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# Trial protocol

**Lifestyle interventions for weight management in patients with serious mental illness: A systematic review, meta-analysis and meta-regression analysis exploring the moderators and mediators of treatment effects**

**Background**

Schizophrenia is a severe and life shortening disease, with life expectancy being reduced by up to 20 years for males and 15 years for females compared to the general population.1 About 60% of the excess mortality is due to physical illness, with cardiovascular disease being the single largest cause of death.2 The unhealthy lifestyle of patients with schizophrenia is a modifiable factor contributing to the high risk of cardiovascular disease3. Indeed, recent randomized clinical trials4–6 have succeeded in initiating weight loss through individual health promotion, leading to a number of reviews7, guidelines8,9 and meta-analyses10–12 concluding that lifestyle interventions for patients with SMI can now be called evidence-based practice. We fully recognize the urgent need for action, but we have concerns about high degree of heterogeneity and the real-world effectiveness of these interventions. To prevent premature recommendations, it is important to be aware of the different moderators and mediators of efficacy of healthy lifestyle interventions for patients with SMI. These will be explored in this analysis, with special focus on internal validity measured as risk of bias, and external validity measured as effectiveness in the real world as opposed to efficacy.

The quality, or risk of bias, can be assessed with several tools. Methodological studies show that trials with unclear or inadequate methodological quality regarding bias domains may be associated with bias (systematic error, the overestimation of benefits, and the underestimation of harms) when compared to trials using adequate methodology.13–15

The ability to address real-world effectiveness can be assessed using rating scales to quantify to which degree the design is pragmatic.16,17 RCTs can be categorized as explanatory (exploring efficacy) or pragmatic (exploring effectiveness), neither being intrinsically superior to the other, but answering different research questions. The explanatory trial investigates a potential causal mechanism under highly controlled settings, answering the question “Can this work?”, while the pragmatic trial investigates whether an intervention is feasible in a real-world setting, answering the question “Will this work?”. Most trials exist on a continuum between these two extremities. A clearly defined research question is crucial in planning a clinical trial, but similarly important in planning meta-analyses, as pooling all RCTs could be misleading due to heterogeneity in trial design.

Equally important questions are “In whom will this work?” and “What part of these complex interventions works?” To answer these questions, an exploratory approach to characteristics of populations and interventions is desired to identify leads for defining design that are associated with greater benefits or harms.

Behavioural interventions addressing lifestyle in patients with SMI need special considerations. The composition of the sample results from exclusion/inclusion criteria and the process of recruitment. Patients with severe symptoms of SMI, substance abuse, unstable medication and comorbid medical disorder, are often excluded, resulting in limited external validity. Furthermore, individuals volunteering to behavioural trials are likely to be more motivated and well functioning than the clinical population as a whole. Behavioural interventions are defined as interventions designed to affect the actions a person takes regarding health. Financial resources and human engagement in clinical trials will often exceed possibilities in clinical settings, enabling interventions that are not transferable to real world. Based on these considerations, explanatory trials are more likely to report positive results.

**Aim and hypotheses**

We aim to summarize the effect of non-pharmacologic weight loss and healthy lifestyle interventions compared to a randomized control condition in the severely mentally ill. We further aim to investigate moderators and mediators of treatment effects, including trial design, patient and intervention characteristics, with a particular focus of efficacy versus effectiveness trials and study bias/quality.

Based on prior literature, we hypothesized that healthy lifestyle interventions can be successful in reducing body weight and improving metabolic status in the severely mentally ill. However, we further hypothesized that the overall effect size will be modest and that the effect size is diminished in trials with a pragmatic as opposed to explanatory design, as well as trials with less bias as opposed to trials with high risk of bias.

## Methods/design

**Design**

Systematic review and meta-analysis with sensitivity, subgroup and meta-regression analyses.

**Search strategy**

The search will be conducted in the following electronic databases: CENTRAL, MEDLINE, EMBASE, and Science Citation Index (Web of Science), using MeSH terms or similar when possible. Search terms will include the following:

*Schizophrenia or schizophrenic or psychotic or schizoaffective disorder or serious mental illness or major depression or severe mental disorder or bipolar disorder or mania or severe mental illness*

*AND*

*Weight or weight loss or weight management or weight gain or BMI or body mass index or weight reduction or cardiovascular risk or obesity or abdominal obesity*

*AND*

*Lifestyle intervention or health promotion or physical activity or exercise or diet or nutrition*

*AND*

*Random or randomized or randomly*

Additional Sources: reference lists of relevant reviews and included studies

Search Date: From database inception to September 2016

**Inclusion criteria**

* Participants should be diagnosed with major depression, schizophrenia, schizoaffective psychosis or bipolar disorder
* Participants aged >17 years of both sexes.
* Individual lifestyle interventions, defined as interventions designed to affect the action a person takes regarding health from an individual level:
  + Interventions to manage weight include efforts to modify energy balance through improved diet or increased physical activity or both. The approaches might include elements theoretically founded techniques to modify behavior, like psychoeducation, psychological counseling, motivational interviewing, stages of change or cognitive therapy
  + Studies of lifestyle interventions for weight loss can be delivered across any type of setting, including community settings, mental health settings or primary care settings
  + Randomized clinical trials. Allocation is perceived as randomized when terms including ‘randomly’, ‘random’, and ‘randomization’ are used.
* No restriction with regards to type of publication (that is, we will include abstracts and full text reports).
* No restriction with regards to language (that is, we will translate foreign language articles)
* The trials had to allocate participants to a lifestyle intervention versus a concurrent control group or using lifestyle intervention as an add-on to treatment as usual.
* Reporting on either weight gain prevention or weight loss

**Exclusion criteria**

* Trials investigating the effect of structural or environmental modifications
* Trials using combination of lifestyle interventions and any pharmacological agents

**Outcomes**

The two primary questions to be answered in this meta-analysis are:

1. Does lifestyle interventions work to manage weight, and is the effect clinically significant and sustainable?
2. Are there any adverse effects?

Thus the two primary outcomes are 1) weight measured on a continuous scale and as number needed to treat (NNT) to reach clinically significant effect on weight (≥5%) using results immediately post intervention and follow up; 2) adverse events: self-reported (such as perceived health, quality of life) and weight gain. Secondary outcomes are1) systolic blood pressure; 2) hemoglobin A1c; 3) total cholesterol 4) waist circumference. Exploratory outcomes includes the analyses of mediators and moderators answering the following questions:

Can this work (internal validity)?

Will this work (external validity)?

For whom will it work (population characteristics)?

What kind of interventions will work (intervention characteristics)?

Is the effect sustainable?

1. Internal validity
   1. risk of bias (high vs low as per Cochrane Risk of Bias Tool)
   2. data analysis (Intent-to-treat, i.e., last-observation-carried-forward or mixed models, vs observed cases analyses
2. External validity
   1. study origin (Europe, vs North-America vs Asia vs rest)
   2. % drop out in intervention vs control conditions
   3. high vs low explanatory /pragmatic design (ASPECT-R score)
3. Population characteristics
   1. Mean age
   2. Gender distribution
   3. Diagnoses
   4. Baseline weight
   5. Illness duration
   6. Global assessment functioning
   7. Negative symptoms
   8. Cognitive functioning
   9. % living in supported housings
   10. % using illegal drugs
   11. inpatient/daypatient vs outpatient
   12. Pattern of medication
   13. Prevention (starting healthy lifestyle intervention together with a weight-gain producing psychotropic medication) vs intervention (starting healthy lifestyle intervention after weight gain has already occurred on psychotropic treatment)
4. Interventions characteristics
   1. Duration
   2. Number of attended sessions
   3. Intervention modality (exercise, diet or both)
   4. Intervention setting (group vs individual vs mixed group and individual treatment)
   5. Program fidelity (number of sessions attended)
   6. Maintenance effect

**Study selection**

Two investigators (HS + KBJ) will independently examine titles and abstracts to remove obviously irrelevant reports. Two investigators (HS + KBJ) will examine the remaining full text reports to identify eligible studies. Any disagreement in the initial search and full text review process will be resolved by consensus or discussion with CH or JK. The final list of included studies will be reviewed independently by all researchers (HS, xx, xx,) to ensure consensus.

**Data extraction**

Two authors (HS, ASJ) will independently extract data, using pre-piloted forms and ASPECT-R working sheets. Any discrepancies in the data extraction or inclusion/exclusion of trials will be resolved by referring to the original papers. CH or JK will assist as adjudicators in case of disagreement. The authors have previously published trial reports assessing the effect of lifestyle counseling. To avoid academic bias, a third assessor (xx) will perform the assessment of bias and design for this trial.

**Risk of bias assessment**

Methodological studies have shown that trials with unclear or inadequate methodological quality regarding bias domains may be associated with bias (systematic error, the overestimation of benefits, and the underestimation of harms) compared to trials using adequate methodology.13–15 Definitions in the assessment of bias risk of a trial18 will be used according to the Cochrane Handbook for Systematic Reviews of Interventions including the following domains: allocation sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, for-profit bias, and other bias. Trials with low risk of bias in all domains are characterized as low risk. However, as lifestyle trials do not have the opportunity to blind participants and personnel, we defined that trials with low risk of bias in the domains of allocation concealment, blinding of outcome assessors and intention-to-treat will be characterized as trials with ‘lower risk of bias. To be conservative, trials with no report on any of these three domains will be characterized as high risk.

**Aspect-R**

The ASPECT-R (A Study Pragmatic-Explanatory Characterization Tool-Rating; ©2014 Janssen Pharmaceuticals, Inc.), assessing six domains that are specifically related to the explanatory-pragmatic spectrum, was developed to permit post-hoc evaluation of these domains in published RCTs.19–21 The six domains covered with ASPECT-R, are i) eligibility criteria ii) intervention flexibility iii) practice setting/practitioner experience iv) follow up intensity/duration v) outcome(s) vi) participant compliance assessment. The authors have provided definitions of terminology and descriptive anchors for each of the six domains. The domains are rated from 0 to 6, where 0 is considered extremely explanatory and 6 extremely pragmatic. Using an Excel®-based file with cover page cells for entry of the study objective(s) and study population of interest, the ASPECT-R instrument has individual domain-related worksheets where the user rates each of the six domains. Each of the six domain worksheets has a section provided for the user to summarize and record the rationale for their domain scoring.

**Data synthesis and analysis**

This meta-analysis will be conducted using Comprehensive Meta-Analysis V3 (<http://www.meta-analysis.com>).

In order to pool results from studies reporting either body weight or BMI related outcomes, estimates of standardized mean difference (SMD) for each individual study will be carried out. SMD is the mean difference in weight between the healthy lifestyle intervention and control groups dived by the pooled standard deviation. The result is a unitless effect size measure. By convention, SMD effect sizes of 0.2, 0.5, and 0.8 are considered small, medium, and large, respectively.22 For the calculations, we will use either change from baseline to endpoint (preferred) or endpoint scores (only preferred if change score results were skewed, i.e., SD >twice the mean). Additionally, weighted mean difference (WMD) will calculated for weight change in kilograms (kg) and BMI (kg/m2) to generate clinically intuitive results. If long term follow up is reported, these will be used in subgroup analyses. For dichotomous variables, we will calculate the relative risks with a 95% confidence interval. Intention-to-treat (ITT) data will always be preferred, but observed cases (OC) data will also allowed. Results from random-effects analyses23 will be used throughout.

The degree of heterogeneity will be quantified using the I-squared statistic24 and the chi-square test of homogeneity) with I-squared >50% may represent substantial heterogeneity, and >75% may represent considerable heterogeneity. Heterogeneity will be explored by analysis of sub-groups and meta-regression.

Publication bias will be assessed by visual inspection of a funnel plot and by Egger’s test.25

**Subgroup analyses and meta-regression**

The possible effects of a number of variables on the primary outcome is categorized as exploratory outcomes. These will be explored in subgroup analyses for categorical variables and meta-regression for continuous variables.

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# **Search strategy**

Bibliographic search for PubMed:

Search **((random OR randomly OR randomized)) AND (((((weight OR obesity OR overweight OR BMI OR "body mass index" OR "abdominal obesity" OR "weight gain")) OR (((("Obesity, Abdominal"[Mesh]) OR "Obesity"[Mesh]) OR "Body Weight Changes"[Mesh]) OR "Body Mass Index"[Mesh]))) AND (((((((("Depressive Disorder, Major"[Mesh]) OR "Bipolar Disorder"[Mesh]) OR "Schizophrenia"[Mesh]) OR "Antipsychotic Agents"[Mesh] "antidepressants" OR mood stabilizers")) AND ((schizophrenia[Text Word] OR bipolar[Text Word] OR psychosis[Text Word] OR major depression[Text Word] OR schizoaffective[Text Word] OR psychotic[Text Word] OR antipsychotics[Text Word])))) AND ((((diet[Text Word] OR dietary[Text Word] OR coaching[Text Word] OR counselling[Text Word] OR health education[Text Word] OR nutrition[Text Word] OR physical activity[Text Word] OR exercise[Text Word] OR health promotion[Text Word] OR behavior intervention[Text Word] OR "weight reduction programs"[Text Word]))) OR (((((((("Life Style"[Mesh]) OR "Risk Reduction Behavior"[Mesh]) OR "Health Promotion"[Mesh]) OR "Health Education"[Mesh]) OR "Counseling"[Mesh]) OR "Diet"[Mesh]) OR "Exercise"[Mesh]) OR "Weight Reduction Programs"[Mesh]))))**

# **Table S1: Trial, Population and Treatment Characteristics**

Legend: Trial characteristics. FEP: first episode patients; AP: Antipsychotics; AD: Antidepressants; ANX: Anxiolytica; MS: Mood Stabilisers; OP: Outpatients; IP: Inpatients; WL: Weight loss; Prev.: Prevention;

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | N | Age mean | % Male | Diagnoses | Medication | Duration weeks | Sessions, numbers | Baseline BMI | Intervention | Control | Setting | Aim |
| Alvarez-Jimenez et al. 2006 | 61 | I:26 | 75.4 | FEP | AP: 100 % | 12 | 12 | 24.2 | Behavior therapy and psychoeducation. | Advice. Equal frequency of therapist contact | OP | Pre |
| Europe |  | C:27.5 |  |  | AD: 1.6% |  |  |  | Diet and exercise |  |  |  |
|  |  |  |  |  | ANX: 24.5%: |  |  |  | Individual |  |  |  |
| Attux et al. 2013 | 134 | I:36.2 | 60 | Schizophrenia: 88.1% | AP: 98.75% | 12 | 12 | 29,1 | Psychoeducation and behavioral techniques | Outpatient program. regular psychiatrist | OP | Pre |
| South America |  | C:38.3 |  | Others: 9.4% |  |  |  |  | Diet and exercise |  |  |  |
|  |  |  |  |  |  |  |  |  | Individual and group |  |  |  |
| Bartels et al. 2013 | 133 | 43.8 | 38 | Schizophrenia: 18% |  | 52 | 52 | 36.8 | Fitness club membership. Health coach. MI | Fitness club membership | OP | WL |
| USA |  |  |  | Schizoaffective:13% |  |  |  |  | Diet and exercise |  |  |  |
|  |  |  |  | Major depression: 34% |  |  |  |  | Individual |  |  |  |
|  |  |  |  | Bipolar: 35 % |  |  |  |  |  |  |  |  |
| Bartels et al. 2015 | 210 | 43.9 | 49 | Scizophrenia: 23% | AP: 100% | 52 | 50 | 36.8 | Fitness club membership. Health coach. MI | Fitness club membership | OP | Pre |
| USA |  |  |  | Schizoaffective: 32% | AD: 16.5% |  |  |  | Diet and exercise |  |  |  |
|  |  |  |  | Major depression 16% | MS: 48.5% |  |  |  | Individual |  |  |  |
|  |  |  |  | Bipolar: 29 % |  |  |  |  |  |  |  |  |
| Battaglia et al. 2013 | 18 | I:36 | 100 | Schizophrenia: 100% | AP: 100 % | 12 | 24 | 28.5 | Football | Treatment as usual | OP | Pre |
| Europe |  | C:35 |  |  |  |  |  |  | Exercise |  |  |  |
|  |  |  |  |  |  |  |  |  | Group |  |  |  |
| Beebe et al. 2005 | 10 | 52 | 80 | Schizophrenia: 100% | AP: 100 % | 16 | 48 | 32.5 | Treadmill exercise program | Outpatient program | OP | WL |
| USA |  |  |  |  | AD: 20% |  |  |  | Exercise |  |  |  |
|  |  |  |  |  | ANX: 10% |  |  |  | Group |  |  |  |
| Brar et al. 2005 | 72 | I:40 | 41 | Schizophrenia: 53.5% | AP: 100 % | 14 | 20 | 101.3 kg | Didactic behavioral program | Monthly weighins | OP | WL |
| USA |  | C:40.5 |  | Schizoaffective: 46.5% | AD: 17% |  |  |  | Diet and exercise |  |  |  |
|  |  |  |  |  | ANX: 7.1% |  |  |  | Group and individual |  |  |  |
| Cordes et al. 2014 | 74 | I:38.2 | 43 | Schizophrenia: 100% | AP: 100 % | 24 | 12 | 27.3 | Psychoeducation and behavioral therapy | Monitoring | OP | Pre |
| Europe |  | C:35.8 |  |  | AD: 14% |  |  |  | Diet and exercise |  |  |  |
|  |  |  |  |  | MS: 16.6% |  |  |  | Group |  |  |  |
|  |  |  |  |  | ANX: 64.5% |  |  |  |  |  |  |  |
| Daumit et al. 2013 | 291 | 45.3 (11.3) | 49.8 | Schizophrenia: 29.2% | AP: 89.7% | 24 | 82 | 36.0 | Tailored behavioural weight management. | Information about lifestyle | OP | WL |
| USA |  |  |  | Schizoaffective: 28.9% | AD: 60.1% |  |  |  | Diet and exercise |  |  |  |
|  |  |  |  | Major depression 12% | MS: 45.5% |  |  |  | Group and individual |  |  |  |
|  |  |  |  | Bipolar: 22 % |  |  |  |  |  |  |  |  |
| Evans et al. 2005 | 51 | I:34.6 | 43.1 | Scizophrenia: 31.4 | AP: 100 % | 12 | 6 | 28.8 | Educational sessions | Treatment as usual | OP | Pre |
|  |  | C:33.6 |  | Schizoaffective: 23.5% |  |  |  |  | Diet |  |  |  |
| USA |  |  |  | Major depression 9.8% |  |  |  |  | Individual |  |  |  |
|  |  |  |  | Bipolar: 15.7% |  |  |  |  |  |  |  |  |
| Font et al. 2015 | 332 | I:46.3 | 55 | Schizophrenia: 67.2% | AP: 100% | 12 | 24 | 32.3 | Sessions on exercise and nutrition | Treatment as usual | OP | WL |
| Europe |  | C:47.1 |  | Schizoaffective: 17.2% |  |  |  |  | Diet and exercise |  |  |  |
|  |  |  |  | Bipolar: 15.6% |  |  |  |  | Group and individual |  |  |  |
| Forsberg et al. 2008 | 41 | I:39.8 | 58.7 | Schizophrenia: 73.2% | AP: 73.2 % | 52 | 104 | 31.1 | Sessions on nutrition and group exercise | Study circle on aesthetic techniques | OP | Both |
| Europe |  | C:42.8 |  | Bipolar: 7.3% |  |  |  |  | Diet and exercise |  |  |  |
|  |  |  |  |  |  |  |  |  | Group |  |  |  |
| Gaughran et al. 2018 | 406 | 44.1 | 55 | Psychosis: 100% |  | 36 |  | 31.2 | Cognitive therapy  And MI | Treatment as usual | OP/IP | Both |
| Europe |  |  |  |  |  |  |  |  | Diet and exercise |  |  |  |
|  |  |  |  |  |  |  |  |  | individual |  |  |  |
| Gillhoff et al. 2010 | 50 | 48 | 54 | Bipolar: 100% |  | 20 | 31 | 28.4 | Behavior therapy | Usual care | OP | WL |
| Europe |  |  |  |  |  |  |  |  | Diet and exercise |  |  |  |
|  |  |  |  |  |  |  |  |  | Group |  |  |  |
| Goldberg et al. 2013 | 71 | 52 | 81 | Schizophrenia: 37% | AP: 100 % | 26 | 22 | 84.1 kg | Behavior therapy | Written information on helathhealth subjects | OP | WL |
| USA |  |  |  | Major depression: 14% |  |  |  |  | Diet and exercise |  |  |  |
|  |  |  |  | Bipolar: 25 % |  |  |  |  | Group and individual |  |  |  |
| Green et al. 2015 | 200 | 47.2 | 28 | Schizophrenia: 29% | AP: 91 % | 24 | 24 | 38.3 | Behavior therapy | Treatment as usual | OP | WL |
| USA |  |  |  | Bipolar: 69% | AD: 16.5% |  |  |  | Diet and exercise |  |  |  |
|  |  |  |  |  | MS: 48.5% |  |  |  | Group |  |  |  |
| Holt et al. 2018 | 412 | 40 | 50.9 | Schizophrenia: 69.1%  Schizoaffective: 16.0% | AP: 100% | 52 | 7 | 35.7 | Cognitive behavior therapy | Treatment as usual | OP | WL |
| Europe |  |  |  | First episode: 15.3% |  |  |  |  | Diet and exercise |  |  |  |
|  |  |  |  |  |  |  |  |  | Group |  |  |  |
| Iglesias-Garcia et al. 2010 | 15 | 39.9 | 68.8 | Schizophrenia: 100% | AP: 100 % | 12 | 12 | 32 | Structured education | Weekly weighings | OP | WL |
| Europe |  |  |  |  |  |  |  |  | Diet and exercise |  |  |  |
|  |  |  |  |  |  |  |  |  | Group |  |  |  |
| Khazaahl et al. 2007 | 61 | 40.7 | 45.9 | Schizophrenia: 73.8% | AP: 100 % | 12 | 12 | 30 | Cognitive behavioral therapy | Brief nutritional information | OP | WL |
| Europe |  |  |  | Bipolar: 8.3% | MS: 23% |  |  |  | Diet and exercise |  |  |  |
|  |  |  |  |  |  |  |  |  | Group |  |  |  |
| Kilbourne et al. 2012 | 68 | 45.3 | 39 | Bipolar: 100% | AP: 11 % | 24 | 9 | 35.2 | Tailored psychotherapy and caremanagement | Quarterly wellness newsletters | OP | WL |
| USA |  |  |  |  | MS: 26% |  |  |  | Diet and exercise |  |  |  |
|  |  |  |  |  |  |  |  |  | Group and individual |  |  |  |
| Kilbourne et al. 2013 | 118 | 52.8 | 83 | Bipolar: 97.5 % | AP: 50 % | 52 | 16 | 33.2 | Tailored psychotherapy and caremanagement | Quarterly wellness newsletters | OP | WL |
| USA |  |  |  | Schizoaffective: 2.5% | MS: 77.1% |  |  |  | Diet and exercise |  |  |  |
|  |  |  |  |  |  |  |  |  | Group and individual |  |  |  |
| Kilbourne et al. 2016 | 45 | 55.3 | 84.6 | Schizophrenia: 7.3% | AP: 38 % | 24 | 9 | 33.3 | Tailored psychotherapy and caremanagement | Quarterly wellness newsletters | OP | WL |
| USA |  |  |  | Major depression: 57.1% | AD: 83.5% |  |  |  | Diet and exercise |  |  |  |
|  |  |  |  | Bipolar: 24% | MS: 52.1 |  |  |  | Group and individual |  |  |  |
| Kwon et al. 2006 | 48 | 30.9 | 31 | Schizophrenia: 100% | AP: 100 % | 12 | 10 | 26.81 | Cognitive behavioral therapy | Routine care with verbal recommendations | OP | WL |
| Asia |  |  |  |  |  |  |  |  | Diet and exercise |  |  |  |
|  |  |  |  |  |  |  |  |  | Individual |  |  |  |
| Lee et al. 2014 | 22 | 44.1 | 54.5 |  | AP: 100 % | 8 | 8 | 33.4 | Pedometers and eight weekly phone calls | Written information on physical activity | OP | WL |
| USA |  |  |  |  |  |  |  |  | Exercise |  |  |  |
|  |  |  |  |  |  |  |  |  | Individual |  |  |  |
| Littrell et al. 2003 | 70 | 33.7 | 61.4 | Schizophrenia: 77% |  | 16 | 16 | 26.3 | Psychoeducation | Usual care | OP | Prev |
| USA |  | 34.5 |  | Schizoaffective: 33% |  |  |  |  | Diet and exercise |  |  |  |
|  |  |  |  |  |  |  |  |  | Group |  |  |  |
| Lovell et al. 2014 | 89 | 25.7 | 60 | Schizophrenia: 83% |  | 24 | 8 | 32.7 | Motivational and behavioral therapy | Usual care | OP | Prev |
| Europe |  |  |  | Schizoaffective: 2% |  |  |  |  | Diet and exercise |  |  |  |
|  |  |  |  |  |  |  |  |  | Group and individual |  |  |  |
| Marzolini et al. 2009 | 13 | 44.6 | 61 | Schizophrenia: 100% | AP: 100 | 12 | 24 | 27.2 | Exercise twice weekly | Usual care | OP |  |
| canada |  |  |  |  | AD: 15 |  |  |  | Exercise |  |  |  |
|  |  |  |  |  | MS: 53 |  |  |  | Group |  |  |  |
| Mauri et al. 2008 | 33 | 38.9 | 42.8 | Schizoaffective: 10.2 % |  | 12 | 12 | 30 | Psychoeducation | Usual care | OP | WL |
| Europe |  |  |  | Major depression 2% | AP: 100 % |  |  |  | Diet |  |  |  |
|  |  |  |  | Bipolar: 87.7 % |  |  |  |  | Individual |  |  |  |
| McKibbin et al. 2006 | 57 | I:53.1 | 64.9 | Schizophrenia: 84.2% | AP: 100 % | 24 | 24 | 33.6 | Health education classes | Written material on healthy lifestyle | OP | WL |
| USA |  | C:54.8 |  | Schizoaffective: 15.8% |  |  |  |  | Diet and exercise |  |  |  |
|  |  |  |  |  |  |  |  |  | Group and individual |  |  |  |
| Methapatara et al. 2011 | 64 | 40.4 | 64 | Schizophrenia: 100% |  | 12 | 5 | 28.4 | Group education. Pedometer walking | Written material on healthy lifestyle | OP | WL |
| Asia |  |  |  |  |  |  |  |  | Diet and exercise |  |  |  |
|  |  |  |  |  |  |  |  |  | Group and individual |  |  |  |
| Milano et al. 2007 | 36 | 45 (N/A) | 44 |  | AP: 100 | 12 | 27 | 27.2 | Calorie restriction and exercise three times a week | Usual care | OP | Both |
| Europe |  |  |  |  |  |  |  |  | Diet and exercise |  |  |  |
|  |  |  |  |  |  |  |  |  | Group and individual |  |  |  |
| Osborn et al. 2018 | 327 | 32 | 47 | Schizophrenia:35% | AP: 72% | 26 | 13 | 51 | Behavioral wheel | Usual care | OP | WL |
|  |  |  |  | Bipolar:46% |  |  |  |  | Diet and exercise |  |  |  |
|  |  |  |  | Psycoses: 19% |  |  |  |  | Individual |  |  |  |
| Scheewe et al. 2013 | 54 | I:29.2 | 73 | Schizophrenia: 76% | AP: 100 % | 24 | 48 | 26.6 | Strict protocol physical exercise twice weekly | Occupational therapy | IP/OP | WL |
| Europe |  | 30.1 |  | Schizoaffective: 24% |  |  |  |  | Exercise |  |  |  |
|  |  |  |  |  |  |  |  |  | Group |  |  |  |
| Scocco et al. 2006 | 18 | 46.4 | 55 | Schizophrenia: 75% | AP: 100 % | 8 |  | 29 | Weight control education | Usual care | OP | Both |
| Europe |  |  |  | Schizoaffective: 25% |  |  |  |  | Diet |  |  |  |
|  |  |  |  |  |  |  |  |  | Individual |  |  |  |
| Skrinar et al. 2005 | 20 | I:39.7 | 33 | Schizophrenia: 100% | AP: 100 | 12 | 48 | 32.9 | Four weekly training sessions. | Recordkeeping on physical activity | IP/OP | Both |
| USA |  | C:36.3 |  |  |  |  |  |  | Diet and exercise |  |  |  |
|  |  |  |  |  |  |  |  |  | Group and individual |  |  |  |  |
| Speyer et al. 2016 | 280 | 38.6 | 44 | Schizophrenia: 90% |  | 52 | 42 | 34.2 | Tailored healthcoach. MI | Care coordination | OP | WL |  |
| Europe |  |  |  | Schizoaffective: 10% |  |  |  |  | Diet and exercise |  |  |  |  |
|  |  |  |  |  |  |  |  |  | Group and individual |  |  |  |  |
| Ratliff et al. 2012 | 30 | 50.1 | 35 | Schizophrenia 60% |  | 8 | 8 | 41.6 | Financial reimbursment | Wait list | OP | WL |  |
| USA |  |  |  |  |  |  |  |  | Diet and exercise |  |  |  |  |
|  |  |  |  |  |  |  |  |  | Group |  |  |  |  |
| Usher et al. 2013 | 101 |  | 54.5 | Schizophrenia: 84.2% | AP: 100 % | 12 | 12 | 33.3 | Weekly health education | Usual care | OP | WL |  |
| Australia |  |  |  | Major depression: 6.9% |  |  |  |  | Diet and exercise |  |  |  |  |
|  |  |  |  | Bipolar: 6.9% |  |  |  |  | Group |  |  |  |  |
| Weber et al. 2006 | 157 |  | 29 | Schizophrenia: 100% | AP: 100 % | 16 | 16 | 33 | Cognitive behavioral therapy | Usual care | OP | WL |  |
| USA |  |  |  |  |  |  |  |  | Diet and exercise |  |  |  |  |
|  |  |  |  |  |  |  |  |  | Group |  |  |  |  |
| Wu et al. 2007 | 53 | I:42.2 | 41.51 | Schizophrenia: 100% | AP: 100 % | 12 | 11 | 30.3 | Psychoeducation | Monthly treadmill test and weighing | IP | WL |  |
| Asia |  | C:39 |  |  |  |  |  |  | Diet and exercise |  |  |  |  |
|  |  |  |  |  |  |  |  |  | Group and individual |  |  |  |  |
| Wu et al. 2008 | 64 | 26.3 | 64 | Schizophrenia: 100% | AP: 100 % | 24 | 72 | 24.5 | Dietary and training program | Usual care | IP | WL |  |
| Asia |  |  |  |  |  |  |  |  | Diet and exercise |  |  |  |  |
|  |  |  |  |  |  |  |  |  | Individual |  |  |  |  |

# **Figure S1: Flow chart**

Records identified through database searching  
(n =1774 )

Additional records identified through other sources  
(n = 6)

Identification

## Identification

## Identification

## Identification

Records after duplicates removed  
(n = 1441)

ScreeningRecords after duplicates removed  
(n = 1441)

## Screening

ScreeningRecords after duplicates removed  
(n = 1441)

ScreeningRecords after duplicates removed  
(n = 1441)

Screening

## Screening

## Screening

## Screening

Records excluded  
(n = 1228)

Records screened  
(n =1441)

Full-text articles excluded:  
Not randomized (n =98)

Not reporting body weight (n = 40)

Not lifestyle (n = 13)

Not SMI (n=11)

Secondary publications (n = 11)

Other (n = 2)

Full-text articles assessed for eligibility  
(n =213)

EligibilityFull-text articles assessed for eligibility  
(n =213)

## Eligibility

IncludedEligibilityFull-text articles assessed for eligibility  
(n =213)

EligibilityFull-text articles assessed for eligibility  
(n =213)

Eligibility

## IncludedEligibility

## IncludedEligibility

## IncludedEligibility

Additional search   
(n =3)

Additional search   
(n =2)

Additional search   
(n =2)

Additional search   
(n =2)

Studies included in quantitative synthesis (meta-analysis)  
(n = 41)

Studies included in quantitative synthesis (meta-analysis)  
(n = 40)

Studies included in quantitative synthesis (meta-analysis)  
(n = 40)

Studies included in quantitative synthesis (meta-analysis)  
(n = 40)

Included

# 

# **Table S2: Risk of bias assessments.**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study name** | **Year** | **Random sequence generation** | | | **Allocation concealment** | | | **Blinding of participants and personnel** | | | **Blinding of outcome assessment** | | | **Incomplete outcome data** | | | **Selective reporting** | | |
|  |  | low | high | unclear | low | high | unclear | low | high | unclear | low | high | unclear | low | high | unclear | low | high | unclear | |
| Beebe | 2005 | X |  |  |  |  | X |  | X |  | X |  |  | X |  |  | X |  |  | |
| Wu | 2007 |  |  | X |  |  | X |  | X |  |  | X |  |  | X |  |  |  | X | |
| Skrinar | 2005 |  |  | X |  |  | X |  | X |  |  |  | X |  | X |  |  |  | X | |
| Methapatara | 2011 | X |  |  | X |  |  |  | X |  |  | X |  | X |  |  | X |  |  | |
| Bartels | 2015 | X |  |  | X |  |  |  | X |  | X |  |  | X |  | x | X |  |  | |
| Bartels | 2013 |  |  | X |  |  | X |  | X |  | X |  |  | X |  |  |  | X |  | |
| Green | 2015 | X |  |  | X |  |  |  | X |  | X |  |  |  | X |  |  |  | X | |
| Littrell | 2003 | X |  | X |  |  | X |  | X |  |  | X |  |  |  | X | X |  |  | |
| Khazaal | 2007 |  |  | X |  |  | X |  | X |  |  | X |  |  | X |  | X |  |  | |
| Evans | 2005 |  |  | X |  |  | X |  | X |  |  | X |  |  | X |  |  |  | X | |
| Wu | 2008 | X |  |  | X |  |  |  | X |  | X |  |  | X |  |  | X |  |  | |
| Alvarez-jiminez | 2006 | X |  |  | X |  |  |  | X |  |  |  |  | X |  |  | X |  |  | |
| Attux | 2013 |  |  | X |  |  | X |  | X |  |  | X |  |  |  | X | X |  |  | |
| Battaglia | 2013 | X |  |  |  |  | X |  | X |  | X |  |  |  | x | X | X |  |  | |
| Cordes | 2014 | X |  |  |  |  | X |  | X |  |  |  | X | X |  |  | X |  |  | |
| Daumit | 2013 | X |  |  | X |  |  |  | X |  | X |  |  | X |  |  |  |  | X | |
| Forsberg | 2008 | X |  |  |  |  | X |  | X |  |  | X |  |  | X |  |  |  | X | |
| Gillhoff | 2010 |  |  | X |  |  | X |  | X |  |  | X |  | X |  |  |  |  | X | |
| Iglesias-garcia | 2010 | X |  |  |  |  | X |  | X |  | X |  |  | X |  |  |  |  | X | |
| Kilbourne | 2012 |  |  | X |  |  | X |  | X |  | X |  |  |  | X |  | X |  |  | |
| Kwon | 2006 |  |  | X |  |  | X |  | X |  |  | X |  |  |  | X |  | X |  | |
| Lee | 2014 | X |  |  |  |  | X |  | X |  | X |  |  |  | X |  |  |  | X | |
| Lovell | 2014 | X |  |  | X |  |  |  | X |  | X |  |  | X |  |  | X |  |  | |
| Marzolini | 2009 | X |  |  | X |  |  |  | X |  |  | X |  | X |  | X |  |  | X | |
| Mauri | 2008 |  |  | X |  |  | X |  | X |  |  | X |  | X |  | X |  |  | X | |
| Mckibbin | 2006 |  |  | X |  |  | X |  | X |  | X |  |  | X |  |  |  |  | X | |
| Scheewe | 2013 | X |  |  | X |  |  |  | X |  | X |  |  |  | X |  |  |  | X | |
| Scocco | 2006 |  |  | X |  |  | X |  | X |  |  | X |  |  | X |  |  |  | X | |
| Uscher | 2013 | X |  |  | X |  |  |  | X |  | X |  |  | X |  |  |  |  | X | |
| Weber | 2006 |  |  | X |  |  | X |  | X |  | X |  |  | X |  |  |  |  | X | |
| Milano | 2007 |  | X |  |  |  | X |  | X |  |  | X |  | x |  | X |  |  | X | |
| Speyer | 2016 | X |  |  | X |  |  |  | X |  | X |  |  | X |  |  |  | X |  | |
| Kilbourne | 2012 | X |  |  | X |  |  |  | X |  | X |  |  |  | X |  |  |  | X | |
| Kilbourne | 2016 | X |  |  | X |  |  |  | X |  | X |  |  |  | X |  | X |  |  |
| Goldberg | 2013 | X |  |  | X |  |  |  | X |  | X |  |  | X |  |  | X |  |  |
| Font | 2015 | X |  |  | X |  |  |  | X |  | X |  |  | X |  |  | X |  |  |
| Brar | 2005 |  |  | X |  |  | X |  | X |  |  |  | X | X |  |  | X |  |  |
| Gaughran | 2018 | X |  |  | X |  |  |  | X |  | X |  |  | x |  |  | X |  |  |
| Osborn | 2018 | X |  |  | X |  |  |  | x |  | X |  |  | x |  |  | X |  |  |
| Holt | 2018 | X |  |  | X |  |  |  | x |  | x |  |  | x |  |  | x |  |  |

# **Table S3: ASPECT-R scores**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Studies** | **Total score (0-24)** | **Eligibility**  **(0-6)** | **Flexibility**  **(0-6)** | **Expertise**  **(0-6)** | **Duration**  **(0-6)** |
| Battaglia 2013 | 6 | 0 | 0 | 3 | 3 |
| Wu 2008 | 6 | 0 | 1 | 3 | 2 |
| Brar 2005 | 8 | 1 | 1 | 4 | 2 |
| Iglesias-Garcia 2010 | 10 | 1 | 3 | 3 | 3 |
| Wu 2007 | 7 | 1 | 1 | 3 | 2 |
| Attux 2013 | 12 | 2 | 2 | 4 | 4 |
| Cordes 2014 | 10 | 2 | 2 | 2 | 4 |
| Evans 2005 | 17 | 2 | 5 | 5 | 5 |
| Kwon 2006 | 12 | 2 | 3 | 4 | 3 |
| Methapatara 2011 | 7 | 2 | 2 | 1 | 2 |
| Milano 2007 | 9 | 2 | 2 | 3 | 2 |
| Scheewe 2013 | 7 | 2 | 1 | 2 | 2 |
| Bartels 2013 | 14 | 3 | 4 | 4 | 3 |
| Bartels 2015 | 14 | 3 | 4 | 4 | 3 |
| Daumit 2013 | 11 | 3 | 2 | 3 | 3 |
| Font 2015 | 13 | 3 | 4 | 4 | 2 |
| Littrell 2003 | 12 | 3 | 3 | 3 | 3 |
| Mauri 2008 | 11 | 3 | 2 | 3 | 3 |
| Scocco 2006 | 16 | 3 | 4 | 4 | 5 |
| Alvarez-Jimenez 2006 | 14 | 4 | 5 | 2 | 3 |
| Beebe 2005 | 11 | 4 | 1 | 4 | 2 |
| Forsberg 2008 | 18 | 4 | 5 | 5 | 4 |
| Goldberg 2013 | 15 | 4 | 4 | 4 | 3 |
| Khazaahl 2007 | 15 | 4 | 5 | 3 | 3 |
| Lee 2014 | 16 | 4 | 3 | 4 | 5 |
| Lovell 2014 | 18 | 4 | 6 | 4 | 4 |
| Usher 2013 | 14 | 4 | 3 | 3 | 4 |
| Weber 2006 | 14 | 4 | 3 | 4 | 3 |
| Gillhoff 2010 | 20 | 5 | 5 | 5 | 5 |
| Green 2015 | 17 | 5 | 5 | 3 | 4 |
| Kilbourne 2012 | 15 | 5 | 3 | 4 | 3 |
| Kilbourne 2013 | 16 | 5 | 4 | 4 | 3 |
| Kilbourne 2016 | 16 | 5 | 4 | 4 | 3 |
| Marzolini 2009 | 17 | 5 | 4 | 5 | 3 |
| Mckibbin 2006 | 15 | 5 | 3 | 4 | 3 |
| Skrinar 2005 | 11 | 5 | 2 | 3 | 1 |
| Speyer 2016 | 20 | 6 | 6 | 4 | 4 |
| Gaughran 2017 | 19 | 4 | 6 | 5 | 4 |
| Holt 2018 | 18 | 4 | 5 | 5 | 4 |
| Osborn 2018 | 29 | 5 | 6 | 4 | 5 |

# **Table S4: Grades of Recommendation, Assessment, Development and Evaluation (GRADE): Summary of findings**

|  | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| **Lifestyle intervention compared to treatment as usual for weight management in people with severe mental illness** | | | | | | |
| Outcomes | **Anticipated absolute effects\*** (95% CI) | | Relative effect (95% CI) | № of participants  (studies) | Quality of the evidence (GRADE) | Comments |
| **Risk with treatment as usual** | **Risk with Lifestyle intervention** |
| BMI post-intervention | The mean BMI post-intervention was **0** kg/m2 | The mean BMI post-intervention in the intervention group was 0,57 kg/m2 lower (-0,98 lower to -0,17 lower) | - | 4237 (40 RCTs) | ⨁◯◯◯ VERY LOW a,b,c |  |
| BMI long term | The mean BMI long term was **0** kg/m2 | The mean BMI long term in the intervention group was 0,63 kg/m2 lower (-1.3 lower to 0.04 higher) | - | 1412 (17 RCTs) | ⨁◯◯◯ VERY LOW a,d |  |
| Clinically significant weight loss | 21.708 per 100.000 | **27819 per 100.000** (17.782 to 40.746) | **OR 1.5** (1.07 to 2.13) | 1121 (9 RCTs) | ⨁◯◯ VERY LOW a |  |
| Quality of Life | The mean quality of Life was **0** SMD | The mean quality of Life in the intervention group was 0.03 SMD higher (-0.11 lower to 0.17 higher) | - | 1309 (15 RCTs) | ⨁◯◯◯ VERY LOW a |  |
| Waist circumference | The mean waist circumference was **0** cm | The mean waist circumference in the intervention group was 2.13 cm lower (-2.98 lower to -1,28 lower) | - | 2128 (24 RCTs) | ⨁◯◯◯ VERY LOW a,b |  |
| Fasting glucose | The mean fasting glucose was **0** mg/dl | The mean fasting glucose in the intervention group was 0.04 mg/dl lower (-0.20 lower to 0.28 higher) | - | 1056 (12 RCTs) | ⨁◯◯◯ VERY LOW a,b |  |
| Cholesterol | The mean cholesterol was **0** | The mean cholesterol in the intervention group was 0,06 lower (-0.14 lower to -0.01 higher) | - | 1658 (15 RCTs) | ⨁◯◯◯ VERY LOW a,b |  |
| Systolic bloodpressure | The mean systolic blood pressure was **0** mmHg | The mean systolic blood pressure in the intervention group was -0.58 mmHg lower (-1.70 lower to 0.54 higher) | - | 1733 (18 RCTs) | ⨁◯◯◯ VERY LOW a,b |  |
|  | | | | | | |
|  | | | | | | |

\***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** Confidence interval; **OR:** Odds ratio

**GRADE Working Group grades of evidence**

**High quality:** We are very confident that the true effect lies close to that of the estimate of the effect  
**Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different  
**Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect  
**Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

# **Trial Sequential Analysis**

## **Figure S2: Trial sequential analysis of BMI:**

![Et billede, der indeholder kort, tekst

Beskrivelse, der er oprettet med meget høj sikkerhed]()

Trial sequential analysis for weight, DARIS = diversity-adjusted required information size

## **Figure S3: Trial sequential analysis of 5% weight loss**

**Et billede, der indeholder kort, tekst, skærmbillede

Beskrivelse, der er oprettet med meget høj sikkerhed**

## **Figure S4: Trial sequential analysis of quality of life:**

**Et billede, der indeholder kort, tekst

Beskrivelse, der er oprettet med meget høj sikkerhed**

# **Funnel plots**

## **Figure S5: Funnel plot of weight (BMI)**



## Figure S6: Funnel plot of weight (kg)



## Figure S7: Funnel plot of weight (BMI) (maintenance):



## Figure S8: Funnel plot of weight quality of life



## Figure S9: Funnel plot of weight cholesterol



## Figure S10: Funnel plot of systolic blood pressure



## Figure S11: Funnel plot of waist circumference



## Figure S12: Funnel plot for all-cause discontinuation



# **Forest plots**

## **Figure S13: Forest plot of weight (kg)**



## **Figure S14: Forest plot of quality of life**



## **Figure S15: Forest plot of systolic blood pressure**



## 

## Figure S16: Forest plot of total cholesterol



## **Figure S17: Glucose**



## **Figure S18: Waist circumference**



## **Figure S19: Forest plot of all-cause discontinuation:**



**Figure S20: Forest plot of deaths:**



**Figure S21: Forest plot of somatic hospitalisations:**



**Figure S22: Forest plot of psychiatric hospitalisations:**

