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**Efeito de Intervenções de Mudança no Estilo de Vida na Perda e
Manutenção da Perda de Peso em Obesos:
Revisão Sistemática com Metanálise e *Trial Sequential Analysis***

Porto Alegre, 2019

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Orientadora: Prof^a Dr^a Jussara Carnevale de Almeida

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“Conheça todas as teorias,
domine todas as técnicas,
mas ao tocar uma alma humana,
seja apenas outra alma humana”

Carl Jung

RESUMO

A obesidade é uma doença crescente na população mundial, definida como um acúmulo excessivo de gordura, sendo identificada como fator de risco para uma série crescente de doenças crônicas. Para reverter este quadro, diretrizes recomendam dieta balanceada, com restrição calórica, atividade física e estratégias comportamentais como opções de tratamento. No entanto, para atingir os benefícios da perda de peso, é necessária a manutenção do peso perdido, que ainda é um dos maiores desafios, visto que o reganho de peso é comum. Desta forma, o objetivo deste trabalho é revisar sistematicamente a literatura para verificar o efeito de programas de mudança de estilo no vida para perda de peso e manutenção em longo prazo em pacientes obesos. Além disso, para determinar se a evidência atualmente disponível é suficiente, *Trial Sequential Analysis* (TSA) foi aplicada. O planejamento, a condução e o relatório desta revisão sistemática seguiram as diretrizes descritas na declaração *Preferred Reporting Items for Systematic Reviews e Meta-Analyzes*. O protocolo de revisão foi registrado no Registro Internacional de Revisões Sistemáticas - PROSPERO (Identificador: CRD42017075187). Foram incluídos ensaios clínicos randomizados das bases de dados PubMed, EMBASE e Lilacs Para avaliação de risco de viés foi utilizado o instrumento da Colaboração Cochrane. Foi utilizado o programa STATA para realizar a metanálise e calcular a diferença ponderada das médias a partir do modelo de efeito randômico. Foi adotado o método do inverso da variância para as análises. Os resultados das metanálises mostraram que a restrição calórica apresenta efeito na redução de peso corporal aos 12 meses e aos 24 meses e a TSA mostrou que a literatura existente é suficiente para esta conclusão. No entanto, aos 36 meses a perda de peso não é significativa e a TSA mostrou que ainda são necessários mais estudos com uma amostra de 1515 participantes para avaliar este desfecho neste período. Esta revisão demonstrou que a restrição calórica leva a perda de peso em até dois anos, no entanto, ainda são necessários mais ensaios com tamanhos amostrais maiores para avaliar a manutenção da perda de peso no longo prazo.

Palavras-chave: Obesidade. Perda de Peso. Estilo de Vida. Revisão.

ABSTRACT

Obesity is a worldwide growing disease, defined as an excessive fat accumulation and it is identified as a risk factor for many chronic diseases. Guidelines recommend a balanced diet with calorie restriction, physical activity and behavioral strategies as treatment options. However, weight loss maintenance is necessary to maintain the benefits and it is still a challenge due weight regain. The objective of this study was to systematically review the literature to verify the effect of lifestyle change programs for weight loss and long-term maintenance in obese and, to determine whether the currently available evidence was sufficient, the Trial Sequential Analysis (TSA) was applied. The planning, conduct and reporting of this systematic review adhered to the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. Review protocol has been registered in PROSPERO International Prospective Register of Systematic Reviews (Identifier: CRD42017075187). The databases searched were MEDLINE, EMBASE and Lilacs/Bireme and were included randomized clinical trials. Risk of bias was assessed using the risk of bias assessment tool developed by the Cochrane Collaboration. Data were pooled using inverse-variance random-effects meta-analysis and expressed as weighted mean differences (WMD) with 95% confidence intervals (CI) using STATA software. Meta-analysis showed that caloric restriction was effective to promote weight loss at 12 months and 24 months and TSA showed firm evidence of effect. However, at 36 months there were no differences in body weight change and the meta-analysis included less patients than the required information size (1515) according to TSA. This review suggested that calorie restriction is effective to weight loss up to two years. For weight loss maintenance greater than three years, large-scale trials are required to support these findings.

Key-words: Obesity. Weight Loss. Lifestyle. Review.

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ABREVIATURAS E SIGLAS

BMI - Body Mass Index

CI - Confidence Interval

IC - Intervalo de confiança

IMC - Índice de massa corporal

OMS - Organização Mundial da Saúde

PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyses

RCT - Randomized Clinical Trial

TSA - Trial Sequential Analysis

WHO - World Health Organization

WMD - Weighted Mean Difference

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FORMATO DA DISSERTAÇÃO

Esta dissertação de Mestrado segue o formato proposto pelo Programa de Pós-Graduação em Ciências Médicas: Endocrinologia da Universidade Federal do Rio Grande do Sul, sendo apresentada através de uma breve revisão da literatura e manuscrito referente ao tema estudado:

Capítulo I. Referencial teórico

Capítulo II. Artigo de revisão sistemática de literatura a ser submetido para publicação no periódico *Nutrition Reviews* (Medicina I, A1, ISSN 0029-6643), redigido conforme as normas do periódico (ANEXO 1).

CAPÍTULO I - REFERENCIAL TEÓRICO

A obesidade pode ser compreendida como um agravo de caráter multifatorial que é identificado como fator de risco para uma série crescente de doenças crônicas, incluindo doenças cardiovasculares, diabetes melito, doença renal crônica, vários tipos de câncer e distúrbios musculoesqueléticos (AFSHIN et al., 2017). Além do desbalanço entre consumo e o gasto energético, entre as causas de obesidade estão fatores biológicos, ecológicos, econômicos, sociais, culturais e políticos (OMS, 2000).

Em todo o mundo, a prevalência da obesidade quase dobrou desde a década de 80. Em 2014, 11% dos homens e 15% das mulheres com 18 anos ou mais foram classificados como obesos de acordo com o Índice de Massa Corporal – IMC (OMS, 2014). No Brasil, o aumento de obesidade ocorre no mesmo sentido. Segundo o levantamento brasileiro chamado de “Vigilância de Fatores de Risco e Proteção para Doenças Crônicas por Inquérito Telefônico – VIGITEL”, em 2006 cerca de 11,8% dos adultos se autodeclararam obesos e, atualmente, 19,8% da população adulta brasileira residente nas capitais relatam estar com obesidade (BRASIL, 2019).

O excesso de peso tem como determinantes proximais o padrão alimentar e o gasto energético. Segundo a Organização Mundial da Saúde (OMS) quando se preparam políticas nacionais e diretrizes dietéticas deve-se seguir as recomendações de limitar a ingestão de energia das gorduras totais, de açúcar adicionado e do sal (sódio) de todas as fontes alimentares, assim como aumentar o consumo de frutas, legumes e leguminosas (OMS, 2004). No entanto, os padrões alimentares atuais identificados por pesquisas nacionais evidenciam justamente o inverso, ou seja, um padrão de consumo caracterizado pelo elevado percentual de alimentos ricos em açúcar, gorduras saturadas, *trans*-insaturadas e sal e, ainda, pelo baixo consumo de carboidratos complexos e fibras (IBGE, 2011). Em nível mundial, de acordo com o estudo *Global Burden of Disease* (AFSHIN et al., 2019), observou-se um consumo sub-ótimo de alimentos saudáveis: baixo consumo de frutas (< 250 g/d), vegetais (< 360 g/d), leguminosas (< 60 g/d), grãos integrais (< 125 g/d), oleaginosas e sementes (< 21 g/d) e fibras (< 24 g/d). Ainda, paralelamente, a ingestão diária de todos os alimentos e nutrientes não saudáveis excedeu o nível considerado ideal: elevado consumo de carne vermelha (> 23 g/d) e processada (> 2 g/d), bebidas açucaradas (> 3 g/d), gordura *trans*-insaturadas (> 0,5 % das necessidades dietéticas diárias) e sódio (> 3 g/d).

Considerando que a causalidade da obesidade é multifatorial, seu tratamento é

complexo e preconiza-se que seja multidisciplinar. A escolha do tratamento deve assim basear-se na gravidade do problema, na presença de complicações associadas e no contexto nos quais os indivíduos estão inseridos (ABESO, 2016). Além disto, deve ser realizada a avaliação dos estágios de mudança em relação à perda de peso para então serem estabelecidas metas personalizadas (BRASIL, 2014).

O sobrepeso é considerado um estágio intermediário onde os indivíduos estão com o peso acima do ideal e possuem maior risco de desenvolver obesidade e suas complicações. A diretriz de 2014 da *American College of Cardiology, American Heart Association, Task Force on Practice Guidelines and The Obesity Society* propõe um algoritmo para manejo da obesidade onde os indivíduos com sobrepeso que não possuem complicações devem ser orientados a evitar o ganho de peso enquanto os que possuem comorbidades associadas devem, como forma de tratamento, perder peso (JENSEN et al., 2014).

Diretrizes internacionais (GARVEY et al., 2016; YUMUK et al., 2015) e nacionais (ABESO, 2016; BRASIL, 2014) referem que o manejo e tratamento da obesidade têm objetivos mais amplos do que a perda de peso isolada, onde benefícios clínicos significativos podem ser alcançados mesmo por modesta perda de peso (ou seja, 5 – 10 % do peso corporal inicial), e modificação do estilo de vida. Uma perda de peso maior (20 % ou mais) pode ser considerada para aqueles com maior grau de obesidade ($IMC \geq 35 \text{ kg/m}^2$) (YUMUK et al., 2015).

Em relação à dieta, há fortes recomendações de que esta deva ser prescrita de forma individualizada, levando em consideração o estado de saúde, as preferências do paciente, mantendo a adequação de nutrientes, reduzindo a ingestão calórica e com metas realistas. A restrição calórica de 500 a 1000 kcal é o principal componente de qualquer intervenção para perda de peso de 0,5 a 1 kg por semana, sendo esta considerada eficiente e factível. Planos alimentares considerados balanceados são caracterizados por serem compostos de 20 % a 30 % de gorduras, 55 % a 60 % de carboidratos e 15 % a 20 % de proteínas. Em casos especiais, dietas de muito baixas calorias (10 kcal por kg de peso atual) com adição de suplementos ou substitutos de refeições, drogas antiobesidade e cirurgia bariátrica são opções a serem consideradas (GARVEY et al., 2016; ABESO, 2016; YUMUK et al., 2015).

Além da intervenção dietética, a atividade física faz parte do tratamento, devendo ser prescrita como um componente da intervenção na mudança de estilo de vida. A prescrição inicial requer aumento progressivo de frequência e intensidade do exercício onde o objetivo final deve ser atingir pelo menos 150 min/semana de exercício aeróbico moderado realizado durante três a cinco vezes por semana, combinado com pelo menos três sessões semanais de

exercícios resistidos para aumentar a força muscular, preservar massa magra e auxiliar na perda de gordura corporal (GARVEY et al., 2016; YUMUK et al., 2015).

Intervenções comportamentais são descritas como auxiliares na mudança de estilo de vida, e entre as opções estão: auto-monitoramento (de peso, dieta e atividade física), definição clara e razoável de metas, redução de estresse, controle de estímulos que antecedem os transtornos de comportamento, terapia cognitivo comportamental, entrevista motivacional, abordagens sistemáticas para resolução de problemas, reestruturação cognitiva, mobilização de estruturas de apoio social e atenção plena na consciência de comer (GARVEY et al., 2016; ABESO, 2016; YUMUK et al., 2015).

Existem inúmeras intervenções dietéticas propostas para a perda de peso e, independente da composição de macronutrientes da dieta, a perda de peso melhora marcadores metabólicos, reduzindo fatores de risco cardiovasculares relacionados à obesidade. Porém, os indivíduos com excesso de peso apresentam divergências quanto à preferência pelas distintas intervenções e à capacidade de adesão as mesmas. Além disso, sustentar a perda de peso em longo prazo continua a ser o maior desafio, o qual é dificultado pelo fato de, na grande maioria das vezes, os indivíduos com excesso de peso estarem expostos a um ambiente "obesogênico", bem como pelas adaptações biológicas que acompanham a perda de peso (THOM; LEAN, 2017).

Duas revisões sistemáticas seguidas de metanálises que avaliaram o efeito de intervenções não cirúrgicas na perda e manutenção de peso em adultos foram publicadas em 2014 (DOMBROWSKI et al., 2014; SCHWINGSHACKL et al., 2014), porém uma incluiu pacientes com sobrepeso e se limitou a estudos publicados apenas na língua inglesa (SCHWINGSHACKL et al., 2014) e a outra incluiu intervenções com uso de substitutos de refeição (DOMBROWSKI et al., 2014), o que pode dificultar a aplicabilidade na prática clínica, especialmente no sistema de saúde brasileiro.

Schwingshackl e colaboradores (2014) compararam a eficácia em 12 meses de dieta e exercício (combinados e cada um de forma isolada) para perda de peso sobre resultados antropométricos e fatores de risco cardiovasculares em pacientes com excesso de peso e obesidade. Foram incluídos 21 ensaios clínicos randomizados publicados somente na língua inglesa (seguimento entre 12 e 72 meses) totalizando 3521 participantes. Em relação às intervenções dietéticas, a maior parte dos estudos incluídos (11) recomendou dietas com redução de calorias a partir da restrição do teor de gordura (≤ 30 % de gordura da energia total), baixo teor de gorduras saturadas, e aumento de fibras a partir do consumo de frutas, verduras e legumes. Em comparação com dieta isolada, dieta combinada com exercício

resultou numa redução de 1,38 kg (IC95% de -1,98 a -0,79) no peso corporal. As intervenções com dieta e exercício apresentaram melhores resultados em comparação com exercício isolado, com redução de 4,13 kg (IC95% de -5,62 a -2,64) no peso. Quando comparado intervenções somente com exercícios com intervenções somente com dieta, a dieta resultou em uma diminuição mais pronunciada no peso corporal (-2,93 kg, IC95% de -4,18 a -1,68) (SCHWINGSHACKL et al, 2014).

Dombrowski e colaboradores (2014) tiveram o objetivo de avaliar quais estratégias foram mais efetivas para a manutenção de um ano (até trinta meses) após uma perda ponderal de pelo menos 5% do peso inicial. Incluíram 37 ensaios clínicos randomizados com intervenções comportamentais e de mudança de estilo de vida (dieta e exercício), mas também com uso de fármacos, suplementos e substitutos de refeições. Intervenções distintas, com foco em dieta, atividade física e mudança de comportamento (25 comparações; n = 2949 participantes) resultaram em uma diferença média de -1,56 kg (IC95% de -2,27 a -0,86 kg) no reganho de peso em comparação com o grupo controle. Aos 18 meses, sete estudos incluindo 13 comparações puderam ser sumarizados e a diferença média de peso foi -1,96 kg (IC95% de -2,73 a -1,20 kg). Aos 24 e 30 meses, dois estudos relataram resultados e diferenças médias na mudança de peso permaneceram significativas aos 24 meses (-1,48 kg, IC95% de -2,27 a -0,69 kg), mas não aos 30 meses (-0,85 kg, IC95% de -1,81 a 0,11 kg). Já o medicamento Orlistat adicionado a mudança de estilo de vida (oito comparações, n = 1738 participantes) resultou em uma diferença de -1,80 kg (IC95% de -2,54 a -1,06) quando comparado ao placebo em 12 meses. Apenas um estudo fornecia resultados em 18 e 36 meses.

Se por um lado a manutenção em longo prazo da perda de peso é muito importante, o efeito de diferentes padrões alimentares na sustentação desta perda de peso em grande parte ainda é desconhecida (GARVEY et al., 2016). O reganho de peso é comum após o período de acompanhamento, pelo menos 50% dos pacientes que atingiram 5% de perda de peso recuperaram este peso em 2 anos (FILDES et al., 2015).

A probabilidade anual de um adulto com obesidade retornar a um IMC dentro da faixa de normalidade é baixa: cerca de um em 210 homens e uma em 124 mulheres (FILDES et al., 2015). Além disto, conforme aumenta o IMC aumenta também o risco de morte e do desenvolvimento de comorbidades associadas (AFSHIN et al. 2017). A cada 5 kg/m², o alto IMC é associado, em média, a uma mortalidade geral 30 % maior (Taxa de risco 1,29 [IC95% 1,27 a 1,32]) (PSC et al., 2009). Apesar da maior parte das revisões publicadas incluírem indivíduos com IMC \geq 25 Kg/m² para avaliar a perda de peso, aqui iremos focar em indivíduos com obesidade, uma vez que o tratamento e os riscos diferem conforme o IMC.

Ainda que as diretrizes nacionais e internacionais recomendem os programas de mudança de estilo de vida na perda de peso, não há consenso na literatura científica de forma sumarizada e atualizada a respeito da manutenção da perda de peso em longo prazo. De 2014 (ano de publicação das últimas metanálises sobre o tema) até a presente data, pelo menos 4252 ensaios clínicos sobre o assunto são rastreados no Pubmed, reforçando a importância de uma atualização sobre o tema. O objetivo desta revisão sistemática foi determinar quais as intervenções de mudança de estilo de vida são efetivas na alteração de peso corporal, prevenção e manejo de fatores de risco e eventos cardiovasculares. Na presente dissertação serão apresentados os resultados destas intervenções na perda de peso e manutenção em indivíduos com obesidade. Além disso, para determinar se a evidência atualmente disponível é suficiente, a *Trial Sequential Analysis* (TSA) foi aplicada.

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**CAPÍTULO II - ARTIGO DE REVISÃO PARA PUBLICAÇÃO NO PERIÓDICO
NUTRITION REVIEWS, REDIGIDO CONFORME AS NORMAS DO PERIÓDICO**

Lead Article

Effect of lifestyle intervention programs on weight-loss and maintenance of weight-loss in obese adults: a systematic review with meta-analysis and trial sequential analysis

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ABSTRACT

Context: For obesity management, current guidelines recommend lifestyle modification to promote weight-loss. There is, however, a lack of evidence on the appropriate approach for weight-loss maintenance. **Objective:** To evaluate the effect of lifestyle change programs on weight-loss and its maintenance in obese individuals. The trial sequential analysis (TSA) was applied to determine whether the currently available evidence is sufficient. **Data Sources:** The PubMed, EMBASE and Lilacs databases were searched for randomized clinical trials published before May of 2018. **Data extraction:** Data were pooled using an inverse-variance random-effects meta-analysis and expressed as weighted mean differences (WMD) with 95% confidence intervals (CI). Heterogeneity was quantified and explored using subgroup analyses. **Results:** Eleven trials (12 publications, 1416 participants) were considered eligible to be included in this meta-analysis. Caloric restriction was effective to promote weight-loss at 12 months [WMD -3.79kg (95%CI -4.78 to -2.79), $I^2=87.5\%$] and 24 months [WMD -6.20kg (95%CI -10.81 to -1.59), $I^2=71.2\%$] and TSA showed convincing evidence of an effect. At 36 months, there were no differences in body weight change [-2.06kg (95%CI -7.00 to 2.89), $I^2=0.0\%$] and the meta-analysis included less patients than the required information size according to TSA. Subgroup analyses suggest improved weight-loss for caloric restrictions that are greater than 501 Kcal, Dietitian as the interventionist, intensity of intervention twice a month and dropout rates of <20%. **Conclusions:** For obesity management in clinical practice, caloric restriction is effective to promote weight-loss for up to two years, preferably with a caloric deficit that is greater than 501 Kcal, if performed by registered Dietitian and if associated with a behavioral component and at least twice-monthly contact with a health team. For weight-loss maintenance greater than three years, large-scale trials are required to support these findings.

Key-word: Obesity, weight-loss; lifestyle; systematic review

268/270 words

INTRODUCTION

Worldwide, obesity has nearly tripled since 1975, and during 2016, 650 million adults 18 years of age or older were considered obese.¹ Epidemiologic studies have identified high BMI as a risk factor for an expanding set of chronic non-communicable diseases, including diabetes mellitus, cardiovascular and chronic kidney diseases, many types of cancer, and an array of musculoskeletal disorders. In 2015, high BMI contributed to 4 million deaths, which represents 7.1 % of the deaths from any cause.²

Guidelines recommend that treatment should constitute lifestyle modifications (diet, exercise and behavior change) for appropriate management of obesity and, if necessary, medication and bariatric surgery.^{3,4} Intentional weight-loss of at least 3% to 5% improves some clinical parameters associated to obesity, but to sustain these benefits, this degree of weight-loss needs to be maintained.⁵

Prevention of weight regain in the long-term remains the biggest challenge.⁶ While there is no standard definition for the length of time for the maintenance of weight-loss to be considered successful, a duration of one year is often used.⁵ Importantly, at least 50% of patients who achieved 5% weight-loss regained this weight within 2 years.⁷

Previous reviews⁸⁻¹⁰ that evaluated non-surgical interventions for weight-loss and its maintenance in adults concluded that behavioral interventions that included both diet and physical activity have small but significant benefits on weight-loss maintenance. However, these reviews included studies that used meal replacements,^{8,10} overweight individuals and even language limitations.⁹ It is important to determine if weight-loss intervention studies are applicable to the clinical management of obese patients, that is, if it is also applicable in real-world settings.¹¹

Besides the need for an update, to the best of our knowledge, no meta-analysis study has compared the long-term effects of combined dietary strategies with exercise and behavioral

components, without the use of meal replacements, to improve the feasibility of interventions in clinical practice for weight-loss and weight maintenance in obese adults, without language restriction. Therefore, the objective of this study was to systematically review the literature to verify the effect of lifestyle change programs for weight-loss and for the long-term maintenance of weight-loss in obese subjects. To determine if the currently available evidence is sufficient, the Trial Sequential Analysis (TSA) was applied.

METHODS

The planning, development and reporting of this systematic review adhered to the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (**Table S1 in the Supporting Information Online**).¹²

Protocol and registration

The search strategy and review protocol has been registered in PROSPERO International Prospective Register of Systematic Reviews (Identifier: CRD42017075187). The present systematic review and meta-analysis focuses on weight outcome.

Search strategy and Study selection

The databases searched were MEDLINE/Pubmed, EMBASE and Lilacs/Bireme (with date of publication from inception until May of 2018) with no restrictions to language and calendar date and using search terms specific for each database (**Table S2 in the Supporting Information Online**). Terms entered in variable combinations included “obesity,” “lifestyle,” and “body mass index”. The reference lists from the previously published systematic review were checked to search for further relevant studies.

Eligibility criteria

Studies were evaluated using the PICOS (Population, Intervention, Comparators, Outcome, and Study design) model shown in **Table 1**. Studies were excluded if they did not report post-intervention mean values (or change-from-baseline value scores) with standard deviation or basic data to calculate: standard error or 95% confidence interval (CI).¹³

Process of study selection

Title and abstract screening was divided between four trained authors (JPP, FMS, TAS, JDB) and conducted independently using EndNote X7.4. Subsequently, full-texts were evaluated to determine if articles met the inclusion/exclusion criteria using the same protocol. Disagreements were resolved by a fifth author (VCL).

Data extraction

Data extraction was performed by two authors (JPP, TAS) in Google Forms® and exported to Microsoft Office Excel®. Characteristics extracted from each study included: first author's name, publication year, study location, sex and age of participants, sample size, follow-up time, sequence generation, allocation sequence concealment, blinding, characteristics of intervention, dropout rates, post-intervention mean values of outcomes change-from-baseline value scores with corresponding standard deviation. Authors were contacted in case of doubts regarding the study.

Assessment of study quality

Full articles were independently assessed for methodological quality by two authors (JPP, TAS) using the risk of bias assessment tool developed by the Cochrane Collaboration.¹⁴ The criteria used for judging risk of bias (in the tool) were those recommended by the Handbook.¹³ However, because this is a review of behavioral interventions and it was not

possible for all participants or study personnel to be blinded to group assignment, the criteria adopted for a judgment of “Low risk” of bias for “blinding of participants and personnel” was if the author had explained the reason that participants or study personnel were not blinded. For other biases, the following criteria was used: “food provided, market voucher or financial incentives” the criteria for a judgment of “Low risk” of bias was reserved for cases in which financial or food incentives were not provided and “High risk” if these incentives were provided. When the intervention was performed by a nutritionist, it was considered “Low risk”, and when the facilitator was not trained in nutrition, it was considered “High risk”. When there was insufficient information about the incentives or the facilitator of the intervention in order to permit a judgment of “Low risk” or “High risk”, it was categorized as ‘Unclear risk’. For "adherence to intervention", it was considered “Low risk” when the authors described in detail how they evaluated adherence to dietary intervention(s), using a standard method such as a food diary or 24 h diet recall, for example, and “High risk” of bias was deemed if the article did not describe the method, or used invalidated methods. When a diet assessment tool was used but the result of adherence to the diet was not presented it was categorized as “Unclear risk”.

Data synthesis and statistical analysis

The initial mean weight (Kg) of each group was directly extracted from the manuscript with its respective standard deviation, as well as the change from the baseline weight value at the following measures times: 12, 24, and 36 months. When the study reported only the initial and final means, the mean change from baseline for each treatment group was obtained by subtracting the final mean from the baseline mean. The standard deviations were imputed assuming a correlation coefficient of 0.5 between the baseline and measures within each group; this is outlined in the Cochrane Handbook through the formula of Follmann.¹³

To proceed with the meta-analysis, we selected the interventions that had caloric restriction as

a dietary strategy for at least one of the comparator groups and presented the weight change in kilogram (kg) as the outcome. The pooled weighted mean difference (WMD) and 95% CI were calculated using the random effects model (inverse-variance approach). We assessed heterogeneity using the Cochran's test (Q test) and I^2 values. An I^2 value of greater than 50% suggested substantial heterogeneity.¹⁵ To test the potential of publication bias, we assessed the symmetry of the funnel plots and applied Begg's¹⁶ and Egger's¹⁷ regression tests to detect small study effects and $P < 0.05$ was considered indicative of small-study effects. Potential sources of heterogeneity among trials were investigated using meta-regression analyses (covariates: age, randomized sample and study length) and the following subgroup analyses were conducted: caloric restriction (CR) ≥ 500 or < 500 Kcal (categorized as binary variables considering the mean values of this variable in the included studies), exercise or behaviour therapy in intervention group versus no exercise and no behaviour therapy in the control group, registered dietitian as interventionist versus other professional, dropout $<$ or ≥ 20 % and frequency of contact with staff $<$ or \geq twice a month (categorized as binary variables as mentioned above). When authors did not describe the covariates, we opted for a more conservative position and we considered the CR < 500 Kcal, dropout $\geq 20\%$, without registered dietitian and frequency less than 2 times a month. Meta-analysis may result in type I errors due to bias or random errors due to sparse data and repeated significance testing when updating meta-analysis with new trials. Trial Sequential Analysis (TSA) controls the risks for type I and type II errors and helps to clarify whether additional trials are needed¹⁸ and the required sample size for such trials.¹⁹ To determine whether the current evidence is sufficient, we applied TSA using $\alpha = 0.05$ (two sided) and $\beta = 0.20$ (power of 80%).

Data were analyzed using STATA software version 14.2 (STATA corp, College Station, TX, USA).²⁰ Risk of bias summary was produced using the Review Manager (RevMan 5.3).²¹ The TSA was performed with TSA software version 0.9.5.10 Beta (Centre for Clinical

Intervention Research Department, Copenhagen, Denmark).²²

RESULTS

The study's selection process is shown as a flow chart in **Figure 1**. The database search identified 22,948 articles and seven were included from reference lists from previously published reviews; 22,599 were excluded on the basis of duplicate and/or irrelevant titles and abstracts. A total of 356 studies were reviewed in full, and of those, 26 randomized clinical trials (RCT) from 29 publications²⁰⁻⁴⁶ were included in this review with 4,221 obese participants.

Study characteristics are summarized in **Table 2** and more details from the interventions are listed in **Table S3 (Supporting Information Online)**. All trials were parallel RCT. The duration of each study ranged between 12 and 36 months and RCTs were published between 2002 and 2018. Most studies (n = 21) were conducted in the United States^{23-26,28-32,34,36,38-43,45,46,48,50} and others in Finland,³⁵ Cuba,⁴⁴ Italy,⁴⁹ Australia²⁷ and Israel.⁵¹ Sample sizes ranged from 27³⁸ to 612 participants,³¹ the mean age ranged from 35 to 70 years and ten studies were conducted only with women (100%).^{26,28,30,36,40,43,44,48-51}

Inspections of the funnel plots suggests a small study bias (**Figure S1 in the Supporting Information Online**), although both Begg's and Egger's tests for small-study effects did not suggest publication bias (p = 0.583 and p = 0.203, respectively). The heterogeneity was explored using meta-regression analysis (**Table S4 in the Supporting Information Online**). Randomized sample was the only variable that influenced the heterogeneity (adjusted R - square = 43.94 %).

Regarding quantitative synthesis, 11 trials^{23-25,30,35,43-46,48} were considered eligible with 1,416 obese participants. Three RCTs assessed more than two randomized groups in the study and were included as independent reports.^{23,25,45} Therefore, a total of 15 comparisons were made in the meta-analysis.

Among the comparisons that performed caloric restriction, twelve reduced calories following a balanced diet with 20% to 30% fat, 55% to 60% carbohydrate and 15% to 20% protein and three utilized strategies with different proportions of macronutrients. As a comparator group, in three studies, the control arm was a non-calorie restricted prudent diet, four used usual diet, two applied a calorie-free diet (according to internal signals), two used general advice, one focused on fiber intake and one was a carbohydrate-restricted diet.

At month 12 during follow-up, 13 comparisons ($n = 1162$) revealed a weighted mean difference in the change in participant body weight -3.79 kg (95%CI -4.78 to -2.79), $I^2 = 87.5$ % (**Figure 2 A**). TSA (**Figure 3**) shows that information size has been reached as the z-curve crosses all TSA boundaries for benefit.

Sensitivity analysis comparing caloric restriction greater than 500 Kcal *versus* up to 500 Kcal indicates that a more distinctive reduction in body weight could be observed with a caloric restriction of at least 501 Kcal [WMD: -8.05 kg (95% CI -12.86 to -3.25), $I^2 = 92.5$ %] (**Figure S2 in the Supporting Information Online**). Including a dietitian in the intervention group caused a similar result [WMD: -5.35 kg (95% CI -7.85 to -2.85), $I^2 = 93.6$ %] (**Figure S3 in the Supporting Information Online**) and a frequency of at least two visits per month during the intervention (**Figure S4 in the Supporting Information Online**) was found to be beneficial for weight-loss [WMD: -4.56 kg (95% CI -5.62 to -3.49), $I^2 = 92.1$ %]. Sensitivity analysis, including studies with a behavioral strategy in the intervention arm, found a WMD of -8.68 kg (95% CI -10.19 to -7.17), $I^2 = 0.0$ %, compared with controls (**Figure S5 in the Supporting Information Online**), but did not occur with the physical activity component in the intervention group [WMD: -4.57 kg (95%CI -9.85 to 0.72), $I^2 = 37.6$ %] (**Figure S6 in the Supporting Information Online**). A dropout rate greater than 20% (**Figure S7 in the Supporting Information Online**) indicates that weight-loss is less accurate [WMD: -5.45 kg (95% CI -9.74 to -1.17), $I^2 = 68.3$ %].

TSA showed that the z-curve crosses all TSA boundaries for benefit and that the information size has been reached for sensitively analysis for caloric restriction > 500 Kcal, dietitian in the intervention group, frequency of at least two visits per month and dropout rates < 20 % (**Figure S8 to S11 in the Supporting Information Online**).

At 24 months, four comparisons (n = 307) showed a weighted mean difference in the change in body weight -6.20 kg (95% CI -10.81 to -1.59), $I^2 = 71.2$ % (**Figure 2 B**). TSA shows that the number of participants does not reach the information size, but that the cumulative Z-curve does cross the monitoring boundary, which indicates firm evidence of an effect that at 24 months, calorie restriction provides weight-loss (**Figure S12 in the Supporting Information Online**). At 36 months (n = 129), only two comparisons showed a weighted mean difference in the change in body weight -2.06 kg (95% CI -7.00 to 2.88), $I^2 = 0.0$ % (**Figure 2 C**). The TSA shows that these two trials did not reach the required information size (1515) and that the cumulative Z-curve does not pass through the trial sequential monitoring boundary, nor the conventional $P = 0.05$ ($Z = 1.96$) level for a beneficial or harmful effect.

According to **Figure 4**, the risk of selection bias was low in six of the 11 included studies. In eight studies, the allocation was unclear. Risk of performance bias was unclear in eight studies, and was also unclear for detection bias in seven studies. Risk of attrition was low in eight studies and was low for reporting bias in 10 studies. Two studies were high in risk for food provided, market voucher or financial incentives. Seven studies were low in risk for interventionist and four studies did not report this information. Regarding adherence to dietary intervention, the majority (nine) was unclear.

DISCUSSION

The present systematic review and meta-analysis revealed that different dietary strategies and strategies affecting behavior and exercise components were used in the included trials to promote weight-loss in obese subjects. Caloric restriction was the predominant dietary

intervention and the pooled results reveal an overall significant weighted mean difference that is in favor of this approach at 12 and 24 month time points, with firm evidence of an effect. However, at 36 months, the meta-analysis included fewer participants than the required information size and the observed changes were not significant.

To the best of our knowledge, there is no systematic review of lifestyle change interventions with trial sequential analysis on weight-loss and its maintenance in obesity. Most systematic reviews report that more evidence is needed to document the effect(s) of caloric restriction on long term weight-loss maintenance. In this study, the TSA showed that enough patients were randomized at 12 and 24 months, and that it is unlikely that the accumulation of additional studies will change these findings. However, the meta-analysis included fewer patients than the required information size at 36 months. An ideal sample size was found to be 1,515 participants, which was not reached to clarify this literature gap.

Caloric restriction is effective as a method of achieving weight-loss in studies with follow-ups that are greater than 12 months. This result is similar to a previous meta-analysis⁹ that compared the long-term effects of diet on the outcomes of anthropometric measures, although their study included overweight participants.

Our subgroup analyses revealed results that are useful for clinical practice. According to current guidelines, caloric restriction of at least 500 kcal is appropriate for weight-loss;^{3,4} similar results were found in this review using subgroup analyses that revealed greater weight-loss when compared with energy deficits of ≤ 500 kcal. Additionally, interventions with behavioral components also was found to lead to more pronounced weight-loss and it this strategy is also recommended in the guidelines.^{3,4} A previous review showed that higher adherence to the low-calorie diet predicts a lower level of weight regain over 2 years,⁵² but we could not assess the effect of diet adherence because only five trials^{23,24,43,46,49} reported initial and final calories. More pronounced weight-loss was found to occur during interventions

provided by dietitians, when compared to other health professionals. This result is similar to other author's findings.^{5,53} In fact, the expertise of registered dietitians is described as 'essential' for the development, implementation, and evaluation of any intervention designed to reduce weight and obesity.⁵

Also, our subgroup analyses suggests that interventions that utilize a frequency of contact of two times per month results in greater weight-loss. This effects is in agreement with The American College of Cardiology, American Heart Association and Task Force Obesity Management Guidelines that recommend high-intensity (i.e., ≥ 14 sessions in 6 months) treatment sessions each month in order to produce greater weight-loss.⁵⁴

Physical activity was not found to have a significant effect on weight-loss, possibly due to there being only a few included studies that evaluated the isolated effect of exercise (n = 3).^{24,45,46} The combination of diet and exercise was found to be associated with improved weight-loss for up to 36 months and has been described as an effective strategy for weight-loss since 2004.⁵⁵ This strategy is also recommended for the prevention of weight regain.^{3,4,54}

Potential limitations of our study should be considered. First, the interventions vary according to the dietary strategy used, the intensity of intervention, and the presence or absence of a behavioral and/or physical activity component strategy. The differences between trials result in substantial heterogeneity and the randomized sample size reveals this heterogeneity to be 43.94 %, using meta-regression analysis. The Assessment of risk of bias was limited for many studies due to a lack of reporting. Few domains were classified to be high risk of bias, which did not allow for subgroup risk of bias analyses. Dropout rates exceeded 20% in five trials that were included in the meta-analysis, which is expected in randomized clinical trials,⁵⁶ but in these studies there was no reference to an intention-to-treat analysis in order to protect against bias. The results should be interpreted with caution due to these limitations. Even though recent strategies have been proposed for obesity management (such as intermittent

fasting) these were not included in this review due to an absence of long-term studies and the chosen BMI eligibility criteria. A recent meta-analysis⁵⁷ that examined the effectiveness of intermittent energy restriction for the treatment for overweight individuals and obesity in adults revealed that there is insufficient evidence to make any firm recommendations given the small number of reliable studies and due to very little follow-up (included studies ranged from three to twelve months). Differences in the fasting strategy used and limited possibility of generalization were also issues in creating sound recommendations.

Strengths of this review include a pre-register protocol that did not limit the sensitive literature search to specific language or periods. This study also assessed lifestyle interventions among trials with the cardiovascular risk factor included in a substantial proportion of the available scientific literature. These studies would not have been included if our analysis was limited to studies that focused exclusively on weight-loss. Trial Sequential Analysis was used to assess the optimal sample size for future studies. The applicability in clinical practice is a great asset in our review due to its applicability to obese participants and widely applied interventions.

CONCLUSION

The findings in this systematic review with meta-analysis and trial sequential analysis are relevant for clinical practice and applicable in real world settings. In the context of lifestyle change for obesity management, prudent diet with caloric restriction of at least 500 Kcal is effective to promote weight-loss for up to two years. Lifestyle intervention performed by a registered dietitian, associated with a behavioral component and twice-monthly health appointments should be considered. Future trials should investigate the long-term weight maintenance with caloric deficit using large-scale trials and a follow-up of greater than three years to reach the additional information size needed to obtain firm evidence.

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Author contributions

J.P.P., J.C.A., F.M.S. and V.C.L. designed and conceptualized this study. J.P.P. and V.C.L. conducted the literature search. J.P.P., T.A.S., J.D.B. and F.M.S. assessed eligibility. J.P.P. and T.A.S. conducted extraction of data and performed risk of bias assessment. F.M.S. and J.P.P. performed the statistical analysis. J.P.P. and J.C.A. drafted and reviewed the manuscript. All authors contributed to the critical revision of the manuscript, read and approved the final version.

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Declaration of interest

The authors declare no conflict of interest.

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Table 1 PICOS criteria for inclusion and exclusion of studies

Category	Definition	Exclusion criteria
Population	Obese adult (BMI ≥ 30 kg/m ²)	< 18 years old, pregnant, individuals with co-morbidities such as polycystic ovary syndrome, obstructive sleep apnea, cushing's syndrome
Intervention	Lifestyle change program with 6 month (minimum) intervention period and a follow-up of 12 months	Medication therapy, bariatric surgery, physical activity intervention only, meal replacement
Comparator	Control group	None
Outcome	Nutrition-related outcomes such as anthropometric measurements (e.g, body weight)	No nutrition-related outcomes
Study Design	Randomized clinical trials	Pre-post design quasi-experimental studies, systematic reviews, reviews, qualitative studies, cross-sectional studies, book chapters, case-control, cross-sectional studies, case reports, opinion, letter

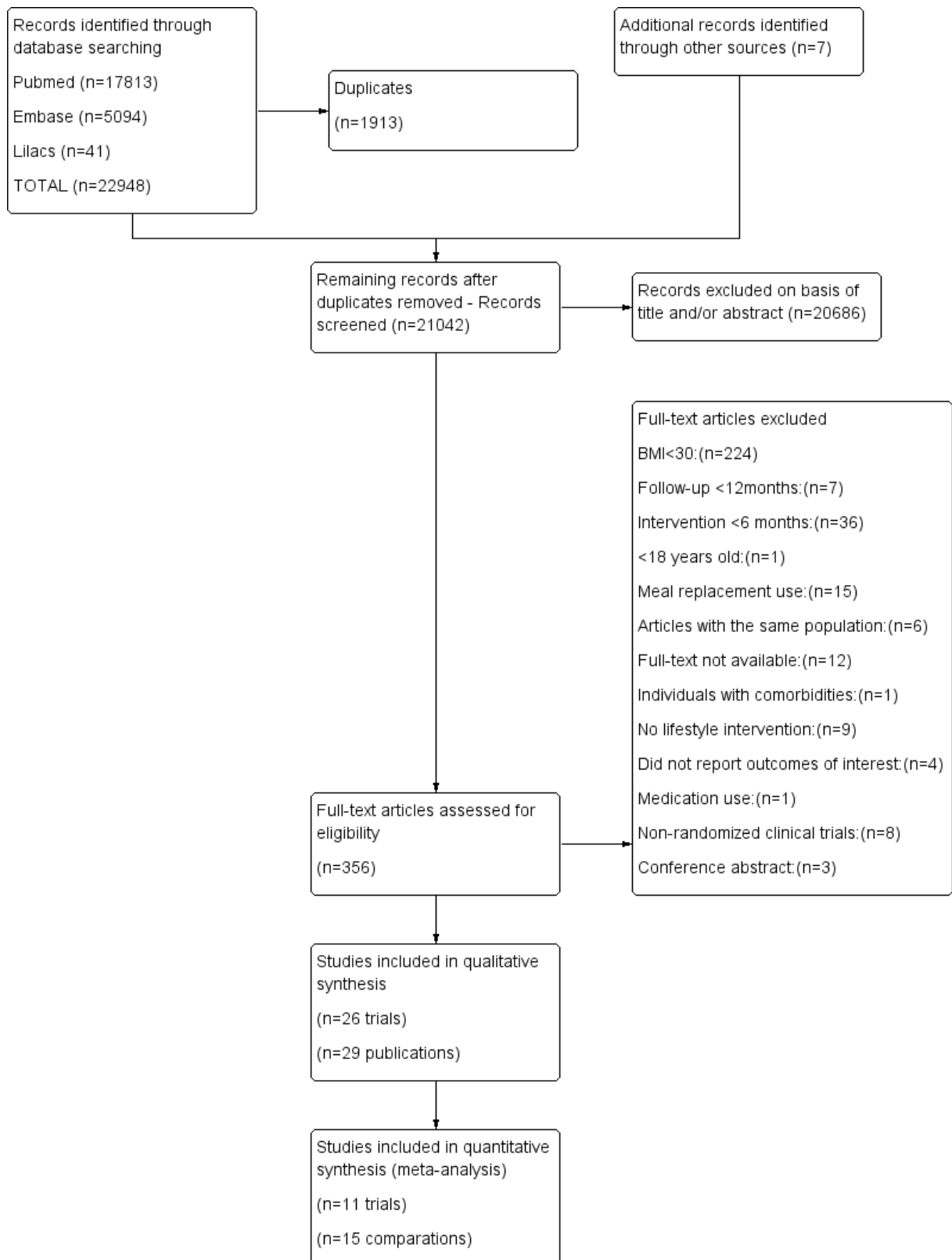


Figure 1 Flow diagram of the literature search process

Table 2 Characteristics of randomized clinical trials included in review

First author (Year) Journal Study name	Population	Duration Incentives	Interventions Interventionist	Control Conducted by	Dropout (%)
Randomized clinical trials included in meta-analysis					
Ard et al. (2018) ²³ J Gerontol A Biol Sci Med Sci The CROSSROADS	n = 164 70 ± 5 y 62 % females United States	<u>Intervention:</u> 12 months <u>Follow-up:</u> None Financial incentives	I: Prudent diet with caloric restriction (500 kcal/d) + 90-150 min/wk of exercise + behavioral recommendations Registered dietitian	C1: Prudent diet + 90-150 min/wk of exercise + behavioral recommendations Registered dietitian C2: Usual diet + 90-150 min/wk of exercise + behavioral recommendations Exercise trainer	I = 12.7 C1 = 16.4 C2 = 16.7
Mensinger et al. (2016) ³⁰ Appetite	n = 80 40 ± 4 y 100 % females United States	<u>Intervention:</u> 6 months <u>Follow-up:</u> 18 months Financial incentives	I: The LEARN Program with caloric restriction (> 500 kcal/d) Registered dietitian	C: HUGS Program : principles of eating for well-being and pleasure, size acceptance, and the importance of engaging in physical activity for personal enjoyment and fulfillment Psychologist and exercise trainer	I = 47.5 C = 52.5
Ma et al. (2015) ²⁴ Ann Intern Med	n = 240 52 ± 10 y 72 % females United States	<u>Intervention:</u> 12 months <u>Follow-up:</u> none Financial incentive: n.d.	I: Prudent diet with caloric restriction (500 - 1000 kcal/d) and < 7% of total energy from saturated fat + no physical activity recommendations Unclear	C: No caloric goals + increase fiber intake (> 30 g/d) + no physical activity recommendations Registered dietitian	I = 12.6 C = 9.9
Nurkkala et al. (2015) ³⁵ Eat Behav	n = 120 45 ± 11 y 78 % females Finland	<u>Intervention:</u> 9 months <u>Follow-up:</u> 27 months Financial incentive: n.d.	I: Prudent diet with caloric restriction (500-1000 kcal/d) + gradually increase physical activity at least 150 min/wk Registered dietitian	C: Booklet with principles of healthy diet and eating and physical activity Nurse	I = 34.4 C = 43.3
Nackers et al. (2013) ⁴³ Obesity	n = 125 52 ± 11 y 100 % females United States	<u>Intervention:</u> 6 months <u>Follow-up:</u> 6 months Financial incentive: n.d.	I: Prudent diet with 1000 kcal/d + 10.000 steps/d (~280 min) + cognitive and behavioral skills Unclear	C: Prudent diet with 1500 kcal/d + 10.000 steps/d + cognitive and behavioral skills Unclear	I = 12.3 C = 10.0
Soca et al. (2012) ⁴⁴	n = 150	<u>Intervention:</u>	I: Prudent diet with caloric restriction (300 kcal/d)	C: Usual diet and physical activity	I = 25.0

Aten Primaria	55 ± 1 y 100 % females Cuba	12 months <u>Follow-up:</u> None Financial incentive: n.d.	+ 90 - 240 min/wk of exercise Unclear		C = 11.4
Villareal et al. (2011) ⁴⁵ N Engl J Med	n = 107 70 ± 4 y 63 % females United States	<u>Intervention:</u> 6 months <u>Follow-up:</u> 6 months Financial incentive: n.d.	I1: Prudent diet with caloric restriction (500-750 kcal/d) + daily calcium and vitamin D supplement + behavioral therapy Registered dietitian I2: Prudent diet with caloric restriction (500-750 kcal/d) + daily calcium and vitamin D supplement + 270 min/wk of exercise+ behavioral therapy	C1: Usual diet+ daily calcium and vitamin D supplement C2: Usual diet (advice only) + daily calcium and vitamin D supplement + 270 min/wk of exercise Physical therapist	I1 = 11.5 I2 = 10.7 C1 = 14.8 C2 = 15.4
Cardillo et al. (2006) ⁴⁶ Eur Rev Med Pharmacol Sci Stern et al. (2004) ⁴⁷ Ann Intern Med	n = 132 53 ± 9 y 17 % females United States	<u>Intervention:</u> 12 months <u>Follow-up:</u> 24 months Financial incentive: n.d.	I:Registered dietitian and physical therapist Prudent diet with caloric restriction (500 kcal/d) with < 30% of calories derived from fat Experts in nutritional counseling	C: Carbohydrate intake < 30 g/d Experts in nutritional counseling	I = 61.8 C = 57.8
Bacon et al. (2005) ⁴⁸ J Am Diet Assoc	n = 78 39 ± 4 y 100% females United States	<u>Intervention:</u> 6 months <u>Follow-up:</u> 18 months	I: Prudent diet + 150 - 210min/wk of moderate exercise + behaviour change based on LEARN Program Registered dietitian	C: Health at every size program: Internal regulation of eating + body acceptance, eating behavior, nutrition, activity and social support Counselor	I = 51.3 C = 51.3
Esposito et al. (2003) ⁴⁹ JAMA	n = 120 35 ± 5 y 100 % females Italy	Unclear <u>Intervention:</u> 24 months <u>Follow-up:</u> None Financial incentive: n.d.	I: Prudent diet with 1300-1500kcal/d with <30% of total energy from fat + physical activity was individually tailored + behavioral counseling Registered dietitian	C: Lifestyle advices n.d.	I = 5.0 C = 8.3
Fleming (2002) ²⁵ Prev Cardiol.	n = 100 43 ± 8 y 53 % females United States	<u>Intervention:</u> 12 months <u>Follow-up:</u> None Financial incentive: n.d.	I1: Caloric intake 1400-1500 kcal/d with < 100g carbohydrate, 25-30 % protein and 55 - 65 % of total energy from fat +180 - 300 min/wk of exercise I2: Caloric intake 1500-1600 Kcal/d with caloric restriction (350-500 kcal/d) with 70 % carbohydrate, 15 % protein and 15 % of total energy from fat + 180-300 min/wk of exercise	C: Caloric intake 2000-2200Kcal/d with 60% carbohydrate, 15% protein and 20-30% of total energy from fat + 180-300 min/wk of exercise Unclear	n.d.

		I3: Caloric intake 1300-1400 kcal/d with 75 % carbohydrate, 15 % protein and 10 % of total energy from fat + daily multivitamin supplement + 180-300 min/wk of exercise			
		Unclear			
Randomized Clinical Trial included in review					
Annesi et al. (2017)²⁶	n = 107 49 ± 7 y 100 % females United States	<u>Intervention:</u> 12 months (I) 6 months (C) <u>Follow-up:</u> 12 months (I) 18 months (C) Financial incentive: n.d.	I: Caloric intake based on each participant's weight + 150 min/wk of moderate exercise + coach approach exercise-support protocol + cognitive-behavioral methods Unclear	C: Caloric intake 1200 kcal/d + 150 min/wk of moderate exercise + review of a written manual The LEARN Program + cognitive-behavioral methods Unclear	n.d.
Rieger et al. (2017)²⁷	n = 201 47 ± 12 y 74 % females Australia	<u>Intervention:</u> 12 months <u>Follow-up:</u> 12 months Financial incentive: n.d.	I: Caloric intake 1500 Kcal/d + physical activity was individually tailored + cognitive behaviour therapy with support person (motivational interviewing) Psychologist	C: Caloric intake 1500 Kcal/d + physical activity was individually tailored + cognitive behaviour therapy Psychologist	I = 56.1 C = 49.5
Spring et al. (2017)²⁸	n = 96 39 ± 12 y 100 % females United States	<u>Intervention:</u> 6 months <u>Follow-up:</u> 6 months Competition for financial incentives	I1: Caloric intake 1200 - 2000 kcal/d with 25% of total energy from fat (calorie and fat gram counting book) + gradually increase physical activity to 175 min/wk+ coaching calls + daily paper self-monitoring diaries Psychologist and coaches I2: Caloric intake 1200 - 2000 kcal/d with 25 % of total energy from fat (calorie and fat gram counting book) + gradually increase physical activity to 175 min/wk + coaching calls + android smartphone ENGAGED app and accelerometer Psychologist and coaches	C: Caloric intake 1200 - 2000 kcal/d with 25 % of total energy from fat (calorie and fat gram counting book) + gradually increase physical activity to 175 min/wk + daily paper self-monitoring diaries + group lifestyle balance DVDs adapted from the DPP curriculum No interventionist contact	I1 = 12.5 I2 = 3.1 C = 25.0
Lillis et al. (2016)²⁹	n = 162 50 ± 11 y 88 % females United States	<u>Intervention:</u> 12 months <u>Follow-up:</u> 12 months	I: Caloric intake 1200 - 1800 kcal/d with 25 % of total energy from fat + gradually increase physical activity to 250 min/wk + standard behavioral strategies + acceptance and mindfulness strategies	C: Caloric intake 1200 - 1800 kcal/d with 25 % of total energy from fat + gradually increase physical activity to 250 min/wk + standard behavioral strategies+ cognitive and emotional control strategies	I = 22.2 C = 21.0

			Registered dietitian	Registered dietitian	
		Financial incentive: n.d.			
Perri et al. (2014) ³¹	n = 612	<u>Intervention:</u>	I: Caloric intake 1200 - 1800 kcal/d with 25 % of total energy from fat + 30 min/d of exercise + training in behavior modification strategies (based on DPP)	C: Lifestyle advices	I1 =24.3
Obesity	52 ± 11 y	6 months	The sessions available for discussion varied according to the dose of treatment	Cooperative extension service family and consumer sciences agents	I2 =16.4
The Rural LITE	78 % females	<u>Follow-up:</u>	I1: Low dose treatment		I3 = 21.7
	United States	18 months	I2: Moderate dose treatment		C = 16.0
		Financial incentive: n.d.	I3: High dose treatment		
			Cooperative extension service family and consumer sciences agents		
Trief et al. (2014) ³²	n = 257	<u>Intervention:</u>	I: DPP adapted for phone delivery (conference calls)	C: DPP adapted for phone delivery individually	I = 43.7
Diabetes Res Clin Pract	52 ± 13 y	24 months	in group	Registered dietitian	C = 51.2
Weinstock et al. (2013) ³³	75 % females	<u>Follow-up:</u>	Registered dietitian		
United States		12 months			
J Gen Intern					
The SHINE					
		Financial incentive: n.d.			
Fitzgibbon et al. (2010) ⁵⁰	n = 213	<u>Intervention:</u>	I: Low-fat, high-fiber diet + 90 - 120 min/wk of moderate to vigorous exercise + walk ≥ 10.000 steps/d + motivational interviewing	C: Newsletters that covered general health and safety topics	I = 13.1
Obesity	46 ± 8 y	6 months			C = 8.5
The ORBIT	100 % females	<u>Follow-up:</u>		Unclear	
	United States	12 months	Unclear		
		Financial incentive: n.d.			
Foster et al. (2010) ³⁴	n = 307	<u>Intervention:</u>	I: Limit carbohydrate intake to 20 g/d gradually increased (5 g/d per week)+ daily multivitamin supplement + gradually increase physical activity to 200 min/wk + behavioral treatment	C: Prudent diet with 1200 - 1800kcal/d + daily multivitamin supplement+ gradually increase physical activity to 200 min/wk + behavioral treatment	I = 41.8
Ann Intern Med.	45 ± 10 y	24 months			C = 31.8
	68 % females	<u>Follow-up:</u>			
	United States	None	Registered dietitian or psychologist	Registered dietitian or psychologist	
		Financial incentive: n.d.			
Kalter-Leibovici et al. (2010) ⁵¹	n = 201	<u>Intervention:</u>	I: Prudent diet with 1200 – 1500 kcal/d+ sessions with exercise trainer + 150 min/wk of moderate exercise + written educational materials in arabic	C: Prudent diet with 1200-1500kcal/d + 150 min/wk of moderate exercise + written educational materials in arabic on healthy diet and physical exercise	I = 17.0
Arch Intern Med	44±6 y	12 months			C = 9.9
	100% females	<u>Follow-up:</u>	Intensive lifestyle intervention	Moderate lifestyle intervention	
	Israel	None			
		Financial incentive: n.d.	Registered dietitian	Registered dietitian	
Perri et al. (2008) ³⁶	n = 234	<u>Intervention:</u>	I1: Prudent diet with 1200 kcal/d+ 210 min/wk of exercise + training in behavior modification	C: Prudent diet with 1200 kcal/d+ 210 min/wk of exercise + training in behavior modification	I1 = 6.9
Arch Intern Med	59 ± 6 y	6 months			I2 = 10.8
Radcliff et al.	100 % females				C = 6.7

(2012) ³¹ J Acad Nutr Diet The TOURS	United States	<u>Follow-up:</u> 12 months Financial incentive: n.d.	Follow-up with individual telephone counseling Cooperative extension service family and consumer sciences agents I2: Prudent diet with 1200kcal/d + 210 min/wk of exercise + training in behavior modification Follow-up with face-to-face counseling Cooperative extension service family and consumer sciences agents	C: Follow-up with newsletters Cooperative extension service family and consumer sciences agents	
Villareal et al. (2008) ³⁸ J Clin Endocrinol Metab	n = 27 70 ± 5 y 67 % females United States	<u>Intervention:</u> 6 months <u>Follow-up:</u> 6 months Financial incentive: n.d.	I: Prudent diet with caloric restriction (500 - 750 kcal/d)+ daily multivitamin supplement + 270 min/wk of exercise + behavioral therapy Registered dietitian	C: Usual diet and activities	I = 7.4 C = 10.0
Ebbeling et al. (2007) ³⁹ JAMA	n = 73 28 ± 4 y 79 % females United States	<u>Intervention:</u> 6 months <u>Follow-up:</u> 12 months Financial incentives	I: Diet with 40 % carbohydrate (low-glycemic), 25 % protein and 35 % of total energy from fat + 150-210 min/wk of moderate exercise Registered dietitian	C: Diet with 55% carbohydrate, 25% protein and 20% of total energy from fat + 150-210 min/wk of moderate exercise Registered dietitian	I = 22.2 C = 37.8
Ello-Martin et al. (2007) ⁴⁰ Am J Clin Nutr	n = 97 45 ± 13 y 100 % females United States	<u>Intervention:</u> 6 months <u>Follow-up:</u> 6 months Financial incentives	I: Ad libitum diet and recommendations for reducing fat consumption and increase intake of water-rich foods + gradually increase steps to 10.000/d + behavior therapy Registered dietitian	C: Ad libitum diet and recommendations for reducing fat consumption+ gradually increase steps to 10.000/d + behavior therapy Registered dietitian	I = 27.1 C = 26.5
Thompson et al. (2005) ⁴¹ Obes Res	n = 90 41 ± 9 y 85 % females United States	<u>Intervention:</u> 12 months <u>Follow-up:</u> None Financial incentive: n.d.	I1: Prudent diet with caloric restriction (500 kcal/d) with increase amount of fiber and four servings of dairy+ 120 min/wk of exercise Registered dietitian I2: Prudent diet with caloric restriction (500 kcal/d) with four servings of dairy+ 120 min/wk of exercise Registered dietitian	C: Prudent diet with caloric restriction (500 kcal/d) with two servings of dairy+ 120 min/wk of exercise Registered dietitian	I1 = 22.6 I2 = 26.7 C = 10.3

Kumanyika et al. (2005) ⁴² Prev Med The HELP	n = 128 43 ± 10 y 91 % females United States	<u>Intervention:</u> 21 months <u>Follow-up:</u> None Gifts as incentives	I1: Prudent diet with 1200-1500kcal/d + advice to increase physical activity was individually tailored + behavioral change + Counseling classes Registered dietitian I2: Prudent diet with 1200 - 1500kcal/d + advice to increase physical activity was individually tailored + behavioral change + Self-directed weight management facilitated by a staff member Registered dietitian	C: Prudent diet with 1200 - 1500kcal/d + advice to increase physical activity was individually + behavioral change + Usual care (clinic visits only) Registered dietitian and personal physicians	I1 = 34.9 I2 = 34.9 C = 26.2

Abbreviations: n, number of participants; I, intervention group; C, control group; n.d., no data; CROSSROADS, Calorie Restriction in Overweight Seniors: Response of Older Adults to a Dieting Study; LEARN: lifestyle, exercise, attitudes, relationships, nutrition; HUGS, Health-focused, Understanding lifestyle, Group supported, and Self-esteem building; ENGAGED; E-Networks Guiding Adherence to Goals in Exercise and Diet; DPP, Diabetes Prevention Program; LITE, Lifestyle Intervention Treatment Effectiveness; SHINE, Support, Health Information, Nutrition and Exercise; ORBIT, Obesity Reduction Black Intervention Trial; TOURS, Treatment of Obesity in Underserved Rural Settings

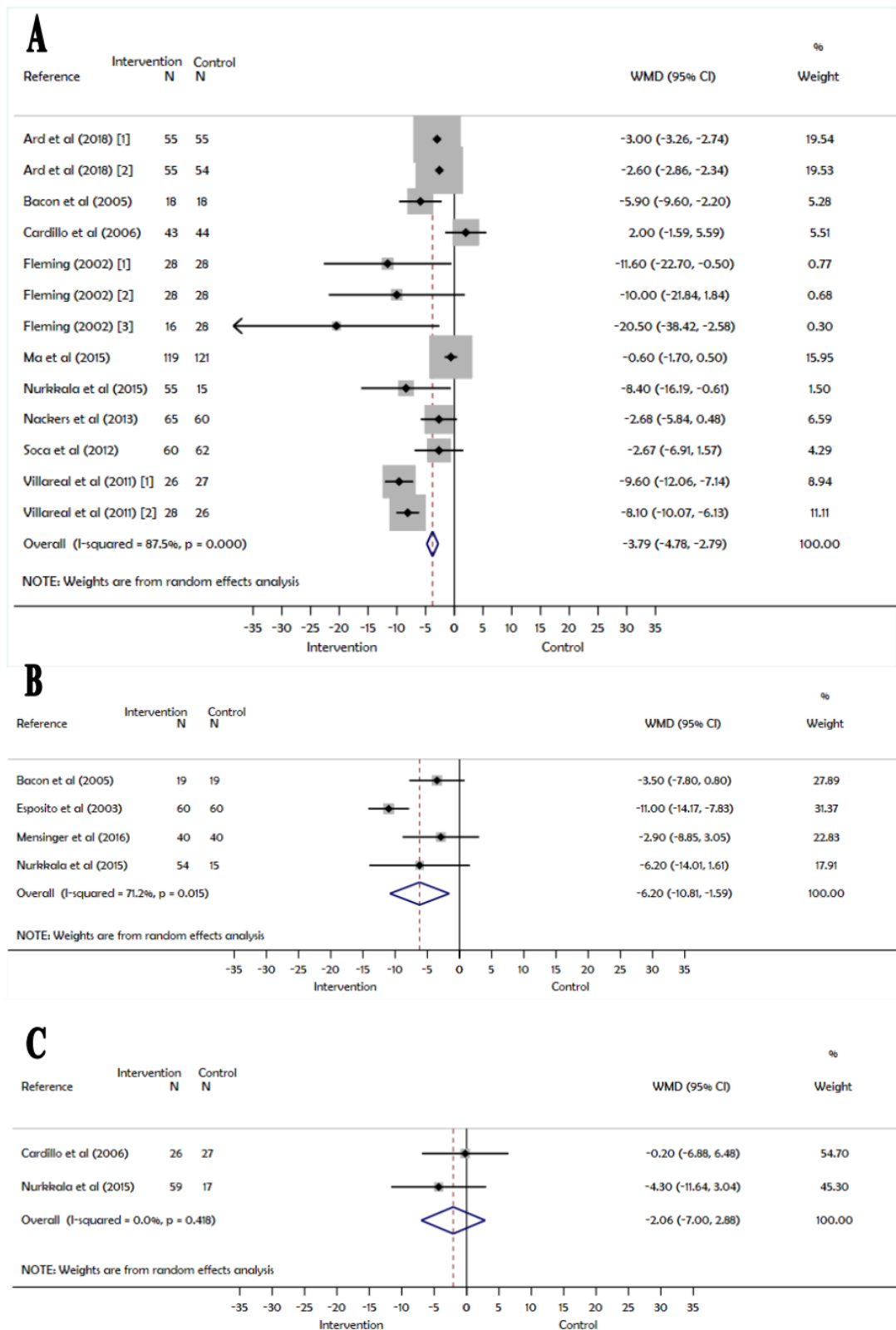
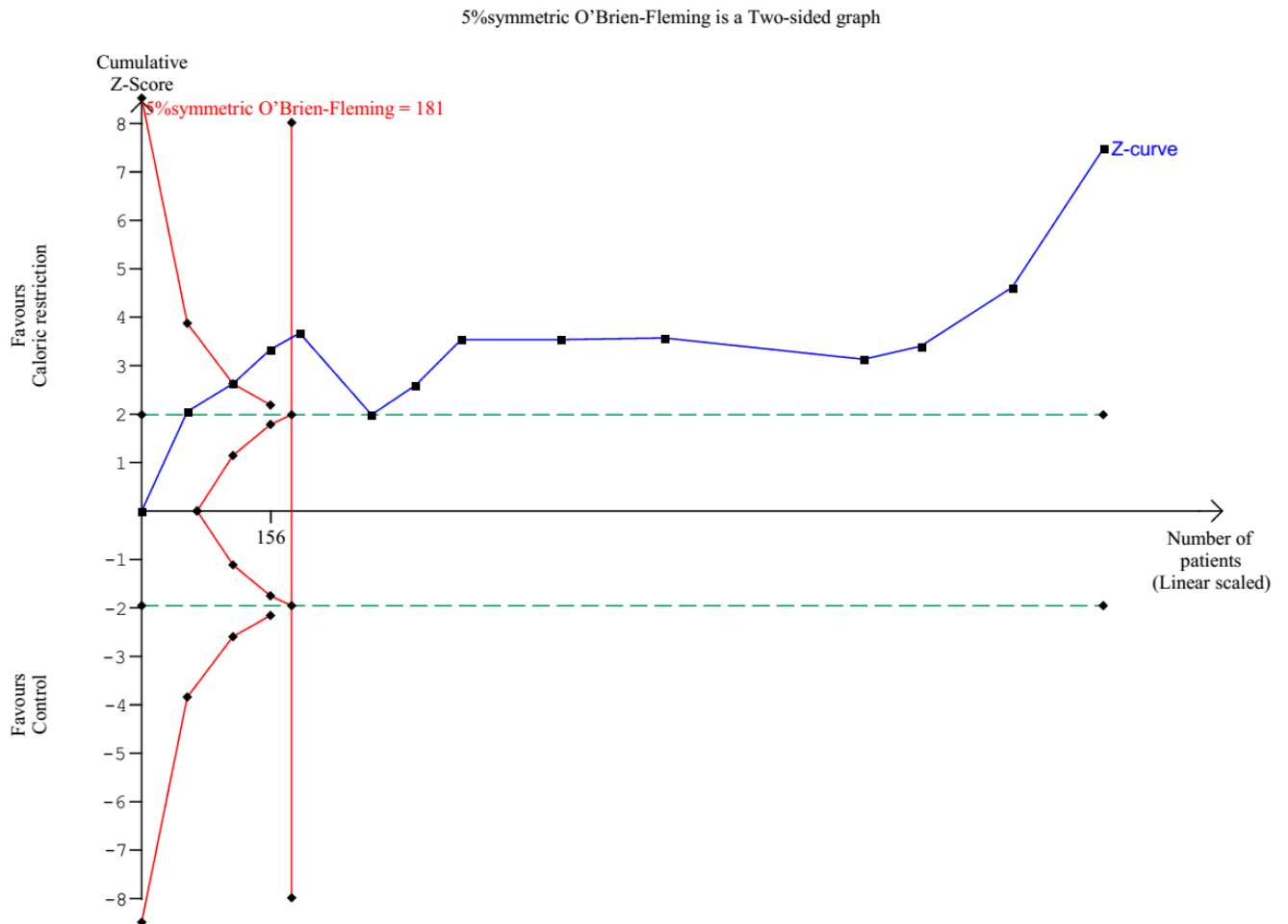


Figure 2 Forest plot of the effect of caloric restriction on body weight (Kg). **A**, at 12 months (n = 1162 participants); **B**, at 24 months (n = 307 participants); **C**, at 36 months (n = 129 participants). Abbreviations: N, number of participants; WMD, weighted mean difference; CI, confidence interval; I^2 , Higgins's inconsistency statistic



	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Food provide, market voucher or financial incentives	Interventionist	Adherence to dietary intervention
Ard et al (2018)	+	+	+	+	+	+	+	+	?
Bacon et al (2005)	?	?	?	?	+	+	+	+	?
Cardillo et al (2006)	+	?	+	?	?	?	+	?	?
Esposito et al (2003)	+	?	+	+	+	+	+	+	?
Fleming (2002)	?	?	?	?	?	+	+	?	-
Ma et al (2015)	+	?	?	+	+	+	-	+	?
Mensinger et al (2016)	+	+	?	?	+	+	-	+	?
Nackers et al (2013)	?	?	?	?	+	+	+	?	+
Nurkkala et al (2015)	?	?	?	?	?	+	+	+	?
Soca et al (2012)	+	+	?	?	+	+	+	?	?
Villareal et al (2011)	?	?	?	+	+	+	+	+	?

Figure 4 **Cochrane Risk of bias summary.** Low risks of bias are green, unclear risk of bias are yellow, high risk of bias are red

Supporting Information

Table S1. PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	p. 1
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	p. 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	p. 3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	p. 4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., web address), and, if available, provide registration information, including a registration number.	p. 4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility and providing rationale.	p. 18 (Table 1)
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and also the date last searched.	p. 4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	p. 32 (Table S 2)
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in the systematic review and, if applicable, included in the meta-analysis).	p. 5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes used to obtain and confirm data from investigators.	p. 5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	p. 5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level) and how this information is to be used for any data synthesis.	p. 5-6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	p. 6
Synthesis of results	14	Describe the methods of handling data and combining the results of studies (if done) including measures of consistency (e.g., I^2) for each meta-analysis.	p. 6-7
Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	p. 7
Additional analyses	16	Describe methods for additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicate which were pre-specified.	p. 7
RESULTS			

Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review. Include with reasons for exclusions at each stage, ideally with a flow diagram.	p. 19 (Figure 1)
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide citations.	p. 20-25 (Table 2)
Risk of bias within studies	19	Present data on the risk of bias for each study and, if available, any outcome level assessment (see item 12).	p. 28 (Figure 4)
Results of individual studies	20	For all outcomes considered (benefits or harms), present for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	p. 26; p. 44-46
Synthesis of results	21	Present results of each completed meta-analysis, including confidence intervals and measures of consistency.	p. 26; p. 44-46
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	p. 8; p. 43
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	p. 8-10
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	p. 10-13
Limitations	25	Discuss limitations at the study and outcome levels (e.g., risk of bias), and at the review-level (e.g., incomplete retrieval of identified research, reporting bias).	p. 12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence and the implications for future research.	p. 13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	p. 14

Table S 2 Search Strategy for PUBMED/MEDLINE

#1	<i>("Obesity"[MeSH Terms] OR "Obesity, Abdominal"[MeSH Terms] OR "Obesity, Morbid"[MeSH Terms])</i>
#2	<i>("life style"[MeSH Terms] OR "healthy lifestyle"[MeSH Terms] OR "life change events"[MeSH Terms] OR "health behavior"[MeSH Terms] OR "diet"[MeSH Terms] OR "healthy diet"[MeSH Terms] OR "caloric restriction"[MeSH Terms] OR "Diet, Reducing"[MeSH Terms] OR "weight reduction programs"[MeSH Terms] OR "behavior therapy"[MeSH Terms] OR "health education"[MeSH Terms])</i>
#3	<i>("body mass index"[MeSH Terms] OR "adiposity"[MeSH Terms] OR "weight-loss"[MeSH Terms] OR "body weight changes"[MeSH Terms] OR "waist circumference"[MeSH Terms] OR "abdominal fat"[MeSH Terms] OR "body composition"[MeSH Terms] OR "body weight"[MeSH Terms] OR "body weight maintenance"[MeSH Terms] OR "body weight changes"[MeSH Terms] OR "Cholesterol, LDL"[MeSH Terms] OR "Cholesterol, HDL"[MeSH Terms] OR "arterial pressure"[MeSH Terms] OR "blood pressure"[MeSH Terms] OR "blood glucose"[MeSH Terms] OR "triglycerides"[MeSH Terms] OR "Diabetes Mellitus"[MeSH Terms] OR "Diabetes Mellitus, Type 2"[MeSH Terms] OR "Cardiovascular Diseases"[MeSH Terms] OR "Metabolic Syndrome"[MeSH Terms])</i>
#4 ⁵⁸	<i>((("clinical"[Title/Abstract] AND "trial"[Title/Abstract]) OR "clinical trials as topic"[MeSH Terms] OR "clinical trial"[Publication Type] OR "random*"[Title/Abstract] OR "random allocation"[MeSH Terms] OR "therapeutic use"[MeSH Subheading]))</i>
#5	<i>"animal*"[Title/Abstract]</i>
Search	<i>#1 AND #2 AND #3 AND #4 NOT #5</i>

Table S3 Strategies for weight-loss and weight maintenance

First author (year)	Diet	Exercise	Behaviour
Annesi et al. (2017) ²⁶	<p>I: Increased fruit and vegetable intake, overall healthy diet was emphasized in which energy intake was based on each participant's weight and participants were encouraged to review the USDA's website www.ChooseMyPlate.gov for nutrition information</p> <p>C: Caloric intake kept to 1200 kcal/d and The LEARN Program sections about nutrition were reviewed.</p>	<p>I: 6 personal meetings of coach approach and exercise-support protocol that included the development of self-regulatory skills such as long- and short-term goal setting linked with progress monitoring, cognitive restructuring, stimulus control, behavioral contracting, dissociation from discomfort, controlling behavioral cues and triggers, and relapse prevention; these were intended to overcome barriers to maintain regular exercise.</p> <p>C: Participants were informed of the recommended 150 min of moderate exercise/wk and reviewed The LEARN Program sections related to physical activity behavioral change (e.g., "maximizing the pleasure of walking").</p>	<p>I: 10 group sessions were focused on applying self-regulatory methods to both losing and maintaining the lost weight and were based on each participant's weight-loss goals. <i>6 individual sessions and 10 group session</i></p> <p>C: 12 groups reviewing The LEARN Program sections that were related to eating behavioral change (e.g., "conquering the cravings") and psychological factors (e.g., "developing a positive body image") + 12, 15 minute phone conversations. <i>12 sections and 12, individual calls</i></p> <p>I and C: Treatments were based on social cognitive and self-efficacy theory and cognitive-behavioral methods intended to develop self-regulatory skills to overcome barriers to behavioral change and increase perceptions of competence.</p>
Rieger et al. ²⁷ (2017)	<p>I and C: Caloric intake was kept to 1500 Kcal/d and patients were provided a book and website addresses for calculating their caloric intake and structure of eating (three meals and two to three snacks each day), daily self monitoring of eating was also instituted.</p>	<p>I and C: Daily self monitoring of physical activity and stimulus were used to increase physical activity.</p>	<p>I and C: 26, 90 - minute group sessions comprised of eight weekly, 16 fortnightly, and two monthly sessions that were focused on teaching cognitive-behavioral skills for dietary modification and increasing physical activity, sessions taught a range of cognitive and behavioral skills to assist with weight control, such as goal setting, strategies for managing cravings, strategies for managing social situations that trigger overeating, strategies for managing emotional triggers of overeating, problem-solving skills, identifying and challenging dysfunctional thoughts that trigger overeating, graded physical activity, and targeting body dissatisfaction</p> <p>I: 10, 90 - minute group developed on the basis of published motivational interviewing and programs for support people in the context of substance misuse and eating disorders + the aim of the intervention to help increase patients' perceived importance of weight-loss, increase their self efficacy for weight-loss reviewing their weight goals, and identifying the strategies the patient uses to achieve these goals or the obstacles that are impeding goal attainment <i>36 group sessions</i></p> <p>C: <i>26 group sessions</i></p>
Spring et al. ²⁸ (2017)	<p>I1, I2 and C: Caloric intake 1200 - 2000 kcal/d</p> <p>I1: Calorie and fat gram counting book and daily paper self-monitoring diaries.</p>	<p>I1, I2 and C: Gradually increase physical activity to 175 min/wk.</p> <p>I1 and I2: 30-minute guided walking exercise</p>	<p>I1 and I2: For the first 8 weeks, 90-minute group sessions focused on nutrition, physical activity, and behavior change strategies + weekly for the first 8 weeks and monthly from</p>

	<p>I2: ENGAGED App to self-monitor dietary intake and body weight and showed traffic-light colors depicting calorie and fat gram allowances remaining for that day and two-four personalized messages/wk</p> <p>C: 1, 60-minute group session during which treatment assignment was revealed and participants received their weight-loss target, calorie and fat gram counting book and daily paper self-monitoring diaries.</p>	<p>was offered after group sessions</p> <p>I2: Accelerometer to objectively measure physical activity.</p>	<p>months 3 to 6, participants received 10 to 15-minutes calls during which trained coaches reviewed self-monitoring and goal attainment and helped participants solve problems. <i>8 group sessions and 12 individual coach calls</i></p> <p>C: DVDs presenting 12 mock group treatment sessions adapted from the original DPP curriculum were used. <i>1 group session</i></p>
Ard et al.* (2018) ²³	<p>I: Prudent diet and goal to reduce caloric intake by 500 kcal/d below estimated total energy needs based on measured resting energy expenditure, with a minimum intake of 1000 kcal/d.</p> <p>C1: Prudent diet</p> <p>C2: Usual diet</p>	<p>I, C1 and C2: 90-150 min/wk of cardio-aerobic exercise + written program to guide participation in two sessions/wk of resistance training using resistance bands focused on major muscle groups of the extremities + after behavioral group, 30 minutes of supervised exercise using resistance band exercises.</p>	<p>I, C1 and C2: Weekly 30 min, behavioral group counseling for the first 24 weeks of the intervention, then, every 2 weeks for the remainder of the intervention with discussions related to diet, exercise or behavioral topics. <i>36 group sessions</i></p>
Lillis et al. ²⁹ (2016)	<p>I and C: Caloric intake 1200 - 1800 kcal/d with 25% of total energy from fat, sample meal plans are provided and participants are given a fat/calorie guidebook and instructed to self-monitor their daily calorie and fat intake in their food diaries.</p>	<p>I and C: gradually increase physical activity to 250 min/wk.</p>	<p>I: 1h, groups meeting weekly during months 1 to 6, then biweekly during months 6 to 9, and monthly during months 9 to 12, for a total of 32 sessions of acceptance and mindfulness strategies: mindful awareness of/detachment from problematic thoughts, acceptance of unwanted emotions and food cravings, values clarification techniques and commitment to values-consistent behavior in the presence of difficult thoughts, feelings, and cravings + standard behavioral strategies. <i>32 group sessions</i></p> <p>C: Weekly 1h groups meetings during months 1 to 6, then biweekly during months 6 to 9, and then monthly during months 9 to 12, for a total of 32 sessions. With standard behavioral strategies: cognitive and emotional control techniques, stopping/replacing negative thoughts, distraction techniques, relaxation skills and environmental control methods <i>32 group sessions</i></p>
Mensingher et al.* (2016) ³⁰	<p>I: Group based on LEARN Program met weekly for 90-min sessions for 6 months. Food intake recommendations were based on external prescriptions and caloric restriction <i>24 group sessions</i></p> <p>C: Group met weekly for 90-min sessions for 6 months, based on HUGS Program emphasizing the principles of eating for well-being and pleasure and size acceptance. Weight-neutral program taught strategies to recognize and respond to internal physiological signs of hunger and satiety to</p>	<p>I: Recommendations based on LEARN Program</p> <p>C: Emphasized the importance of engaging in physical activity for personal enjoyment and fulfillment</p>	<p>I: Participants received the LEARN manual, the LEARN Weight Stabilization and Maintenance and the LEARN Program CD set</p> <p>C: Participants received the books, Staying Off of the Diet Roller Coaster and Tailoring Your Tastes, in addition to a booklet of psycho-educational worksheets and a set of affirmation CDs produced by HUGS Inc.</p>

Ma et al.* (2015) ²⁴	<p>determine food intake. 24 group sessions I: Prudent diet based on American Heart Association dietary guidelines with caloric restriction. <i>Unclear</i></p>	I and C: No physical activity recommendations	I and C: Unclear
Nurkkala et al.* (2015) ³⁵	<p>C: 2 individual sessions and 12 group sessions focus on educating individuals about fiber and how to increase consumption by eating a variety of fiber-rich foods. Individuals are instructed to gradually increase fiber intake. Each participant received a manual containing intervention materials organized by session, home activity worksheets, resources, recipes, and suggestions for choosing high-fiber meals in restaurants. 2 individual sessions and 12 group sessions I: During the first year the intervention group was given individual weight counseling and were instructed to reduce energy intake 500 to 1000 kcal/d lower than their current energy expenditure three times by a nutritionist and eleven times by a qualified nurse. During the second year, the individuals met the nurse four times and during the third year, two times. The goal was to achieve and sustain a 10 % decrease in weight. 20 individual sessions C: Subjects met a nurse individually once at the beginning and also received a booklet concerning the principles of weight management: contained information about healthy diet and eating (e.g. eating of vegetables, quality of fats, fiber, regular eating, plate size, etc.) and physical activity.</p>	<p>I: The participants were instructed to gradually increase moderate aerobic physical activity for at least 150 min/wk and muscle-strengthening and balance training 2 times a week. Short bouts, 10 - 15 min, of exercise sessions 2 - 3 times/d were encouraged to meet the exercise goal. The participants were also advised by qualified nurse to decrease their sedentary time and were instructed to maintain these dietary recommendations throughout the study period, unless the agreed body weight was achieved.</p>	<p>I: Eating behavior was taken into account during the counseling using questionnaires, exercises and diaries about supporting permanent change in eating behavior to achieve successful weight-loss management.</p>
Perri et al. (2014) ³¹	<p>1 individual sessions I1, I2 and I3: Caloric intake 1200 - 1800 kcal/d with 25 % of total energy from fat, cooking demonstrations to illustrate low-calorie preparation. The intervention content and the accompanying written materials provided to participants were the same for the interventions, but the time available for discussion varied according to the dose of treatment I1: 8 group sessions (based on DPP) + 8 individual calls + 1 campaign (enhance motivation by setting specific weight-loss targets and providing</p>	<p>I1, I2 and I3: 30 min/d of walking above baseline levels C: Lecture on a topic relevant to physical activity.</p>	<p>I1, I2 and I3: Based on DPP, training in behavior modification strategies including goal setting, self-monitoring, stimulus control, cognitive restructuring, and problem solving. C: Lecture on a topic relevant to weight control. The information presented in the lectures was derived from resources available from US government agencies.</p>

Trief et al. (2014) ³² Weinstock et al. (2013) ³³	<p>motivational incentives) I2: 16 group sessions + 16 individual calls + 2 campaign I3: 24 group sessions + 24 individual calls + 3 campaign C: 8 group sessions + 8 individual calls and 1 campaign. Lecture on a topic relevant to nutrition DPP materials were adapted for delivery by telephone. The 16 - session core curriculum, which included goal-setting, self-monitoring, diet modification and problem-solving. Topics were presented weekly for the first 5 weeks, then monthly. A modified 12-session curriculum was used during year 2. <i>28 group session by telephone and ~17 individual coach calls</i></p>	I and C: Activity modification	I and C: Coaches made monthly calls, individually. During year 2, each participant could request up to six coach contacts. They answered questions, provided goal setting and feedback, and problem solved behavior change barriers.
Nackers* et al. (2013) ⁴³	<p>C: DPP adapted for phone delivery individual I and C: Months 0-6 involved an initial treatment of 24 weekly group sessions; Months 7-12 with six monthly group sessions. The prescribed diet (according to recommendations) from the USDA and the National Institutes of Health's Dietary Approaches to Stop Hypertension. <i>30 group session</i></p>	I and C: Participants were encouraged to increase walking to 10000 steps/d (or by 3000 steps above baseline levels). To assist in accomplishing these behavioral goals, participants were instructed to maintain detailed daily written records of physical activity with provided pedometers.	I and C: Training in cognitive and behavioral skills including stimulus control, self-reinforcement, cognitive restructuring, and problem solving. Each group session involved a private weigh-in, review of participants' progress toward goals, feedback, encouragement from group leaders and other group members, and a brief presentation related to nutrition, physical activity, stress management, or behavioral management of eating and physical activity.
Soca* et al. (2011) ⁴⁴	<p>I: Prudent diet with 1000 kcal/d C: Prudent diet with 1500 kcal/d I: Prudent diet with caloric restriction (300 kcal/d) <i>Unclear</i> C: Usual diet</p>	I: The exercise program was structured for 48 weeks, with 3 times/wk according to the principles: the specificity of the training, the overload, the increase progressive of the load, the individuality, the reversibility, the systematic functions and the adequate relation work-rest.	I and C: None
Villareal* et al. (2011) ⁴⁵	<p>I1 and I2: Prudent with an energy deficit of 500 to 750 kcal/d from daily energy requirement + daily calcium and vitamin D supplement. Participants met as a group with a dietitian for adjustments to their</p>	<p>C: Usual physical activity I1 and C1: Usual physical activity I2 and C2: Individuals participated in three group exercise-training sessions/wk. Each</p>	<p>I1 and I2: Participants met weekly as a group for behavioral therapy and instructed to set weekly behavioral goals. C1 and C2: None</p>

Fitzgibbon et al. (2010) ⁵⁰	<p>caloric intake. They attend weekly weigh-in sessions. Food diaries were reviewed, and new goals were set on the basis of diary reports.</p> <p><i>52 group sessions</i></p> <p>C1 and C2: Usual diet, just general information about a healthy diet and daily calcium and vitamin D supplement.</p> <p>I: participants were encouraged to adopt a low-fat, high-fiber diet with increased fruit and vegetable consumption</p> <p><i>48 group sessions and 12 individual motivational interviewing</i></p> <p>C: newsletters that covered general health and safety topics on a weekly basis throughout the 6- month period and every month during the maintenance period.</p> <p><i>36 newsletters</i></p>	<p>session was approximately 90 minutes in duration and consisted of aerobic exercises, resistance training, and exercises to improve flexibility and balance.</p> <p>I: Exercise objectives included exercising at a moderate to vigorous level a minimum of 3-4 times/wk for at least 30 minutes. Participants also received pedometers and were asked to increase their physical activity to a level equivalent to 10000 steps/d. The didactic session was followed by a physical activity session that incorporated aerobic activity as well as strength and flexibility training. To increase the variety, some physical activity sessions included salsa dancing, African dancing, belly dancing, yoga, and pilates. The second meeting of each week was 60 minutes in length and included a 30-40 minute physical activity class and discussion of topics related to increasing regular physical activity.</p> <p>C: none</p>	<p>I: The development and delivery of the interventions were based on Social Cognitive Theory and thus, focused on changes in cognition, behaviors, and social support related to weight-loss. The weight-loss intervention (6 months) was conducted in a small group format and met weekly and consisted of a weekly weigh-in, a didactic session. In months 7-12, the group met twice weekly for 45-60 minutes, and each member received monthly motivational interviewing sessions (face to face or by calls). During the group meetings, the didactic sessions were replaced with a support group conducted by the participants. During months 13-15, women continued to receive monthly MI. Finally, during months 16-18, there were no face-to face group meetings, but women continued to receive MI.</p> <p>C: none</p>
Foster et al. (2010) ³⁴	<p>I: During the first 12 weeks of treatment, participants were instructed to limit carbohydrate intake to 20 g/d in the form of low- glycemic index vegetables. After the first 12 weeks, participants gradually increased carbohydrate intake (5 g/d per week) by consuming more vegetables, a limited amount of fruits, and eventually small quantities of whole grains and dairy products, until a stable and desired weight was achieved. They followed guidelines described in Dr. Atkins' New Diet Revolution, which limited carbohydrate intake but allowed unrestricted consumption of fat and protein and a multivitamin supplement</p> <p>C: Prudent diet with 1200 - 1800kcal/d and multivitamin supplement.</p>	<p>I and C: All participants were prescribed the same level of physical activity (principally walking), beginning on week 4, with 4 sessions of 20 minutes each and progressing by week 19 to 4 sessions of 50 minutes each.</p>	<p>I and C: All participants received comprehensive, in-person group behavioral treatment weekly for 20 weeks, every other week for 20 weeks, and then every other month for the remainder of the 2-year study period. Topics included self-monitoring, stimulus control, and relapse management. Group sessions reviewed participants' completion of their eating and activity records, as well as other skill builders. There was 1 brief (15 minute) individual session at week 30 that focused on assessing progress and goal setting for the future.</p> <p><i>~38 group sessions</i></p>
Kalter-Leibovici et al. (2010) ⁵¹	<p>I and C: 1500 kcal/d target was set for participants who consumed 2500 kcal/d or more at baseline and a 1200 kcal/d target for women who reported consuming less than 2500 kcal/d.</p>	<p>I: 2 monthly group sessions: muscle strengthening, aerobic exercise, and provision of instructions for home exercise and at least 150 minutes/wk of leisure physical activity of</p>	<p>I and C: The themes discussed, such as social norms and women's role in Arab society and in the family, were addressed in the intervention design.</p>

		moderate intensity.	
	I: Monthly individual counseling session and a monthly group meeting with a dietitian. <i>12 individual sessions + 36 group sessions</i>	C: At least 150 minutes/wk of leisure physical activity of moderate intensity	
Perri et al. (2008) ³⁶ Radcliff et al. (2012) ³⁷	C: <i>3 individual sessions and 2 group sessions</i> II, I2 and C: The initial 6-month program delivered to groups (based on DPP) included a low-calorie eating plan (at least 1200 kcal/day), cooking demonstrations, strategies for coping with a lack of family support for weight-loss, and techniques for healthful eating while away from home. Then, participants were randomized for the follow-up. II: Individual telephone counseling that included bi-weekly sessions were provided during extended care (12 months). The 15-20 minute sessions addressed barriers to maintain eating and exercise behaviors required for sustaining lost weight, 5-stage problem-solving model were used <i>26 individual calls</i> I2: Group sessions, with 60-minute addressed barriers to the maintenance of eating and exercise behaviors required for sustaining lost weight during 12 months, the 5-stage problem-solving model was used. <i>26 face-to-face group sessions</i> C: During follow up, 26 biweekly newsletters that contained tips for maintaining weight-loss progress along with recipes for low-calorie meals <i>26 biweekly newsletters</i>	II, I2 and C: The initial 6-month program included strategies to increase physical activity (30 min/d of walking).	II, I2 and C: The initial 6-month program included a training in behavior modification strategies, such as goal setting and self-monitoring of daily food intake and during the follow up of all participants were encouraged to continue using behavioral weight-control strategies and were asked to complete written self-monitoring logs of food intake.
Villareal et al. (2008) ³⁸	I: Subjects met weekly as a group. Participants were prescribed a balanced diet to provide an energy deficit of 500-750 kcal/d of a prudent diet. In addition, subjects were given a daily multivitamin supplement and were counseled to consume adequate dietary calcium and vitamin D Total calorie intake was adjusted to prevent more than a 1.5 % loss of body weight/wk. <i>52 group sessions</i> C: Usual diet	I: Exercise training sessions were conducted as a group on three non-consecutive days each week. Each session lasted about 90 min: 15 min of flexibility exercises, 30 min of endurance exercise, 30 min of strength training, and 15 min of balance exercises. Subjects exercised at moderate intensity (75 % of peak heart rate), and the intensity of exercise was gradually increased over several weeks to between 80 and 90% of peak heart rate. C: Usual diet	I: Standard behavioral techniques were used to change eating habits.
Ebbeling et al.	I and C: The same intervention of a 6-month	I and C: Physical activity recommendations	I and C: Principles of non-formal adult education and

(2007) ³⁹	<p>intensive intervention period and a 12-month follow-up period was implemented for both groups. Diets were prescribed using an ad libitum approach that relied on intrinsic control of energy intake based on the presumption that these diets would decrease hunger, increase satiation and/or satiety, and therefore, promote a negative energy balance <i>23 group sessions and 1 individual session and 5 motivational calls</i></p> <p>I: Participants were counseled to consume low-glycemic load foods (particularly non-starchy vegetables, legumes, and temperate fruits) and to limit intake of high-glycemic load foods, such as refined grains, starchy vegetables, fruit juices, and sweets. Attention was also directed toward consuming sources of healthy fat including, nuts, seeds, and oils.</p> <p>C: Participants were counseled to consume low-fat grains, vegetables, fruits, and legumes and to limit intake of added fats, sweets, and high-fat snacks. The intervention was designed to prescribe a diet consistent with low-fat guidelines.</p>	<p>were consistent between groups and based on public health guidelines: 150-210 min/wk of moderate exercise.</p>	<p>participant-centered counseling were applied to promote adherence to the diets. The primary objective of the workshops was to foster knowledge and skills necessary to follow the respective diets, and the purpose of the telephone calls was to enhance motivation for translating knowledge and skills to change dietary behaviors. Dietitians directed the negotiation of goals with participants and empathetic when assisting them to overcome adherence challenges.</p>
Ello-Martin et al. (2007) ⁴⁰	<p>I and C: During the first 6 months, participants met individually with a dietitian once/wk for 30 min. During the second 6 months, participants attended one small group session (topics for practical review: holiday eating, cooking and recipe modification, appropriate portion sizes, label reading, dining out, and grocery shopping) and one individual session with a dietitian each month. Subjects were instructed in cooking and recipe modifications and grocery shopping and dining-out strategies and were provided with meal and snack ideas. <i>32 individual sessions + 6 group sessions</i></p>	<p>I and C: Physical activity information for both groups focused on walking and using a pedometer to set goals and track progress. Subjects' baseline step counts were determined over 7 days during the first week of the study. Subjects set goals to gradually increase their step counts by 20 % of their baseline measure or 2000 steps/d and the long-term goal for subjects was to reach 10000 steps/d.</p>	<p>I and C: Subjects in both groups received the same behavior therapy recommendations based on social cognitive theory. It emphasized increasing self-efficacy for lifestyle changes. Some key topics incorporated into the intervention were self-monitoring, goal setting, social support networks, coping with emotional eating, managing stress and the environment, overcoming obstacles, problem solving, and handling setbacks.</p>
Cardillo* et al. (2006) ⁴⁶ Stern et al. (2004) ⁴⁷	<p>I and C: The two diet groups attended separate, two-hour group-teaching sessions each week for four weeks, followed by monthly one-hour sessions for eleven additional months. Subjects received a diet</p>	<p>I and C: Usual physical active</p>	<p>None</p>

overview handout, instructional nutrition labels, sample menus and recipes, and a book on counting calories and carbohydrates.

15 group sessions

I: Subjects received instruction in the accordance with the obesity-management guidelines including caloric restriction sufficient to create a deficit of 500 calories/d, with 30% (or less) of total calories derived from fat.

C: Subjects were instructed to restrict carbohydrate intake to 30 g/d or less. No instruction on restricting total fat intake was provided. Vegetables and fruits with high fiber to carbohydrate ratios were recommended.

Bacon* et al. (2005)⁴⁸

I and C: Both treatment groups included weekly sessions, each 90 minutes in length. Following this, six monthly aftercare sessions were offered, and were described as optional group support.

24 group sessions

I: Participants were taught to moderately restrict their fat and energy intake and were encouraged to monitor their diet by maintaining a food diary. Material was presented on topics such as how to count fat grams and exchanges, understanding food labels and shopping for food.

C: Standard nutritional instruction regarding diet quality was given, however, the emphasis was on regulating the quality and quantity of food intake according to internal cues for hunger, appetite and satiety

Thompson et al. (2005)⁴¹

I1, I2 and C: Subjects completed a 2-week weight maintenance run-in phase in which they kept daily food records and exercise logs that they reviewed with the dietitian once weekly. After, subjects were given a meal plan based on their calorie level an intervention group.

Individual sessions

I1: The prudent diet was calculated at an energy deficit of 500 calories with an increased amount of fiber (through additional whole grains, fruits, and vegetables) and with a reduction in the glycemic index.

I2: The prudent diet was calculated at an energy

I: Exercise at an intensity within the training heart range delineated in the guidelines was encouraged.

C: The activity component of the intervention focused on helping participants to identify and transform the barriers to becoming active, such as attitudes towards their bodies, and to find activity habits that were fun and appealing.

I: Behavioral treatment based on the LEARN Program for Weight Control manual that includes self-monitoring, stimulus control, reinforcement and cognitive change

C: Initial treatment focused on enhancing body-acceptance and self-acceptance, and subjects were supported in leading as full a life as possible, regardless of their body weight or whether they succeed at weight control. The goal was to first help participants disentangle feelings of self worth from their weight and a secondary phase focused on eating behavior.

Esposito* et al. (2003) ⁴⁹	<p>deficit of 500 calories and four servings of dairy were prescribed, at least two of which were fluid milk.</p> <p>C: The prudent diet was calculated at an energy deficit of 500 calories and the diet was designed to provide an average level of calcium and fiber; two servings of dairy were prescribed.</p> <p>I: Monthly sessions with the nutritionist and exercise trainer for the first year and bimonthly sessions for the second year. Subjects received education on reducing dietary calories, personal goal setting, and self-monitoring (food diaries) through a series of monthly small group sessions. The mean caloric intake goal of a prudent diet was set at 1300 kcal/d for the first year and 1500 kcal/d for the second year.</p> <p><i>18 group sessions</i></p>	<p>I: Subjects received individual guidance on increasing physical activity, mainly by walking, but also with swimming or aerobic ball games.</p> <p>C: General oral and written information about exercise at baseline and at subsequent monthly visits</p>	<p>I: Behavioral and psychological counseling was offered.</p> <p>C: none</p>
Fleming* (2002) ²⁵	<p>C: General oral and written information about healthy food choices at baseline and at subsequent monthly visits</p> <p>I1: Caloric intake 1400-1500 kcal/d with < 100g carbohydrate, 25 – 30 % protein and 55 - 65% of total energy from fat. Patients ate until satiated.</p> <p>I2: Caloric intake 1500-1600Kcal/d with caloric restriction (350-500 kcal/d) with 70 % carbohydrate, 15 % protein and 15 % of total energy from fat with no more than 5 g of saturated fat intake/d</p> <p>I3: Caloric intake 1300-1400 kcal/d with 75 % carbohydrate, 15% protein and 10 % of total energy from fat + daily multivitamin supplement</p> <p>C: Caloric intake 2000 – 2200 Kcal/d with 60% carbohydrate, 15 % protein and 20 - 30% of total energy from fat. Patients consumed 10-12 calories per pound/d.</p> <p><i>12 individual sessions</i></p>	<p>I1, I2, I3 and C: Each individual was instructed to exercise an average of 3-5 times/wk, beginning with stretching for 15 minutes, followed by walking for 30 minutes, and then relaxing and stretching for an additional 15 minutes.</p>	None
Kumanyika et al. (2005) ⁴²	<p>I1, I2 and C: No specific diet or caloric intake level was specified, except that women and men were advised to consume at least 1200 and 1500 kcal, respectively/d. Participants were encouraged to set personal goals for gradual behavior change using the provided guidance about how to identify and track sources of fat and calories in their usual eating patterns and to make healthful, lower calorie substitutions.</p>	<p>I1, I2 and C: Advice to increase physical activity was individually tailored to ability and preferences.</p>	<p>I1, I2 and C: Initial phase with 10-week group counseling program HELP adapted from The Trial of Non-pharmacological interventions in the Elderly program with self-monitoring, stimulus control, goal setting and planning, overcoming motivational barriers, cognitive restructuring, assertive responding, and relapse prevention and management. Participants were then randomized into phase 2.</p> <p><i>10 group sessions</i></p> <p>I1: Participants assigned to continue in Healthy Eating and</p>

Lifestyle Program Classes were offered six 1-h classes, twice a month, followed by monthly classes until the end of follow-up, with new topics, expansion on or review of prior topics, designed to facilitate weight-loss maintenance or additional weight-loss.

~21 group sessions

I2: Participants were given a Self-HELP Kit containing a personalized calendar, a packet describing local resources for healthy eating and physical activity, a personal diary, and a pedometer, and ad hoc telephone support from a HELP outreach worker to facilitate long-term weight management, designed to facilitate weight-loss maintenance or additional weight-loss.

C: The only study contacts during the follow-up were during the semi-annual clinic visits with their personal physicians.

*Randomized Clinical Trials included in meta-analysis

Abbreviations: I, intervention; C, control; USDA, United States Department of Agriculture; LEARN, lifestyle, exercise, attitudes, relationships, nutrition; ENGAGED, E-Networks Guiding Adherence to Goals in Exercise and Diet; HUGS, Health-focused, Understanding lifestyle, Group supported, and Self-esteem building; DPP, Diabetes Prevention Program; MI, Motivational Intervention; HELP, Healthy Eating and Lifestyle Program

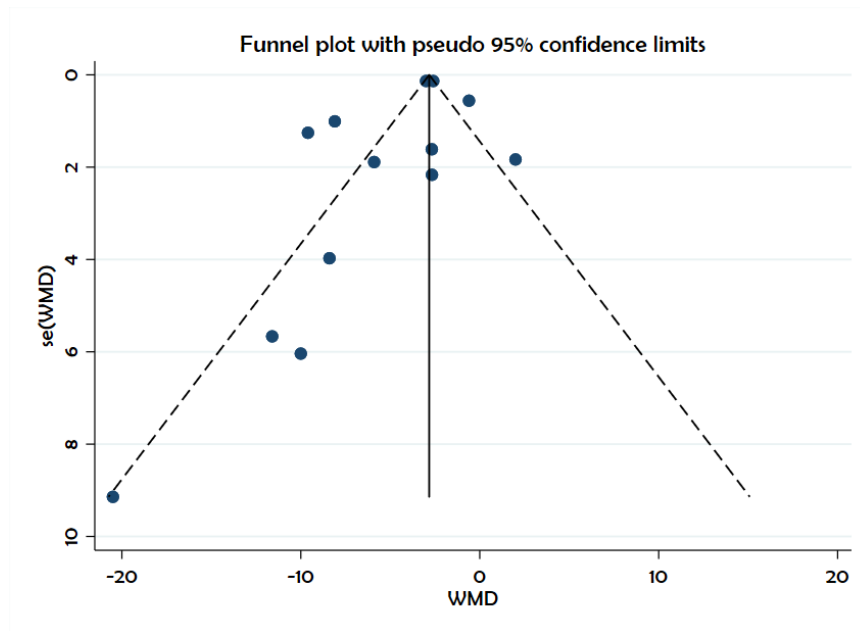


Figure S 1 **Funnel plots assessing publication bias.** The solid line represents the pooled effect estimate expressed as the mean difference for each analysis. The dashed lines represent pseudo 95% confidence intervals.

Table S 4 **Meta-regression analysis of the effect of lifestyle change on weight**

Covariate	Weight (Kg)	
	Adjusted R-square (%)	$P > t $
Participants age	-17.01 %	0.885
Study follow-up	-3.52 %	0.455
Randomized Sample	43.94 %	0.027

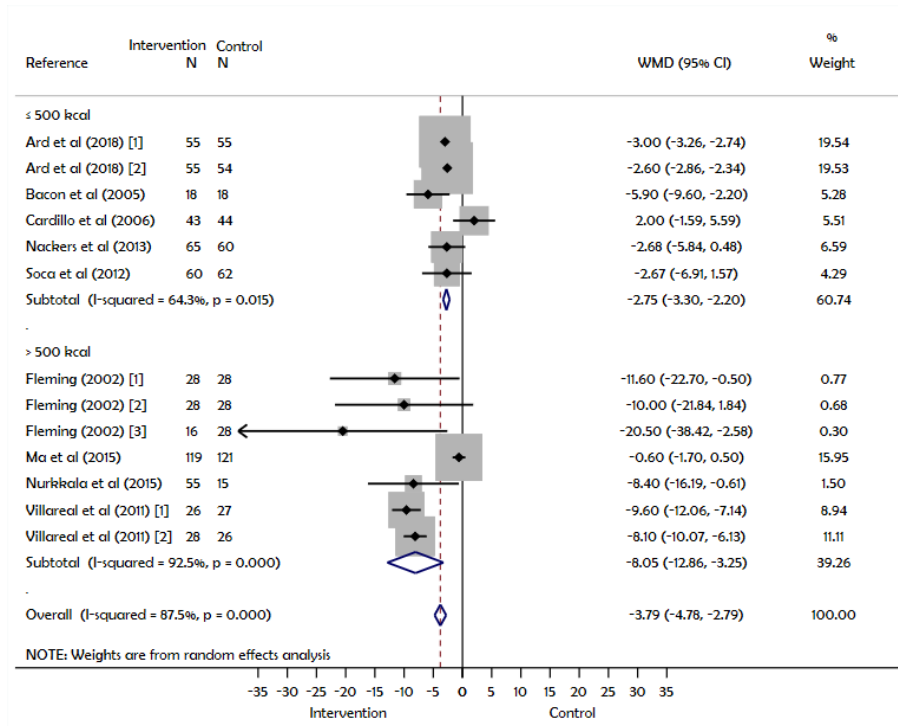


Figure S 2 Subgroup analyses investigating the effect of caloric restriction ≤ 500 or > 500 Kcal on body weight at 12 months. Abbreviations: N, number of participants; WMD, weighted mean difference; CI, confidence interval; I^2 , Higgins's inconsistency statistic.

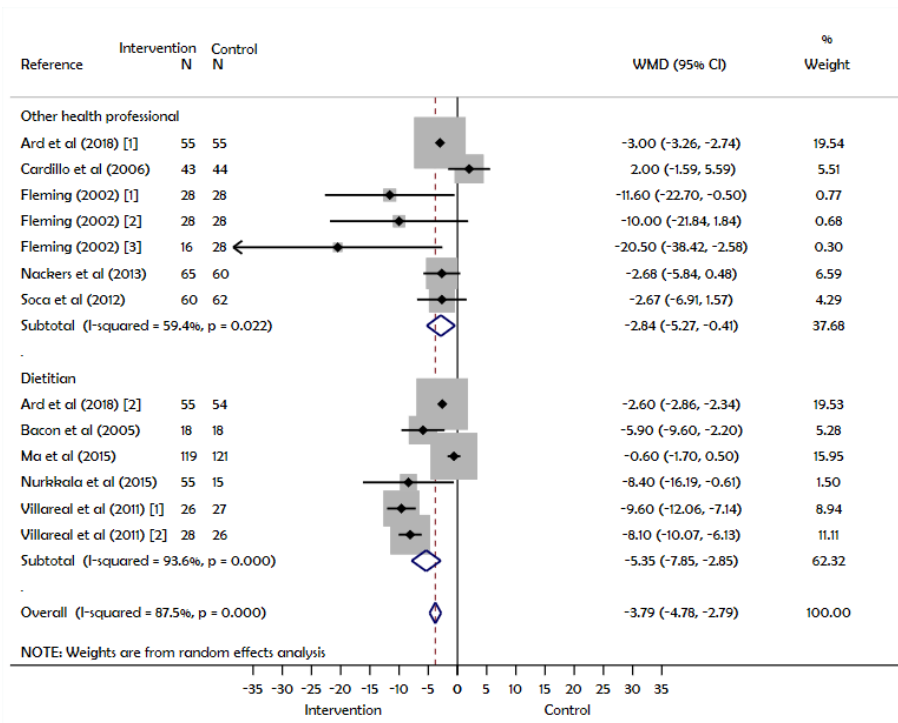


Figure S 3 Subgroup analyses investigating the effect of the intervention facilitator on body weight at 12 months. Abbreviations: N, number of participants; WMD, weighted mean difference; CI, confidence interval; I^2 , Higgins's inconsistency statistic

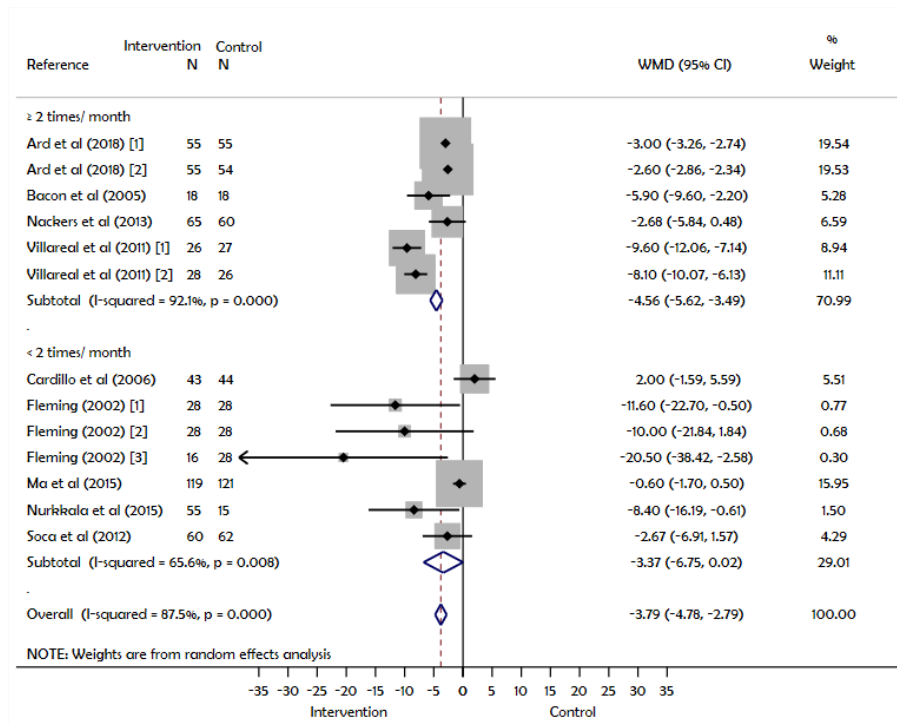


Figure S 4 Subgroup analyses investigating the effect of frequency (< or ≥ 2 times / month) of contact with staff on body weight at 12 months. Abbreviations: N, number of participants; WMD, weighted mean difference; CI, confidence interval; I², Higgins's inconsistency statistic.

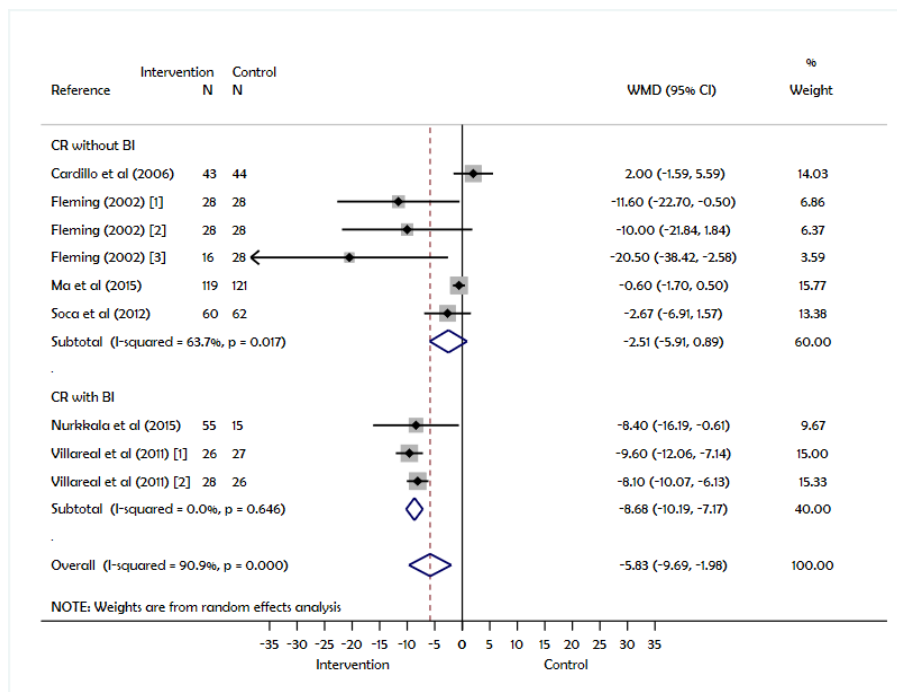


Figure S 5 Subgroup analyses investigating the effect of caloric restriction with or without Behaviour Intervention on body weight at 12 months. Abbreviations: N, number of participants; WMD, weighted mean difference; CI, confidence interval; I², Higgins's inconsistency statistic.

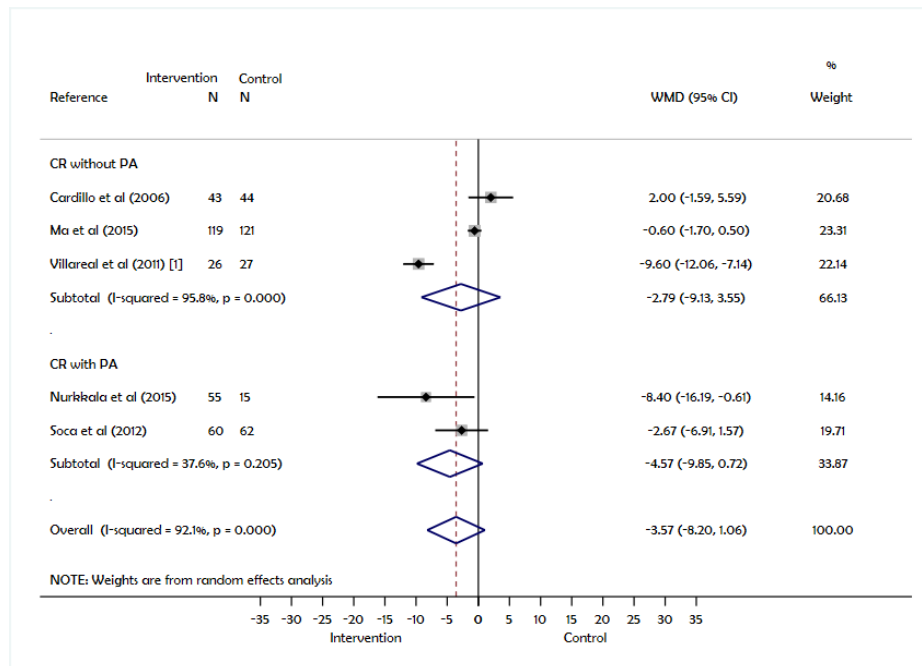


Figure S 6 **Subgroup analyses investigating the effect of caloric restriction (CR) with or without Physical Activity (PA) on body weight at 12 months.** *Abbreviations:* N, number of participants; WMD, weighted mean difference; CI, confidence interval; I^2 , Higgins's inconsistency statistic.

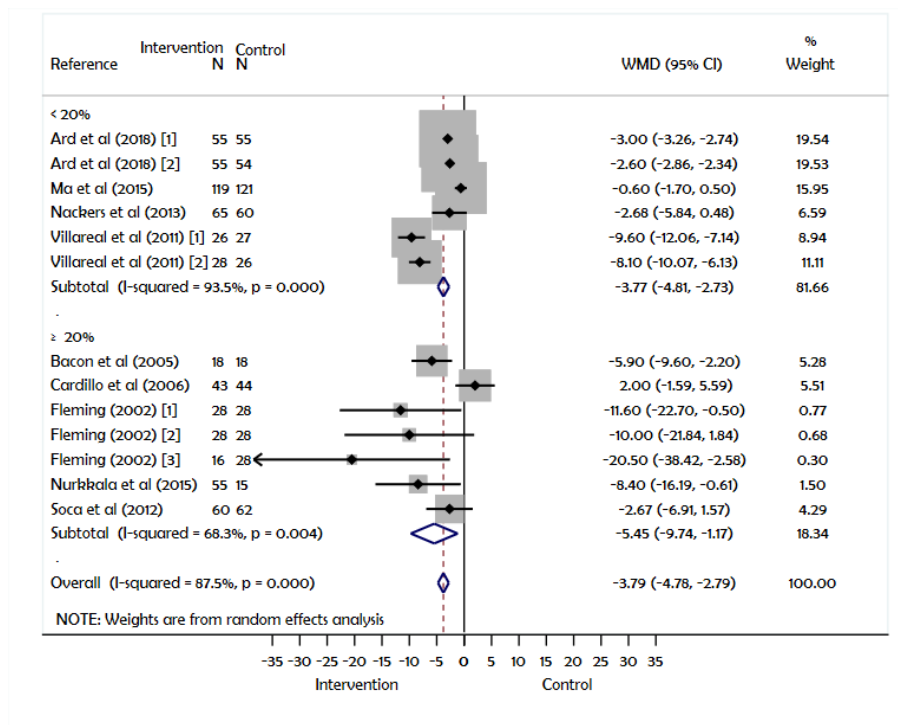


Figure S 7 **Subgroup analyses investigating the effect of intervention dropout on body weight at 12 months.** *Abbreviations:* N, number of participants; WMD, weighted mean difference; CI, confidence interval; I^2 , Higgins's inconsistency statistic.

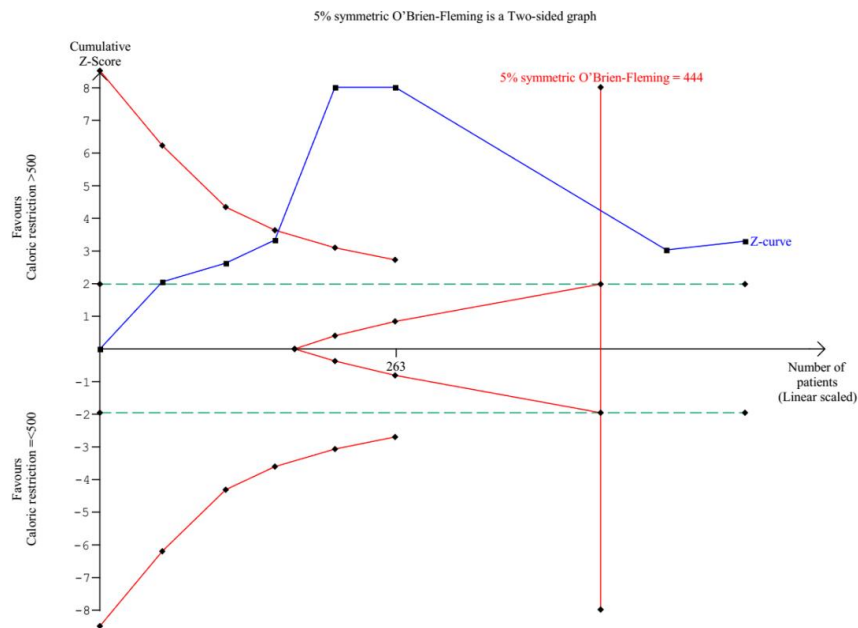


Figure S 8 Trial sequential analysis on pooled result of effects of caloric restriction > 500 Kcal on body weight at 12 months. Complete blue line represents cumulative Z-curve, which crossed conventional boundary (dashed green line), the trial sequential monitoring boundary (red line) and required information size (vertical red line).

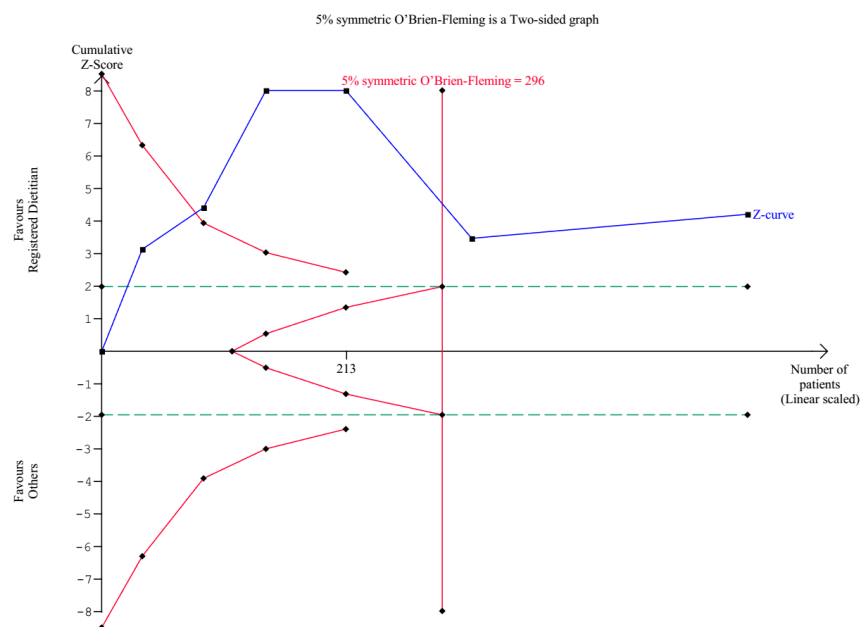


Figure S 9 Trial sequential analysis on pooled result of the effects of registered dietitian as interventionist on body weight at 12 months. Complete blue line represents cumulative Z-curve, which crossed conventional boundary (dashed green line), the trial sequential monitoring boundary (red line) and required information size (vertical red line).

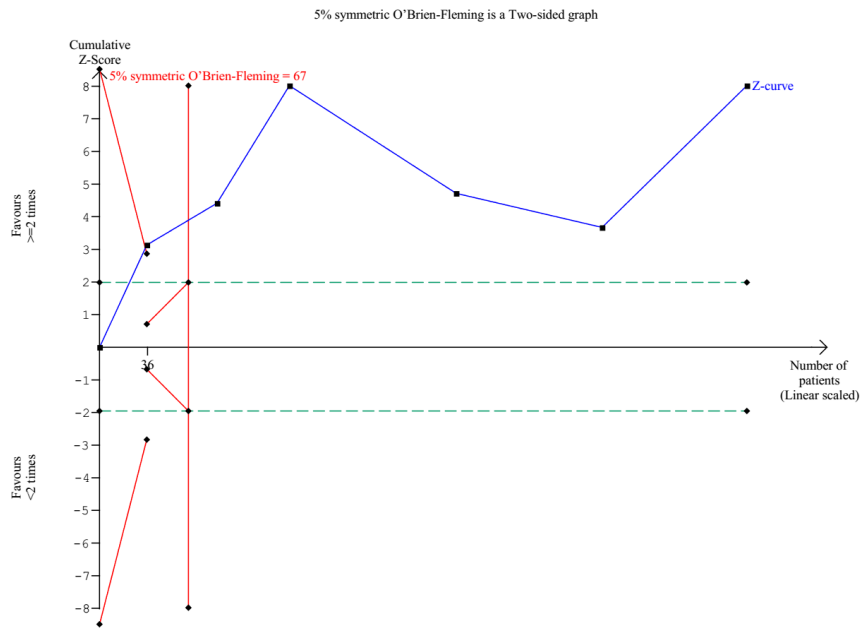


Figure S 10 Trial sequential analysis on pooled result of the effects of frequency of intervention twice a month on body weight at 12 months. Complete blue line represents cumulative Z-curve, which crossed conventional boundary (dashed green line), the trial sequential monitoring boundary (red line) and required information size (vertical red line).

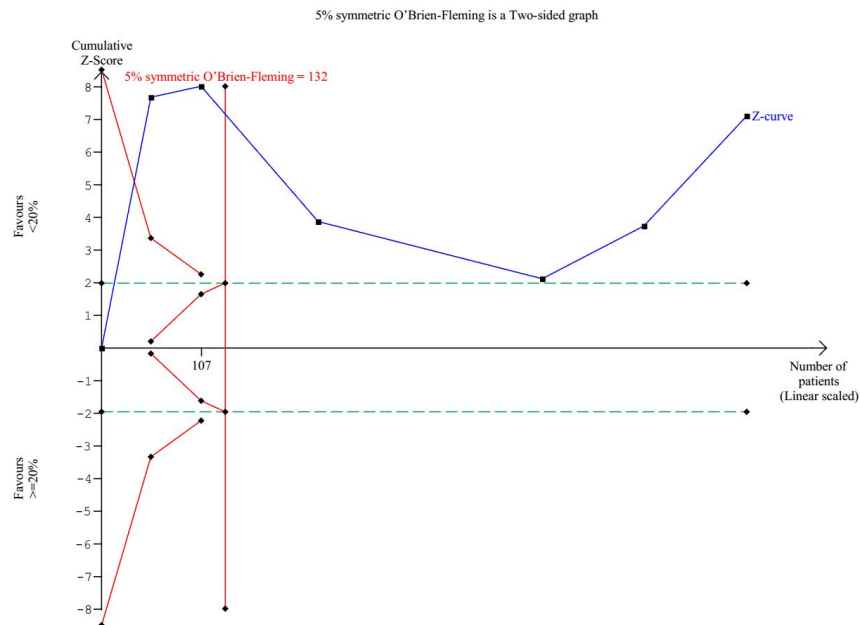


Figure S 11 Trial sequential analysis on pooled result of the effects of dropout $< 20\%$ on body weight at 12 months. Complete blue line represents cumulative Z-curve, which crossed conventional boundary (dashed green line), the trial sequential monitoring boundary (red line) and required information size (vertical red line).

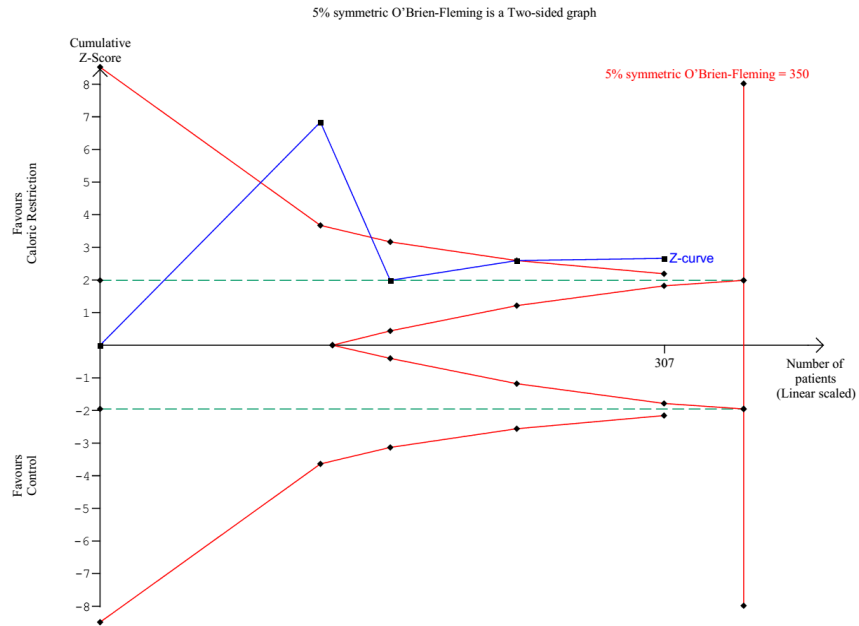


Figure S 12 **Trial sequential analysis on pooled result of the effects of caloric restriction on body weight at 24 months.** Complete blue line represents cumulative Z-curve, which crossed conventional boundary (dashed green line), the trial sequential monitoring boundary (red line) and did not cross required information size (vertical red line).

ANEXO I- Normas para publicação de artigo na revista *Nutrition Reviews*

Article types

Nutrition Reviews publishes review articles in both the narrative and systematic review formats. Systematic reviews must address a clearly defined research question that is articulated in the abstract; they must also follow recognized approaches to the literature selection, analysis, and conclusions, as outlined in accepted guidelines, such as PRISMA or MOOSE. Scoping reviews that investigate the available literature on a topic in order to determine if more research is required, or if there is sufficient available literature for a full review, fall outside of the journal's scope and are not considered for publication. Submissions in the following article categories are welcome:

- *Lead Article*: Comprehensive review of a broad topic;
- *Special Article*: Comprehensive review focused on a niche topic, a specific aspect of a broad topic, or new methods in nutrition science;
- *Nutrition in Clinical Care*: Presentation of clinically relevant brief reviews of evidence-based information and tools to facilitate translation into clinical practice;
- *Emerging Science*: Discussion of an important current study or group of studies in nutrition research presented in the context of the larger body of research on that topic;
- *Nutrition Science ↔ Policy*: Review of the interaction between scientific research and national and international health and nutrition policy;
- *Letter to the Editor*: Addition to the discourse regarding certain topics covered in recent issues of the journal.

Systematic reviews may be submitted for any category except Emerging Science and Letter to the Editor. Articles in the categories of Lead Article, Special Article, Nutrition in Clinical Care, Emerging Science, and Nutrition Science ↔ Policy are subject to peer review. Letters to the Editor are published at the discretion of the editors.

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letter.

Authorship and originality

To qualify for authorship, individuals must meet all of the following criteria: 1) contributed significantly to the work's conception, design, data collection (as applicable), or data interpretation and analysis; 2) participated in the writing or critical revision of the article in a manner sufficient to establish ownership of the intellectual content; and 3) read and approved the version of the manuscript being submitted. All authors share responsibility for ensuring the manuscript complies with the journal's style requirements and terms of consideration. Any requests for changes to author names, or order of appearance, that are received post submission will need to be approved in writing by all authors.

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Manuscript preparation

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- *Abstract.* An abstract clearly outlining the topic and primary objective of the review, methods of data sourcing and extraction, data synthesis (as applicable), and conclusions must be included with each article. The length should not exceed 170 words for Lead, Special, and Nutrition Science ↔ Policy papers or 125 words for Emerging Science and Nutrition in Clinical Care papers. Abstracts exceeding these word limits will be shortened during copyediting. References, tables, and figures should not be cited in the abstract.
- *Key words.* At least three to five key words or phrases should be provided.

Sections and headings

Narrative reviews. Each manuscript should contain the following sections in addition to the abstract:

- Introduction (directly following the abstract)
- Conclusion (at the end of the text)
- Acknowledgements (after the Conclusion)
- Funding and sponsorship (as part of the Acknowledgments)
- Declaration of interest (as part of the Acknowledgments)
- References (after the Acknowledgments).

Between the Introduction and Conclusion, headings and subheadings are at the discretion of the author. They should be used to organize the text and guide the reader.

Systematic reviews. Articles of this type should be prepared in accordance with relevant, existing guidelines (e.g., PRISMA, MOOSE) and be structured accordingly. If the guidelines used include a checklist, the completed checklist should be uploaded as Supporting Information during the manuscript submission process. Questions regarding the acceptability of chosen guidelines can be sent to the journal's editorial office via e-mail (nutritionreviews@ilsa.org).

Abbreviations and acronyms. Abbreviations and acronyms should not be used unless they are widely recognized and generally understood, e.g. BMI, FDA. These should only be used for terms used more than four times in the text. If that criterion is met, the term should be spelled out on first use followed by the abbreviation or acronym in parentheses. The abbreviated form should be used consistently thereafter, except in section headings, where it should continue to

be spelled out.

References. The number of references cited should be tailored to the material being reviewed and be from reputable sources. As a general rule, articles in the Lead, Special, and Nutrition Science ↔ Policy categories do not typically include more than 200 references, while articles in the Emerging Science and Nutrition in Clinical Care categories do not typically have more than 120.

References should be numbered sequentially upon first appearance in text, tables, and figures. They should be typed as superscripts and placed after commas and periods but before colons and semicolons. When citing a series of consecutive numbers, provide the first and last with a dash between them (e.g., ⁵⁻⁷). When referring to a group of authors in the text, the format “Smith et al.²³” should be used.

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Entire book: Gibson GR, Rastall RA. Prebiotics: Developments and Application. Hoboken, NJ: Wiley; 2006.

Government bulletin: Guidance on Labeling of Foods That Need Refrigeration by Consumers. College Park, MD: Office of Food Labeling, US Food and Drug Administration; 1997. Docket No. 96D-0513.

Internet citation: American College of Surgeons. National Trauma Data Bank Report 2006,

Version 6.0. Chicago, USA. Available at: <http://www.facs.org/trauma/ntdb/ntdbannualreport2006.pdf>. Accessed on October 22, 2007.

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