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Acute and maintenance effects of non-pharmacologic interventions for antipsychotic associated weight gain and metabolic abnormalities: A meta-analytic comparison of randomized controlled trials

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ABSTRACT

Objective: To evaluate the efficacy of non-pharmacological interventions for antipsychotic-associated weight gain.
Methods: Systematic literature search and meta-analysis of randomized controlled trials comparing behavioral interventions with control groups to ameliorate antipsychotic-associated weight gain.
Results: Across 17 studies (n = 810, mean age: 38.8 years, 52.7% male, 40.8% White, 85.6% with schizophrenia-spectrum disorders), non-pharmacological interventions led to a significant reduction in weight (−3.12 kg; CI: −4.03, −2.21, p < 0.0001) and body mass index (BMI) (−0.94 kg/m^2; CI: −1.45, −0.43, p = 0.0003) compared with control groups. Intervention benefits extended to all secondary outcomes, except for high density-lipoprotein-cholesterol and systolic blood pressure. Compared to controls, intervention patients experienced significant decreases in waist circumference (WMD = −3.58 cm, CI: −5.51, −1.66, p = 0.03), percent body fat (WMD = −2.82%, CI: −5.35, −0.30, p = 0.03), glucose (WMD = −5.79 mg/dL, CI: −9.73, −1.86, p = 0.004), insulin (WMD = −4.93 uIU/mL, CI: −7.64, −2.23, p = 0.0004), total cholesterol (WMD = −20.98 mg/dL, CI: −33.78, −8.19; p = 0.001), low density-lipoprotein-cholesterol (WMD = −22.06 mg/dL, CI: −37.80, −6.32, p = 0.006) and triglycerides (WMD = −61.68 mg/dL, CI: −92.77, −30.59, p = 0.0001), and less weight gain ≥7% (29.7% vs. 61.3%; RR = −0.52, CI: −0.35, −0.78, p = 0.002; number-needed-to-treat = 4). Up to 12 months after the intervention ended (mean = 3.6 months), benefits endured regarding weight (WMD = −3.48 kg, CI: −6.37, −0.58, p = 0.02), but not BMI (p = 0.40). Subgroup analyses showed superiority of non-pharmacological interventions irrespective of treatment duration, individual or group, cognitive behavioral or nutritional interventions, or prevention versus intervention trials. However, weight and BMI were significantly improved only in outpatient trials (p < 0.0001), but not in inpatient or mixed samples (p = 0.09–0.96).
Conclusion: Behavioral interventions effectively prevented and reduced antipsychotic-associated weight gain and cardiometabolic perturbations, at least in outpatients agreeing to participate in trials aimed at improving physical health. Effective treatments ranged from nutritional interventions to cognitive behavioral therapy.
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1. Introduction

Antipsychotic efficacy for psychotic disorders (Leucht et al., 2009), bipolar disorder (Correll et al., 2010), major depressive disorders (Nelson and Papakostas, 2009) and irritability/aggression associated with autism (Correll et al., 2011a), as well as off-label use in other psychiatric conditions (Maher et al., 2011) is counterbalanced by significant weight gain and cardiometabolic risk (Allison et al., 1999; American Diabetes Association et al., 2004; Lieberman et al., 2005; Kahn et al., 2008; De Hert et al., 2012). This weight gain is problematic as it may adversely affect adherence, quality of life (Allison et al., 2003), and especially, cardiovascular morbidity and mortality (Newcomer, 2005; Correll et al., 2011b; De Hert et al., 2011).

Pharmacologic interventions to ameliorate antipsychotic weight gain have had moderate success. Out of 15 agents examined in a recent meta-analysis, only five showed significant benefit versus placebo, and three were already taken off the market due to adverse effects (fenfluramine, sibutramine, reboxetine). Metformin and topiramate

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reduced antipsychotic-related weight gain compared to placebo by 2.5–3 kg after 8–12 weeks of treatment (Maayan et al., 2010). Pharmacologic interventions can cause additional side effects (Maayan and Correll, 2010). Metformin carries a risk of lactic acidosis, particularly in the elderly and in those with compromised renal function, and its use can be limited by nausea, vomiting and diarrhea. Topiramate has been associated with cognitive blunting (Narula et al., 2010).

Conversely, non-pharmacological interventions do not have such side effects and have shown promise. In a meta-analysis of 10 randomized controlled (RCTs) (n = 482) Alvarez-Jimenez et al. (2008) reported that non-pharmacological interventions led to 2.56 kg less weight gain and 0.91 kg/m^2 less BMI increase than the control condition and that nutritional counseling was equivalent to cognitive behavioral therapy (CBT). While this meta-analysis provided support for non-pharmacological interventions, the small number of studies precluded secondary analyses regarding metabolic outcomes, and the mediating impact of treatment duration. A more recent, systematic review included the same 10 RCTs plus 6 additional, but non-randomized studies (Gabriele et al., 2009), reporting similar results.

The current study expands upon the prior publications (Alvarez-Jimenez et al., 2008; Gabriele et al., 2009) by (1) including additional RCTs , and (2) analyzing effects on insulin, glucose, high density lipoprotein (HDL), low density lipoprotein (LDL), total cholesterol, triglycerides, and systolic blood pressure. In addition we also aimed to assess maintenance effects after the behavioral interventions ended.

2. Materials and methods

2.1. Search

A literature search was conducted in PsycInfo, Medline, PubMed, CINAHL, and the Cochrane Library using the following search terms: 'weight,' 'antipsychotic,' and 'intervention' plus 'behavioral,' 'psychoeducation,' 'exercise,' or 'cognitive'. Reference lists of relevant articles were searched for additional studies. When required data was missing, first/corresponding authors were contacted for additional information.

Included in this meta-analysis were RCTs of non-pharmacological interventions aimed at preventing or reducing antipsychotic associated weight gain (see Fig. 1 for the search results and flow).

2.2. Data extraction and outcomes

All data were extracted by one author and verified at a later point by a second author. Inconsistencies were reviewed and resolved.

2.3. Calculations and analyses

Data were analyzed using randomized effects models in Review Manager 5.0 (RevMan 5.0.24 (PC version), Cochrane Collaboration, Oxford, UK). All tests were two-sided and α was set at 0.05. For continuous outcomes, the weighted mean difference (WMD) with 95% confidence intervals (CI) was calculated. For dichotomous outcomes, Risk Ratio (RR) $\pm$ CI was calculated and number-needed-to-treat (NNT) was derived by dividing 1 by the risk difference. Study heterogeneity was measured using the I-squared statistic, with I-squared > 50% indicating significant heterogeneity.

The co-primary outcomes were (a) body weight and (b) body mass index (BMI). Secondary outcomes included change in waist circumference, body fat percentage, total, HDL-, and LDL-cholesterol, triglycerides, fasting glucose, insulin, and systolic sitting blood pressure and all-cause discontinuation.

To examine potential moderator variables, five a priori planned sensitivity analyses were conducted: (1) CBT (N = 6) vs. nutritional and/or exercise interventions (N = 11); (2) trial duration $\leq$ 3 months (N = 9) vs. trial duration > 3 months (N = 8); (3) prevention trials (i.e., non-pharmacologic intervention initiated within 4 weeks of starting the antipsychotic: N = 6) vs. intervention trials (i.e., non-pharmacologic intervention initiated after antipsychotic weight gain had occurred: N = 11); (4) individual interventions (N = 5) vs. group interventions (N = 12); and (5) inpatient status (N = 3) vs. mixed (N = 2) vs. outpatient status (N = 12).

3. Results

We identified 17 RCTs, including 810 participants, that had a comparison group (Table 1). Data were extracted from an 18th publication (Alvarez-Jimenez et al., 2010) for follow-up information on an active treatment study (Alvarez-Jimenez et al., 2006). Treatment duration ranged from 8 to 72 weeks (8 studies (47%) with > 12 week duration, mean: 19.6 weeks). Treatment involved CBT (N = 7, 41%) and nutritional and/or exercise interventions (N = 10, 59%). Participants' mean age was 38.1 years in the intervention

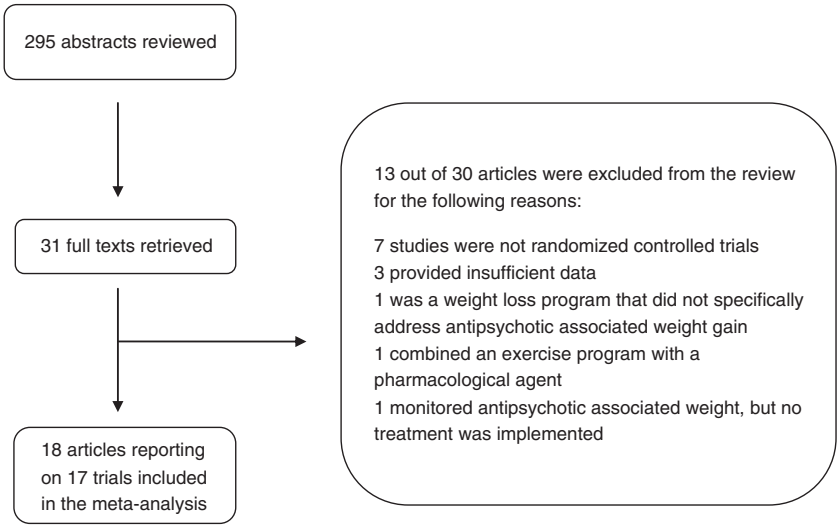


Fig. 1. Flow chart of systematic review.

group and 37.2 years in the control group. Overall, 52.3% of the participants in the intervention group and 54.9% in the control group were men. In the intervention group, 47% of the participants were Caucasian, 36% were Asian, 10.7% were African American, 0.8% were Hispanic, and 5.5% were reported as "Other". In the control group, 51.3% of the participants were Caucasian, 31.7% were Asian, 10.9% were African American, 3% were Hispanic, and 3.9% were reported as "Other" (8 studies with data). Trials were conducted in the USA (N = 6), Europe (N = 5), Asia (N = 3), Australia (N = 1), Canada (N = 1), and Israel (N = 1). The mean BMI was 29.6 kg/m^2 for the intervention group and 28.5 kg/m^2 for the control group. Out of the 810 participants, 423 (52.2%) were diagnosed with schizophrenia, schizoaffective disorder, or schizophreniform (85.6% of patients with diagnostic information), 46 (5.7%) were diagnosed with unipolar or bipolar disorder,and in 341 patients (42.1%) diagnostic information was missing.

All but three studies included weight data (82%), with 57% of those studies (N = 8) reporting weight change data and 43% (N = 6) providing endpoint weight. Similarly, 94% of the studies (N = 16) reported BMI data, with 44% of the studies (N = 7) reporting BMI change data and 56% (N = 9) reporting endpoint BMI. Only 6 studies (35%) reported change or endpoint for glucose and waist circumference, 5 studies (29%) provided total cholesterol endpoint data, 4 (24%) reported end point data in HDL-cholesterol and triglycerides, 3 (18%) reported change or end point in LDL-cholesterol, insulin, body fat percentage, and weight gain $\geq$ 7%, and 2 studies (12%) reported endpoint for systolic sitting blood pressure.

In six studies, changes in weight and/or BMI change were reported 2–12 months (mean: 3.6 months for weight, 5.8 months for BMI) after the intervention ended.

3.1. Co-primary outcomes

Non-pharmacological interventions were associated with a pooled weight change of −3.12 kg(CI: −4.03, −2.21; p<0.0001; I^2: 42%) (Fig. 2) and a pooled BMI change of −0.94 kg/m^2 (CI: −1.45, −0.43; p = 0.0003; I^2: 75%) compared to controls (see Fig. 3).

3.2. Secondary outcomes

3.2.1. Waist circumference, percent body fat, and weight gain $\geq$ 7%

The waist circumference in the intervention group decreased significantly compared with the control group (N = 6, n = 349, WMD = −3.58 cm, CI: −5.51, −1.66, p = 0.03; I^2 = 65%). Percentage of body fat decreased significantly in the intervention group compared with controls (N = 3, n = 83, WMD = −2.82%, CI: −5.35, −0.30, p = 0.03; I^2 = 0%). Lastly, in the intervention group significantly less patients gained $\geq$ 7% compared to the control group (N = 3, n = 126, 29.7% vs. 61.3%; RR = −.52, CI: −0.35, −0.78, p = 0.002; I^2 = 67%, NNT = 4).

3.2.2. Insulin and glucose

Compared with the control group, insulin levels (N = 3, n = 150, WMD = −4.93 uIU/mL, CI: −7.64, −2.23, p = 0.0004; I^2 = 0%) and fasting glucose levels (N = 6, n = 348, WMD = −5.79 mg/dL, CI: −9.73, −1.86, p = 0.004; I^2 = 58%) were significantly lower in the intervention group.

3.2.3. Blood lipids

Total cholesterol decreased significantly in the intervention group compared to control group (N = 5, n = 273, WMD = −20.98 mg/dL, CI: −33.78, −8.19; p = 0.001; I^2 = 41%) (Fig. 4). The same was true for LDL-cholesterol (N = 3, n = 200, WMD = −22.06 mg/dL, CI: −37.80, −6.32; p = 0.006; I^2 = 58%) (Fig. 4) and triglycerides (N = 4, n = 253, WMD = −61.68 mg/dL, CI: −92.77, −30.59; p = 0.0001; I^2 = 0%) (Fig. 4). Conversely, group differences were not significant regarding HDL-cholesterol (N = 4, n = 220, WMD = 2.89 mg/dL, CI: −5.67, 11.45, p = 0.51; I^2 = 85%) (Fig. 4).

3.2.4. Systolic blood pressure

No significant group differences existed for systolic blood pressure (N = 2, n = 128, WMD = −3.88, CI: −8.79, 1.03, p = 0.12; I^2 = 0%).

3.2.5. All-cause discontinuation

All-cause discontinuation rates were similar between treatment (16.6%) and control groups (15.1%) (N = 15, n = 858; RR: 1.03, CI: 0.68–1.56, p = 0.88; I = 30%).

3.3. Sensitivity analyses

Across five sensitivity analyses to determine the effects of potential moderators, no significant subgroup differences emerged, except that weight and BMI were only significantly improved in outpatient trials (p<0.0001), but not in inpatient or mixed samples (p = 0.09–0.96) (Table 2).

There were numerically larger reductions for nutritional and/or exercise interventions compared to CBT regarding weight (−3.76 kg (CI: −4.78, −2.74) vs. −1.95 kg (−3.26, −0.64)) and BMI (−1.04 kg/m^2 (−1.66, −0.42) vs. −0.64 kg/m^2 (−1.14, −0.14)).

3.4. Maintenance effects after discontinuation of the intervention

Across 5 studies with follow-up data after the end of the weight loss intervention, significantly greater weight loss persisted in favor of the intervention group compared to control group after a mean of 3.6 months (range: 2–12 months) (N = 5, n = 220, WMD = −3.48 kg, CI: −6.37, −0.58, p = 0.02; I^2 = 4%) (Fig. 5). However, the five studies which included BMI follow-up data (two of which were different from those reporting weight outcomes), did not show continued benefit for treatment over the control group (N = 5 n = 211 WMD = −0.72 kg/m^2, CI: −2.36, 0.93, p = 0.40, I^2 = 53%) (Fig. 5).

3.5. Publication bias

Funnel plots for studies reporting on weight change (Supplemental Fig. 1) or BMI change (Supplemental Fig. 2) showed no evidence of publication bias.

4. Discussion

In this largest to date meta-analysis of 17 studies, including 810 participants, non-pharmacologic interventions were significantly more effective than the respective control condition regarding the reduction in weight and all metabolic parameters, except for HDL-cholesterol and systolic blood pressure. The interventions resulted in 3.12 kg less weight gain and a 0.94 kg/m^2 lower BMI unit increase compared to the control conditions. In addition, at least regarding body weight, beneficial effects endured for a mean of 3.6 months after the intervention ended. Although the same benefit was not shown for BMI, data on maintenance effects were relatively scarce, suggesting that additional studies are needed to further clarify the degree and duration of potentially enduring benefits of non-pharmacologic interventions beyond the active treatment phase.

Although study methodologies and samples differed, the magnitude of weight and BMI advantage for behavioral interventions were generally comparable to that achieved with the two available weight loss medications, metformin and topiramate, when added to antipsychotic medications. In a recent meta-analysis, metformin (N = 7, n = 334) was associated with 2.94 kg less weight gain and 1.36 kg/m^2 less BMI increase than placebo (Maayan et al., 2010). For topiramate, the weight loss was 2.52 kg compared to placebo

Table 1
Design and patient characteristics of studies of non-pharmacologic interventions for antipsychotic-related weight gain and metabolic abnormalities.

Study	Design	Duration (weeks)	Group	N[a]	Age (yrs)	Male (%)	White (%)	Diagnosis [n_t/n_p][b]	Anti-psychotic dose (daily dose)	Weight Δ (kg) or BMI Δ (kg/m^2) [n][c]
Alvarez-Jimenez et al. (2006)	Cognitive Behavioral Therapy	13	Early behavioral intervention	28	26.0 ± 15.5	71.4	_–	Psychotic disorder [28/33]	Olanzapine 13.1 ± 3.3 mg/day, Risperidone 4.2 ± 0.9 mg/day, Haloperidol 4.9 ± 1.4 mg/day	4.10 ± 3.99* [28] after 24 week follow up: 6.32 ± 5.94
Alvarez-Jimenez et al. (2010)			Control	33	27.5 ± 8.5	78.8				6.98 ± 4.50 [33] after 24 week follow up: 8.98 ± 5.61
Beebe et al. (2005)	Exercise Program	16	Exercise intervention	4	Overall: mean: 52 range: 40–63	Total: 80	Total: 80	Schizophrenia	Atypicals (90%), typicals (20%)	**BMI: Baseline: 32.51 ± 7.39 Endpoint: 31.27 ± 8.55 [4] Baseline: 30.07 ± 4.54 End point: 29.93 ± 4.74 [6]
			Control	6						
Brar et al. (2005)	Cognitive Behavioral Therapy	14	Behavioral treatment	34	40.0 ± 10.1	47.1	52.9	Schizophrenia and schizoaffective disorders [34/37]	Switched from olanzapine to risperidone	− 2.0 ± 3.79 [34]
			Control	37	40.5 ± 10.6	35.1	45.9			− 1.1 ± 3.11 [37]
Cordes et al. (in press)	Weight Management Program	24 + 24 week follow up	Prevention	13	44.1 ± 7.5	30.7	–	Schizophrenia and schizoaffective disorders	Started new treatment with olanzapine	Baseline: 81.9 ± 15.1 Endpoint (week 48 after 24 week follow up): 88.9 ± 16.6 Change during intervention (week 24):3.4 ± 4.2 [13]
			Control	18	40.7 ± 11.7	61.1	–			Baseline: 79.0 ± 15.0 Endpoint (week 48 after 24 week follow up): 89.0 ± 12.1 Change during intervention (week 24): 4.5 ± 6.1[18]
Evans et al. (2005)	Nutritional counseling program	12 + 12 week follow up	Nutritional Counseling	29	34.6 ± 9.6	38	–	Schizophrenia [9/3], schizoaffective disorder [4/6], schizophrenoform psychosis [4/6], bipolar disorder [4/4], depression [2/3]	Olanzapine 13.9 ± 3.3 mg/day 10.6 ± 4.8 mg/day	2.0 ± 3.6* [29] After follow up: 2.0 ± 5.0* [11]
			Control	22	33.6 ± 11.6	50				6.0 ± 2.6 [22] After follow up: 9.9 ± 7.4* [8]
Khazaal et al. (2007)	Cognitive behavioral therapy	12 + 12 week follow-up	CBT	31	43.0 ± 9.8	42	–	Schizophrenia and schizoaffective [25/20], bipolar [1/4], schizotypal [2/2], depression and personality disorders [3/4]	Olanzapine, risperidone, clozapine, quetiapine, amisulpride	Baseline: 90.9 ± 16.6 After 12 week intervention: 88.0 ± 14.9 Endpoint after 12 week follow up: 87.4 ± 14.8 [31]
			Control	30	38.3 ± 10.4	50	–			Baseline:84.3 ± 17.2 After 12 week intervention: 83.5 ± 17.2 [30] Endpoint after 12 week follow up: 83.5 ± 17.4 [30]
Kwon et al. (2006)	Cognitive behavioral therapy	12	Weight management	33	32.0 ± 9.2	30.3	–	Schizophrenia and schizoaffective disorders [33/15]	Olanzapine 5–20 mg/day	3.94 ± 3.63* [33]
			Control	15	29.8 ± 6.1	33.3				− 1.48 ± 1.88 [15]
Littrell et al. (2003)		16 + 8 week follow up	Nutritional Counseling	35	33.7 ± 9.2	62.9	74.3		Olanzapine [35/35] 5–20 mg/day	0.81 ± 8.97 [35] after follow up

	Nutritional counseling program		Control	35	34.5 ± 10.0	60.0	74.3	Schizophrenia and schizoaffective disorders [35/35]		0.06 ± 9.43* [35] 7.17 ± 9.16 [35] after follow up 9.57 ± 12.98 [35]
Mauri et al. (2008)	Psychoeducational Program	12	Psychoeducational Control	15 18	Total: mean: 38.9 range: 19–60	46.7 38.9	–	Bipolar I [41], Bipolar II [2], Schizoaffective [5], Depression [1]	Olanzapine 5–20 mg/day	−3.6 ± 2.6* 0.2 ± 2.9
McKibbin et al. (2006)	Cognitive behavioral therapy	24	Diabetes awareness rehabilitation training Control	28 29	53.1 ± 10.4 54.8 ± 8.2	67.9 62.1	50 72.4	Schizophrenia and schizoaffective disorder and type-2 diabetes mellitus [29/28]	Typical or atypical with low weight liability (aripiprazole, ziprasidone) [7/6]; Atypical with moderate weight liability (risperidone, quetiapine) [13/14]; Atypical with high weight gain liability (clozapine, olanzapine) [8/9]	2.30 ± 5.70* [28] 3.10 ± 4.60 [29]
Melamed et al. (2008)	Nutrition and Exercise Program	12 + 52 week follow-up	Nutritional Counseling Control	28 31	Total mean: 46.2 ± 11.9	Total: 72.9	–	Schizophrenia and schizoaffective disorders [−/−]	First or second generation or both	**BMI: baseline: 34.1 ± 4.8 after 12 week intervention: 31.6 ± 4.8 endpoint after 52 week follow-up: 31.3 ± 4.1 [28] Baseline: 30.6 ± 3.2 after 12 week intervention: 31.4 ± 4.4 endpoint after 52 week follow-up: 30.4 ± 3.4 [31]
Poulin et al. (2007)	Nutritional and exercise program	72	Diet and exercise Control	59 51	36.1 ± 6.1 35.3 ± 5.2	53 51	100 100	Schizophrenia [19/15], Schizoaffective [19/17], Bipolar [21/19]	Clozapine, Olanzapine, Risperidone, Quetiapine	−3.1* [59] 3.6 [51]
Scocco et al. (2006)	Psychoeducational and Nutritional Counseling	8	Psychoeducational intervention/ nutritional counseling Control	9 8	51.7 ± 12.4 39.2 ± 9.9	33.3 87.5	–	Schizophrenia and schizoaffective disorders [9/8]	Olanzapine	0.99 ± 3.34 [9] 2.96 ± 3.08 [8]
Skrinar et al. (2005)	Psychoeducational and exercise program	12	Healthy Lifestyle Control	9 11	39.7 ± 8.17 36.3 ± 11.3	–	–	Mood or psychotic disorder	Any antipsychotic	**BMI: baseline: 33.0 ± 6.7 endpoint: 32.3 ± 7.6 [9] baseline: 31.8 ± 3.9 endpoint: 32.3 ± 4.1 [11]
Weber and Wyne (2006)	Cognitive behavioral therapy	16	Cognitive/behavioral Control	8 9	– –	37.5 22.2	25.0 33.3	Schizophrenia and schizoaffective disorders [8/9]	Olanzapine, Risperidone, Ziprasidone, Quetiapine	−2.45 ± 2.97 [8] −0.62 ± 3.34 [9]
Wu et al. (2007)	Nutritional and exercise program	24	Diet and exercise Control	28 25	42.2 ± 7.5 39.0 ± 6.7	39 44	0 0	Schizophrenia [28/25]	Clozapine [28/25] ≥ 300 mg/day	−4.2 ± 4.4* [28] 1.0 ± 3.4 [25]
Wu et al. (2008)	Nutritional and exercise lifestyle program	12	Diet and exercise Control	32 32	26.4 ± 1.6 25.8 ± 1.7	53 50	0 0	Schizophrenia [32/32]	Clozapine [9/10], Olanzapine [10/7], Risperidone [6/8], Sulpiride [7/7]	−1.4 ± 0.6* [32] 3.1 ± 0.7 [32]

All values represent mean ± standard deviation, unless otherwise stated or it was not reported.
"–" indicates data were not provided.
Summary data are presented as total number of participants in treatment and placebo groups for the above intervention.
The overall percentage in % Male and % White categories is calculated using studies with available data only. If the data was not reported for that trial, the trial was not utilized in the summary statistic and its population was not included in the overall calculation.
Beebe et al. (2005), Melamed et al. (2008), Skrinar et al. (2005) reported only means for BMI endpoint data, and not weight mean change.
* $p<0.05$.
[a] N = total number of subjects randomized in the study.
[b] $[n_t/n_p]$ = number of subjects in the treatment group/number of subjects in the placebo group with the diagnosis.
[c] [n] = number of subjects included in analysis.

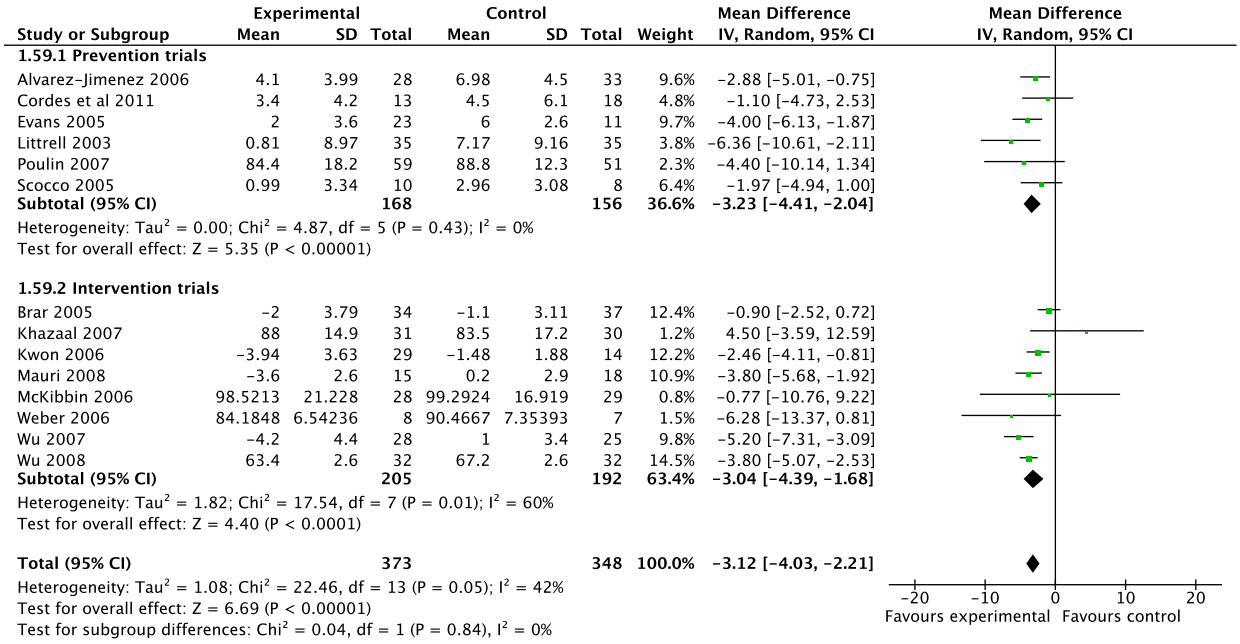


Fig. 2. Differences in weight (kg) between behavioral interventions and control groups and separately analyzed by prevention and intervention trials.

(Maayan et al., 2010). In addition, the NNT of 4 for less weight gain of at least 7% with behavioral interventions is also similar to the NNT of 3 for metformin (Maayan et al., 2010). However, the only direct head-to-head comparison of a non-pharmacologic intervention with metformin showed that metformin outperformed the behavioral intervention (−3.2 kg [95% CI: −3.9, −2.5] vs. −1.4 kg [95% CI: −2.0, −0.7]), while combined metformin and behavioral intervention was even more effective (−4.7 kg [95% CI: −5.7, −3.4]) (Wu et al., 2008). As this was an inpatient study and most non-pharmacologic intervention trials were conducted in outpatient settings, this research deserves replication.

In addition to the significant results regarding change in weight and BMI, our study demonstrated for the first time in a pooled meta-analysis that non-pharmacological interventions decrease waist circumference, total body fat percentage, glucose levels, insulin levels, total and LDL-cholesterol, and triglyceride levels compared to the control conditions. These differences are not only statistically, but also clinically relevant, especially for waist circumference and

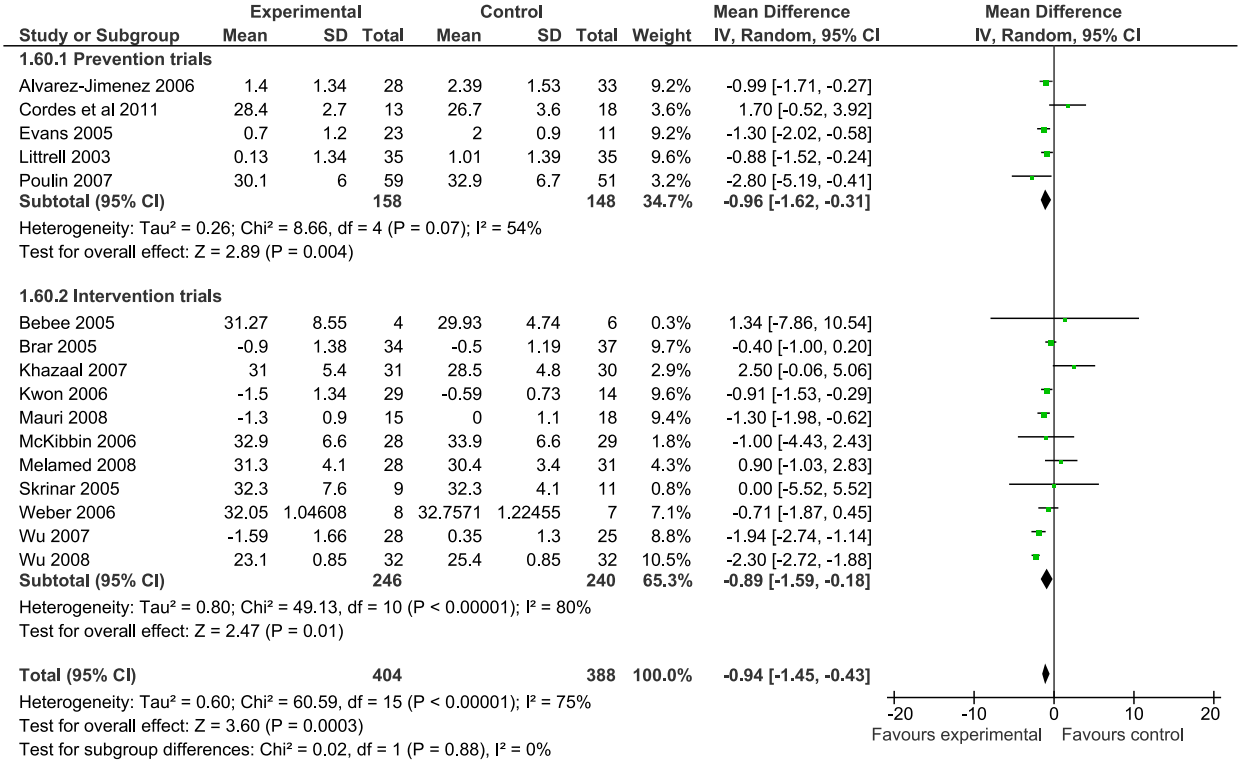


Fig. 3. Differences in body mass index (kg/m^2) between behavioral interventions and control groups and separately analyzed by prevention and intervention trials.

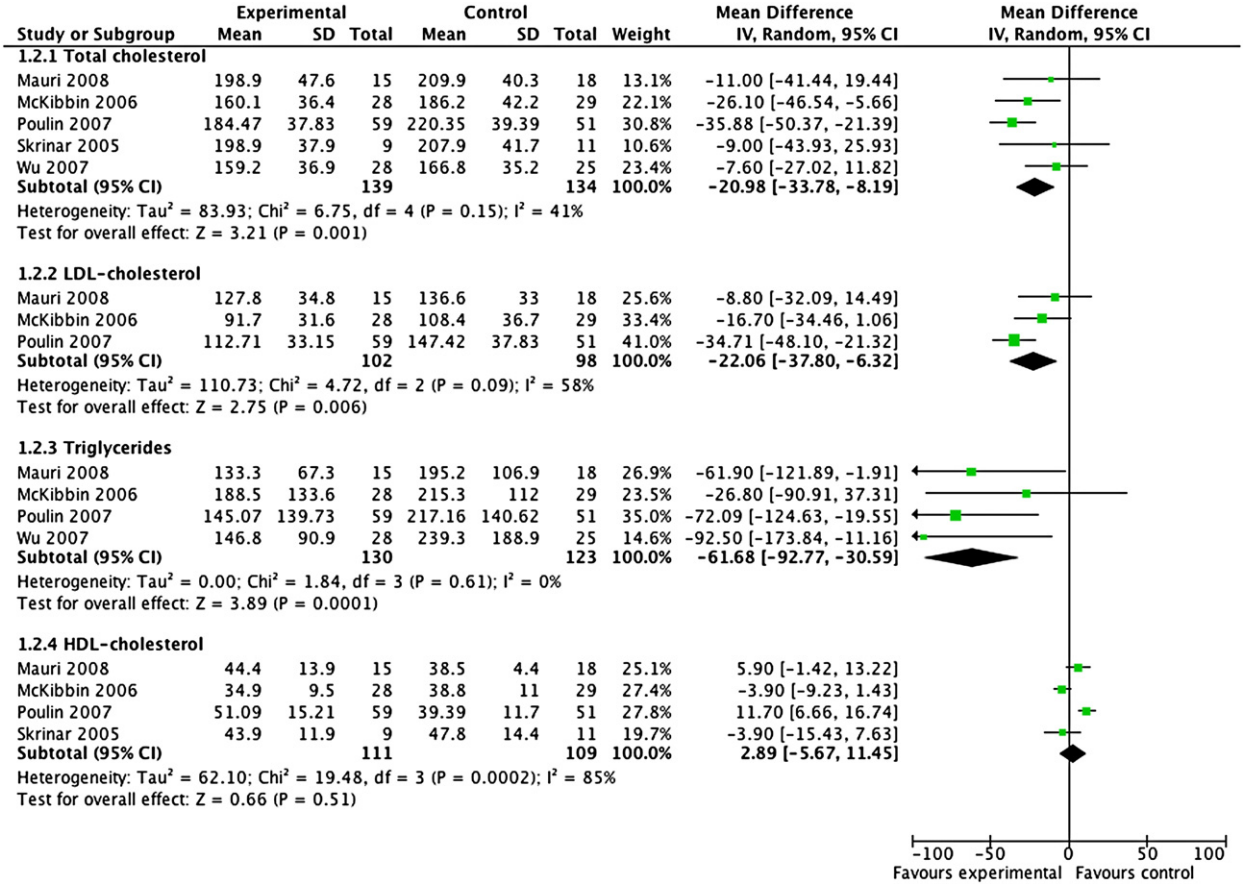
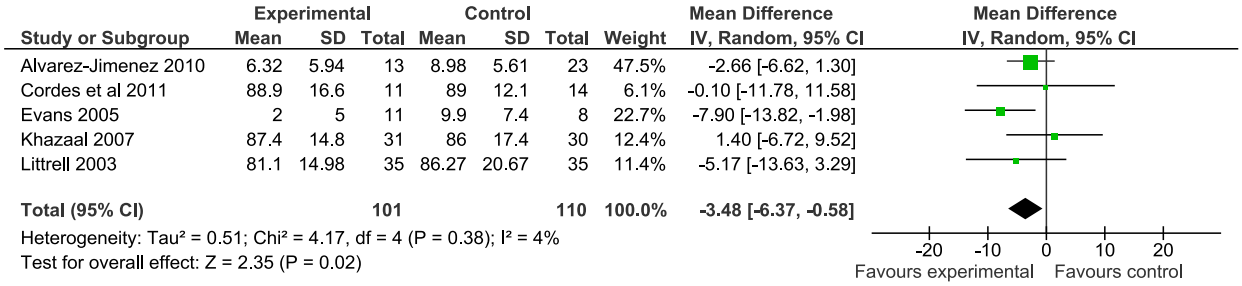


Fig. 4. Differences in total, LDL- and HDL-cholesterol as well as triglycerides change (mg/dL) between behavioral interventions and control groups.

triglyceride changes, because of their role as cardiometabolic risk factors (Haffner, 2006). For example, insulin resistance and increased LDL-cholesterol are primary targets of coronary artery disease prevention (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001). Unfortunately, only five studies measured HDL-cholesterol and two measured systolic blood pressure. This made it difficult to fully explore these factors and the results for these two metabolic outcomes were non-significant. However, it is also known that HDL-cholesterol is less readily affected by changes in weight, as exercise levels seem to affect HDL-cholesterol the most (Correll et al., 2011b). Nevertheless, it is crucial for future studies to examine the impact of interventions on all cardiometabolic

Table 2
Five sensitivity analyses of potential moderator variables.

Sensitivity analysis	Outcomes	Number of studies	n	Mean difference	95% C.I.	p value
Cognitive-behavioral	Weight (kg)	6	308	−1.95	−3.26, −0.64	0.003
	BMI (kg/m^2)	6	308	−0.64	−1.14, −0.14	0.01
Nutrition and/or exercise	Wt (kg)	8	413	−3.78	−4.57, −2.98	<0.00001
	BMI (kg/m^2)	10	484	−1.22	−1.87, −0.56	0.003
Trial duration ≤ 3 months	Weight (kg)	7	314	−3.23	−4.04, −2.42	<0.00001
	BMI (kg/m^2)	8	375	−0.96	−1.67, −0.25	0.008
Trial duration > 3 months	Weight (kg)	7	407	−2.96	−5.09, −0.82	0.007
	BMI (kg/m^2)	8	417	−0.89	−1.58, −0.19	0.01
Prevention	Weight (kg)	6	324	−2.98	−4.20, −1.76	<0.00001
	BMI (kg/m^2)	5	306	−0.96	−1.62, −0.31	0.004
Intervention	Weight (kg)	8	397	−3.04	−4.39, −1.68	<0.00001
	BMI (kg/m^2)	11	486	−0.89	−1.59, −0.18	0.01
Group treatment	Weight (kg)	9	501	−2.82	−4.58, −1.05	0.002
	BMI (kg/m^2)	12	590	−0.66	−1.29, −0.04	0.04
Individual treatment	Weight (kg)	5	220	−3.24	−4.05, −2.44	<0.00001
	BMI (kg/m^2)	4	202	−1.40	−2.16, −0.65	0.0003
Inpatients	Weight(kg)	2	84	−3.43	−7.41, 0.55	0.09
	BMI (kg/m^2)	3	143	0.06	−2.44, 2.57	0.96
Mixed (both inpatients and outpatients)	Weight (kg)	1	71	−0.90	−2.52, 0.72	0.28
	BMI (kg/m^2)	2	91	−0.40	−0.99, 0.20	0.20
Outpatients	Weight (kg)	11	566	−3.30	−4.03, −2.58	<0.00001
	BMI (kg/m^2)	11	596	−1.29	−1.81, −0.77	<0.00001



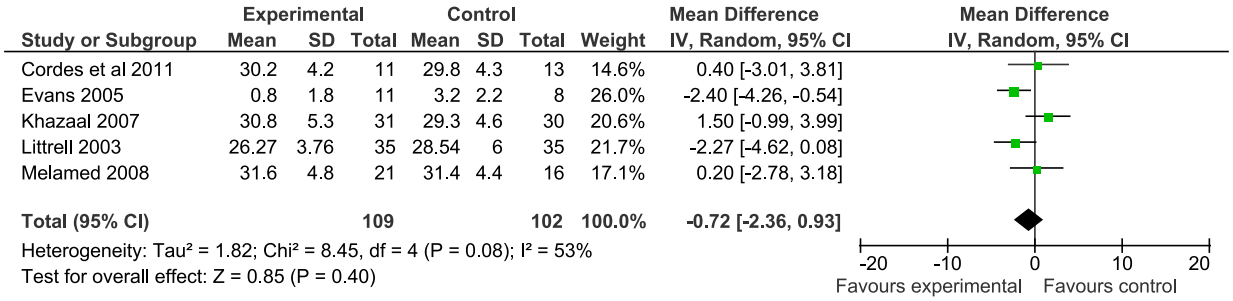


Fig. 5. Differences in weight (kg) and body mass index (kg/m^2) between behavioral interventions and control groups during follow up after the end of the intervention.

factors. This should also include measures of insulin resistance, inflammatory markers and coagulation factors, which were generally not assessed.

Importantly, the superiority of behavioral interventions for antipsychotic-associated weight gain was independent of treatment modality, treatment duration, group versus individual treatment, and prevention versus intervention design. We cannot exclude that some of these factors may show differences, given larger groups, as a non-significant trend was observed in that nutritional interventions produced a slightly larger effect size than CBT. While this speaks favorably for simpler nutritional interventions, a closer analysis reveals overlapping aspects of each intervention. Specifically, components of CBT included psychoeducation, self-monitoring, teaching behavioral change strategies and/or cognitive restructuring. Nutritional and/or exercise interventions consisted of supervised exercise programs, psychoeducation regarding healthy lifestyles, and/or nutritionist and dietician consultations. However, many CBT programs also included dietary and even exercise management, while many of the nutritional and/or exercise programs utilized behavioral techniques, such as reinforcers to encourage compliance and self-monitoring. Therefore, the distinction between the two treatment modalities is not clearly demarcated, making comparisons difficult.

Treatment setting however, did play a role in outcome, as only outpatients, but not inpatients and mixed in- and outpatient samples, showed significant benefits from the behavioral interventions compared to the control conditions in the pooled analyses. This discrepancy could be due to the lower number of inpatient trials and participants compared to outpatient trials, reducing the power to find significant differences. Conversely, it is also possible that a more controlled food delivery in inpatient settings may confer advantages for the control condition. However, it is also possible that more acutely ill patients are less likely to comply with the behavioral intervention or that there are less opportunities for exercise during an inpatient stay.

Although our results suggest that behavioral treatments are potentially comparable to metformin and topiramate in reducing antipsychotic related weight gain, it needs to be borne in mind that this is an indirect comparison only and that patients agreeing to each of these interventions may differ. However, our results also show that individuals with schizophrenia and other psychiatric illnesses can respond well to behavioral weight loss programs and that interventions may not need to be much more complicated than nutritional counseling. This suggests further, that at least in individuals motivated to initiate a non-pharmacologic intervention program, non-pharmacologic interventions should be tried first, before attempting pharmacologic augmentation strategies. In fact, a recent 1-year study suggested that compared to the obese in the general population, psychiatric outpatients with psychotropic medication related obesity referred to a cognitive behavioral weight management program were less likely to drop out of that program, leading to greater weight loss, at least in last-observation-carried-forward analyses (Zhang et al., 2012). In our analyses, the all-cause discontinuation rates were low in both the behavioral intervention and control groups (17% and 15%), almost 50% lower than the rates found for pharmacologic weight loss interventions in antipsychotic treated patients (23% and 22%, respectively) (Maayan et al., 2010). This finding underscores that there are at least subgroups of psychiatric patients in whom behavioral weight management approaches are acceptable and effective. For some patients, especially those in whom a switch to a lower risk antipsychotic (Mukundan et al., 2010; Stroup et al., 2011) may not be an option and who do not normalize cardiovascular risk markers sufficiently with non-pharmacologic interventions alone, combined treatment with a pharmacologic agent might also be an option (Wu et al., 2008).

The results of this meta-analysis have to be interpreted in light of its limitations. Although we were able to add another 7 RCTs (70.0%) and 328 patients (68.0%) to the previous meta-analysis, the number of studies and participants is still relatively small. In addition, studies only lasted between 8 and 24 weeks and while there were data to assess enduring maintenance effects for weight and BMI 2–12 months following the cessation of treatment, these came from only five studies for each of these outcomes. Moreover, while we were able to report on metabolic outcomes, our conclusions are clearly limited in that area because only 6/17 studies reported these and other secondary outcomes. Furthermore, there are no behavioral studies in youth, a group particularly vulnerable to antipsychotic weight gain (Correll et al., 2009; De Hert et al., 2011, 2012; Maayan and Correll, 2011). We were also not able to investigate the effect of diagnosis on outcome, as in 42.1% of patients diagnostic information was not

available. In addition, the sensitivity analyses found that only outpatients benefitted from the intervention. This may be partially explained by the lack of insight and possible lower likelihood of agreement of some acutely ill patients, who are more likely to be hospitalized, to participate in behavioral interventions. Therefore, motivational factors predicting agreement and success with behavioral weight loss interventions should be investigated in future studies. Further, treatment adherence was not formally assessed. Finally, relevant outcomes, including insulin resistance, inflammatory and coagulation factors, were not reported and only one study compared directly non-pharmacologic vs. pharmacologic weight loss interventions in patients treated with antipsychotics (Wu et al., 2008). Nevertheless, this is the largest meta-analysis of non-pharmacologic interventions for antipsychotic-induced weight gain and metabolic complications, an important area in the clinical care of patients requiring antipsychotics.

Future studies of behavioral interventions should include larger samples, last longer and assess participants' maintenance of weight loss after cessation of the intervention, possibly compared against infrequent booster sessions. Maintenance studies also need to focus on metabolic outcomes. Moreover, a broader range of cardiometabolic risk markers, as well as mechanisms and predictors of weight loss should also be investigated. In addition, it would be valuable to assess if an improvement in aspects of the physical health of those affected by antipsychotic-associated weight gain has a positive effect on psychiatric outcomes. As mentioned above, more studies are needed in high-risk samples, such as first episode and pediatric patients, and motivational factors predicting or preventing successful participation in behavioral weight management programs for antipsychotic related weight gain require investigation. Finally, studies are needed that directly compare the effectiveness of pharmacological, non-pharmacological, and combined treatments. At a minimum, more placebo-controlled, pharmacologic intervention trials should have a behavioral intervention arm for comparison in order to further inform clinical practice.

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Contributors

Mrs. Caemmerer undertook the literature search, statistical analysis, and wrote the first draft of the manuscript. Drs. Correll and Maayan designed the meta-analysis, provided intellectual guidance and contributed to the procurement of studies to be included in the meta-analysis and to later drafts of the manuscript. All authors contributed significantly to and have approved the final manuscript.

Conflict of interest

Mrs. Caemmerer has nothing to disclose.

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