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Research

Treatment for overweight and obesity in adult populations: a systematic review and meta-analysis

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Abstract

Background: Obesity is a major public health issue. This review updates the evidence on the effectiveness of behavioural and pharmacologic treatments for overweight and obesity in adults.

Methods: We updated the search conducted in a previous review. Randomized trials of primary care–relevant behavioural (diet, exercise and lifestyle) and pharmacologic (orlistat and metformin) with or without behavioural treatments in overweight and obese adults were included if 12-month, postbaseline data were provided for weight outcomes. Studies reporting harms were included regardless of design. Data were extracted and pooled wherever possible for 5 weight outcomes, 6 secondary health outcomes and 4 adverse events categories.

Results: We identified 68 studies: most consisted of short-term (≤ 12 mo) treatments using diet (n = 8), exercise (n = 4), diet and exercise (n = 10), lifestyle (n = 19), orlistat (n = 25) or metformin (n = 4). Compared with the control groups, intervention participants had a greater mean weight loss of –3.02 kg (95% confidence interval [CI] –3.52 to –2.52), a greater reduction in waist circumference of –2.78 cm (95% CI –3.34 to –2.22) and a greater reduction in body mass index of –1.11 kg/m^2 (95% CI –1.39 to –0.84). The relative risk for loss of ≥ 5% body weight was 1.77 (95% CI 1.58 to 1.99; number needed to treat 5, 95% CI 4 to 7), and the relative risk for loss of ≥ 10% body weight was 1.91 (95% CI 1.69 to 2.16; number needed to treat 9, 95% CI 7 to 12). Incidence of type 2 diabetes was lower among prediabetic intervention participants (relative risk 0.62, 95% CI 0.50 to 0.77; number needed to treat 17, 95% CI 13 to 29). With prevalence rates for type 2 diabetes on the rise, weight loss coupled with a reduction in the incidence of type 2 diabetes could potentially have a significant benefit on population health and a possible reduction in need for drug treatments for glycemic control.

Interpretation: There is moderate quality evidence that behavioural and pharmacologic plus behavioural treatments for overweight and obesity in adults lead to clinically important reductions in weight and incidence of type 2 diabetes in prediabetic populations. Registration: PROSPERO no. CRD42012002753

Overweight and obesity are defined by a body mass index (BMI) of 25–29.9 and ≥ 30 kg/m^2, respectively. An estimated one billion adults are overweight and at least 300 million are obese worldwide, with prevalence increasing in most countries.[1] Obese adults are at increased risk for developing major diseases, such as type 2 diabetes, coronary artery disease, stroke, depression and certain cancers.[2–4] It is estimated that one in 10 premature adult deaths is directly attributable to overweight and obesity.[5,6]

We provide an updated synthesis of the effectiveness of behavioural and pharmacologic interventions for treating overweight and obesity in adults. Whereas most systematic reviews on this topic have focused on anthropometric (e.g., weight and waist circumference)[7,8] and biochemical outcomes (e.g., cholesterol and blood pressure),[9–11] we aimed to also assess the effects of nonsurgical weight-loss interventions on clinically meaningful outcomes (e.g., 5% weight loss and incidence of type 2 diabetes).

Methods

Search strategy

A recent high-quality (9/11 AMSTAR rating)[12] review by the United States Preventive Services Task Force[13] examined interventions for preventing obesity in overweight and obese populations. To avoid duplication, our protocol was designed to update their search. We searched MEDLINE, Cochrane Central Register of Controlled Trials, PsycINFO and Embase

Competing interests: See end of article.

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from September 2010 (the date of the last United States Preventive Services Task Force search) up to and including Apr. 19, 2013. The full search strategy is provided in Appendix 1 (available at www.cmajopen.ca/content/2/4/E306/suppl/DC1). Reference lists from other systematic reviews were searched for studies not captured by our search.

Population, intervention, comparator, outcome and setting statement

Details regarding the population, intervention, comparator, outcomes and setting for this review are provided in Box 1.

Inclusion and exclusion criteria

The inclusion and exclusion criteria for this review are provided in Box 2.

Study selection, quality assessment and data abstraction

Titles and abstracts of papers were reviewed independently by 2 team members. Any citation marked for inclusion by either team member went on to full-text screening, which was also done independently by 2 researchers. Randomized controlled trials were assessed using the Cochrane Collaboration's tool for risk-of-bias assessment[14] (Appendix 2, available at www.cmajopen.ca/content/2/4/E306/suppl/DC1). Overall strength of the evidence (identified as high, moderate, low or very low quality) was determined using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework (GRADEpro version 3.2).[15] One team member completed full-data abstraction, and a second member verified all extractions. All data were checked in a third round of verification before analysis. Unadjusted immediate postassessment data were extracted where available. For a small number of studies, there were no immediate postassessment data; we chose the data point closest to the end of the intervention. For another small group of ongoing studies, we extracted interim data (at 12 mo). We extracted data for all reported adverse events. At all levels, inter-rater disagreements were resolved through discussion.

Data analysis

For meta-analyses, immediate post-treatment data (means and standard deviations) were used for continous outcomes such as weight in kg, whereas number-of-events data were used for binary outcomes such as loss of ≥ 5% baseline body weight. The DerSimonian and Laird random-effects model with an inverse variance method was used to generate the summary measures of effect in the form of mean difference

Box 1: Description of population, intervention, comparator, outcomes and setting

Population

- Overweight (BMI 25–29.9 kg/m^2) and obese (BMI 30–39.9 kg/m^2) adults aged 18 years and older

Interventions

- Behavioural (diet, exercise or lifestyle) and pharmacologic (orlistat or metformin) treatments for weight loss

Comparator

- Treatment effectiveness: no intervention, usual care, placebo or minimal intervention (e.g., newsletter or single information session on healthy living)
- Treatment harms: any type of comparison group or no comparison group

Outcomes

- Treatment effectiveness: Primary weight outcomes: weight change in kg, loss of ≥ 5% and ≥ 10% baseline body weight, change in BMI, change in waist circumference. Secondary health outcomes: total cholesterol, low density lipoprotein cholesterol, fasting blood glucose, incidence of type 2 diabetes, and systolic and diastolic blood pressure
- Treatment harms: Any adverse events, serious adverse events (requiring admission to hospital or urgent medical care), gastrointestinal events, and withdrawal from the study because of adverse events

Settings

- Generalizable to Canadian primary care or feasible for conducting in or referral from primary care; surgical and metabolic unit interventions were excluded as representing a level of obesity and comorbid conditions that would be less commonly used as referral points from primary care

Box 2: Inclusion and exclusion criteria

Studies were included if they met the following criteria:

- Behavioural (diet, exercise or lifestyle strategies), pharmacologic (orlistat or metformin) or combined strategy trial of weight loss treatment or management
- Intervention focused on adults ≥ 18 years old who were overweight (BMI 25–29.9 kg/m^2) or obese (BMI 30–39.9 kg/m^2)
- Randomized controlled trial with a no-intervention, usual care, placebo or minimal component (e.g., single newsletter or information session on general health) comparison group (this condition applied only to studies assessing treatment effectiveness)
- Reported data for one or more specified weight outcomes (i.e., weight change in kg, loss of ≥ 5% and ≥ 10% of baseline body weight, change in waist circumference, and change in BMI)
- Reported data for outcomes of interest at least 12 months postbaseline assessment
- No restrictions on study design, comparison group, reporting of weight outcome or timing of assessment were applied to studies that reported data for harms of treatment
- Results were published in English or French

Studies were excluded if:

- Treatment involved a surgical intervention or a drug other than orlistat or metformin
- Intervention focused on morbidly obese adults (BMI ≥ 40 kg/m^2) or specifically enrolled participants who were pregnant, had an eating disorder or a condition in which weight gain was a cardinal manifestation (e.g., metabolic syndrome or polycystic ovarian disease).
- Intervention was conducted in an inpatient hospital, institutional or occupational setting or involved a school-based or faith-based program
- The only available results were published in a language other than English or French

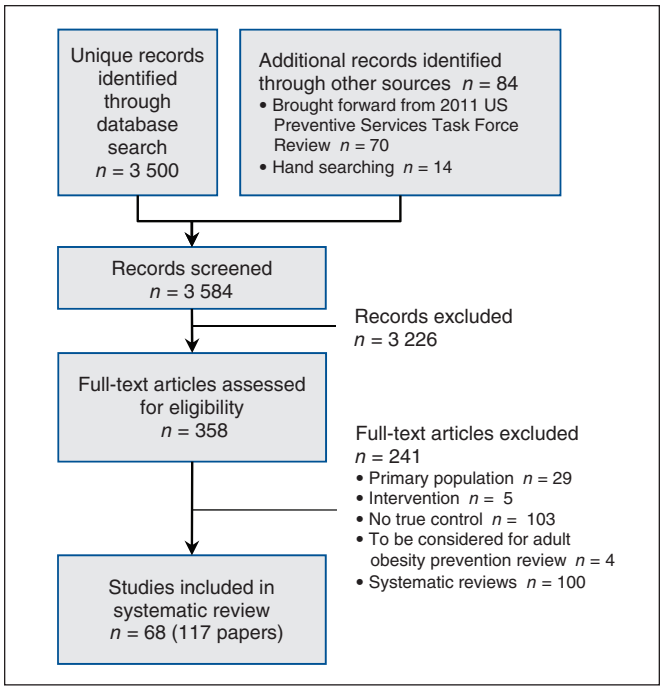

Figure 1: Search and selection flow diagram for articles on treatment of overweight and obesity in adults.

for continuous outcomes and risk ratio (RR) for binary outcomes.[16] For studies with more than one treatment arm, we took different approaches depending on the similarity of the interventions. For similar interventions (e.g., 2 arms of a lifestyle intervention, one using phone contact and one using in-person support) we pooled the data to do a pairwise comparison with the control group. Alternatively, if groups were substantially different (e.g., low-calorie diet and high-intensity aerobic exercise) we included the data for each arm compared with the control group but split the sample size for the control group to avoid a unit-of-analysis error and double counting.[14] All orlistat studies included an intervention of 120 mg thrice daily. Some studies also assessed smaller doses, but we only extracted data for effects of the consistently reported 120 mg dosage. Cochran's Q ($\alpha = 0.10$) and I^2 statistics were used to quantify heterogeneity within and between subgroups. Sensitivity analyses were performed to evaluate statistical stability and effect on statistical heterogeneity. For the outcome of weight in kg, we did subgroup analyses by focus of intervention (behavioural and pharmacologic plus behavioural) for all outcomes and comparisons (except sex for weight in kg and gastrointestinal adverse effects, which included studies in a single group).

Table 1: Summary of study characteristics

Design	• Sixty-eight studies (66 randomized controlled trials, 2 single-group pre–post designs [included for harms outcomes only])
Populations	• All studies included overweight (body mass index [BMI] 25–29.9) or obese (BMI 30–39.9) adults • Two interventions targeted seniors (≥ 65 yr); all other studies included adults aged 18 years or older • Sixty-four studies included both sexes (1 reported data only for men); 3 included only women, 1 included only men • Twenty-six studies (38%) were directed at populations with a high risk for cardiovascular disease (i.e., screened or identified as high risk or diagnosed with type 2 diabetes, hypertension or dyslipidemia)
Interventions	• Forty-one behavioural intervention arms (8 diet, 4 exercise, 10 diet plus exercise and 19 lifestyle) in 39 studies • Twenty-nine pharmacologic (25 studies involved orlistat [dosages: 23 studies, 120 mg three times daily; in 2 studies, 60 mg three times daily, included only for harms]; and 4 studies involved metformin (dosages: 500 mg once daily, 850 mg once daily, 850 mg twice daily, 1500 mg once daily]) plus behavioural (hypocaloric diet and encouragement to increase physical activity level) intervention arms in 27 studies • Median intervention duration was 12 mo; 49 interventions (72%) were ≤ 12 mo; 19 interventions (28%) lasted 13–60 mo: most ran for ≤ 2 yr
Comparator	• In behavioural intervention trials, control participants received usual care from their physicians or no intervention; in 7 studies they received a minimal component (e.g., printed materials on weight loss and healthy lifestyles) • In trials using orlistat or metformin, control participants followed the same diet and exercise instructions as the intervention participants but received placebo instead of active medications
Outcomes	• Primary weight outcomes (weight change in kilograms, loss of ≥ 5% baseline bodyweight, loss of ≥ 10% baseline body weight, change in BMI and change in waist circumference) • Secondary health outcomes (total cholesterol, low-density lipoprotein cholesterol level, fasting blood glucose level, incidence of type 2 diabetes, systolic blood pressure and diastolic blood pressure) • Treatment harms (any adverse events, serious adverse events, gastrointestinal events and withdrawal from the study because of adverse events)
Quality assessment	• Sixty-two of the randomized controlled trials (94%) were rated as having unclear or high risk of bias primarily because of a lack of information or a lack of procedures to ensure random sequence generation, allocation concealment and blinding of participants, personnel and outcome assessment • Most outcomes received moderate quality Grading of Recommendations Assessment, Development and Evaluation ratings (downgraded for risk of bias); occasional low-quality ratings were applied because of added concerns primarily regarding reporting bias
Study locations	• Two studies were conducted in Canada, 26 in the US, 31 in European countries, 1 co-located in the US and Europe, 6 in Australia or New Zealand, 1 in Japan and 1 in China
Publication dates	• Thirty-five studies (51%) were published between 2009 and 2013; 33 studies were published between 1985 and 2008

Results

The search and selection process is presented in Figure 1. Sixty-eight studies (117 papers) were eligible for inclusion in this review.[17–84] Thirty-six of these studies were brought forward from the 2011 USPSTF review[13] that met our inclusion criteria, and 32 studies were found in the recent literature. Of the 68 studies, 54 randomized controlled trials reported weight outcome data that could be pooled; 2 others provided eligible weight data that could not be pooled.[51,55] The remaining 12 studies (2 studies were single-group pre–post designs, 1 study had a more active comparison group, and 9 studies reported outcomes at < 12 mo) were only included in analyses of adverse events.[24,29,57,63,75–81,83] High within-group heterogeneity was common; however, the direction of treatment effect was consistent across most studies, and the confidence intervals overlapped. This statistical heterogeneity is likely due to small versus large treatment effects observed across studies. Table 1 presents a summary of the features of this body of evidence; details for individual studies are provided in Appendix 3 (available at www.cmajopen.ca/content/2/4/E306/suppl/DC1).

Weight outcomes

Forty-nine studies were included in the meta-analysis assessing weight change in kg.[17–23,25–28,31,33–47, 49,50,52–54,56,59–61,64–74,82,84] Intervention participants had a significantly greater reduction in weight compared with the control group (Table 2 and Figures 2A and 2B). There was no evidence that the effect of treatment differed based on focus of intervention (behavioural or pharmacologic plus behavioural). Weight loss was greater in intervention participants than in control participants for both behavioural interventions and pharmacologic plus behavioural interventions. The test for subgroup differences based on type of behavioural intervention in the behavioural trials (diet, exercise, diet + exercise and lifestyle) was significant: interventions using exercise alone did not lead to significantly greater reductions in weight, whereas diet alone showed the largest difference between groups (Table 2). In the behavioural trials, the test for subgroup differences based on cardiovascular disease risk status was also significant: compared with the control group, changes in weight were greater for participants with low baseline risk than those with high baseline risk (Table 2). There was no evidence that the effect of treatment differed based on any of the other variables considered in the sub-

Table 2: Effect of intervention on weight (kg), by intervention focus and subgroup

Intervention focus; subgroup	Meta-analysis, mean difference (95% CI)	Statistical heterogeneity (within group) p value (I^2 value, %)	Test for between-group differences p value (I^2 value, %)	No. of participants	No. of studies	Quality of evidence rating
Overall	–3.02 (–3.52 to –2.52)	< 0.00001 (91)	NA	22 615	49	Moderate
Behavioural	–3.13 (–3.88 to –2.38)	< 0.00001 (92)	0.62 (0)	10 829	33	Moderate
Pharmacologic + behavioural	–2.89 (–3.49 to –2.29)	< 0.00001 (87)		11 786	17	Moderate
Behavioural						
Diet	–4.71 (–6.22 to –3.21)	0.0003 (72)	0.03 (67.8)	913	8	Moderate
Exercise	–1.49 (–3.32 to 0.35)	0.0002 (85)		598	4	Low
Diet + exercise	–3.83 (–5.49 to –2.16)	< 0.00001 (90)		2 382	10	Low
Lifestyle	–2.52 (–3.54 to –1.49)	< 0.00001 (93)		6 936	17	Low
≤ 12 mo duration	–3.43 (–4.32 to –2.55)	< 0.00001 (88)	0.07 (23.4)	4 780	21	Low
> 12 mo duration	–2.53 (–3.81 to –1.24)	< 0.00001 (95)		6 049	12	Low
Male	–4.65 (–6.20 to –3.09)	< 0.00001 (89)	0.23 (31.5)	2 131	8	Moderate
Female	–3.33 (–4.80 to –1.86)	< 0.00001 (87)		1 800	8	Moderate
High cardiovascular disease risk	–1.89 (–2.69 to –1.08)	< 0.00001 (75)	0.005 (87.6)	2 951	12	Low
Low cardiovascular disease risk	–3.66 (–4.59 to –2.74)	< 0.00001 (92)		7 878	21	Moderate
Pharmacologic + behavioural						
Metformin	–1.92 (–2.94 to –0.89)	0.11 (60)	0.07 (68.8)	1 938	2	Moderate
Orlistat	–3.05 (–3.75 to –2.35)	< 0.00001 (88)		9 848	15	Moderate
≤ 12 mo duration	–2.89 (–3.90 to –1.88)	< 0.00001 (91)	0.72 (0)	4 418	11	Moderate
> 12 mo duration	–2.69 (–3.00 to –2.38)	0.36 (9)		7 368	6	Moderate
High cardiovascular disease risk	–2.93 (–4.08 to –1.79)	< 0.00001 (92)	0.80 (0)	3 411	9	Moderate
Low cardiovascular disease risk	–2.77 (–3.27 to –2.28)	0.03 (54)		8 375	8	Moderate

Note: CI = confidence interval, NA = not applicable.

group tests (i.e., intervention duration, sex, type of drug and cardiovascular disease risk in pharmacologic trials) (Table 2).

Twenty-four studies were included in the meta-analysis assessing loss of ≥ 5% baseline body weight.[17,19,20,27,33,36,38,39,45,53,54,58–60,62,64–68,70,72–74] Figure 3 shows intervention participants were more likely to lose ≥ 5% of their baseline body weight compared with control participants. There was no evidence that the effect of treatment differed based on focus of intervention (Table 3).

Similarly, 16 studies were included in the meta-analysis assessing loss of ≥ 10% baseline body weight.[19,20,36,58–60,62,64–70,72,74] Intervention participants were more likely to lose ≥ 10% of their baseline body weight compared with controls. There was no evidence that the effect of treatment differed based on focus of intervention (Table 3).

Twenty-six studies were included in the meta-analysis assessing change in BMI from baseline.[18–23,25–28,30,32,37,46–50,52–54,56,61,66,73,84] Intervention participants had a greater reduction in

	Experimental		Control		Mean difference (95% CI)
Study* (Behavioural)	**Mean ± SD**	***n***	**Mean ± SD**	***n***	
Andrews et al.[22] (1)	−1.5 ± 7.63	246	−0.4 ± 8.34	47	−1.10 (−3.67 to 1.47)
Andrews et al.[22] (2)	−2.4 ± 7.41	240	−0.4 ± 8.34	47	−2.00 (−4.56 to 0.56)
Appel et al.[19]	−4.84 ± 8.73	272	−0.8 ± 6.81	129	−4.04 (−5.61 to −2.47)
Balducci et al.[25]	0.44 ± 1.76	62	0.4 ± 1.21	20	0.04 (−0.65 to 0.73)
Bennett et al.[27]	−1.53 ± 4.96	180	−0.5 ± 4.76	185	−1.03 (−2.03 to −0.03)
Burke et al.[34] (F)	−4.3 ± 4.7	59	−1.2 ± 4.49	54	−3.10 (−4.79 to −1.41)
Burke et al.[34] (M)	−4.4 ± 4.8	47	−0.8 ± 4.99	44	−3.60 (−5.61 to −1.59)
Christian et al.[33]	−0.08 ± 4.95	141	0.63 ± 4.81	132	−0.71 (−1.87 to 0.45)
Cohen et al.[35]	−0.88 ± 4	15	1.3 ± 3	15	−2.18 (−4.71 to 0.35)
de Mello et al.[50]	−3.5 ± 5.1	231	−0.9 ± 5.4	203	−2.60 (−3.59 to −1.61)
Dekkers et al.[17]	−1.65 ± 6.03	526	−0.7 ± 5.68	266	−0.95 (−1.81 to −0.09)
DPP[84] (1)	−6.76 ± 5.58	1079	−0.42 ± 3.95	541	−6.34 (−6.81 to −5.87)
Foster-Schubert et al.[49] (1F)	−7.1 ± 5.85	118	−0.7 ± 5.55	29	−6.40 (−8.68 to −4.12)
Foster-Schubert et al.[49] (2F)	−8.9 ± 5.03	116	−0.7 ± 5.55	29	−8.20 (−10.42 to −5.98)
Foster-Schubert et al.[49] (3F)	−2 ± 5.52	117	−0.7 ± 5.55	29	−1.30 (−3.55 to 0.95)
Haapala et al.[36]	−4.5 ± 5	42	−1.1 ± 5.8	40	−3.40 (−5.75 to −1.05)
Janus et al.[53]	−2.65 ± 4.44	38	−0.6 ± 2.11	41	−2.05 (−3.60 to −0.50)
Kirby et al.[23]	−2.9 ± 8.64	34	0 ± 9.64	34	−2.90 (−7.25 to 1.45)
Kulzer et al.[37]	−3.8 ± 5.2	91	−1.4 ± 4	91	−2.40 (−3.75 to −1.05)
Langford et al.[38]	−4 ± 5	67	−0.46 ± 3.6	77	−3.54 (−4.98 to −2.10)
Lim et al.[31]	−2.96 ± 5.33	82	0.8 ± 5	22	−3.76 (−6.15 to −1.37)
Ma et al.[47]	−5.39 ± 8.08	160	−2.4 ± 8.1	81	−2.99 (−5.15 to −0.83)
Martin et al.[39] (F)	−1.38 ± 3.69	68	−0.16 ± 3.63	69	−1.22 (−2.45 to 0.01)
Morey et al.[46]	−1.48 ± 5.99	180	−0.84 ± 5.81	122	−0.64 (−1.99 to 0.71)
Nakade et al.[52] (F)	−4 ± 4.02	58	−0.1 ± 4.73	56	−3.90 (−5.51 to −2.29)
Nakade et al.[52] (M)	−5 ± 3.83	57	0.2 ± 5.5	55	−5.20 (−6.96 to −3.44)
Nanchahal et al.[54]	−2.39 ± 5.57	103	−1.31 ± 5.07	114	−1.08 (−2.50 to 0.34)
Parikh et al.[45]	−3.27 ± 3.31	35	−1.09 ± 3.67	37	−2.18 (−3.79 to −0.57)
Patrick et al.[18] (M)	−0.9 ± 7.06	224	−0.2 ± 6.87	217	−0.70 (−2.00 to 0.60)
Ross et al.[28] (F)	−1.24 ± 7.01	175	−1.24 ± 6.89	169	0.00 (−1.47 to 1.47)
Ross et al.[28] (M)	−1.48 ± 5.42	74	0.39 ± 5.18	72	−1.87 (−3.59 to −0.15)
Stevens et al.[40] (F)	−1.6 ± 5.2	83	0.2 ± 5.2	85	−1.80 (−3.37 to −0.23)
Stevens et al.[40] (M)	−4.7 ± 7.06	212	0 ± 7.06	151	−4.70 (−6.17 to −3.23)
Stevens et al.[41] (F)	0.7 ± 6.18	203	1.5 ± 5.99	170	−0.80 (−2.04 to 0.44)
Stevens et al.[41] (M)	−0.7 ± 5.68	344	1.9 ± 5	384	−2.60 (−3.38 to −1.82)
ter Bogt et al.[21]	−1.1 ± 5.3	171	−0.5 ± 5	186	−0.60 (−1.67 to 0.47)
Vissers et al.[26] (1)	−4.3 ± 4.8	12	1.3 ± 3.7	9	−5.60 (−9.24 to −1.96)
Vissers et al.[26] (2)	−7.94 ± 6.43	32	1.3 ± 3.7	9	−9.24 (−12.53 to −5.95)
Wadden et al.[20]	−2.9 ± 8.01	131	−1.7 ± 7.98	130	−1.20 (−3.14 to 0.74)
Wood et al.[42] (1M)	−7.2 ± 3.7	42	0.6 ± 3.7	21	−7.80 (−9.74 to −5.86)
Wood et al.[42] (2M)	−4 ± 3.9	47	0.6 ± 3.7	21	−4.60 (−6.54 to −2.66)
Wood et al.[43] (1F)	−4.1 ± 5.5	31	1.3 ± 5.2	20	−5.40 (−8.39 to −2.41)
Wood et al.[43] (1M)	−5.1 ± 5.8	40	1.7 ± 4.8	20	−6.80 (−9.57 to −4.03)
Wood et al.[43] (2F)	−5.1 ± 5.3	42	1.3 ± 5.2	20	−6.40 (−9.19 to −3.61)
Wood et al.[43] (2M)	−8.7 ± 5.7	39	1.7 ± 4.8	20	−10.40 (−13.16 to −7.64)
Woollard et al.[44]	0.75 ± 5.21	97	2 ± 5.1	53	−1.25 (−2.97 to 0.47)
Subtotal (95% CI)		**6463**		**4366**	**−3.13 (−3.88 to −2.38)**
Heterogeneity: I^2 = 92%					

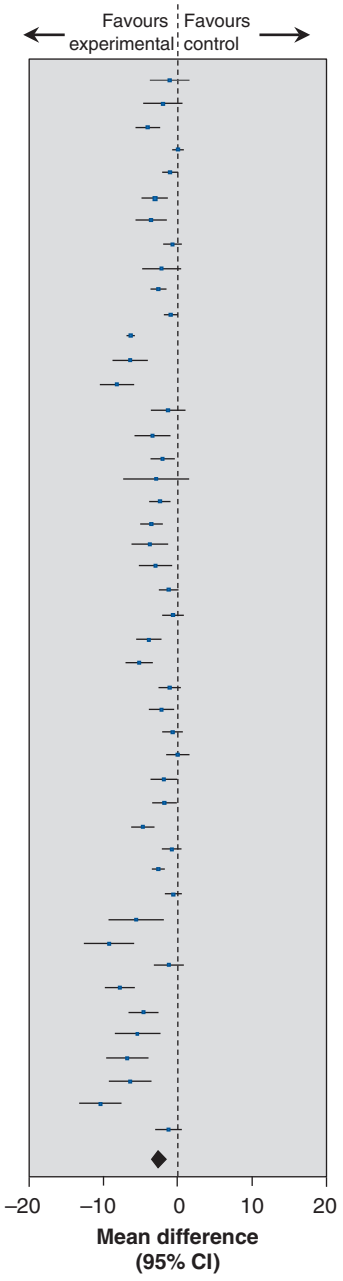

Figure 2A: Effect of behavioural treatment interventions on weight in kilograms. Note: 1 = intervention arm 1; 2 = intervention arm 2; F = females only; M = males only: 1F, 2F and 3F represent female participants in different intervention arms; 1M and 2M represent male participants in different intervention arms; CI = confidence interval; DPP = Diabetes Prevention Program; SD = standard deviation.

BMI compared with the control groups. There was no evidence that the effect of treatment differed based on focus of intervention (Table 4).

Thirty-three studies were included in the meta-analysis assessing change in waist circumference from baseline.[17–22,25,26,28,33,34,36,37,45–47,49,50,52–54,56,58,59,61,65,66,69,71–74,84] Intervention participants had a greater reduction in waist circumference compared with controls. There was no evidence that the effect of treatment differed based on focus of intervention (Table 4).

Secondary outcomes

Meta-analyses showed greater improvements in intervention participants compared with control participants across all continuous secondary outcomes: total cholesterol,[17,19–23,25,28,31,33,37,42,43,46–48,50,53,56,58,59,61,62,64,65,67–71,73,74,82] low-density lipoprotein cholesterol,[19–23,25,28,31,33,42,43,45–47,53,56,58,59,61,62,64,65,67–71,73,74,82] fasting blood glucose,[19–22,26,28,31,37,45–48,50,53,56,58,64–72,74,82,84] and systolic[17,19–22,25–28,31–34,37,40,42,43,45,47,53,54,58–61,64,66–74,82,84] and diastolic[17,19–22,25–28,31–34,37,40,42,43,45,47,53,54,58–61,64,66,67,69–74,82,84] blood pressure (Table 4). For all but 2 of these outcomes, there was no evidence that the effect of treatment differed based on focus of intervention. The tests for subgroup differences were significant for total cholesterol and fasting glucose (Table 4). In both cases, when compared with the control groups, benefits were greater for participants in pharmacologic plus behavioural interventions than for those taking part in behavioural interventions alone.

Nine studies were included in a meta-analysis assessing the risk of type 2 diabetes in prediabetic patients.[45–47,50,51,55,72,82,84] A diagnosis of new onset type 2 diabetes was less likely to occur in intervention participants compared with the control group (Table 3). There was no evidence that the effect of treatment differed based on focus of intervention (Table 3).

Adverse effects

Very few behavioural studies reported adverse events. When they did, harms were usually minor and related to injuries sustained during physical activity (e.g., joint, back or muscle pain; minor abrasions, bruises or blisters; and fractures). Most (about 80%) adverse events that occurred in orlistat trials (and some in metformin trials) were gastrointestinal disturbances. Commonly reported symptoms across studies were fatty or oily stool, increased defecation, increased urgency, abdominal pain, soft stools, oily spotting and flatulence. Most studies reported that the gastrointestinal events were typically mild or moderate in intensity and occurred only once or twice in the participants, usually near the beginning of treatment.

Across the 17 studies with data that could be pooled, intervention participants were more likely to have an adverse event compared with control participants (Table 5).[58–61,64,66,67,69–74,82,84] However, as indicated by the test for subgroup differences, participants in the 15 pharmacologic interventions were significantly more likely to have an adverse event (Table 5).

Study* (Pharmacologic and behavioural)	Experimental Mean ± SD	Experimental *n*	Control Mean ± SD	Control *n*	Mean difference (95% CI)
Bakris et al.[73]	–5.4 ± 6.4	267	–2.7 ± 6.4	265	–2.70 (–3.79 to –1.61)
Broom et al.[59]	–5.8 ± 8.5	259	–2.3 ± 6.4	263	–3.50 (–4.79 to –2.21)
Davidson et al.[60]	–8.76 ± 9.48	657	–5.81 ± 10.01	223	–2.95 (–4.45 to –1.45)
Derosa et al.[61]	–8.6 ± 1	25	–7.6 ± 0.7	23	–1.00 (–1.49 to –0.51)
Derosa et al.[56]	–9.5 ± 5	113	–2.6 ± 3.79	121	–6.90 (–8.04 to –5.76)
DPP[84] (2)	–2.72 ± 5.57	1073	–0.42 ± 3.95	541	–2.30 (–2.77 to –1.83)
Fontbonne et al.[82]	–2 ± 6.21	164	–0.8 ± 5.49	160	–1.20 (–2.48 to 0.08)
Hauptman et al.[64]	–7.94 ± 8.26	210	–4.14 ± 8.15	212	–3.80 (–5.37 to –2.23)
Hollander et al.[65]	–6.19 ± 6.49	162	–4.31 ± 7.19	159	–1.88 (–3.38 to –0.38)
Kelley et al.[74]	–3.89 ± 4.4	266	–1.27 ± 4.59	269	–2.62 (–3.38 to –1.86)
Krempf et al.[66]	–5.3 ± 9.3	346	–2.4 ± 9.35	350	–2.90 (–4.29 to –1.51)
Lindgärde[67]	–5.6 ± 5.2	190	–4.3 ± 5.9	186	–1.30 (–2.43 to –0.18)
Miles et al.[68]	–4.7 ± 4.74	250	–1.8 ± 4.78	254	–2.90 (–3.73 to –2.07)
Rossner et al.[69]	–7.4 ± 7.1	242	–4.3 ± 7.4	237	–3.10 (–4.40 to –1.80)
Sjöström et al.[70]	–10.3 ± 9.3	343	–6.1 ± 9.3	340	–4.20 (–5.59 to –2.81)
Swinburn et al.[71]	–4.7 ± 7.7	170	–0.9 ± 4.2	169	–3.80 (–5.12 to –2.48)
Torgerson et al.[72]	–5.8 ± 5.58	1640	–3 ± 5.58	1637	–2.80 (–3.18 to –2.42)
Subtotal (95% CI)		**6377**		**5409**	**–2.89 (–3.49 to –2.29)**
Heterogeneity: I^2 = 87%					
Total (95% CI)		**12 840**		**9 775**	**–3.02 (–3.52 to –2.52)**
Heterogeneity: I^2 = 91%					
Test for subgroup differences: I^2 = 0%					

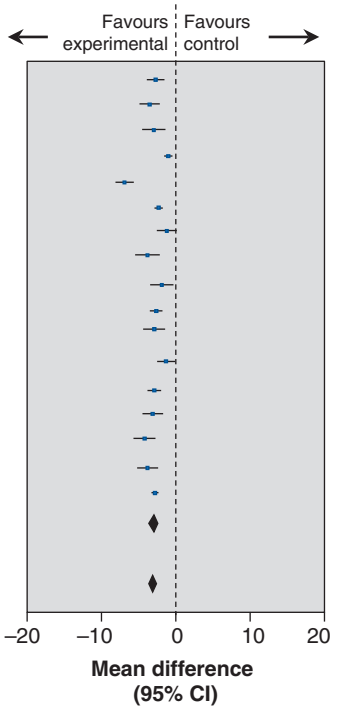

Figure 2B: Effect of pharmacologic plus behavioural treatment interventions on weight in kilograms. Note: 2 = intervention arm 2; CI = confidence interval; DPP = Diabetes Prevention Program; SD = standard deviation.

Serious adverse events were defined as those requiring urgent medical care or admission to hospital, as well as those defined as serious by the primary authors. A meta-analysis of 14 studies showed no difference between the intervention and control groups for the risk of having serious adverse events, and there was no evidence that the effect of treatment differed based on focus of intervention (Table 5).[20,27,57,59,61,66,67,70–73,77,79,84] Gastrointestinal events were reported only in studies that used drug interventions and in the 23 studies with data that could be pooled; those taking active medications were more likely to report these events than control participants.[57,59,61–69,71–77,79,81–84] Likewise, participants in 25 pharmacologic studies were more likely to withdraw from their study because of adverse events compared with control participants (Table 5).[46,56,58–77,79,81,82]

Interpretation

Main findings

There are 3 principal findings from this review. First, the pooled-effect estimates for all weight outcomes were statistically significant in favour of the interventions and, compared with the control groups, intervention participants had, on average, a 3.02 kg greater weight loss, a 2.78 cm greater reduction in waist circumference, and a 1.11 kg/m^2 greater reduction in BMI, and were more likely to lose ≥ 5% (RR 1.77) and ≥ 10% (RR 1.91) of their baseline body weight. Every kilogram of weight loss in people with impaired glucose tolerance is associated with a 16% reduction in the incidence of type 2 diabetes.[85] Second, there was no significant difference

Study*	Events, *n/N* Experimental	Control	Risk ratio (95% CI)
Behavioural			
Appel et al.[19]	107/272	24/129	2.11 (1.43–3.12)
Bennett et al.[27]	36/180	36/185	1.03 (0.68–1.55)
Christian et al.[33]	30/141	14/132	2.01 (1.11–3.61)
Dekkers et al.[17]	104/526	35/266	1.50 (1.06–2.14)
Haapala et al.[36]	19/42	8/40	2.26 (1.12–4.57)
Janus et al.[53]	12/38	0/41	26.92 (1.65–439.61)
Langford et al.[38]	31/67	9/77	3.96 (2.03–7.70)
Martin et al.[39] (F)	7/68	8/69	0.89 (0.34–2.31)
Nanchahal et al.[54]	35/103	22/114	1.76 (1.11–2.79)
Parikh et al.[45]	16/47	6/43	2.44 (1.05–5.66)
Wadden et al.[20]	34/131	28/130	1.21 (0.78–1.87)
Subtotal (95% CI)	**1615**	**1226**	**1.75 (1.35–2.27)**
Total events	431	190	
Heterogeneity: I^2 = 57%			
Pharmacologic and behavioural			
Bakris et al.[73]	122/267	60/265	2.02 (1.56–2.61)
Berne et al.[58]	51/96	12/94	4.16 (2.38–7.29)
Broom et al.[59]	144/259	64/263	2.28 (1.80–2.90)
Davidson et al.[60]	432/657	97/223	1.51 (1.29–1.77)
Finer et al.[62]	39/110	23/108	1.66 (1.07–2.59)
Hauptman et al.[64]	106/210	65/212	1.65 (1.29–2.10)
Hollander et al.[65]	79/162	36/159	2.15 (1.55–2.99)
Kelley et al.[74]	87/266	35/269	2.51 (1.76–3.58)
Krempf et al.[66]	130/223	74/196	1.54 (1.25–1.91)
Lindgärde[67]	103/190	76/186	1.33 (1.07–1.65)
Miles et al.[68]	98/250	40/254	2.49 (1.80–3.44)
Sjöström et al.[70]	235/343	167/340	1.39 (1.23–1.59)
Torgerson et al.[72]	449/850	210/564	1.42 (1.25–1.61)
Subtotal (95% CI)	**3883**	**3133**	**1.79 (1.57–2.04)**
Total events	2075	959	
Heterogeneity: I^2 = 76%			
Total (95% CI)	**5498**	**4359**	**1.77 (1.58–1.99)**
Total events	2506	1149	
Heterogeneity: I^2 = 69%			
Test for subgroup differences: I^2 = 0%			

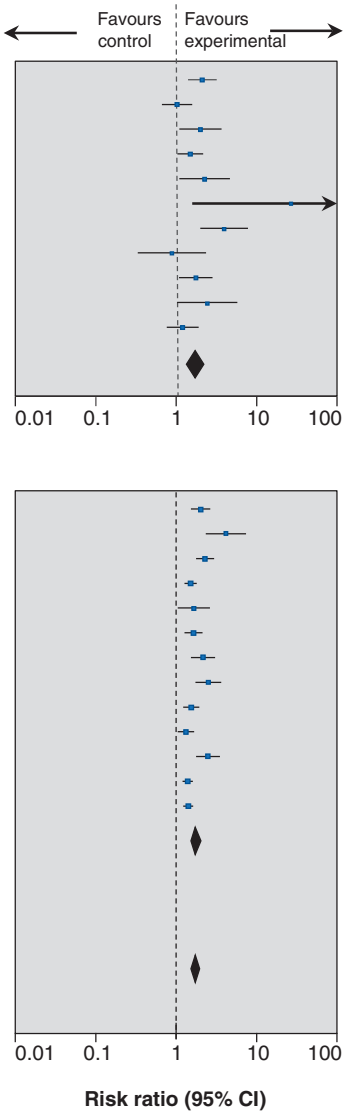

Figure 3: Effect of treatment interventions on loss of ≥ 5% baseline body weight: overall and by focus of intervention (behavioural and pharmacologic plus behavioural). Note: CI = confidence interval; F = females only.

between behavioural and pharmacologic interventions for any weight outcomes, although the potential for adverse outcomes appears greater with pharmacologic treatments. Third, modest weight reduction, corresponding to loss of ≥ 5% and ≥ 10% of baseline body weight (number needed to treat 5 and 9, respectively) had clinically important effects, most notably a 38% reduction in the incidence of type 2 diabetes in prediabetic populations (number needed to treat 17). With prevalence rates for type 2 diabetes in the US and the European Union of 9.3% and 10%, respectively,[86] coupled with its increasing prevalence, extrapolation of a 38% reduction in the incidence of type 2 diabetes could have a significant benefit on population health. Intervention participants also had small improvements in secondary outcomes; these effects may be of minor clinical significance at the individual level, but important at the population level.

The benefits of treatment should be weighed against the harms. Few behavioural studies reported adverse events; those that did found a small absolute excess in the risk of injuries associated with physical activity. Participants on active medications reported significantly milder to moderate gastrointestinal disturbances than those on placebo.

Comparison with other studies

Updating the United States Preventive Services Task Force review search[13] added 32 studies, but did not point to changes in any important outcomes. We used a more comprehensive approach of subgrouping studies based on behavioural interventions such diet, exercise and lifestyle changes to better reflect the evidence in the current literature. In addition to a modest reduction observed for measures of adiposity such as weight in kilograms, BMI and waist circumference, our review also found associated reductions in intermediate physiological outcomes such as blood pressure and incidence of type 2 diabetes, which reinforces the findings of other systematic reviews[87,88,89] documenting reduction in the need for pharmacologic therapy for blood pressure and glycemic control as a potential clinical benefit of modest weight loss.

Limitations

Most evidence was derived from studies that could not be assessed comprehensively for risk of bias. Two-thirds of the pharmacologic studies had prerandomization run-in periods that involved low-calorie diets with or without placebo, which may have exaggerated the potential benefits of treatment. Potential reporting bias was identified across a number of outcome and comparison-based study groupings. The relatively high attrition rates in many studies leads to further risk of bias. These methodological limitations reduced the strength of evidence, resulting in moderate- and sometimes low-quality ratings, which reduce confidence in the pooled estimates of effect. Results presented for the secondary outcomes should be interpreted with caution because we only included interventions where the focus was on weight loss. Adverse events may be overestimated; data were extracted as reported even when the connection to the intervention was not clear and even if run-in events were included. The search included papers in English or French only and thus may have missed studies in other languages. Most studies were of relatively short duration (≤ 12 mo), and there was a lack of evidence to address the question of whether (and for how long) weight loss is maintained after interventions are completed.

Table 3: Effect of intervention on weight loss and diabetes outcomes, by intervention focus

Outcome; intervention focus	Effect on % weight loss: RR (95% CI)	Absolute risk reduction, %	No. needed to treat (95% CI)	Statistical heterogeneity (within group) p value (I^2 value, %)	Test for between-group differences p value (I^2 value, %)	No. of participants	No. of studies	Quality of evidence rating
Loss of ≥ 5% baseline body weight								
Overall	1.77 (1.58–1.99)	20.42	5 (4–7)	< 0.00001 (69)	NA	9 857	24	Low
Behavioural	1.75 (1.35–2.27)	11.67	9 (5–18)	0.01 (57)	0.88 (0)	2 841	11	Low
Pharmacologic + behavioural	1.79 (1.57–2.04)	24.26	4 (3–6)	< 0.00001 (76)		7 016	13	Low
Loss of ≥ 10% baseline body weight								
Overall	1.91 (1.69–2.16)	11.24	9 (7–12)	0.27 (16)	NA	7 523	16	Low
Behavioural	2.04 (1.30–3.21)	8.01	12 (6–44)	0.81 (0)	0.81 (0)	744	3	Moderate
Pharmacologic + behavioural	1.92 (1.67–2.21)	11.81	8 (6–12)	0.14 (31)		6 779	13	Low
Incidence of type 2 diabetes								
Overall	0.62 (0.50–0.77)	5.75	17(13–29)	0.02 (54)	NA	8 624	9	Moderate
Behavioural	0.55 (0.42–0.72)	8.88	11 (9–18)	0.25 (23)	0.11 (60)	3 198	7	Moderate
Pharmacologic + behavioural	0.72 (0.59–0.87)	3.60	28(19–60)	0.26 (27)		5 426	3	Moderate

Note: CI = confidence interval, NA = not applicable, RR = risk ratio.

Conclusion

In summary, modest weight reduction confers clinically important benefits and a substantial reduction in the incidence of type 2 diabetes in prediabetic populations, with the potential to improve population health. Future research should include longer term follow-up to observe maintenance of weight loss, to study the effects of repeated weight loss and regain, and to determine if improvements in health outcomes are related to the intervention apart from weight loss.

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Table 4: Effect of intervention on body mass index, waist circumference and secondary health outcomes, by intervention focus

Outcome; intervention focus	Meta-analysis, mean difference (95% CI)	Statistical heterogeneity (within group) p value (I^2 value, %)	Test for between-group differences p value (I^2 value, %)	No. of participants	No. of studies	Quality of evidence rating
Primary weight outcomes						
Body mass index, kg/m^2						
Overall	−1.11 (−1.39 to −0.84)	< 0.00001 (93)	NA	10 611	26	Moderate
Behavioural	−1.09 (−1.43 to −0.75)	< 0.00001 (93)	0.59 (0)	7 487	22	Moderate
Pharmacologic + behavioural	−1.27 (−1.82 to −0.72)	< 0.00001 (93)		3 124	5	Moderate
Waist circumference, cm						
Overall	−2.78 (−3.34 to −2.22)	< 0.00001 (91)	NA	16 565	33	Moderate
Behavioural	−3.05 (−3.86 to −2.24)	< 0.00001 (90)	0.18 (44.4)	7 770	22	Moderate
Pharmacologic + behavioural	−2.29 (−3.04 to −1.55)	< 0.00001 (91)		8 795	12	Moderate
Secondary health outcomes						
Total cholesterol, mmol/L						
Overall	−0.21 (−0.29 to −0.13)	< 0.00001 (86)	NA	10 039	33	Moderate
Behavioural	−0.10 (−0.18 to −0.03)	< 0.0001 (63)	0.0001 (93.1)	4 282	18	Low
Pharmacologic + behavioural	−0.33 (−0.42 to −0.24)	< 0.00001 (81)		5 757	15	Moderate
Low-density lipoprotein cholesterol, mmol/L						
Overall	−0.21 (−0.29 to −0.12)	< 0.00001 (90)	NA	9 313	30	Low
Behavioural	−0.14 (−0.29 to −0.002)	< 0.00001 (90)	0.11 (60.1)	3 556	15	Moderate
Pharmacologic + behavioural	−0.28 (−0.38 to −0.19)	< 0.00001 (89)		5 757	15	Moderate
Fasting blood glucose, mmol/L						
Overall	−0.26 (−0.38 to −0.13)	< 0.00001 (96)	NA	12 646	28	Moderate
Behavioural	−0.14 (−0.23 to −0.05)	< 0.00001 (81)	0.02 (80.7)	5 106	15	Moderate
Pharmacologic + behavioural	−0.43 (−0.66 to −0.20)	< 0.00001 (98)		7 540	14	Moderate
Systolic blood pressure, mm Hg						
Overall	−1.70 (−2.23 to −1.17)	0.002 (41)	NA	16 668	37	Moderate
Behavioural	−1.76 (−2.61 to −0.91)	0.0009 (50)	0.91 (0)	7 644	22	Moderate
Pharmacologic + behavioural	−1.70 (−2.28 to −1.13)	0.24 (19)		9 024	16	Moderate
Diastolic blood pressure, mm Hg						
Overall	−1.42 (−1.88 to −0.96)	< 0.00001 (63)	NA	16 158	36	Moderate
Behavioural	−1.60 (−2.27 to −0.93)	< 0.00001 (63)	0.45 (0)	7 690	22	Moderate
Pharmacologic + behavioural	−1.24 (−1.88 to −0.61)	0.0002 (65)		8 468	15	Moderate

Note: CI = confidence interval, NA = not applicable.

Table 5: Effect of intervention on any adverse events, serious adverse events, gastrointestinal events and withdrawals from the study because of adverse events, by intervention focus

Outcome; intervention focus	Effect			Statistical heterogeneity (within group) *p* value (I^2 value, %)	Test for between-group differences *p* value (I^2 value, %)	No. of participants	No. of studies	Quality of evidence rating
	RR (95% CI)	Absolute risk increase, %	No. needed to harm (95% CI)					
Any adverse events								
Overall	1.16 (1.09–1.23)	9.31	11 (7–19)	< 0.00001 (73)	NA	5 512	17	Moderate
Behavioural	0.19 (0.03–1.16)	—	—	0.41 (0)	0.05 (74)	561	3	Low
Pharmacological + behavioural	1.16 (1.09–1.23)	10.36	10 (7–17)	< 0.00001 (75)		4 951	15	Moderate
Serious adverse events								
Overall	1.07 (0.96–1.20)	—	—	0.74 (0)	NA	10 811	14	Low
Behavioural	0.995 (0.80–1.24)	—	—	0.68 (0)	0.44 (0)	2 174	3	Low
Pharmacological + behavioural	1.10 (0.97–1.25)	—	—	0.62 (0)		8 637	12	Low
Gastrointestinal events								
Pharmacological + behavioural	1.58 (1.47–1.70)	18.72	5 (4–7)	< 0.00001 (71)	NA	12 954	23	Low
Study withdrawal because of adverse events								
Overall	1.69 (1.43–2.00)	3.05	33 (23–53)	0.65 (0)	NA	12 987	26	Moderate
Behavioural	3.40 (0.16–70.16)	—	—	NA	0.65 (0)	302	1	Low
Pharmacological + behavioural	1.68 (1.42–2.00)	3.09	32 (22–47)	0.25 (15)		12 685	25	Moderate

Note: CI = confidence interval, NA = not applicable, RR = risk ratio.

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