similar findings were found in a review, without meta-analysis, carried out by Calcagno et al. (2019) [6], in which a higher TEF can be induced after consuming meals with high energy content and meals rich in proteins and carbohydrates. In another review, it was noted that an increase in energy intake by 100 kJ (23.90 kcal) contributed to an increase of 1.1kJ/h (0.26 kcal/h) in TEF, as well as greater results after consumption of meals rich in these nutrients, when compared to lipids [9], although our results did not show an association with carbohydrates. Further corroborating our findings, Westerterp (2004) [23] reported that the energy content of the meal is a determinant of TEF, as well as the protein fraction of the diet. A review conducted by Park et al. (2020) [10], in individuals with obesity, concluded that the results in this population were not constant between studies, however, the possible differences in TEF were related, among other findings, to the proportions of macronutrients, with a disadvantage for the percentage of fat in the diet.

It is also worth highlighting that the effects of macronutrient percentages on the TEF in this review are evident in meals with up to 1000 kcal. On the other hand, the proportion of macronutrients does not seem to have contributed in meals with an energy content above 1000 kcal. It is believed that the participation of macronutrients in this component of energy expenditure is similar to the oxidation process of energy substrates, with proteins being primarily oxidized and making the greatest contribution to increasing TEF, followed by carbohydrates and lipids. Furthermore, among macronutrients, proteins require a greater energy demand for their metabolism [23]. However, we found unexpected results, since the proportion of proteins in the meal was related to TEF only in specific subgroup analyses, whereas the proportion of lipids in the meals showed a consistent negative association with TEF in all analysis.

4.3. Limitations

This review has some limitations: 1) the methodological variations of the studies, mainly related to the measurement time, contributed to a smaller number of studies being included in the meta-analysis; 2) variations in expressions of results to report TEF (area under the curve, respiratory coefficient, volume of oxygen consumption, and % above BMR) reduced the number of studies grouped to perform statistical analyses; 3) the heterogeneity of the energy content of the test meals may have led to variability in the results, therefore, it was decided to stratify the contents of these meals into 3 categories and, thus, obtain more reliable results and 4) the limitation of the inclusion criteria, such as: liquid meals, specific physiological conditions (pregnant women, athletes, hospitalized individuals), measurement of TEF over 4 hours and other measurement methods (other than calorimetry).

We chose to include only solid meals as they are metabolized differently than liquids, especially in terms of time and work spent during the process [21]. Furthermore, the aim of this review was to evaluate the effects of TEF in common clinical conditions. Measurements over 4 hours were generally accompanied by more than one test meal, which would make it difficult to obtain TEF after ingesting a specific meal, and measurements taken less than 6 hours may be sufficient to reach TEF responses [24,25]. Restricting other measurement methods was necessary since the number of studies found with these characteristics was small and did not allow them to be grouped for analysis purposes.

On the other hand, this review has some strong points: the non-restriction of time for publication of studies, which guarantees a greater scope of findings and inclusion of different age groups and nutritional classes. These criteria allowed us to reach and consolidate evidence of the components intrinsic to individuals, factors that are scarce and little addressed in systematic reviews, but of fundamental importance in the knowledge of thermogenesis, and to delve deeper into the particularities of the meals offered that influence TEF.

5. Conclusion

From the consolidation and analysis of the studies present in this review, it is concluded that the TEF presents a peak value between 60 and 120 minutes after eating a meal, and it is higher in males and in individuals with normal BMI classification, although BMI was not associated with TEF in the meta-regression analysis only in the subgroup analysis. Age was not associated with TEF. Furthermore, the degree of food processing of the meals influenced thermogenesis during the first hour after the meal, whereas the energy content of the meal showed positive associations with TEF, regardless of the measurement time. The %PTN and %LIP were also associated, positively and negatively, respectively, with the TEF, however this relationship was more evident for lipids than for proteins, since in the analysis containing all meals, only lipids showed some significant association with TEF, while proteins showed no relationship. In the subgroup analysis, in meals with up to 500 kcal, proteins maintained an association with TEF only between 180 and 240 minutes whereas lipids showed an association for most of the time, except during the second hour of measurement; In meals with 500-1000 kcal, proteins maintained a relationship until the first 180 minutes and lipids until 120 minutes and between 180 and 240 minutes.

Despite the inclusion of some studies with low methodological quality and high heterogeneity, these results highlight the relevance of TEF as a potential therapeutic target. Future research with high methodological rigor is also highlighted, aiming to standardize measurement methods, time spent, kcal in meals, sample size and equitable proportion between age groups are warranted.

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Declaration of interest

The authors declare that there are at the conflicts of interest.

Author Contributions

NBB designed the project. KMMA, MBGS, MLM conducted the search. KMMA, MBGS, DTCP, GCOC, MDRB and TCGR extracted data. KMMA and MBGS assessed the risk of bias and study quality, write the first draft with input from NBB. NBB critically reviewed the manuscript. All authors read and approved the final manuscript.

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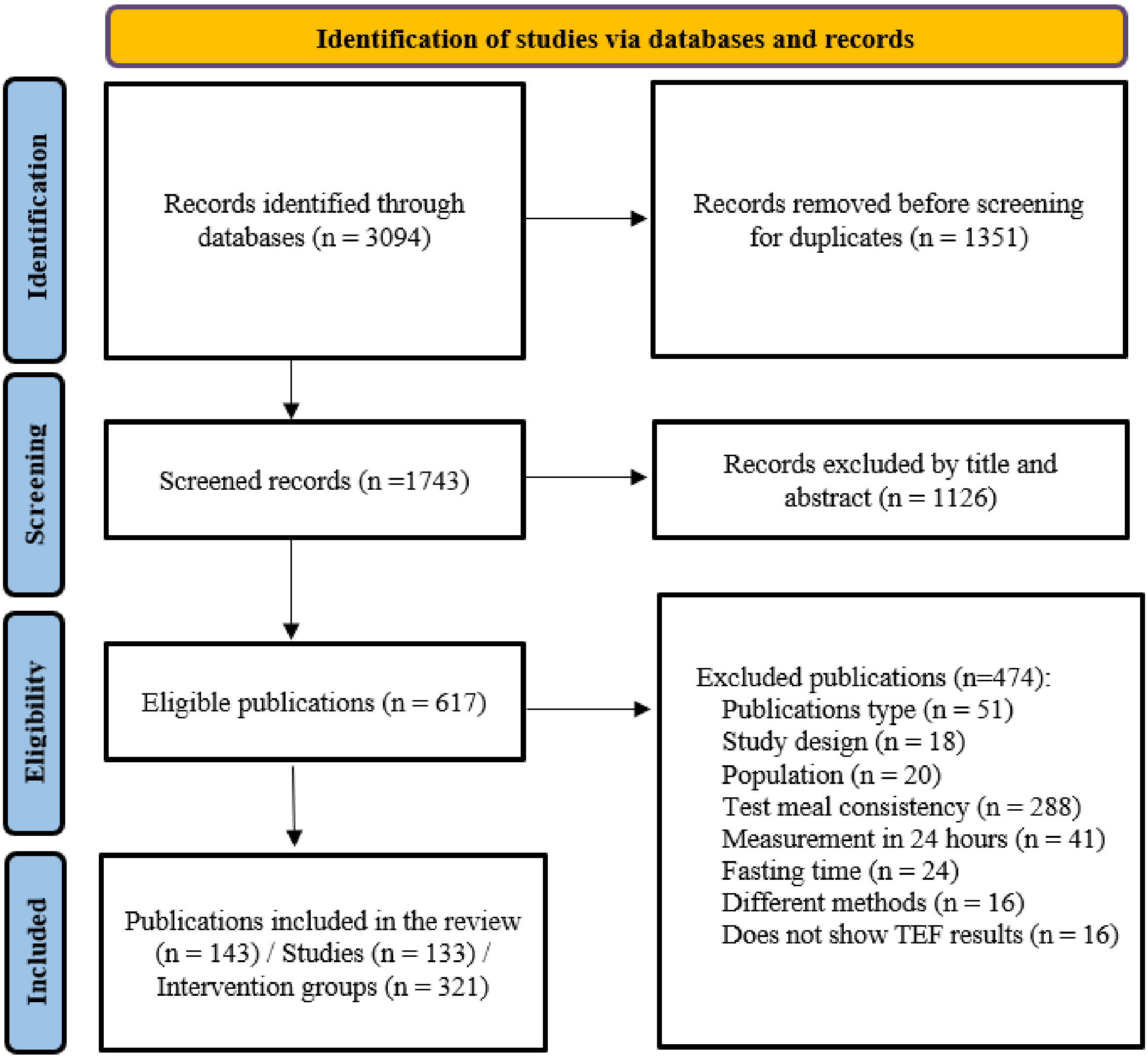


Figure 1. Flowchart of studies included in the review.

Table 1. Characteristics of selected studies (n= 133)

	n	%
Continent		
North America	59	44,36
South America	5	3,76
Asia	22	16,54
Europe	35	26,32
Oceania	11	8,27
South America and Europe	1	0,75
Study design		
Parallel	28	21,05
Crossover	90	67,67
Single group	15	11,28
Fasting time		
8 – 12 pm	101	75,94
> 12h	2	1,50
Overnight fast	16	12,03
Uninformed*	14	10,53
Test meal		
Breakfast	129	96,99
Lunch	3	2,26
Brunch	1	0,75
Characteristics of the interventions**		
High in carbohydrates	9	6,77
Low in carbohydrates	2	1,50
Low or high glycemic index	1	0,75
Distinct types of carbohydrates	5	3,76
High in proteins	5	3,76
Distinct types of proteins	3	2,26
Different protein proportions	7	5,26
High in fat	10	7,52
Low in fat	2	1,50
Distinct types of fats	15	11,28
Distinct lipid proportions	1	0,75
Hypercaloric	1	0,75
Distinct caloric densities	7	5,26
(Ovo)lactovegetarian	2	1,50
Whole, processed or gluten-free	1	0,75
Low or high in fiber	2	1,50
Combined characteristics	4	3,01
TEF measurement moment		
≤ 60 min after meal	5	3,76
61 – 120 min after meal	11	8,27
121 – 180 min after meal	24	18,05
181 – 240 min after meal	51	38,35

> 240 min after meal	29	21,80
Uninformed	13	9,77
Calorimetry time		
< 30 min	42	31,58
≥ 30 min	85	63,91
Uninformed	6	4,51
Measurement method		
Direct calorimetry	5	3,76
Indirect calorimetry	128	96,24

n: sample number; h: hours; min: minutes; TEF: thermal effect of the food. *Presence of fasting state, but period not specified. **Most common characteristics of test meals found in studies.

Table 2. Characterization of the research groups (n = 321)

	n	%
Age range		
Adults	249	77,57
Elderly	16	4,98
Mixed	29	9,03
Uninformed	27	8,41
Sex		
Male	125	38,94
Female	108	33,65
Mixed	88	27,41
BMI		
<25 kg/m²	162	50,47
≥ 25 kg/m²	107	33,33
Uninformed	52	16,20
Clinical conditions		
Asthma / SAH / Depression	3	0,93
Diabetes	2	0,62
Hypercholesterolemia	2	0,62
Metabolic syndrome	1	0,31
Hyperinsulinemia	2	0,62
No comorbidities	311	96,89
Energy content		
≤ 500 kcal	82	25,55
501 – 1000 kcal	135	42,06
> 1000 kcal	43	13,39
Uninformed	61	19,00
Energy distribution		
Carbohydrates		
< 45 %	110	34,27
≥ 45 %	164	51,10
Uninformed	47	14,64
Proteins		
< 15 %	125	38,94
≥ 15 %	149	46,42
Uninformed	47	14,64
Lipids		
< 35 %	142	44,24
≥ 35 %	132	41,12
Uninformed	47	14,64
Consumption time		
< 15 min	46	14,33
≥ 15 min	181	56,39
Uninformed	94	29,28

Meal classification		
Unprocessed	45	14,02
Processed	39	12,15
Mixed	181	56,39
Uninformed	56	17,45

n:sample number; BMI: body mass index; SAH: systemic arterial hypertension; kcal: kilocalories; min: minutes.

Table 3. Meta-analysis of TEF and subgroups according to sex, age group and BMI classification.

	Up to 60 minutes					Up to 120 minutes				Up to 180 minutes				Up to 240 minutes		
Condition	Groups (n)	Mean TEF (kcal/day)	CI95% (low;high)	p-value	**Condition**	Groups (n)	Mean TEF (kcal/day)	CI95% (low;high)	**Condition**	Groups (n)	Mean TEF (kcal/day)	CI95% (low;high)	**Condition**	Groups (n)	Mean TEF (kcal/day)	CI95% (low;high)
General	129	261,75	235,98; 287,51	<0,001*	133	262,48	242,40; 282,56	<0,001*	146	244,45	225,02; 263,87	<0,001*	111	217,61	191,06; 244,16	<0,001*
Sex	129			0,001*	133			0,001*	146			0,15	111			0,06
Male	49	314,99	266,36; 363,62		56	324,58	278,49; 370,68		52	273,64	235,04; 312,24		51	247,30	203,13; 291,48	
Female	55	219,89	193,03; 246,75		56	223,44	195,38; 251,49		56	222,99	188,21; 257,78		40	216,75	173,29; 260,20	
Mixed	25	266,94	246,87; 287,02		21	234,65	193,79; 275,50		38	241,03	208,81; 273,26		20	154,66	92,04; 217,27	
Age range	118			0,74	120			0,84	137			0,57	96			0,70
Adults	108	263,81	243,72; 283,89		110	256,44	234,25; 278,64		126	247,38	226,33; 268,42		81	216,57	189,39; 243,76	
Elderly	6	246,75	173,03; 320,47		8	256,03	186,67; 325,38		7	204,61	126,28; 282,93		11	187,62	115,87; 259,36	
Mixed	4	250,49	218,02; 282,96		4	247,95	229,16; 266,74		4	250,50	192,10; 308,90		4	206,94	188,40; 225,48	
BMI	83			<0,001*	83			<0,001*	89			<0,001*	60			0,001*
Malnutrition	2	141,79	-6,66; 290,26		2	77,42	-12,60; 167,46		2	88,18	-12,24; 188,61		2	115,20	-5,37; 235,77	
Normal	39	297,71	271,97; 323,45		38	301,65	270,36; 332,94		39	301,91	248,84; 354,98		26	261,85	193,74; 329,97	
Obesity	18	205,92	127,05; 284,78		15	244,13	222,06; 266,21		14	177,38	148,17; 206,58		10	189,97	133,85; 246,09	
Overweight/ Obesity	11	253,54	212,68; 294,39		12	240,22	189,10; 291,33		21	248,42	222,01; 274,83		7	113,40	85,96; 140,83	
Normal/ Overweight	13	189,65	151,25; 228,04		16	166,15	119,69; 212,61		13	122,28	81,97; 162,59		15	130,57	82,16; 178,98	
Degree of processing	121			0,03*	124			0,64	137			0,39	93			0,99
Processed	24	258,45	195,80;		21	245,62	210,90;		20	209,38	122,19;		16	196,19	150,17;	

			321,09			280,34			296,58			242,21
Unprocessed	23	204,52	153,33; 255,70	23	240,63	191,29; 289,98	23	225,59	181,23; 269,95	8	194,76	110,21; 279,31
Mixed	74	277,53	254,44; 300,62	80	262,17	235,64; 288,70	94	252,99	231,08; 274,89	69	194,80	170,28; 219,32

Groups: number of research groups; n: number of participants included; TEF: thermal effect of the food; BMI: body mass index. *$p<0.05$ was considered significant.

Table 4. Meta-regression analysis of subgroups according to age, BMI classification and composition of meals offered by the studies.

	n	β coefficient	CI95% lower	CI95% higher	p-value
Age (years)					
Up to 60min	123	-0,70	-2,62	1,20	0,46
61-120min	121	-0,03	-1,80	1,72	0,96
121-180min	138	-0,96	-2,99	1,05	0,34
181-240min	104	-0,58	-2,57	1,41	0,56
BMI (kg/m²)					
Up to 60min	111	-2,92	-8,07	2,21	0,26
61-120min	110	-1,46	-7,17	4,24	0,61
121-180min	131	-4,18	-10,10	1,73	0,16
181-240min	91	-3,02	-11,89	5,84	0,49
Energy content of the meal (kcal)					
Up to 60min	124	0,22	0,16	0,28	<0,001*
61-120min	118	0,27	0,21	0,34	<0,001*
121-180min	136	0,10	0,05	0,15	<0,001*
181-240min	95	0,28	0,19	0,36	<0,001*
CHO (%)					
Up to 60min	121	1,09	-0,13	2,31	0,08
61-120min	120	0,81	-0,43	2,06	0,19
121-180min	131	0,36	-0,89	1,62	0,57
181-240min	92	1,42	-0,78	3,63	0,20
PTN (%)					
Up to 60min	121	1,53	-0,34	3,41	0,10
61-120min	120	0,95	-1,01	2,93	0,33
121-180min	131	1,83	-0,12	3,80	0,06
181-240min	92	0,15	-3,89	4,20	0,93
LIP (%)					
Up to 60min	121	-1,76	-2,91	-0,60	0,003*
61-120min	120	-1,25	-2,49	-0,01	0,04*
121-180min	131	-1,17	-2,43	0,08	0,06
181-240min	92	-1,53	-3,73	0,66	0,16

n: number of research groups; min: minutes; BMI: body mass index. *$p<0.05$ was considered significant.

Table 5. Meta-regression analysis according to the range of energy content and composition of the meals offered by the studies.

	n	β coefficient	CI95% lower	CI95% higher	p-value
			0 - 500 kcal		
CHO (%)					
Up to 60min	46	1,22	-0,49	2,94	0,15
61-120min	38	0,30	-1,70	2,31	0,76
121-180min	37	1,67	-1,24	4,59	0,25
181-240min	39	-0,00	-2,61	2,61	0,99
PTN (%)					
Up to 60min	46	1,55	-0,31	3,43	0,10
61-120min	38	1,07	-0,92	3,08	0,28
121-180min	37	0,93	-1,94	3,80	0,51
181-240min	39	5,02	2,03	8,00	0,002*
LIP (%)					
Up to 60min	46	-2,60	-4,06	-1,13	0,001*
61-120min	38	-1,47	-3,48	0,53	0,14
121-180min	37	-3,08	-6,08	-0,07	0,04*
181-240min	39	-2,95	-5,46	-0,043	0,02*
			501 - 1000 kcal		
CHO (%)					
Up to 60min	55	1,14	-0,55	2,85	0,18
61-120min	56	0,71	-0,82	2,24	0,35
121-180min	64	-0,15	-1,55	1,24	0,82
181-240min	37	3,27	-0,33	6,88	0,07
PTN (%)					
Up to 60min	55	6,30	1,84	10,76	0,006*
61-120min	56	7,90	4,20	11,61	<0,001*
121-180min	64	8,56	5,29	11,83	<0,001*
181-240min	37	0,60	-9,39	10,59	0,90
LIP (%)					
Up to 60min	55	-2,00	-3,68	-0,33	0,02*
61-120min	56	-1,69	-3,21	-0,16	0,03*
121-180min	64	-0,89	-2,31	0,52	0,21
181-240min	37	-3,99	-7,90	-0,09	0,04*
			> 1000 kcal		
CHO (%)					

Up to 60min	16	-0,55	-3,70	2,58	0,70
61-120min	19	-0,82	-3,38	1,74	0,50
121-180min	25	-0,08	-2,32	2,15	0,93
181-240min	11	-2,03	-6,06	1,98	0,28
PTN (%)					
Up to 60min	16	-2,05	-8,44	4,33	0,50
61-120min	19	-1,89	-7,74	3,95	0,50
121-180min	25	-3,57	-7,64	0,48	0,08
181-240min	11	-3,65	-20,57	13,26	0,63
LIP (%)					
Up to 60min	16	1,02	-1,98	4,03	0,47
61-120min	19	1,25	-1,27	3,79	0,31
121-180min	25	1,04	-1,26	3,35	0,35
181-240min	11	1,89	-1,84	5,63	0,28

n: number of research groups; min: minutes; BMI: body mass index. *$p<0.05$ was considered significant.

MATERIAL SUPLEMENTAR

A – Risk of bias assessment using the tool Risk of Bias 2 (RoB2).

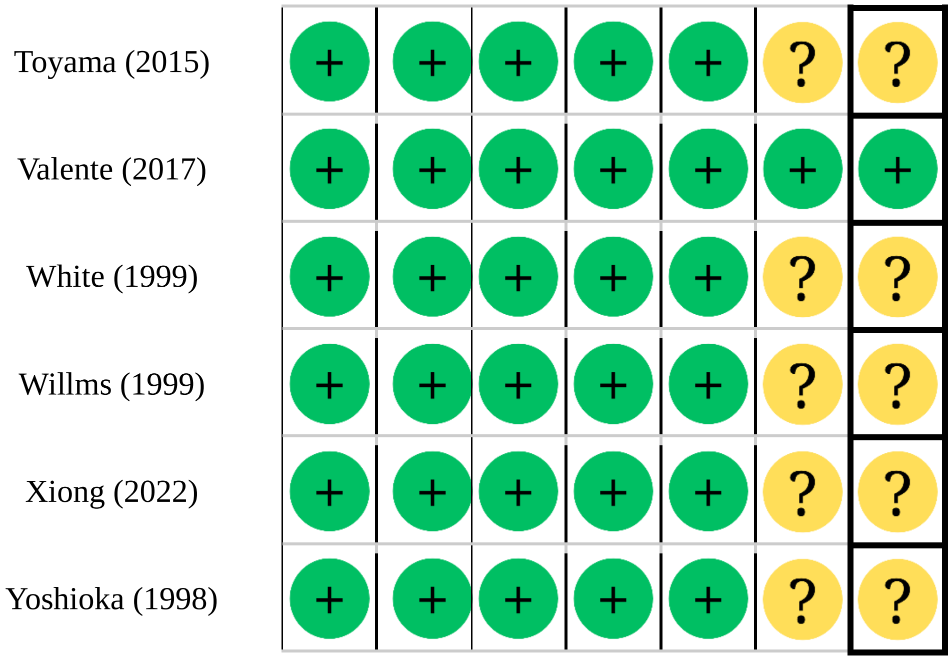
	D1	DS	D2	D3	D4	D5	OR
Agte (1992)	+	+	+	+	+	?	?
Alfenas (2010)	+	+	+	+	+	?	?
Allirot (2013) Allirot (2014)	+	+	+	+	+	+	+
Alves (2013)	+	NA	?	-	+	?	-
Ando (2016)	+	+	+	+	+	+	+
Apolzan (2011)	+	+	+	+	+	+	+
Bahr (1991)	+	+	+	+	+	?	?
Belko (1986)	+	?	+	+	+	?	?
Belko (1987)	+	?	+	+	+	?	?
Bendixen (2002)	+	+	+	+	+	?	?
Binns (2014)	+	+	?	+	+	?	?
Blond (2011)	+	+	?	-	+	?	-
Bo (2015)	+	+	+	+	+	?	?
Boschmann (2020)	+	NA	+	+	+	+	+
Brehm (2005)	+	?	?	-	+	?	-

Camps (2019)	+	+	?	-	+	+	-
Casas-Agustench (2009)	+	+	+	+	+	?	?
Chowdhury (2018) Chowdhury (2019)	+	NA	+	+	+	+	+
Clegg (2012)	+	+	+	+	+	?	?
Cummings (2006)	+	+	+	+	+	?	?
Das (2001)	?	NA	?	-	+	?	-
Dioneda (2020)	+	+	+	+	+	+	+
Alves (2014)	+	NA	+	+	+	?	?
Duhita (2017)	+	+	?	-	+	?	-
Duhita (2019)	+	+	+	+	+	+	+
Fagundes (2021)	+	+	+	+	+	+	+
Garrel (1994)	+	?	+	+	+	?	?
Gepner (2016)	+	+	+	+	+	+	+
Gregersen (2012)	+	+	+	+	+	+	+
Hamada (2014)	+	?	+	+	+	?	?
Hamada (2016)	+	+	+	+	+	?	?
Hansen (1998)	+	+	+	+	+	?	?

Hellerstein (1994)	+	?	?	-	+	?	-
Hollis (2007)	+	+	?	-	+	?	-
Hursel (2009)	+	+	+	+	+	?	?
Ishii (2016)	+	+	?	-	+	?	-
Jobin (1996)	+	+	+	+	+	?	?
Johnston (2002)	+	+	+	+	+	?	?
Jones (2008)	+	+	+	+	+	?	?
Jones (1992)	+	+	+	+	+	?	?
Jones (1988)	+	?	+	+	-	?	-
Kennedy (2014)	+	+	?	-	+	?	-
Khossousi (2008)	+	+	+	+	+	?	?
Kinabo (1990)	+	?	?	+	+	?	?
Komai (2016)	+	+	+	+	+	?	?
Lason-Meyer (2010)	+	+	?	-	+	?	-
LeBlanc (1985)	+	?	+	+	+	?	?
LeBlanc (1991)	+	+	+	+	+	?	?
LeBlanc (1984)	+	+	+	+	+	?	?

Li (2016)	+	+	+	+	+	+	+
Luscombe (2003) Luscombe-Marsh (2005)	+	NA	+	+	+	?	?
Luscombe-Marsh (2013)	+	+	+	+	+	+	+
Mahler (2022)	+	NA	+	+	+	+	+
Mansour (2012)	+	?	+	+	+	?	?
Marinangeli (2011)	+	+	?	-	+	?	-
Melanson (2015)	+	NA	?	-	+	+	-
Melanson (1996) Melanson (1998)	+	?	+	+	+	?	?
Mohr (2020)	+	+	+	+	+	+	+
Morris (2015)	+	+	+	+	+	?	?
Nagai (2005)	+	?	+	+	+	?	?
Nguo (2018)	+	+	+	+	+	?	?
Nielsen (1987)	+	+	+	+	+	?	?
Nielsen (2018) Nielsen (2019)	+	+	+	+	+	+	+
Ooi (2021)	+	NA	+	+	+	+	+
Parker (2020)	+	+	+	+	+	?	?
Peracchi (2000)	+	+	+	+	+	?	?

Piers (2002)	+	+	+	+	+	?	?
Ping-Delfos e Soares (2011)	+	+	+	+	+	?	?
Raben (2003)	+	+	+	+	+	?	?
Racette (1995)	?	NA	?	-	+	?	-
Ratcliff (2011)	+	+	?	-	+	?	-
Reeves (2015)	+	+	+	+	+	?	?
Richter (2020)	+	+	+	+	+	+	+
Riggs (2007)	+	+	+	+	+	?	?
Saito (2006)	+	+	+	+	+	?	?
Sawaya (2001)	+	+	+	+	+	?	?
Scazzina (2011)	+	+	+	+	+	?	?
Segal (1983) Segal (1983)	+	+	+	+	+	?	?
Soares (2004)	+	+	+	+	+	?	?
St-Onge (2003)	+	+	?	-	+	?	-
Suen (2003)	+	+	+	+	+	?	?
Sutton (2016)	+	NA	+	+	+	+	+
Tentouloris (2003) Tentouloris (2008) Tentouloris (2011)	+	+	+	+	+	?	?



D1: Domain 1 - Risk of bias arising from the randomization process;
DS: Domain S - Risk of bias due to period and transition effects (only for crossover design studies);
D2: Domain 2 - Risk of bias due to deviations from intended interventions (effect of assignment to intervention);
D3: Domain 3 - Risk of bias due to missing outcome data;
D4: Domain 4 - Risk of bias in measurement of the outcome;
D5: Domain 5 - Risk of bias in selection of the reported result**;**
OR: Overall rating;
NA: Not applicable.

B – Risk of bias assessment using the tool Risk of Bias In Non-randomized Studies – of Interventions (ROBINS-I).

	D1	D2	D3	D4	D5	D6	D7	OR
Acheson (1982)	+	+	+	+	+	?	?	?
Asahara (2016)	+	+	+	+	+	?	?	?
Bennett (1992)	+	+	+	+	+	?	?	?
Bissoli (1999)	+	+	+	+	+	?	?	?
Dalasso (1984)	+	+	+	+	+	?	?	?
Davis (1992)	+	+	+	+	+	?	?	?
De Jonge (1991)	+	+	+	+	+	?	?	?
Den Besten (1988)	+	+	+	+	+	?	?	?
Elia (1988)	+	+	+	+	+	?	?	?
Faraj (2001)	+	+	+	+	+	?	?	?
Fukagawa (1991)	+	+	+	+	+	?	?	?
Fukuda (2017)	+	+	+	+	?	?	?	?
Gougeon (2005)	+	+	+	+	+	?	?	?
Harris (2007)	+	+	+	+	+	?	?	?
Houde-Nadeau (1993)	+	+	+	+	+	?	?	?

Imbeault (2001)	+	+	+	+	+	?	?	?
Kayaba (2014)	+	+	+	+	+	?	?	?
Kopp-Hoolihan (1999)	+	+	+	+	?	?	?	?
LeBlanc (1993)	+	+	+	+	+	?	?	?
LeBlanc (1984)	+	+	+	+	+	?	?	?
Luscombe (2006)	+	+	+	+	?	?	?	?
Marrades (2006)	+	+	+	+	+	?	?	?
Matheson (2011)	+	+	+	+	+	?	?	?
Matsumoto (2000) Matsumoto (2001)	+	+	+	+	+	?	?	?
Mourad (2009)	+	+	+	+	+	?	?	?
Nagai (2006)	+	+	+	+	+	?	?	?
Piers (1995)	+	+	?	+	?	?	?	?
Poehlman (1985)	+	+	+	+	+	?	?	?
Raben (1994)	+	+	+	+	+	?	?	?
Raben (1994)	+	+	+	+	+	?	?	?
Reddy (2015)	+	+	+	+	+	?	?	?
Roberts (1996a) Roberts (1996b)	+	+	+	+	+	?	?	?

Ruddick-Collins (2021)	+	+	+	+	+	?	?	?
Ruddick-Collins (2013)	+	+	+	+	+	?	?	?
Stothard (2020)	+	+	+	+	?	?	?	?
Swaminathan (1985)	+	+	+	+	?	?	?	?
Tremblay (1983)	+	+	+	+	+	?	?	?
Tremblay (1997)	+	+	+	+	+	?	?	?
Treuth (1995)	+	+	+	+	?	?	?	?
Tuttle (1953)	+	+	+	+	+	?	?	?
Votruba (2002)	+	+	+	+	+	?	?	?
Young (1995)	+	+	+	+	+	?	?	?
Watanabe (2006)	+	+	+	+	+	?	?	?
Watts (1990)	+	+	+	+	+	?	?	?

D1: Domain 1 - Bias due to confounding;
D2: Domain 2 - Bias in selection of participants into the study;
D3: Domain 3 - Bias in classification of interventions;
D4: Domain 4 - Bias due to deviationsfrom intended interventions;
D5: Domain 5 - Bias due to missing data;
D6: Domain 6 - Bias in measurement of outcomes**;**
D7: Domain 7 - Bias in selection of the reported result**;**
OR: Overall rating;

C – Strategies and terms to search for reports in the electronic databases

ELECTRONIC DATABASES	STRATEGY AND TERMS FOR SEARCH
MEDLINE	(((((((thermic effect of food) OR (thermic effect of feeding)) OR (thermogenic effect of food))) OR ("specific dynamic action"[All Fields])) OR (dietary induced thermogenesis)) OR (diet* induced thermogenesis)) OR (meal-induced thermogenesis)
Embase	('thermic effect of food' OR 'thermic effect of feeding' OR 'thermogenic effect of food' OR 'specific dynamic action' OR 'dietary induced thermogenesis' OR 'diet* induced thermogenesis' OR 'meal-induced thermogenesis') AND 'human'/de
CENTRAL	'thermic effect of food' OR 'thermic effect of feeding' OR 'thermogenic effect of food' OR 'specific dynamic action' OR 'dietary induced thermogenesis' OR 'diet* induced thermogenesis' OR 'meal-induced thermogenesis' in All Text AND humans in All Text
Web of Science	(((((((ALL=(thermic effect of food)) OR ALL=(thermic effect of feeding)) OR ALL=(thermogenic effect of f ALL=(specific dynamic action)) OR ALL=(dietary induced thermogenesis)) OR ALL=(diet* induced thermogen ALL=(meal-induced thermogenesis)) AND ALL=(Humans)
LILACS	"thermic effect of food" OR "thermic effect of feeding" OR "thermogenic effect of food" OR "specific dynamic action" OR "dietary induced thermogenesis" OR "diet* induced thermogenesis" OR "meal-induced thermogenesis"

D - Articles Included

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E - PRISMA 2020 checklist.

PRISMA 2020 Checklist

Section andTopic	Item	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	3,4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	4,5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify thedate when each source was last searched or consulted.	4
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Appendix C
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each recordand each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	4,5
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	5
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in eachstudy were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	5,6

	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	5,6
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	6
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	5,6
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	5,6
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	6,7
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	6,7
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	6,7
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	6,7
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	6,7
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	6,7
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	6,7
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included inthe review, ideally using a flow diagram.	7
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	20
Study characteristics	17	Cite each included study and present its characteristics.	Appendix F
Risk of bias instudies	18	Present assessments of risk of bias for each included study.	8, Appendix A and B
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimates and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	-

Results ofsyntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	8
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	8, 9, 25 - 29
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	8,9, 25-29
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	8,9, 25-29
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	8
Certainty ofevidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	8, 9, 25 - 29
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	9 - 13
	23b	Discuss any limitations of the evidence included in the review.	9 - 19
	23c	Discuss any limitations of the review processes used.	13, 14
	23d	Discuss implications of the results for practice, policy, and future research.	13, 14
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	4
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	4
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	-
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	14
Competing interests	26	Declare any competing interests of review authors.	15
Availability of data, code andother	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies;	Appendix F

materials		data used for all analyses; analytic code; any other materials used in the review.	

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

CONSIDERAÇÕES FINAIS

4. CONSIDERAÇÕES FINAIS

O metabolismo energético tem se tornado objeto de investigação como potente estratégia terapêutica frente a pandemia do excesso de peso. Considerando a homeostase energética como o equilíbrio entre ganho e gasto de energia, o Efeito Térmico do Alimento (ETA) se faz importante por compreender a parcela energética modificável que se entrelaça entre a ingestão energética, as características biológicas individuais e resposta da energia química e térmica.

Embora os estudos sobre este tema tenham se avançado, ainda há lacunas sobre os possíveis fatores influenciadores neste componente. Visando contribuir com a literatura, esta dissertação investigou o impacto de diferentes características biológicas dos indivíduos e nutricionais das refeições no ETA em humanos por meio de uma revisão sistemática com metarregressão de ensaios clínicos. Diante do exposto, foi possível observar que as características referentes ao sexo e o conteúdo energético influenciaram fortemente na resposta energética, com pico máximo entre uma e duas horas após uma refeição. Além disso, o índice de massa corporal, o grau de processamento dos alimentos e a distribuição de proteínas e lipídios também se relacionaram com o ETA, sendo os lipídios mais consistentemente associados.

Por fim, estes resultados nos mostram a relevância do ETA como potencial alvo terapêutico na prevenção e tratamento do excesso de peso. No entanto, devido à alta heterogeneidade dos estudos, destaca-se a necessidade de pesquisas futuras com alto rigor metodológico a fim de aprimorar a consistências dos resultados e a implementação na prática clínica.

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