



Review article

Non-pharmacological interventions for preventing weight gain in patients with first episode schizophrenia or bipolar disorder: A systematic review.



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ARTICLE INFO

Keywords:

First episode schizophrenia
Bipolar disorder
Weight gain
Non-pharmacological intervention
Prevention

ABSTRACT

Weight gain is a side effect of antipsychotic medication and highly prevalent in people with schizophrenia or bipolar disorder, increasing their overall cardio-metabolic risk. We conducted a systematic review on non-pharmacological interventions for preventing/reducing weight gain or increase in waist-circumference in young, newly diagnosed patients with schizophrenia or bipolar disorder. We searched major electronic databases from inception to 04/2019 on RCTs, pre- and post-test studies, and non-randomized controlled clinical trials. From a potential of 2963 hits, eight studies met the inclusion criteria ($n = 438$, mean age of 18.8 (13–45) years). The interventions comprised supervised and individually adjusted aerobic exercise activities (5 studies), individual lifestyle counselling vs. control condition (2 RCTs), and dietetic counselling and practical training of cooking and shopping (1 study). Physical activity and practical dietetic interventions seem to be more efficient than lifestyle counselling. However, the results shall be taken with caution due to the non-randomized designs and other methodologically deficits in the majority of the included studies.

1. Introduction

Patients with schizophrenia or bipolar disorder have a 15–20 years shorter life-expectancy compared with the general population (Laursen, 2011; Laursen et al., 2014; Nordentoft et al., 2013). Although there is a high risk of suicide among patients with bipolar disorder and schizophrenia (Miller and Bauer, 2014; Palmer et al., 2005) mounting evidence suggests that the increased mortality is primarily due to death from natural causes, in particular cardiovascular disease (CVD) (Ringen et al., 2014; Walker et al., 2015; Hayes et al., 2015; Correll et al., 2017). The metabolic syndrome (MetS), defined as abdominal obesity, raised triglycerides, reduced high density lipoprotein (HDL) cholesterol, elevated blood pressure or raised plasma glucose, significantly increases the risk of CVD as well as type-2-diabetes (T2D) (Alberti et al., 2006; Mottillo et al., 2010). Both MetS and cardio-metabolic abnormalities are highly prevalent in patients with schizophrenia or bipolar disorder compared to the general population (Vancampfort et al., 2015c; Vancampfort et al., 2013a; Vancampfort et al., 2013b; Vancampfort et al., 2015b; Mitchell et al., 2011). According to The International Diabetes Federation abdominal

obesity is the most significant, single risk factor for development of MetS and T2D, therefore preventing weight gain, in particular abdominal obesity, is essential for decreasing the overall cardio-metabolic risk and premature mortality (Alberti et al., 2007). Mounting evidence confirms that weight gain is one of the most significant side-effects of antipsychotic medication (AP) (Allison and Casey, 2001; De Hert et al., 2012; Foley and Morley, 2011) and weight gain occurs after short-time exposure to AP (Perez-Iglesias et al., 2014; Maayan and Correll, 2011; Alvarez-Jimenez et al., 2008a). Further, preventing weight gain seems to be essential for patients as weight gain decreases adherence with treatment as well as the overall quality of life (Dayabandara et al., 2017). Thus, as presented by a recent Lancet Psychiatric Commission interventions targeting the first episode period are of critical importance for preventing further downstream adverse events (Firth et al., 2019).

To date, pharmacological interventions, comprising use of metformin or other statins, or switching to agents with lesser tendency to cause weight gain, as well as non-pharmacological interventions have been investigated to reduce weight gain (Alvarez-Jimenez et al., 2008b; Dayabandara et al., 2017; de Silva et al., 2016; Caemmerer et al.,

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2012). Non-pharmacological interventions have proven to be effective in reducing weight in obese patients with severe mental illness (Caemmerer et al., 2012; Naslund et al., 2017), yet in the recent CHANGE-study this was not confirmed (Speyer et al., 2016; Jakobsen et al., 2017). Preventing obesity is far more efficient than treating the long-term consequences and it can be strongly argued to prescribe life style interventions to patients with schizophrenia or bipolar disorder regardless of metabolic health (Firth et al., 2019). However, very few studies have reported on interventions in relation to young first-episode patients with schizophrenia (FEP) or bipolar disorder (BD) and to the best of our knowledge, no prior systematic review on this topic exists.

Thus, the objectives of this review was to identify and evaluate the effectiveness of non-pharmacological lifestyle interventions for preventing and reducing weight gain in young, first-episode patients with schizophrenia or bipolar disorder.

2. Methods

This systematic review followed the PRISMA reporting guidelines. A protocol for the review was registered at PROSPERO International prospective register of systematic reviews in December 2018: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=117600

2.1. Search procedure

A health research librarian identified studies by performing a systematic literature search in PubMed, EMBASE, Scopus, PsycInfo and Cochrane bibliographic databases from their inception to February 2019. An updated search was performed in March 2019. In addition, the reference lists of included articles were reviewed and so were the citations received by them.

In collaboration the team and the research librarian developed an appropriate search strategy combining medical subject headings (MESH), EMTREE headings and thesaurus term with natural language terms, using the following key-words: (“first episode” OR FEP OR “newly diagnosed” OR naïve OR “early onset” OR “early intervention” OR “early psychosis” OR “adolescent*” OR “young adult*”) AND (“schizoaffective OR schizophr* OR psychosis OR psychotic OR “affective disorder” OR bipolar OR “severe mental illness” OR “serious mental illness” OR mania OR “manic disorder” OR “cyclothymic disorder”) in combination with (“weight gain” OR overweight OR “body weight” OR “weight change*” OR obesity OR “body mass index” OR BMI OR “waist circumference”) AND (diet OR nutrition OR “physical activity” OR exercise* OR “physical training” OR psychoeducation OR “psycho education” OR coaching OR mentoring OR lifestyle OR “life style” OR prevention OR “health promotion” OR counseling OR “health education” OR “physical health” OR “behavioural intervention” OR “behavioral intervention” OR “behavior therapy” OR “behavior therapy” OR “patient compliance” OR “weight reduction program” OR “weight loss program”). The search was restricted to English and Nordic languages and duplicates were removed using EndNote.

2.2. Inclusion criteria

In accordance with the PRISMA reporting guidelines the participants, interventions, comparisons, outcomes, and study design criteria were used to assess study eligibility:

Participants: Young patients with first-episode ICD-10 or DSM-IV diagnosed schizophrenia or bipolar disorder aged between 15–25 years; including studies in which the mean age of participants was < 25 years.

Interventions: Any non-pharmacological interventions aiming at preventing or reducing weight gain or increase in waist-circumference, including exercise or physical activity, nutritional interventions, behavioural counselling, motivational interviewing or Cognitive Behavioural Therapy (CBT).

Comparators: All usual-care or wait list conditions were considered eligible.

Outcomes: The outcome measures had to be changes in kilograms, body mass index (BMI), or centimetres in waist circumference (WC), respectively.

Study design: Included study designs were randomized controlled trials (RCT), pre- and post-test studies without a control group, and non-randomized controlled clinical trials in which the experimental and the control intervention were of similar duration.

2.3. Study selection and data extraction

The selection of studies was conducted in two stages. In the first stage *Title* and *Abstract* of each reference was screened by two independent reviewers (LN, SL) against the criteria mentioned above. In stage two the full text of the included articles was screened for eligibility by the two reviewers, independently; disagreements were solved through discussions or by consulting a third author (BS).

Two reviewers (LN, SL) independently extracted relevant data from the included studies, including study design, characteristics of participants, intervention approach, the nature of the intervention, counselling, diet, nutritional counselling or other, intervention format, duration of intervention, description of comparison intervention. Any conflicts of extraction were resolved through discussion or by consulting a third reviewer (BS).

2.4. Risk of bias assessment

The quality of the included studies was evaluated using the ROBINS-I risk of bias assessment tool for non-randomized studies of interventions (Schunemann et al., 2018; Sterne et al., 2016) and for RCTs the RoB – 2 (Higgins et al., 2016). The quality assessment of studies included confounding and selection of participants for the study, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes and selection of the reported results. Two authors (LN, SL) independently assessed the risk of bias in the included studies; any disagreements were resolved through discussion or consulting of a third author (BS).

3. Results

3.1. Search results and flow of studies through the review

A total of 2960 records were identified in the databases; three additional studies were identified through reference and citation searching. After the first review of title and abstract, 67 full-text articles were screened of which eight studies were identified and included in the review (Abdel-Baki et al., 2013; Curtis et al., 2016; Curtis et al., 2018; Detke et al., 2016; Firth et al., 2018; Lovell et al., 2014; Nuechterlein et al., 2016; Teasdale et al., 2015). Fig 1 presents the flow of studies through the review.

3.2. Characteristics of included trials

Across the eight included studies, three included patients with FEP and five included a mixture of patients with FEP and BD with a mean age of 18.8 (13–45) years and 36.0% females. The length of follow-up differed from 10 weeks to two years. Non-pharmacological interventions were provided for 286 out of 438 patients with FEP; descriptions of articles are presented in Table 1.

Four (Curtis et al., 2016; Detke et al., 2016; Lovell et al., 2014; Nuechterlein et al., 2016) of the included studies were controlled studies of which two were RCTs (Detke et al., 2016; Lovell et al., 2014) whereas the remaining four were prospective pre and post test studies (Abdel-Baki et al., 2013; Curtis et al., 2018; Firth et al., 2018; Teasdale et al., 2015). The mean number of participants was 154 (range

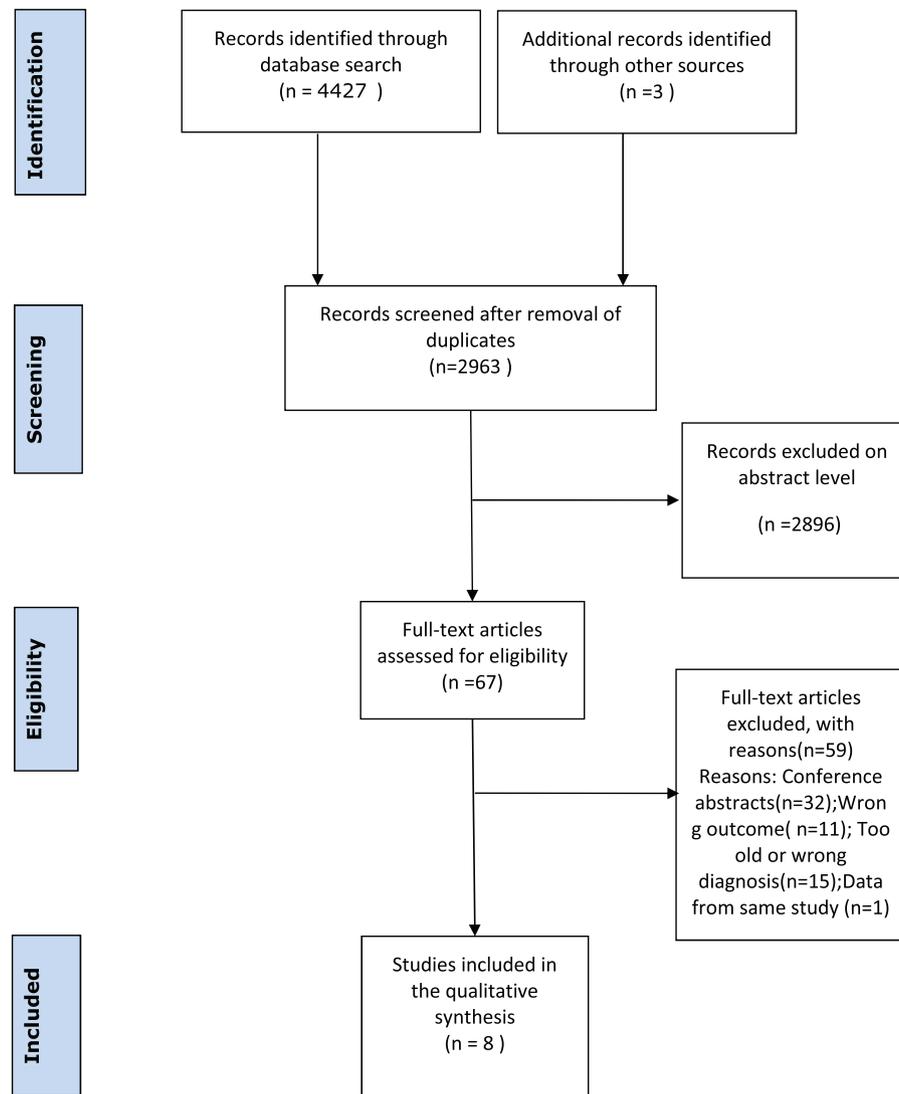


Fig 1. Flowchart describing study selection during literature search.

105–203) in the two RCTs, 25.7 (range 16–33) in the two controlled trials, and 24.5 (range 12–31) in the four pre and post test studies.

In five studies comprising supervised and individually adjusted aerobic exercise activities (Abdel-Baki et al., 2013; Curtis et al., 2016; Curtis et al., 2018; Firth et al., 2018; Nuechterlein et al., 2016) 69 patients with FEP underwent aerobic exercise and 20 participants were assigned to a control condition. The majority of patients had a diagnosis of schizophrenia (86%) and the mean age was 23.7 (17–45) years.

In two RCTs 156 patients were randomized to individual lifestyle counselling and 152 patients to a control condition, respectively (Detke et al., 2016; Lovell et al., 2014). The mean age of patients was 20.75 (13–35) years and the majority of patients had a diagnosis of schizophrenia (62%). A single study covered 30 patients with FEP with a mean age of 20.8 ± 2.6 years who received dietetic counselling and practical training of cooking and shopping (Teasdale et al., 2015).

3.3. Risk of bias

Due to non-randomized designs the majority of studies were assessed having a moderate to severe risk of bias and confounding. In addition, the majority of the studies reported poor adherence to the intervention increasing the risk of bias further (table 2). In all, this led to an assessment of moderate to severe overall risk of bias in the non-randomized trials. The two RCTs were also of moderate quality,

primarily due to insufficient randomization leading to confounding as well as poor adherence to the intervention (table 3).

3.4. Outcome of interventions

Two prospective studies in which participants underwent weekly, supervised aerobic exercise (Abdel-Baki et al., 2013; Firth et al., 2018) found a significant decrease in WC of 4.3 cm ($p = 0.015$) and 2 cm ($p = 0.008$), respectively. Similar, participants receiving 12 weeks of practical dietetic counselling (Teasdale et al., 2015) had a significant decrease in WC of approximately 2 cm ($P = 0.04$). Participants receiving individual, supervised, exercise and dietetic counselling, and peer wellness coaching as described in "Keeping the Body in Mind" (KBIM) (Curtis et al., 2016), had a non-significant increase in WC of 0.1 cm (from -2.1 to 2.2 cm) compared to a significant increase in WC of 7.1 cm (from 4.8 to 10.7 cm; $p < 0.001$) in the standard care group. Further, participants attending KBIM had significantly lower weight gain compared to patients receiving standard care (1.8 kg vs. 7.8 kg; 95% CI -0.4 to 2.8 ($p < 0.001$)). In a 2-year follow-up study of the KBIM intervention the participants (Curtis et al., 2018) had a non-significant ($p = 0.6$) mean weight gain of 1.3 (95% CI -4.0 to 6.6) kg and a non-significant ($p = 0.9$) increase in WC of 0.1 (-4.9 to 5.1) cm.

Two RCTs of behavioural weight and healthy lifestyle counselling (Detke et al., 2016; Lovell et al., 2014) found no significant differences

Table 1
Review of included articles on non-pharmacological interventions for preventing/reducing weight gain and increase in waist circumference (WC).

| Author and year | Study design | Participants | Intervention | Outcomes |
|--------------------------|--------------|--|--|---|
| Abdel-Baki et al. (2013) | Followup | 25 out-patients with FEP Male: 100%; 24.4 (18–35) years | 14 wks./30 min individual, supervised aerobic exercise (treadmill) | Patients completing 14 wks. of exercise had a decrease of WC of 4.3 cm; (p = 0.015). Effect size: 0.4 |
| Curtis et al. (2016) | Casecontrol | 28 out-patients with FEP Male/ female (%): 60.3/29.3; Mean age: 20.7 (17–25)years | 12 wks. individual, supervised dietetic support, exercise program and peer wellness coaches (KBIMI)(n = 16) versus. 12 wks. of individual standard case-management (n = 12) | Patients in KBIMI vs. standard care: Significant lower weight gain 1.8 kg vs. 7.8 kg (95% CI -0.4 to 2.8) (p < 0.001) Non-significant increase in WC of 0.1(-2.1 to 2.2) cm vs. significant increase of WC of 7.8 cm (4.8–10.7) (p<0.001) |
| Curtis et al. (2018) | Follow up | 12 outpatients with FEP Male/ female (%): not informed; Age of years: not informed | 2 years "Step-down program" of KBIMI with continued access to onsite gym, cooking group, nutrition and exercise consultations | Patients followed for 2 years: Non-significant mean weight gain of 1.3(95% CI -4.0 to 6.6)kg; p = 0.6 Non-significant mean increase of WC of 0.1 cm (95% CI -4.9 to 5.1)p = 0.9 |
| Detke et al. (2016) | RCT | 203 in - and outpatients with bipolar disorder (n = 116) or schizophrenia (87) Male/female(%): 52.2/47.8; Mean age: 15.8(13–17)years | 52 wks. of individual, supervised intense (n = 102) vs. standard(n = 101) behavioural weight counselling | High long-term weight gain in both groups. There were no significant differences intense vs. standard in mean change in BMI (+2.8 kg/m2 vs. +3.6 kg/m2; p = 0.150) or weight (+9.6 kg vs. +12.1 kg; p = 0.148) |
| Firth et al. (2018) | Followup | 31 outpatients with FEP Male/female(%):81/19 Mean age: 25.8(18–35)years | 10 wks. of ≥ 90 min/wk. individualized, aerobic exercise of moderate-to-vigorous activity | Patients had: A significant decrease in WC of 2 cm (p = 0.008). Effect size 0.58 A non-significant decrease in BMI (30.2(6.9) vs. 29.8(6.7); p = 0.265). Effect size: 0.23 |
| Lovell et al. (2014) | RCT | 105 outpatients with FEP Male/female(%): 60/40 Mean age: 25.7(16–35)years | 12 months comparison of a healthy living intervention(individual psychoeducation, individualized action plans for changes in physical activity and dietary habits, access to optional group activities)(n = 54) versus treatment as usual(TAU)(n = 51) | Intervention vs. TAU: Non-significant mean decrease in BMI of 0.31 vs. no change. Effect size: 0.11 |

in weight or waist circumference between patients in the intervention groups compared to patients in the control groups.

4. Discussion

To the best of our knowledge, this is the first systematic review on non-pharmacological interventions for preventing/reducing weight gain or increase of waist circumference among young patients with first-episode schizophrenia or bipolar disorder. The review identified eight studies of aerobic exercise, practical dietetic counselling or behavioural weight and lifestyle counselling, respectively. Some participants in the included studies exceeded the age limit of 15–25 years (Abdel-Baki et al., 2013; Firth et al., 2018; Lovell et al., 2014; Nuechterlein et al., 2016), underpinning that studies on young patients are rare. In relation to the chosen age limits this review included significantly fewer female patients, which might be due to the fact that females tend to have a later onset of psychosis. Hence, the findings might be most valid for male patients.

Studies comprising aerobic exercise interventions or practical dietetic counselling had significant impact on either weight or waist circumference. The studies found that a significant decrease in waist circumference was obtained by 10 to 14 weeks of aerobic exercise. Reducing abdominal obesity is essential for preventing T2D and CVD (Alberti et al., 2007). Accordingly, long-term observational data shows that exercise seems to be able to reduce weight gain in patients with first-episode schizophrenia significantly (Alvarez-Jimenez et al., 2008b). Further, preventing weight gain could be essential to reduce weight-related social stigma, to improve overall quality of life and treatment adherence (Firth et al., 2019).

Studies involving behavioural weight and lifestyle counselling did not show any significant impact on either weight or waist circumference. Importantly, in the two RCTs (Detke et al., 2016; Lovell et al., 2014), it was found that there was no benefit of non-pharmacological interventions comprising behavioural weight and healthy lifestyle counselling versus usual care.

Despite the fact that cardio-metabolic risk factors, including weight gain (Vancampfort et al., 2015c; Allison and Casey, 2001), has received increased attention in the past decades in relation to patients with severe mental illness only eight studies on non-pharmacological interventions were identified, highlighting that this is an area of limited research. This calls for more non-pharmacological interventions to be developed in the group of people with first episode schizophrenia or bipolar disorder. Moreover, the results are equivocal, particularly when one considers the most robust data from two RCTs. There could be several explanations for the limited number of studies in this field of research. The adherence to physical activity and healthy lifestyle interventions in the majority of studies was suboptimal. Poor adherence to interventions for changing lifestyle, becoming more physically active or gaining healthier eating habits is a well known phenomena and challenge in general health promotion (Vermeire, 2005; Ekkekakis et al., 2016; Leijon et al., 2011). It is possible that young patients with first-episode schizophrenia or bipolar disorder have additional challenges and difficulties in maintaining healthy lifestyle habits (Vancampfort et al., 2015d; Vancampfort et al., 2014). Moreover, to date, very few of the intervention studies appear to have been underpinned by theoretical frameworks with minimal usage of behavior change techniques which may increase adherence and optimize outcomes (Vancampfort et al., 2015a; Bradshaw et al., 2012).

Future, theoretically derived research is required to determine how patients can be motivated to engage in interventions, and the projects should be developed in corporation with service users in order to increase the patients' adherence (Hawkins et al., 2017). Another serious limitation of the literature is that the majority of patients in this review resolved patients with schizophrenia. People with BD are also at greatly increased risk of cardio-metabolic abnormalities (Vancampfort et al., 2013a) and there is a need for future research to explore interventions

Table 2
Risk of Bias Assessment using ROBINS-I {{2031 Schunemann,H.J. 2018}}.

| Author and year | Bias due to confounding | Bias in selection of participants into the study | Bias in classifications of interventions | Bias due to departure from intended interventions | Bias due to missing data | Bias in measurement of outcomes | Bias in selection of reported result | Overall bias |
|----------------------------|-------------------------|--|--|---|--------------------------|---------------------------------|--------------------------------------|--------------|
| Abdel-Baki et al. (2013) | Serious | Low | Moderate | Serious | Serious | Moderate | Moderate | Serious |
| Curtis et al. (2016) | Moderate | Low | Low | Moderate | Moderate | Moderate | Low | Moderate |
| Curtis et al. (2018) | Moderate | Low | Low | Low | Low | Moderate | Low | Moderate |
| Firth et al. (2018) | Moderate | Low | Low | Low | Moderate | Moderate | Moderate | Moderate |
| Nuechterlein et al. (2016) | Moderate | Low | Moderate | Low | Low | Moderate | No information | Moderate |
| Teasdale et al. (2016) | Moderate | Serious | Moderate | Serious | Serious | Moderate | Low | Serious |

Table 3
Assessment of RCT using risk-of-bias tool for randomized trials (RoB 2){2051 Higgins et al., 2016}}.

| Author and year | Bias arising from the randomization process | Bias due to deviations from the intended intervention | Bias due to missing outcome data | Bias in measurement of the outcome | Bias due to selection of reported outcome | Overall risk of bias |
|----------------------|---|---|----------------------------------|------------------------------------|---|----------------------|
| Detke et al. (2016) | Low | High | | Low | Low | Some concerns |
| Lovell et al. (2014) | Some concerns | High | Low | Low | Low | Some concerns |

in this neglected group.

The findings in this review are primarily limited by the fact that most studies included non-randomised designs which are prone to bias. Further, a majority of studies had short follow-up periods and poor adherence to the interventions. The findings of aerobic exercise and practical dietetic training trumping the effect of behavioural weight and lifestyle counselling could reflect a true difference of efficacy between the interventions or be caused by poor study designs, including shorter lengths in follow-up. These findings should therefore be taken with caution, and consequently, it is not possible to make robust and population specific recommendations about the most optimal manner to prevent weight gain in young patients with first episode schizophrenia or bipolar disorder. In the absence of such data, clinicians should be guided by general guidelines on physical activity and diet (World Health Organization, 2010; Stubbs et al., 2018; World Health Organization; Teasdale et al., 2017). In addition, a recent Lancet Psychiatry Commission recommends that life-style interventions should be provided from the initiation of treatment focusing on both physical and mental health outcomes of these interventions (Firth et al., 2019).

Conclusively, this review might indicate that aerobic exercise and practical dietetic interventions are efficient in preventing/reducing weight gain or increase in waist-circumference in young, first-episode patients with schizophrenia or bipolar disorder despite some methodological weaknesses in some of the included studies. However, there is a need for future methodologically well-designed studies to determine this.

Declaration of Competing Interest

None of the authors has any conflicts of interests.

Acknowledgments

Brendon Stubbs is supported by a Clinical Lectureship (ICA-CL-2017-03-001) jointly funded by Health Education England (HEE) and the National Institute for Health Research (NIHR). Brendon Stubbs is part funded by the NIHR Biomedical Research Center at South London and Maudsley NHS Foundation Trust. Brendon Stubbs is also supported by the Maudsley Charity, King's College London and the NIHR South London Collaboration for Leadership in Applied Health Research and Care (CLAHRC) funding. This paper presents independent research. The views expressed in this publication are those of the authors and not necessarily those of the acknowledged institutions.

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