Psychological Medicine

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The effect of a low-calorie diet on depressive symptoms in individuals with overweight or obesity: a systematic review and meta-analysis of interventional studies

Briana Applewhite[1,2], Brenda W. J. H. Penninx[3], Allan H. Young[1,4], Ulrike Schmidt[1,4], Hubertus Himmerich[1,4] and Johanna L. Keeler[1]

[1]Department of Psychological Medicine, Centre for Research in Eating and Weight Disorders, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK; [2]Department of Psychiatry, Centre for Eudaimonia and Human Flourishing, University of Oxford, Oxford, UK; [3]Psychiatry, Amsterdam Public Health Research Institute, Amsterdam UMC, Vrije Universiteit, Amsterdam, The Netherlands and [4]South London and Maudsley NHS Foundation Trust, London, UK

Original Article

The original version of this article was missing an ORCID ID. A notice detailing this has been published and the ORCID added.

Cite this article: Applewhite B, Penninx BWJH, Young AH, Schmidt U, Himmerich H, Keeler JL (2024). The effect of a low-calorie diet on depressive symptoms in individuals with overweight or obesity: a systematic review and meta-analysis of interventional studies. *Psychological Medicine* **54**, 1671–1683. https://doi.org/10.1017/S0033291723003586

Received: 11 January 2023
Revised: 26 October 2023
Accepted: 13 November 2023
First published online: 12 December 2023

Keywords:
depression; diet; low-calorie diet; obesity; overweight

Corresponding author:
Johanna L. Keeler;
Email: johanna.keeler@kcl.ac.uk

Abstract

Background. Individuals with overweight or obesity are at a high risk for so-called 'atypical' or immunometabolic depression, with associated neurovegetative symptoms including overeating, fatigue, weight gain, and a poor metabolic profile evidenced e.g. by dyslipidemia or hyperglycemia. Research has generated preliminary evidence for a low-calorie diet (LCD) in reducing depressive symptoms. The aim of the current systematic review and meta-analysis is to examine this evidence to determine whether a LCD reduces depressive symptoms in people with overweight or obesity.

Methods. Eligible studies were identified through PubMed, ISI Web of Science, and PsycINFO until August 2023. Standardized mean differences (SMDs) were derived using random-effects meta-analyses for (1) pre-post LCD comparisons of depression outcomes, and (2) LCD v. no-diet-control group comparisons of depression outcomes.

Results. A total of 25 studies were included in the pre-post meta-analysis, finding that depression scores were significantly lower following a LCD (SMD = −0.47), which was not significantly moderated by the addition of exercise or behavioral therapy as a non-diet adjunct. Meta-regressions indicated that a higher baseline BMI and greater weight reduction were associated with a greater reduction in depression scores. The intervention-control meta-analysis ($n = 4$) found that overweight or obese participants adhering to a LCD showed a nominally lower depression score compared with those given no intervention (SMD = −0.29).

Conclusions. There is evidence that LCDs may reduce depressive symptoms in people with overweight or obesity in the short term. Future well-controlled intervention studies, including a non-active control group, and longer-term follow-ups, are warranted in order to make more definitive conclusions.

Introduction

The vicious cycle of obesity and depression has gained increasing scientific and clinical importance (Plackett, 2022). Over 280 million people worldwide suffer from depression and ~2 billion adults are overweight (body mass index (BMI) of ⩾25 kg/m^2); of these, approximately 650 million are obese (body mass index of ⩾30 kg/m^2) (World Health Organization, 2021a, 2021b). Depressive disorders have been attributed as the leading cause of burden in the Global Burden of Disease studies of 1990, 2000, and 2010, and contribute to the burden allocated to suicide and ischemic heart disease (Ferrari et al., 2013). These figures emphasize the magnitude of the burden of depression, overweight, and obesity on public health globally, with associated health complications such as hypertension, coronary artery disease, and an increased risk of mortality (Agha & Agha, 2017; Faith, Matz, & Jorge, 2002; Liu et al., 2020). Moreover, the prevalence of obesity is significantly elevated in people with depression (Opel et al., 2015), and conversely, the prevalence of depression in people who are obese is twice as high as in non-obese individuals (Pereira-Miranda, Costa, Queiroz, Pereira-Santos, & Santana, 2017). There is evidence for large heterogeneity in the symptom profile of depression. In people with overweight or obesity, there is evidence of a preponderance of specific more 'atypical' symptoms related to energy metabolism: increased appetite and body weight, fatigue, hypersomnia, a poor metabolic profile, and leaden paralysis (Lamers, Beekman, Van Hemert, Schoevers, & Penninx, 2016; Milaneschi, Lamers, Berk, & Penninx, 2020).

Low-grade systemic inflammation related to increased pro-inflammatory cytokine release from adipose tissue appears to be a major factor contributing to the pathophysiology of depression in people with overweight or obesity. For example, the pro-inflammatory cytokine tumor necrosis factor (TNF)-α, produced by fat cells and macrophages within adipose tissue, has been found to activate indoleamine-2,3-dioxygenase (IDO). IDO, in turn, degrades the serotonin precursor tryptophan leading to a central deficiency of serotonin (Himmerich, Berthold-Losleben, & Pollmächer, 2009). Additionally, TNF-α activates the reuptake of serotonin from the synaptic cleft, reducing synaptic serotonin, and also activates the hypothalamus–pituitary–adrenal (HPA) axis. An activated HPA axis and reduced serotonin concentration in the brain are consistent biological correlates of depression (Moncrieff et al., 2022; Thormann, Chittka, Minkwitz, Kluge, & Himmerich, 2013; Tichomirowa et al., 2005). Other pro-inflammatory cytokines, for example interleukin (IL)-6, have similar effects on neurotransmitter signaling in the brain (Müller, 2014).

Current therapeutic strategies to treat depression include antidepressants and psychotherapy (National Institute for Health and Care Excellence, 2009). However, many patients do not achieve remission with these therapies, even when they are combined; one study documented low remission rates of between 7% and 30% (Rush et al., 2004; Sinyor, Schaffer, & Levitt, 2010). This failure has been attributed in part to the heterogeneity of depression and the lack of differentiation of treatment in depression subtypes (Akil et al., 2018).

In recent years, studies have found that anti-depressant-like effects occur during periods of prolonged calorie restriction (Hussin, Shahar, Teng, Ngah, & Das, 2013; Redman, Martin, Williamson, & Ravussin, 2008). A probable explanation is that caloric restriction is associated with pronounced physiological adaptations in the immune, the endocrine, and the central nervous system. For example, fasting is associated with reductions in the production of leptin, TNF-α and IL-6 in the adipose tissue. Therefore, fasting reverses the cytokine-induced low-grade inflammation that links overweight and obesity to depression by inducing improvements in neurotransmitter signaling (e.g. the serotonin system [Curzon, Joseph, & Knott, 1972; Igwe, Sone, Matveychuk, Baker, & Dursun, 2021; Michalsen, 2010; Schweiger, Broocks, Tuschl, & Pirke, 1989]). Additionally, fasting has been linked to increased endogenous opioid release (e.g. B-endorphins; (Komaki et al., 1990), opioids; (Molina et al., 1995), cannabinoids; (Hanuš et al., 2003)) as well as an increased production of neurotrophins such as brain-derived neurotrophic factor (Igwe et al., 2021).

Therefore, treating overweight and obesity may constitute an antidepressant strategy in people with additional depression. All major guidelines for the treatment of overweight and obesity (e.g. [Jensen et al., 2014; World Health Organization, 2000]) recommend a calorie-reduced diet and/or physical activity to prevent further weight gain or achieve a moderate weight loss of 5–15% of the body weight. Indeed, recent studies indicate that, at least in the short-term, weight loss due to caloric restriction improves depressive symptoms amongst obese patients with depression (Vaghef-Mehrabany, Ranjbar, Asghari-Jafarabadi, Hosseinpour-Arjmand, & Ebrahimi-Mameghani, 2021). Moreover, a recently published systematic review presented evidence for a low-calorie diet (LCD) in reducing depressive scores in individuals with overweight or obesity as well as non-overweight individuals, emphasizing that people with obesity and depression appear to be a specific subgroup of depressed patients in which calorie-restricted diets might constitute a promising personalized treatment approach (Patsalos et al., 2021).

The current systematic review and meta-analysis aimed to synthesize the available evidence to answer the question 'does a LCD lead to an improvement in depression scores at the end of treatment in individuals with overweight or obesity?'. Our current study extends a review by Patsalos et al. (2021), by meta-analyzing data on the effect of LCDs on depressive symptoms, specifically in individuals with overweight or obesity. (Patsalos et al., 2021). To our knowledge, this study is the first of its kind to meta-analyze the results of interventional studies investigating the effects of a LCD on depressive symptoms in individuals specifically with overweight or obesity. As adjunctive physical exercise and behavioral therapy might have an additional effect (Ein, Armstrong, & Vickers, 2019; Rajaie et al., 2022), we examined the moderating effects of these adjuncts on depressive symptoms specifically in this population.

Methods

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher, Liberati, Tetzlaff, Altman, & Group*, 2009).

Literature search

Three databases (PubMed, ISI Web of Knowledge, PsycINFO) were systematically searched from inception until the 1st August 2023. Studies were identified through Boolean operators by combining the following free-text words: ((depression) OR (depress*) (depression scor*) OR (depress* symptoms) (mood*)) AND ((obesity) OR (obes*) OR (overweight) AND ((diet) OR (diet*) OR (calorie restricted) OR (calorie restrict*) OR (very low calorie diet) OR (very low energy diet) OR (VLCD) OR (weight loss)) OR (weight loss*)). Two authors (B.A. and J.L.K.) independently screened the titles and abstracts of the articles to ascertain whether they fulfilled the inclusion criteria. B.A. conducted supplementary hand searching and citation-chaining by appraising the reference lists of selected articles. The full texts of relevant studies were retrieved and independently assessed for eligibility.

Inclusion and exclusion criteria

Studies were included if they: (i) were published in English; (ii) included adult human participants ($\geqslant$18 years of age); (iii) were clinical intervention studies or randomized controlled trials; (iv) included overweight and/or obese adults with defined BMIs of $\geqslant$25 kg/m^2; (v) utilized a calorie-restricted diet or a very low-energy diet; and (vi) assessed depressive symptoms at baseline and at least once post-intervention. We defined a calorie-restricted or very low-energy diet, as a diet with a deficit of 500–1500 kcal/day or a restriction of at least 30% of normal energy expenditure.

Studies were excluded if they: (i) did not measure weight or BMI change after the intervention; (ii) included participants with a BMI of $\leqslant$25 kg/m^2 (iii) were cross-sectional studies, systematic reviews, meta-analyses, case studies, conference proceedings/abstracts, book chapters, and unpublished theses; or (iv) had a calorie-restricted diet with a deficit of less than 500 kcal/day or less than 30% of normal energy expenditure.

https://doi.org/10.1017/S0033291723003586 Published online by Cambridge University Press

Quality assessment

All studies selected for retrieval were assessed by two independent reviewers (B.A. and J.L.K.) for methodological validity using the standardized critical appraisal instruments from the Joanna Briggs Institute Manual for Evidence Synthesis (Tufanaru, Munn, Aromataris, Campbell, & Hopp, 2017). In the case of conflicting judgments between the reviewers, the third author (H.H.) re-reviewed the assessment to ensure accuracy.

Data extraction

One author (B.A.) extracted data from all included studies into electronic summary tables using Endnote 20 and then Microsoft Excel, which were then checked by both authors (J.L.K. and H.H.). The following data were extracted: Study and participant characteristics: sample and group size, the number of participants in each arm at baseline and post-intervention, the study design (RCT/Intervention), geographical location and duration; Intervention details: the energy restriction, treatment protocol and adjuncts; Comparison details: mean weight loss, pre and post intervention depression score mean and standard deviation, control group depression score mean and standard deviation; Outcome measures: the type of questionnaire, attrition and adherence, statistical significance of main result. Data that were not available in the published manuscript were sought and obtained by contacting authors where possible.

The principal endpoints were the change in mean depression scores between all calorie-restricted and LCDs at baseline and after the intervention, as well as follow-up outcomes in controls given no intervention. Data from the control groups were only extracted if the condition consisted of a non-active control (i.e. no change in diet or continued TAU).

Quantitative synthesis

Two individual meta-analyses were conducted using (a) pre-post LCD intervention depression scores and (b) LCD at post-intervention v. no active intervention depression scores, using the 'meta set' and 'meta summarize' commands in Stata 16 (StataCorp, 2019). All meta-analyses and sub-group analyses were conducted with random-effects models using the Dersimonian & Laird method (DerSimonian & Laird, 1986), which calculated standardized mean differences (SMDs) per study and an overall SMD relative to the sample size of each individual study. The Higgins I^2 metric was used to estimate study heterogeneity, which was considered to be high when $I^2 \geqslant 75\%$. The threshold for statistical significance for all analyses was $p < 0.05$.

We performed meta-regressions using the 'metareg' command, to investigate the effect of age, baseline depressive symptoms, baseline BMI, changes in weight, average energy intake (kcal) of diet, and intervention duration, on the SMD between pre-post measurements of depression in individuals treated with a LCD, where data from ⩾10 studies were available (Borenstein, Hedges, Higgins, & Rothstein, 2021). Additionally, sub-group analyses were run to explore the moderating effects of non-diet interventional adjuncts such as exercise or behavioral therapy on overall effect sizes.

Publication bias was estimated with the Egger's test for small study effects, and funnel plots using the 'meta funnelplot' command in Stata 16. The Duval and Tweedie trim and fill method was used to identify smaller studies causing funnel plot asymmetry and adjust for this asymmetry by imputing missing studies and re-estimating SMDs (Duval & Tweedie, 2000).

Qualitative synthesis

Studies that were not eligible for inclusion in the meta-analysis due to insufficient data reporting were synthesized narratively.

Results

Study characteristics

A total of 14 262 articles were identified and after exclusion of duplicates and those not in the English language, 7329 articles titles and abstracts were screened. After screening, 7259 articles were excluded, and 70 were assessed for eligibility. Of these, 44 were excluded because they did not meet the inclusion criteria (see Fig. 1). In total, 25 studies were included in the meta-analysis, with one study being included in the qualitative synthesis due to being ineligible for inclusion in the meta-analysis.

The majority of included studies were from the United States of America ($n = 12$; (Faulconbridge et al., 2012; 2018; Foster et al., 1992; Geliebter et al., 1997; Imayama et al., 2011; LaPorte, 1990; Ma et al., 2019; Payne et al., 2018; Pearl et al., 2018; Wadden, Stunkard, Brownell, & Day, 1985; Wadden, Stunkard, & Liebschutz, 1988; Wadden, Stunkard, & Smoller, 1986)). Six studies were from Australia (Brinkworth, Buckley, Noakes, Clifton, & Wilson, 2009; Brinkworth et al., 2016; Fuller et al., 2017; Halyburton et al., 2007; Kakoschke et al., 2021; Thomson et al., 2010). The remaining studies were from Canada ($n = 2$; [Buffenstein, Karklin, & Driver, 2000; Sanchez et al., 2017]), Finland ($n = 1$; [Tan et al., 2016]), Iran ($n = 1$; Dolatkhah et al., 2023)), Poland ($n = 1$; [Stefanska, Wendolowicz, Konarzewska, & Ostrowska, 2016]), the Netherlands ($n = 1$; [Snel et al., 2012]) and Spain ($n = 1$; [Rodriguez-Lozada et al., 2019]). The duration of the studies ranged from 4 to 52 weeks and the median was 24 weeks. The mean ± S.D. age of those allocated to LCDs was reported by 22 studies, which across studies was 51.0 ± 11.9 years. The age of participants allocated to control across four studies was 53.4 ± 9.9 years. All studies were conducted on people who were overweight or obese, and the mean ± S.D. BMI at baseline was reported by 20 studies, which when pooled was 34.2 ± 5.5 kg/m^2. For the control groups of four studies, the mean BMI at baseline was 34.9 ± 6.0 kg/m^2. The weight loss following the LCD ranged from −1.1 kg to −25.4 kg. Table 1 provides a summary of the study and sample characteristics for each study.

Quality assessment

online Supplementary Table S1 provides an overview of the quality assessment of the studies included in the meta-analysis and online Supplementary Table S2 provides an overview of the quality assessment of the one study included in the systematic review. All studies screened in the quality assessment were deemed suitable for inclusion in the meta-analysis and qualitative synthesis. Notably, the blinding of the participants and research staff is nearby impossible in lifestyle modification trials, thus the blinding of study participants and research staff were not considered when assessing the overall quality of studies. The full appraisal of the quality of the studies is included in online Supplementary Materials 1.

https://doi.org/10.1017/S0033291723003586 Published online by Cambridge University Press

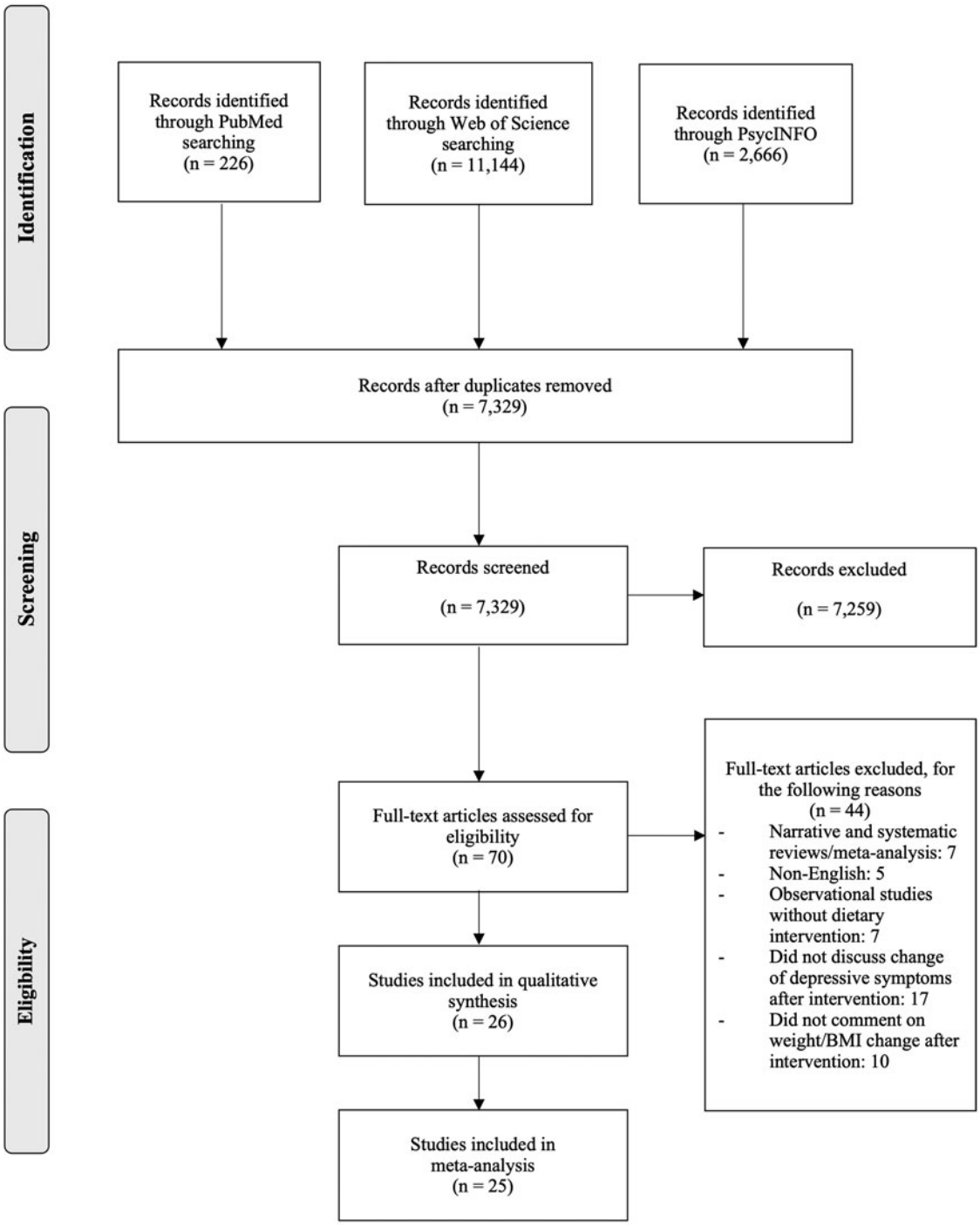

Figure 1. Flow chart of the study selection process according to PRISMA.

Meta-analysis results

Results of the intervention-control meta-analysis and pre-post intervention meta-analysis, and sub-group analysis of depression measurement scales (BDI and CES-D) on pre-post outcomes are presented in Table 2.

Pre-post comparisons

Data from a total of 25 studies using a sample of 4574 participants at the baseline time-point and 4134 at a follow-up time-point were included in this meta-analysis (Brinkworth et al., 2009; Brinkworth et al., 2016; Buffenstein et al., 2000; Dolatkhah et al., 2023; Faulconbridge et al., 2012, 2018; Foster et al., 1992; Fuller et al., 2017; Geliebter et al., 1997; Halyburton et al., 2007; Imayama et al., 2011; Kakoschke et al., 2021; LaPorte, 1990; Ma et al., 2019; Payne et al., 2018; Pearl et al., 2018; Rodriguez-Lozada et al., 2019; Sanchez et al., 2017; Snel et al., 2012; Stefanska et al., 2016; Tan et al., 2016; Thomson et al., 2010; Wadden et al., 1985; Wadden et al., 1988; Wadden et al., 1986). All 25 studies had a control and intervention comparison;

https://doi.org/10.1017/S0033291723003586 Published online by Cambridge University Press

Table 1. Study and sample characteristics of the included studies ($n = 25$)

Author, Year, *Country*	Sample and group size (n)	Gender (n)	Age (years) (M ± s.d. or range)	BMI (kg/m^2) (M ± s.d.	Study design	Control condition	Duration (weeks)	Depression measure	Energy restriction	Treatment protocol	Adherence to intervention	Overall attrition	Mean weight loss (kg)
Brinkworth et al., 2009. *Australia*	Pre *n* = 118 Post *n* = 65	Male = 43; Female = 75	50.0 ± 8.1	33.7 ± 4.2	RCT	Active	52	BDI	1433–1672 kcal/day	Very low-carbohydrate, high fat (LC) diet v. high-carbohydrate, low-fat (LF) diet	68%	42%	−13.7
Brinkworth et al., 2016. *Australia*	Pre *n* = 115 Post *n* = 78	Male = 66; Female = 49	58.5 ± 7.1	34.7 ± 4.3	RCT	Active	52	BDI	1434–1673 kcal/day	Energy-restricted 1434–1673 kcal/day planned isocaloric LC v. high-carbohydrate, low-fat (HC) diet, combined with a supervised exercise program	67%	40%	−9.2
Buffenstein et al., 2000. *Canada*	Pre *n* = 9 Post *n* = 9	All female	20–36	26.1 ± 2.8	Interventional study with no control group	N/A	4	POMS	800 kcal/day	Two weeks of maintaining normal energy intake (baseline), followed by four-week period of 800 kcal/day	100%	0%	−5.8
Dolatkhah et al., 2023. *Iran*	Pre *n* = 30 Post *n* = 30	All female	54.57 ± 8.16	34.54 ± 5.58	RCT	Active	8	BDI-II	500 kcal deficit/day	Randomly assigned to receive either low-calorie diet or anti-inflammatory diet accompanied by a low-calorie diet	65%	10%	0.0.8
Elder et al., 2012 *USA*	Pre *n* = 472 Post *n* = 352	Male = 80; Female = 392	55.0 ± 11.7	33.7 ± 5.2	Interventional study with no control group	N/A	24	PHQ-8	500 kcal deficit/day	Reducing dietary intake by 500 kcal/day; increasing physical exercise to ⩾180 min/week; DASH dietary advice; group weight loss counseling	73%	27%	−6.3
Faulconbridge et al., 2012 *USA*	Pre n = 2563 Post n = 2430	Male + Female (ns)	ns (⩾18)	ns (BMI⩾27)	RCT	Active	52	BDI	1200–1800 kcal/day	Intensive lifestyle intervention (ILI) v. diabetes support and education. ILI = 1200–1800 kcal prescription; exercise of ⩾175 min/week; diet/physical activity counseling.	NR	7%	ns
Faulconbridge et al., 2018 *USA*	Pre *n* = 25; Post *n* = 25	Male = 1; Female = 24	53.7 ± 10.2	36.7 ± 5.3	RCT	Active	20	BDI-II	1200–1800 kcal/day	Behavioral weight control (BWC) v. CBT-D v. BWC + CBT-D. BWC = 1200–1800 kcal prescription, exercise of 180 min/week; self-monitoring	64%	24%	−3.5
Foster et al., 1992. *USA*	Pre *n* = 68 Post *n* = 68	Female = 68	40.6 ± 9.4	37.6 ± 5.5	RCT	Active	24	BDI	240 kcal/d; 660 kcal/day; 800 kcal/day	3 different VLCDs in combination with behavior therapy for 6 months	NR	6%	−20.7

(*Continued*)

Table 1. (*Continued.*)

Author, Year, *Country*	Sample and group size (n)	Gender (n)	Age (years) (M ± s.d. or range)	BMI (kg/m^2) (M ± s.d.	Study design	Control condition	Duration (weeks)	Depression measure	Energy restriction	Treatment protocol	Adherence to intervention	Overall attrition	Mean weight loss (kg)
Fuller et al., 2017 *Australia*	Pre *n* = 70 Post *n* = 70	Male = 26; Female = 44	45.4 ± 11.1	31.1. ± 3.9	RCT	Active	52	BDI-II	500 kcal/day	Randomization to one of two treatment groups with a 500 kcal/day diet; encouraged to increase activity to 10 000 steps over 3 month intervention	NR	29%	−3.75
Geliebter et al., 1997. *USA*	Pre *n* = 22 Post *n* = 22	Male = 8; Female = 14	36.0 ± 8.0	ns	RCT	Active	8	BDI	1286 ± 281 kcal/day	Diet + strength training v. diet + aerobic training v. diet only	NR	20%	−9.5
Halyburton et al., 2007. *Australia*	Pre *n* = 93 Post *n* = 93	Male = 37; Female = 56	50.2 ± 8.1	33.5 ± 4.1	RCT	Active	8	BDI	1434–1673 kcal/day	Energy-restricted low-carbohydrate ketogenic (LCHF) diet v. isocaloric conventional high-carbohydrate (HCLF) diet	95%	11%	−7
Imayama et al., 2011. *USA*	Pre *n* = 235 Post *n* = 235 Control *n* = 87	All female	Pre = 58.1 ± 5.2 Control = 57.4±4.4	Pre = 31.0 ± 4.1 Control = 30.7±3.9	RCT	Non-active	52	BSI-18	1200–2000 kcal/day based on baseline weight	12 months of dietary weight loss (n = 118) v. moderate-to-vigorous aerobic exercise (225 min/week, n = 117) v. combined diet and exercise (n = 117) v. control (no intervention)	86%	9%	−7.2
Kakoschke et al., 2021. *Australia*	Pre *n* = 115 Post *n* = 61	Male = 66; Female = 49	58.5 ± 7.1	34.6 ± 4.3	RCT	Active	52	BDI	500–1000 kcal/day deficit)	LC diet v. isocaloric high unrefined carbohydrate, low-fat diet. Both combined with aerobic/resistance exercise	95%	47%	−10
LaPorte, 1990. *USA*	Pre *n* = 94 Post *n* = 68	Male = 28; Female = 66	ns (⩾21)	37.2 ± ns	Interventional study with no control group	N/A	10	BDI	420–800 kcal/day	VLCD for 10 weeks (Optifast) 420 kcal/day (800 kcal/day in those with pre-existing medical condition)	42%	28%	−17.8
Ma et al., 2019. *USA*	Pre *n* = 204 Post *n* = 184 Control *n* = 205	Male = 122; Female = 287	Pre = 50.9 ± 12.2 Control = 51.0±11.9	Pre = 36.7 ± 6.9 Control = 36.6±5.8	RCT	Non-active	52	SCL-20	500–1000 kcal/day deficit	500 to 1000 kcal deficit per day, ⩾150 min of moderate-intensity physical activity, and behavioral activation therapy. Control = usual care	74%	16%	−2.6
Payne et al., 2018. *USA*	Pre *n* = 67 Post *n* = 67	Male = 14; Female = 53	68.2 ± 5.6	36.9 ± 6.3	RCT	Active	24	CES-D	500 kcal/day deficit	Six-month reduced calorie diet at two protein levels; prescribed a 500 kcal/day energy deficit	86%	30%	−8.4

Pearl et al., 2018. *USA*	Pre *n* = 178 Post *n* = 137	Male = 19; Female = 118	46.1 ± 10.1	40.8 ± 5.9	RCT	Active	14	PHQ-9	1000–1200 kcal/day	Structured 1000 to 1200 kcal/d diet; increasing physical activity to 225 min/week by week 40	NR	16%	−10.7
Rodriguez-Lozada et al., 2019. *Spain*	Pre *n* = 305 Post *n* = 217	Male = 92; Female = 213	45.3 ± 10.7	31.6 ± 3.6	RCT	Active	16	BDI	30% calorie restriction based on individuals energy expenditure	2 different calorie restricted diets: moderately high in protein v. low in fat	95%	33%	−8.6
Sanchez et al., 2017. *Canada*	Pre *n* = 63 Post *n* = 53	Male = 24; Female = 39	37.0 ± 10.0	33.3 ± 3.2	RCT	Active	12	BDI	500 kcal/day deficit	Phase 1: 12-week 500 kcal energy restriction; Phase 2: 12-week weight maintenance program	99%	26%	−3.4
Snel et al., 2012. *Netherlands*	Pre *n* = 27 Post *n* = 27 Control n = 54	Male = 42; Female = 39	Pre = 58.0 ± 8.3; Control = 56.0±1.0	Pre = 37.2 ± 4.7; Control = 37.6±5.1	RCT	Non-active	16	HADS	~450 kcal/day as 3 sachets of Modifast®	16-week VLCD v. VLCD + exercise program. Control = no intervention	NR	0%	−25.4
Stefanska et al., 2016. *Poland*	Pre *n* = 60 Post *n* = 60	All female	52.0 ± 5.3	30.5 ± 3.6	Interventional study with no control group	N/A	24	BDI	1200–1500 kcal/day	Weekly meal plan with caloric intake ranging from 1200–1500	NR	0%	−4.1
Tan et al., 2016. *Finland*	Pre *n* = 28 Post *n* = 26 Control *n* = 21	All male	Pre = 51.0 ± 10.1; Control = 52.6±10.8	Pre = 29.4 ± 3.9; Control = 29.2±4.7	RCT	Non-active	24	Rimon's brief depression scale	300–500 kcal/day deficit	6-month individualized diet intervention with calorie deficit of 300–500 kcal/day; 3 counseling sessions. Control = no intervention	93%	10%	−1.1
Thomson et al., 2010. *Australia*	Pre *n* = 94 Post *n* = 49	All female	29.3 ± 6.8	36.1 ± 4.8	RCT	Active	20	CES-D	1434 kcal/day	Three 20-week lifestyle programs: diet only v. diet and aerobic exercise v. diet and combined aerobic-resistance exercise	NR	48%	−9.5
Wadden et al., 1985. *USA*	Pre *n* = 19 Post *n* = 19	Male = 2; Female = 17	38.1 ± ns	ns	RCT	Active	4	BDI	1200 kcal/day; 400 kcal/day	1000–1200 kcal balanced diet for the first month, then random assignment to protein-sparing-modified fast (PSMF) v. protein-formula-liquid diet. Each diet about 400 kcal daily.	NR	16%	−4.2
Wadden et al., 1986. *USA*	Pre *n* = 28 Post *n* = 28	All female	42.1 ± 5.3	ns	Interventional study with no control group	N/A	24	BDI	1200 kcal/day; 400 kcal/day	1200 kcal diet during month 1 and months 4–6; a very low-calorie diet (400 kcal) for months 2-3.	NR	0%	−19.2
Wadden et al., 1988. *USA*	Pre *n* = 15 Post *n* = 15	Male = 2; Female = 13	44.3 ± 8.7	ns	RCT	Active	24	BDI	400–500 kcal/day; 1200 kcal/day	VLCD v. behavior therapy v. VLCD + behavior therapy	NR	24%	−14.1

Abbreviations: BDI, Beck Depression Inventory; BSI-18, Brief Symptom Inventory 18; CES-D, Centre for Epidemiologic Studies Depression Scale; HADS, Hospital Anxiety and Depression Scale; kcal, kilocalorie; kg, kilograms; M, mean; N/A, not applicable; NR, not reported; N.S., non-significant; POMS, Profile of Mood States; RCT, Randomized Controlled Trial; SCL-20, 20-item Depression Symptom Checklist; SD, standard deviation.

Table 2. Summary of comparative outcomes and heterogeneity for low-calorie diet *v.* no intervention (at follow-up) meta-analysis and low-calorie diet (pre to post diet) meta-analysis and sub-group meta-analyses

Group	N	SMD	95% CI	Z	*p*	Heterogeneity
LCD v. control	N (Diet, Control)					
Overall (*n* = 4)	494, 360	−0.29	−0.60, 0.02	−1.81	0.070	I^2 = 71.4%; *p*(Q) = 0.015*
LCD pre-post	N (Pre, Post)					
Overall (*n* = 25)	4574, 4134	−0.47	−0.59, −0.35	−7.74	<0.001**	I^2 = 75.6%; *p*(Q)<0.001**
Subgroups[a]						
With BI (*n* = 11)	3552, 3344	−0.46	−0.61, −0.31	−6.02	<0.001**	I^2 = 72.3%; *p*(Q)<0.001**
Without BI (*n* = 15)	1161, 874	−0.53	−0.73, −0.33	−5.26	<0.001**	I^2 = 74.2%; *p*(Q)<0.001**
With exercise (*n* = 12)	3534, 3252	−0.64	−0.83, −0.45	−6.48	<0.001**	I^2 = 84.3%; *p*(Q)<0.001**
Without exercise (*n* = 17)	1102, 918	−0.39	−0.55, −0.23	−4.71	<0.001**	I^2 = 61.8%; *p*(Q)<0.001**

Notes. [a]Some studies reported depression scores for separate groups and so were included in each subgroup. **Significant at the $p < 0.01$ threshold. *Significant at the $p < 0.05$ threshold. Abbreviations: BI, behavioral intervention; CI, confidence intervals; LCD, low-calorie diet; N, number; SMD, standardized mean difference.

however, 21 studies included a LCD for the intervention and the control condition was comprised of some other form of active intervention (different diet type, exercise, behavioral therapy etc.). Including all measures of depressive psychopathology, those adhering to a LCD showed a significant reduction in depression scores from baseline to follow-up, with a small-to-moderate effect size (SMD = −0.47; 95% CI −0.59 to −0.35; $p <$ 0.001; see Fig. 2 for a forest plot and Table 2 for the full results).

Subgroup analysis of behavioral intervention and exercise

For the full results of the subgroup analyses, refer to Table 2. A total of 11 studies included a behavioral intervention component (Faulconbridge et al., 2012, 2018; Frost et al., 2007; Geliebter et al., 1997; Imayama et al., 2011; LaPorte, 1990; Ma et al., 2019; Payne et al., 2018; Pearl et al., 2018; Tan et al., 2016; Wadden et al., 1988), although this did not have a significant effect on reductions in depressive symptoms ($Q(1) = 0.32$; $p = 0.574$). A total of 12 studies included exercise as an adjunct (Brinkworth et al., 2016; Faulconbridge et al., 2012; 2018; Foster et al., 1992; Fuller et al., 2017; Geliebter et al., 1997; Imayama et al., 2011; Kakoschke et al., 2021; Ma et al., 2019; Pearl et al., 2018; Snel et al., 2012; Thomson et al., 2010), which trended towards having an effect on depressive symptoms ($Q(1) = 3.81$; $p = 0.051$). In studies where exercise was an adjunct, depression reduced with a medium-to-large effect size (SMD = −0.64; 95% CI −0.83 to −0.45; z = −6.48; $p < 0.001$). However, depressive symptoms also significantly reduced in studies where exercise was not an adjunct, with a small-to-medium effect size (SMD = −0.39; 95% CI −0.55 to −0.23; z = −4.71; $p < 0.001$).

Control group with no change in diet or continued treatment as usual (TAU)

Data from a total of four studies using a sample of 494 participants treated with a LCD and 360 in a non-active control condition were included in this meta-analysis (Imayama et al., 2011; Ma et al., 2019; Snel et al., 2012; Tan et al., 2016). At follow-up, those adhering to a LCD showed a nominally lower depression score compared with those maintaining their usual diet or TAU, although this was non-significant with a small effect size (SMD = −0.29; 95% CI −0.60 to 0.02; $p = 0.070$; see Fig. 3 for a forest plot and Table 2 for the full results).

Meta-regression analyses

Meta-regression analyses were conducted on longitudinal outcomes, which are presented in Table 3. The effects of mean age, baseline BMI, baseline depressive symptoms, weight reduction from baseline to follow-up, average energy intake, and the time interval between baseline and follow-up on changes in depression scores in individuals on a LCD were investigated in six separate meta-regression analyses. Baseline BMI, and the degree of weight reduction, was significantly related to a reduction in depression scores, indicating that a higher BMI at baseline and a greater reduction in weight was associated with a greater reduction in depression from pre-post. The variables of age, baseline depression, time between baseline and follow-up and average calorie intake of the diets were not significantly associated with changes in depression over time.

Sensitivity analyses

Both meta-analyses showed medium-high heterogeneity (50–75%). The Egger's test for small study effects found no evidence of potential publication bias in the main pre-post analysis including all studies ($z = -0.05$; $p = 0.960$) and the LCD v. no intervention analysis ($z = -0.17$; $p = 0.862$). See online Supplementary Figures S1 and S2 (online Supplementary Materials 2) for funnel plots of these two analyses. The Duval and Tweedie trim and fill method found no evidence of missing studies in all meta-analyses.

Qualitative synthesis

One study was not included in the meta-analysis and thus was synthesized qualitatively (Elder et al., 2012). This study explored a behavioral weight loss program in obese individuals targeting sleep, depression, and stress. The weight loss program was linearly associated with changes in both depression (PHQ-8) and stress.

Discussion

In this systematic review and meta-analysis, the primary objective was to determine if a LCD produces a significant reduction in depressive symptoms in people with overweight or obesity. Data from 25 studies were meta-analyzed, revealing that those prescribed a LCD did show a significant reduction in depressive symptoms from baseline to post-treatment, with a moderate effect size. Across four studies, individuals prescribed a LCD showed

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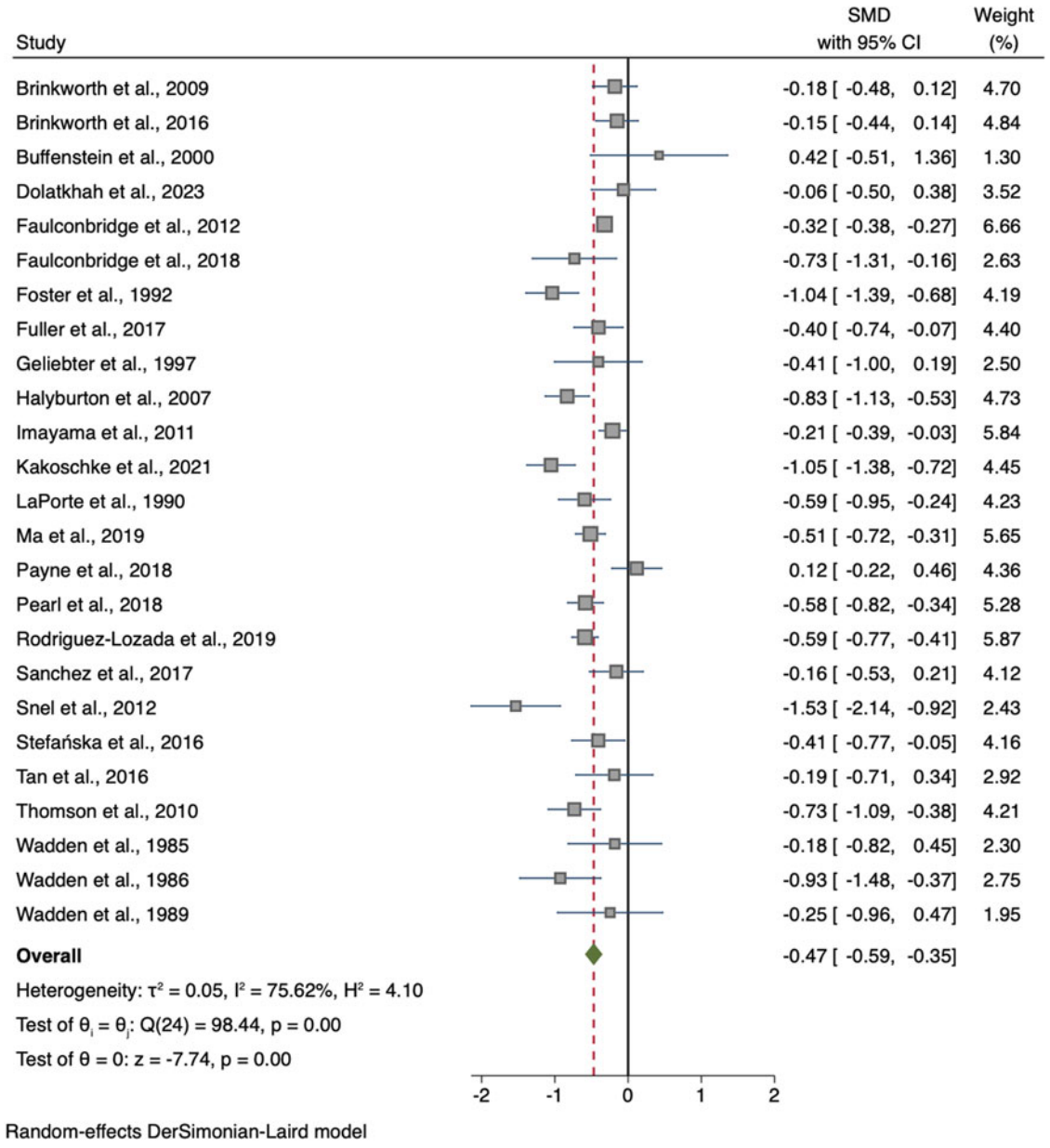

Figure 2. Forest plot of standardized mean difference (SMD) in depression scores from baseline to post low-calorie diet.

lower depression scores than individuals given no intervention, albeit this difference was non-significant, likely owing to a limited number of studies included. These findings extend the findings of an earlier systematic review, which found that a calorie restricted diet resulted in a decrease in depression scores in individuals who were obese (Patsalos et al., 2021).

Earlier meta-analyses have explored the use of LCDs for the treatment of anxiety and depressive symptoms (Ein et al., 2019), as well as the use of exercise as an adjunctive to an energy restrictive diet, and their effects on quality of life and depressive symptoms (Rajaie et al., 2022). However, to the best of our knowledge, this is the first systematic review and meta-analysis that explored the effects of a LCD on depressive symptoms specifically in people with overweight or obesity. In people with overweight or obesity, we found that the addition of a behavioral adjunct to the intervention did not significantly moderate the effect of LCDs in reducing depression scores, in contrast with a previous meta-analysis that found behavioral therapy to be a significant moderator (Ein et al., 2019). However, we found a trend towards an effect whereby the addition of physical exercise moderated the effect of LCDs on depression; LCDs with adjunctive exercise yielded a greater effect on depression than those without exercise, although both had a significant effect on depression scores. This is partially in agreement with the meta-analysis by Ein et al. (2019) but may contrast with another meta-analysis that found no beneficial addition of exercise to energy-restricted diets on depression or quality of life (Rajaie et al., 2022). In summary, our findings indicate that in people with overweight or obesity, adjunctive exercise may be a useful adjunct to a LCD for reducing symptoms of depression.

Six separate meta-regression analyses were performed on the pre-post outcomes, including weight change from baseline to follow up, baseline BMI, age, baseline depression scores, the time

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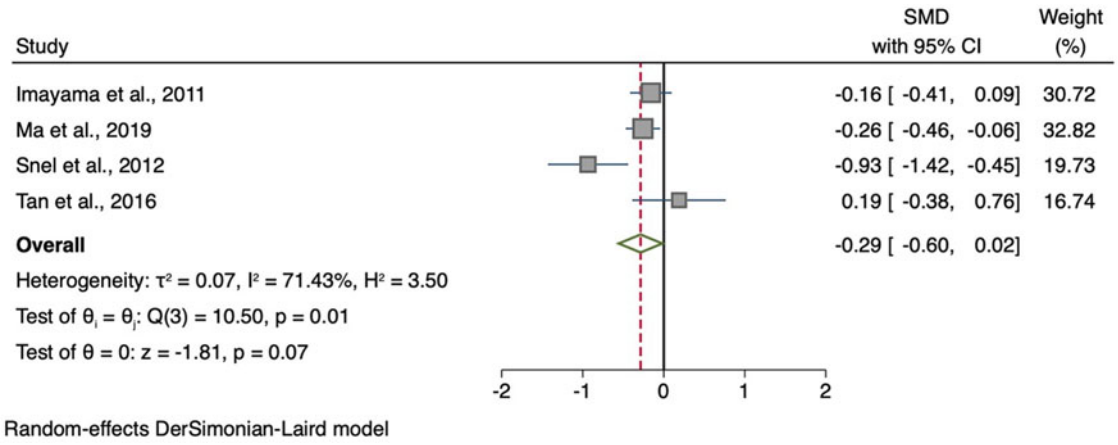

Figure 3. Forest plot of standardized mean difference (SMD) in depression scores between individuals following a low-calorie diet *v.* individuals following their usual diet or treatment as usual.

Table 3. Results of the meta-regression analyses

Variable	N studies included	Beta coefficient (S.E.)	Z	95% CIs	*p*
Pre-post meta-analysis					
Age (years)	22	0.009 (0.008)	1.07	−0.01, 0.02	0.283
Baseline BMI (kg/m^2)	20	−0.050 (0.025)	−2.05	−0.10, −0.002	0.040*
Baseline depressive symptoms	25	0.006 (0.005)	1.07	−0.01, 0.02	0.285
Weight reduction (kg)	24	0.036 (0.011)	3.15	0.01, 0.06	0.002**
Time interval (weeks)	25	0.002 (0.003)	0.69	−0.004, 0.01	0.492
Average energy intake (kcal)	14	0.0002 (0.0002)	0.70	−0.0003, 0.001	0.486

Notes. **Significant at the $p < 0.01$ threshold. *Significant at the $p < 0.05$ threshold. Abbreviations: BMI, body mass index; kcal, kilocalories; kg, kilograms; N, number; SE, standard error.

interval between baseline and follow up and the average calories prescribed in the LCD. Only weight change and baseline BMI showed a significant association, indicating that greater baseline BMI, and greater weight reduction, were linearly related to decreases in depression scores. Time interval between baseline and follow-up, average number of calories in the diet, age, and baseline depression scores were unrelated to changes in depression scores from pre- to post-intervention. Notably, no study included a sample with a mean age ⩾70 years, so these findings are not generalizable to geriatric populations with overweight or obesity. These findings mirror a previous meta-analysis finding that those who lost a high amount of weight, specifically obese individuals, also showed a greater reduction in depressive symptoms (Ein et al., 2019), and imply that the more weight loss, the greater the reduction in depressive symptoms. The improvement regarding depressive symptoms in obese people might be achieved through beneficial changes in the hormone or cytokine system, as well as psychological and behavioral consequences of the weight loss such as increased physical mobility, improved self-esteem or a sense of mastery.

Clinical considerations

The findings have implications for the therapy of patients. As treatment with antidepressants often leads to weight gain, with an associated risk of diabetes and cardiovascular problems (Himmerich, Minkwitz, & Kirkby, 2015), the preliminary results from our meta-analysis suggest that it may be worthwhile to initiate the treatment of a patient who has both obesity and depression, by reducing body weight using a LCD. However, this suggestion should be made with caution as the adverse effects of LCDs and their potential risks for overweight or obese populations have not yet been systematically investigated. Moreover, dietary restrictions may be a contraindication for certain individuals, such as geriatric populations (Volkert et al., 2022) or people with or at risk of developing an eating disorder (Goldschmidt, Wall, Loth, Le Grange, & Neumark-Sztainer, 2012).

One problem is the experience that may people regain weight quickly after strict weight loss, described as weight cycling, which might cause fluctuations in cardiovascular risk factors such as blood pressure, heart rate, sympathetic activity, and circulating levels of glucose, lipids, and insulin (Rhee, 2017). Therefore, helping patients to stabilize their new lower weight during a maintenance phase after the acute weight loss seems important. Data from the National Weight Control Registry indicate that high levels of physical activity, eating a low-calorie and low-fat diet, eating breakfast regularly and self-monitoring weight help to maintain weight (Wing & Phelan, 2005). Studies and guidelines support these measures for weight maintenance. For example, 200–300 min of physical activity per week are recommended by the American College of Sports Medicine for the prevention of weight gain after successful weight loss (Donnelly et al., 2009). This

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recommendation is based on several studies, for example, Jakicic, Marcus, Gallagher, Napolitano, and Lang (2003) which found that after 12 months of intervention, women with greater than 200 min/week (13.6%) had maintained significantly greater percentage of weight loss compared to those who had exercised at 150–199 min/week (9.5%), and less than 150 min/week (4.7%). The dietary and weight advantages of consuming breakfast, especially ones that include grains, cereals, lower-fat milk, and fruit or fruit juice, in contrast to the potential adverse effects of skipping breakfast were reported in the National Health and Nutrition Examination Survey which examined the eating habits of approximately 19 000 adults (O'Neil, Nicklas, & Fulgoni, 2014). Daily weighing might contribute to weight maintenance because it leads to greater adoption of weight control behaviors (Steinberg, Bennett, Askew, & Tate, 2015). However, according to a recent review on weight loss and weight maintenance, there is no single best strategy for weight management. Hence, strategies for weight loss and its maintenance should be individualized, and healthcare providers should choose the best strategy based on patient preferences (Kim, 2021).

Strengths & limitations

To the authors' knowledge, this is the first systematic review and meta-analysis that examines the effects of a LCD on depressive symptoms in overweight or obese populations. A comprehensive literature search of three different databases was performed to identify all potential studies and we utilized a strict inclusion criterion of only clinical trials or RCTs, which considerably strengthens the validity of our research findings. Exploratory analyses such as meta-regression and subgroup analysis enabled the initial exploration of potential mediators and moderators of the relationship between LCDs and decreases in depression in overweight/obese individuals. Furthermore, the quality of studies was assessed in all 26 articles as being of a high standard.

Despite the strengths of the study, there are several limitations. There is high heterogeneity between studies as the LCDs and the depression assessment tools utilized in each study varied drastically. Further, there were only four studies included in the analysis comparing LCD outcomes with a non-active control condition. As pre-post outcomes are dependent on one another, it has been discussed that pre-post effect sizes may be prone to bias, and it has been recommended that between-group (i.e. intervention v. control) effect sizes are preferable (Cuijpers, Weitz, Cristea, & Twisk, 2017). Because of the paucity of studies with non-active control groups, the results and generalizability of our between-group comparisons should be interpreted with caution. Future RCTs relating to our primary research question, including a non-active control group, are necessary to enable future well-powered between-group estimations of effect size. Notably, it has also been highlighted that eliminating pre-post effect sizes entirely, and therefore excluding trials that utilize a single-group design or have heterogeneous control groups, may miss a substantial part of the evidence, thereby introducing new bias (Koesters, 2017).

Additionally, as the reporting of the average calorie deficit was not standardized across studies, including the level of calorie deficit as a regressor in a meta-regression model was not possible, which would have provided additional clinical insights. Furthermore, this review did not assess the adverse effects of LCDs and their potential risks for people who are overweight or obese, as well as the potentially negative effects of a LCD on certain populations (e.g. geriatric populations, those at risk of an eating disorder). Such adverse effects and their careful clinical management should be explored in further research before prescribing this diet type. Future studies should also examine if the effects of LCDs on depressive symptoms in individuals with overweight or obesity are sustained in the long-term as studies selected for this review only lasted between four and 52 weeks.

Conclusions

The results of this systematic review and meta-analysis suggest that a LCD may contribute to a reduction in depressive symptoms in people with overweight or obesity. Given the high risk of physical health complications associated with obesity and depression, such as cardiovascular disease, these findings provide preliminary evidence for the importance of weight loss to alleviate depression and associated symptoms like reduced physical activity, low mood, sleep disturbances and changes in appetite which link obesity and depression (Plackett, 2022). These findings of reduced depression scores in LCDs may be particularly noteworthy for those suffering from depression where symptoms include increased appetite, weight gain, fatigue, hypersomnia, and a poor metabolic profile (Lamers et al., 2016). Further research is warranted, particularly RCTs that have well-defined LCD interventions, non-active control groups, and long-term follow-ups, in order to recommend the prescription of a LCD to ameliorate symptoms in such individuals.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291723003586.

Funding statement. Briana Applewhite, Hubertus Himmerich, Ulrike Schmidt and Allan Young received salary support from the National Institute for Health Research (NIHR) Biomedical Research Centre (BRC) at the South London and Maudsley NHS Foundation Trust (SLaM) and KCL. Johanna Keeler received a PhD stipend from the Medical Research Council (MRC; reference number: MR/N013700/1). The views expressed are those of the author(s) and not necessarily those of the MRC, NHS, NIHR or the Department of Health and Social Care. For the purpose of open access, the author has applied a Creative Commons Attribution (CC BY) license to any Author Accepted Manuscript version arising.

Competing interest. Professor Allan Young has participated in paid lectures and advisory boards for the following companies with drugs used in affective and related disorders: Astrazenaca, Boehringer Ingelheim, Eli Lilly, LivaNova, Lundbeck, Sunovion, Servier, Livanova, Janssen, Allegan, Bionomics, Sumitomo Dainippon Pharma, COMPASS, Sage, Novartis, Neurocentrx. Professor Young is a UK Chief Investigator for two studies funded by COMPASS (COMP006, COMP007) and one study funded by Novartis (MIJ821A12201).

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