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Outcome of a psychosocial health promotion intervention aimed at improving physical health and reducing alcohol use in patients with schizophrenia and psychotic disorders (MINT)

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Abstract

Background: Life expectancy is reduced by 19 years in men and 17 in women with psychosis in Sweden, largely due to cardiovascular disease.

Aim: Assess whether a psychosocial health promotion intervention improves cardiometabolic risk factors, quality of life, and severity of illness in patients with psychotic disorders more than treatment as usual.

Methods: A pragmatic intervention trial testing a manual-based multi-component health promotion intervention targeting patients with psychosis. The Swedish intervention was adapted from IMPaCT therapy, a health-promotion program based on motivational interviewing and cognitive behavioral therapy, designed to be incorporated into routine care. The intervention group consisted of 119 patients and a control group of 570 patients from specialized psychosis departments. Outcome variables were assessed 6 months before intervention during the run-in period, again at the start of intervention, and 12 months after the intervention began. The control group received treatment as usual.

Results: The intervention had no significant effect on any of the outcome variables. However, BMI, waist circumference, systolic BP, heart rate, HbA1c, general health, and Clinical Global Impressions Scale score improved significantly during the run-in period before the start of the active intervention (observer effect). The multi-component design meant that treatment effects could only be calculated for the intervention as a whole.

Conclusion: The results of the intervention are similar to those of the U.K. IMPaCT study, in which the modular health-promotion intervention had little effect on cardiovascular risk indicators. However, in the current study, the run-in period had a positive effect on cardiometabolic risk factors.

Keywords: cardiovascular risk factors, lifestyle intervention, psychiatric care, mental health, psychosis, run-in period.

1. INTRODUCTION

People with schizophrenia or other psychotic disorders have higher risk for cardiovascular disease (CVD) than the general population (Correll et al., 2017). Their diets are poor, they exercise less, and they are often overweight/obese and/or smokers (Gardner-Sood et al., 2015; Jakobsen et al., 2018; Vancampfort et al., 2017). Metabolic risk factors for CVD, such as central obesity, glucose dysregulation, hypertension, and dyslipidemia are highly prevalent in people with psychotic disorders (Gardner-Sood et al., 2015; Olsson et al., 2015). Moreover, in those who take certain antipsychotics (such as clozapine), glucose dysregulation occurs in 55% within three months and before a change in weight (Howes et al., 2004). Additionally, the mortality rate of people with schizophrenia and other psychotic disorders is higher than that of the general population (Hjorthoj et al., 2017; Laursen et al., 2013), mainly because of CVD (Westman et al., 2017). A study on the life expectancy of people with psychosis found that in Sweden, men with schizophrenia spectrum disorders lived 19 fewer years than men in the general population, while women with such disorders lived 17 fewer years than their general population peers (Nordentoft et al., 2013).

Historically, the physical health of psychiatric patients has been neglected. Awareness of the importance of focusing on physical health in these patients is increasing among members of the psychiatric profession, but there is currently no evidence-based method to improve the physical health of patients with psychoses (schizophrenia spectrum disorders). We hypothesized that addressing lifestyle factors such as weight, smoking, and exercise would help reduce the increased exposure to cardiometabolic risk factors. The Metabolic Intervention Therapy in Psychosis (MINT) study partially replicated a U.K. intervention study, called Improving Physical Health and Reducing Substance Use in Psychosis (IMPACT) study. The U.K. IMPACT study was designed to improve the physical health of people with psychosis through behavioral change, by training care coordinators to use motivational interviewing and cognitive behavioral therapy techniques to encourage healthier lifestyle choices (Gaughran et al., 2013a).

MINT was one of the first larger controlled intervention studies on this topic in Sweden, and together with the U.K. IMPACT intervention study (Gaughran et al., 2017) it constitutes a robust evaluation of the effectiveness of motivational interviewing and cognitive behavioral

therapy to improve unhealthy lifestyle habits and well-being in people with psychoses. Our specific aim was to assess whether IMPaCT therapy, adapted for use in Sweden, improves cardiometabolic measures, self-reported health and quality of life, and psychological functioning and severity of illness in patients with psychotic disorders in Sweden more than treatment as usual. In addition, we evaluated how those measures and outcomes changed during a 6-month run-in period before the start of the intervention.

2. METHOD

2.1. Study design and setting

The MINT study partially replicated the IMPaCT health promotion intervention (based on motivational interviewing and cognitive behavioral therapy) from the United Kingdom (Gaughran et al., 2017). To test IMPaCT therapy in Sweden, psychosis departments in Gothenburg, Kristianstad, Hässleholm, and Malmö were recruited to an existing cohort study, the Swedish Study of Metabolic Risks in Psychosis (SMRP). Patients in the control group came from the psychiatric clinics originally included in SMRP. Patients in the intervention group came from the newly recruited psychiatric clinics. In Sweden, specialized psychosis departments are responsible for the treatment of most outpatients in their catchment area who have long-term psychotic disorders. The cost of treatment was covered by the Swedish health insurance system.

The original IMPaCT health promotion intervention, developed at King's College, London, was a manual-guided intervention designed to be integrated into routine care and delivered by care coordinators. These care coordinators received training and supervision in motivational interviewing and manual-based cognitive behavioral therapy techniques. The Swedish intervention was modeled on the U.K. version; the English-language manual was translated into Swedish, and the U.K. research group travelled to Sweden to train the Swedish teams in IMPaCT therapy and to collaborate in the development and implementation of the Swedish study protocol. The MINT research group maintains close collaboration with the IMPaCT research group in the United Kingdom.

2.2. Ethical permission

MINT was part of SMRP and received ethical approval as such from the Stockholm Regional Ethics Review Board (dnr 2011/849-32). MINT was carried out in accordance with the Code

of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

2.3. Participants

2.3.1. Inclusion and exclusion criteria

Patients were eligible to participate in MINT if they were 18 years or older and had been diagnosed with a psychotic disorder (ICD 10 diagnoses F20-29: Schizophrenia, schizotypal and delusional disorders; F31.2: Bipolar affective disorder, current episode manic with psychotic symptoms; and F31.5: Bipolar affective disorder, current episode severe depression with psychotic symptoms). Exclusion criteria included a) a primary diagnosis of learning disability; b) a co-existing physical health problem that would, in the opinion of a medical doctor, independently impact cardiometabolic measures and/or substance use habits; c) current pregnancy or ≤ 6 months post-partum; or d) a life-threatening or terminal medical condition for which the person already received extensive care. Psychiatric diagnoses were confirmed by the treating psychiatrist in accordance with ICD-10 diagnostic criteria.

2.3.2. The intervention group

To select the intervention group, we involved care coordinators who were permanently employed at the intervention departments and had a minimum of four patients. We created a list of each care coordinator's eligible patients, and then a blinded administrator used a random number generator to randomly select four to six of the patients of each care coordinator. The selected patients were then consecutively invited to take part in MINT. If a patient declined to participate, we approached the next patient on the list. Patients in the intervention group received the intervention in addition to treatment as usual.

2.3.3. The control group

The control group consisted of the patients with psychotic disorder from the departments that originally participated in SMRP. None of these departments included any patients in the intervention group. The patients in the control group received treatment as usual but not IMPaCT therapy.

2.4. IMPaCT therapy

IMPACT therapy is described in detail in the protocol for the IMPACT randomized controlled trial that took place in the United Kingdom (Gaughran et al., 2013a) and in the IMPACT Manual, Reference Guide, and patients' handbook "the Better Health Handbook" (Gaughran et al., 2013b), copies of which were given to the participating care coordinators. The materials were developed by specialists in psychiatry and tailored to needs of people with psychosis. Key messages were reinforced via images and text in the materials and repeated by the care coordinators. In the MINT study, the Swedish version of IMPACT therapy was delivered by each patient's care coordinator. The care coordinators in Sweden participated in a week-long educational program about IMPACT therapy jointly run by the U.K. and Swedish teams. The program focused on how to improve lifestyle factors and cardiometabolic outcomes in patients with psychotic disorders via motivational interviewing and specific cognitive behavioral therapy techniques for psychosis.

The IMPACT therapy in the United Kingdom consisted of eight modules designed to improve physical health and reduce substance use in people with psychosis (Gaughran et al., 2013a). IMPACT therapy in Sweden consisted of six of these eight modules: basic cognitive behavioral therapy in mental health, smoking, diabetes, healthy eating, alcohol, and exercise (Table 1). The Swedish version of IMPACT therapy did not include the original U.K. modules on cannabis and other drugs. In Sweden, those with a primary diagnosis of substance use disorder or mixed diagnoses (e.g., substance use disorder and psychosis) are often treated in special addiction units that were not included in this study.

In consultation with their care coordinator, patients participating in MINT chose one or more of the modules to focus on during the intervention. During the following 9 to 12 months, they met their care coordinator each week to work on the modules they had chosen. Individual meetings with care coordinators occurred weekly and lasted approximately 45 minutes. Some modules included optional group activities (e.g., exercise, healthy eating). Group activities also took place weekly and lasted approximately 60 minutes. In the Swedish intervention, all participants took part in the exercise module. In most cases, exercise sessions were led by physiotherapists with experience working with psychiatric patients. Care coordinators used person-centered motivational interview techniques in the individual and group sessions.

Table 1. IMPACT health promotion therapy in Sweden.

2.5. Therapy supervisors in Sweden

In MINT, the care coordinators in each participating geographical area were supported by a specially selected and trained supervisor. The supervisors received a week of additional training from the U.K. IMPaCT team.

2.6 Variables

2.6.1. Sociodemographic variables

Sociodemographic variables were gathered by the care coordinator via a questionnaire. These variables included age, sex, level of education (dichotomized into college or above and less than college). The patient's main psychiatric diagnosis was made in accordance with the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV).

2.6.2. Outcome measures

2.6.2.1 Cardiometabolic and lifestyle measures

Cardiometabolic and lifestyle measures in the study included diagnosis of diabetes, smoking (yes/no, and if yes, number of cigarettes), BMI, central obesity (waist circumference >94 cm for European men and >80 cm for European women in accordance with the International Diabetes Federation consensus definition of the metabolic syndrome) (International Diabetes Federation., 2006), systolic blood pressure, diastolic blood pressure, pulse (heart) rate, triglycerides, total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, fasting serum glucose, long-term blood glucose control as measured by glycated hemoglobin (HbA1c), and tests of liver function (including alanine aminotransferase [ALT], alkaline phosphatase [ALP], and gamma-glutamyl transpeptidase [GGT]). These measures were assessed by the care coordinator in accordance with standard protocols. Other cardiometabolic and lifestyle measures in the study included alcohol consumption and self-reported physical activity (sedentary minutes per day and week) and sedentary behavior (in minutes per day). Alcohol consumption was assessed with the Alcohol Use Disorders Identification Test (AUDIT). AUDIT is a ten-item questionnaire developed by the World Health Organization to assess risk of alcohol abuse.

2.6.2.2. Self-reported health and quality of life

There were three measures of self-reported health and quality of life. The first was the general health question, which asks people to rate their general health on a scale from one ("very

good”) to five (“very bad”). The second was the visual analog scale (EQ VAS) of the EuroQol five dimensions questionnaire (EQ5D). The EQ VAS asks participants to rate their health from "the best health you can imagine" to "the worst health you can imagine." The third was the index assessment of the EQ5D. This index sums the responses to the five variables on the EQ5D.

2.6.2.3. Psychological functioning and severity of illness

These measures include the Global Assessment of Functioning (GAF) scale score (Endicott et al., 1976) and the Clinical Global Impressions (CGI) scale score. A GAF score represents a psychiatrist's assessment of a patient's current social, occupational, and psychological functioning. The psychiatrist chooses one of eleven numerical ranges (0, 1-10, 11-20, and so on, up to 91-100); lower scores indicate worse functioning and higher scores, better functioning. The 7-point CGI scale score represents the psychiatrist's assessment of the current severity of the patient's illness compared to that of other patients with the same illness. Higher scores indicate more severe psychiatric illness.

2.7 Data collection

Measures were assessed at pre-baseline, at baseline, and post-intervention. To study the possible effects of inclusion in the study, pre-baseline measures were taken, in the intervention group only, 6 months before the designated start of the intervention. Subsequently, during the latter part of the following 6-month period, participating care coordinators received training in IMPaCT therapy while patients continued to receive their usual care. Baseline measurements were performed before implementation of the intervention. The Swedish version of IMPaCT therapy was then implemented and actively supervised for 6 months.

2.8. Statistical analysis

The analyses were conducted with SPSS (version 22.0). All variables were summarized with standard descriptive statistics, such as frequency, mean, and standard deviation. Categorical variables; e.g., group and gender, were analyzed with Pearson's chi-squared test or Fisher's exact test if the expected cell frequency was 5 or less. Changes during the 6-month run-in period; that is, between inclusion in the study and the start of the intervention, were analyzed with the Student's t-test for paired observations if the variables were approximately normally

distributed. For observations with skewed distributions, the Wilcoxon signed-rank test was applied.

The significance level in all analyses was 5% (two-tailed). The researchers and statistician who analyzed the outcomes were blind to the treatment group.

The study was powered to detect a weight reduction of 3 kg. Weight reduction of >5% of baseline body weight is considered clinically relevant (Stevens et al., 2006). The average weight in the study population was 90.5 kg at the start of the study, so a >5% weight loss would entail a loss of 4.5 kg.

3. RESULTS

3.1 Patient characteristics

There were few significant differences between the intervention and control groups at the start of the intervention, although the intervention group had higher rates of central obesity; more severe psychiatric illness; and lower functioning scores (GAF scores >50) than the control group (Table 2). Psychiatric diagnoses differed somewhat between the groups. In the intervention group, 88 out of 119 completed all assessments. Of 1020 patients in the SMRP study, 570 control patients were followed up for one year.

Table 2. Pre-baseline characteristics of patients in the intervention group (n= 119) and the control group (n= 1020)

3.2 Pre-baseline measures

During the 6 month run-in period before the start of the intervention, there were significant improvements in BMI, waist circumference, systolic blood pressure, heart rate, glycated hemoglobin (HbA1c), general health, and CGI scores.

Table 3. Changes in the intervention group during the run-in period 6 months before the start of the intervention (n= 119).

3.3 Results of the intervention

Table 4 shows that there was no difference between the intervention group that received the Swedish version of IMPaCT therapy and the control group that received usual care in cardiometabolic and lifestyle measures, including smoking, BMI, waist circumference, systolic blood pressure, diastolic blood pressure, triglycerides, total cholesterol, HDL cholesterol, LDL cholesterol, fasting serum glucose, ALT, ALP, and GGT. Nor was there a differential effect on self-reported health, quality of life, psychological functioning, or severity of psychiatric illness. Although the difference did not reach statistical significance, blood glucose decreased more in the intervention than the control group.

Table 4. Changes in cardiometabolic and lifestyle measures, self-reported health and quality of life, and psychological functioning and severity of illness in the intervention group (n= 88) and control group (n= 570) between the start and the end of the intervention (IMPaCT therapy)

4. DISCUSSION

4.1. Summary

IMPaCT therapy did not significantly improve cardiometabolic and lifestyle measures, self-reported health and quality of life, or psychological functioning and severity of illness in patients with psychotic disorders in Sweden more than treatment as usual. However, before the intervention, during the 6-month run-in period, several cardiometabolic risk factors improved significantly, including BMI, waist circumference, systolic blood pressure, heart rate, long-term blood glucose control, general health, and severity of illness.

4.2. Strengths and limitations

The MINT study had several strengths. First, we used a manual-based, well-described and evidence-based theoretical framework developed by the IMPaCT team at King's College in London. Even though the MINT study was designed to be low budget and incorporated into ordinary care, the participating clinics invested considerable time and effort in the project. Participating in the study represented an important commitment on the part of each clinic, from the manager and from the health care professionals. Clinics paid for the time their staff spent in training and implementation, chose one professional at the clinic to act as study coordinator, and sent their staff to receive training in IMPaCT therapy.

Another strength of the MINT study was the assessment of outcome variables in the intervention group during the 6-month run-in period prior to the start of the intervention. A run-in period is common in pharmacological but not health promotion interventions. A review of 311 weight loss studies showed that only 19% of the studies included a run-in period; the highest frequency was found in pharmaceutical studies. The inclusion of a pre-randomization run-in period was associated with less weight loss ($P = 0.0017$) than the absence of a run-in period (Affuso et al., 2014).

It is important for interventions designed to improve health behavior in people with psychosis to be tested in real-life settings (McGinty et al., 2016). Thus, another strength of the study was the real-life setting and broad inclusion criteria used in MINT, which meant that the study population reflected the actual population of patients at psychosis clinics in Sweden. For instance, potential participants were not excluded on the basis of the severity of their psychiatric disorder or suicidal ideation. Moreover, the multi-component design of the intervention gave patients the power to choose their own health priorities: every patient was free to choose, in dialogue with their care manager, which of the modules they wanted to work with. The multi-component intervention also used health care professionals and patients' time efficiently. Instead of attending individual courses on treating each health problem, staff could attend one course on a multi-component intervention, and patients could participate in one program.

However, the multi-component design of the intervention was also a weakness. It was not possible to trace the effects of each module, as all but 14 patients chose to participate in at least two modules. Another limitation of the study is that although the intervention manual recommended that participants attend a certain number of sessions, we did not measure how adherent they were to this recommendation.

Self-reported outcomes are subject to both recall problems and social desirability bias, which can lead to systematic error. Recall bias in particular can be magnified in people with psychotic disorders. More direct measurement of physical activity (e.g., with accelerometers) would have been preferable. However, limited funding made it unfeasible to use such technology in this study.

Another important weakness of the study was the randomization process. The whole study population was not randomized into intervention and control groups. Instead, patients at the clinics originally participating in SMRP were assigned to the control group, and new clinics were recruited to provide patients for the intervention group. Patients at the newly recruited clinics were then randomly selected to represent the total patient population. Although the randomization method was not optimal, it nevertheless enabled us to assess the effects of the intervention. Few baseline characteristics of the intervention and control groups differed significantly. Thus, the choice of control group and the randomization method used to select the intervention group were not likely to have caused the lack of intervention effect.

Finally, when designing the study, we chose to use validated instruments whenever possible. Many of the instruments chosen have been validated for use in psychiatric patients (Mulhern et al., 2014).

4.3. Comparison with other studies

Many trials that have attempted to improve the health of people with psychiatric disorders have focused on single risk behaviors, such as diet, smoking, or physical inactivity (Ward et al., 2015). The effects of such health promotion interventions in patients with schizophrenia have been positive in some cases (Kimhy et al., 2015; Pajonk et al., 2010; Scheewe et al., 2013), although most have been limited (Gates et al., 2015). Weight-loss and exercise programs have been the most common interventions, and a meta-evaluation showed that several trials had positive outcomes (Singh et al., 2018), whereas others had mixed results (McGinty et al., 2016). A systematic review showed that nonpharmacological interventions led to less weight loss in patients with serious mental illness than in the general population. In patients with serious mental illness, the mean weight loss in randomized controlled trials is 1.6 kg (95% CI, 0.3 to 2.9 kg), whereas it is 3.6 to 5 kg in the general population (Cabassa et al., 2010).

Because smoking is common in patients with serious mental illness, it has also been an important target of behavioral interventions, with mixed results (Cather et al., 2017; McGinty et al., 2016). Smoking rates in patients with serious mental illness have declined much less than in those without such disorders (Cook et al., 2014).

Like our own intervention, other multi-component health behavior interventions have had little or no effect on important outcomes for people with schizophrenia and psychotic disorders, including cardiometabolic risk factors such as blood glucose, HbA1c, blood pressure, and blood lipids. For instance, the Danish CHANGE trial evaluated how care coordination alone, lifestyle coaching plus care coordination, or treatment as usual in adults with schizophrenia spectrum disorders and increased waist circumference affected cardiovascular risk (Speyer et al., 2016). Like the present study, the CHANGE intervention had no effect on cardiometabolic risk factors such as cardiorespiratory fitness, physical activity, weight, diet, or smoking (Jakobsen et al., 2017; Speyer et al., 2016). This is not entirely surprising given that most health promotion and weight loss interventions targeting the general population have modest effects, and people with schizophrenia and psychotic disorders have additional obstacles to overcome. The first report of the results of the ELIPS trial, another cluster-randomized controlled trial targeting health behavior in patients with severe mental illness, showed no effect psychosocial outcomes (Stiekema et al., 2018). At the time of writing, effects on somatic outcomes were not yet available.

Single-component and multi-component intervention studies each have advantages and disadvantages. Complex interventions are often preferable in clinical practice, as they address multiple risk factors at the same time, but they are less straightforward to evaluate scientifically than single-component interventions. However, given our null findings and the lack of findings in similar multi-component health promotion intervention studies, we suggest that future studies evaluate more intense, single-component interventions. Moreover, in light of the modest results of many health promotion interventions in reducing the high burden of metabolic disease in people with schizophrenia and psychotic disorders, it might be time to perform trials of pharmacological interventions such as lipid-lowering medication, glucose lowering medication (Aldossari, 2018; Zheng et al., 2019), and medication for smoking cessation. It could also be relevant to carefully consider surgical interventions for obesity in selected patients with severe obesity who do not respond to health promotion interventions or pharmacotherapy.

In the current study, a number of variables improved during the 6-month run-in period. The improvement may be the result of the observer effect (also referred to as the Hawthorn effect) (Goodwin et al., 2017), which occurs when people modify their behavior in response to the knowledge that they are being observed. For instance, when patients are included in a study,

they tend to increase their adherence to medication, as shown for hypertension (Gardner-Sood et al., 2015). The finding of a significant effect on cardiometabolic risk factors during the run-in period is worth further investigation to see if it could be used in a structured way in clinical practice.

Most trials of health promotion interventions do not include a run-in period prior to evaluating the new approach; such periods have most often been employed in studies on weight loss, especially those involving weight control drugs. Even so, weight change during the pre-randomization (run-in) phase is rarely reported in obesity or other types of health promotion trials (West et al., 2011). Only 19% of the interventions included in a meta-analysis of 311 obesity RCTs included a run-in period, and most of these were trials of pharmaceuticals (Affuso et al., 2014), possibly because the U.S. Food and Drug Administration's 1996 Guidance for the Clinical Evaluation of Weight Control Drugs advocated that RCTs include a 6-week behavioral weight reduction run-in period. Although all intervention types were associated with weight loss (mean=2.80 kg, SD=3.52), the effect of the active intervention was smaller in studies that included a pre-randomization run-in period ($P=0.0017$).

The weak results of previous interventions and our finding of significant reductions in cardiometabolic risk factors after an open run-in period before the start of the active intervention underline the importance of designing studies that make it possible to distinguish between the observer effect and the effect of the intervention itself. During the run-in period, patients' expectations of treatment efficacy can alter behavior, which can lead improved health outcomes (Crow et al., 1999). In addition to increased patient focus on their own health problems and related behaviors, explanations for the significant effects observed during the run-in period could include more attention to patients from clinicians and effects of the training on clinicians' work (Aveyard et al., 2016).

4.4. Conclusions

This study adds to the growing evidence that multi-component health promotion interventions have limited effects on cardiometabolic risk factors in patients with schizophrenia and psychotic disorders. It also showed that several cardiometabolic and lifestyle variables improved during the run-in period. Researchers should consider including run-in periods in similar studies on health promotion interventions to avoid false positive results.

5. AUTHOR DISCLOSURE

5.1 Funding

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5.2. Contributors

The Swedish group, including Jeanette Westman, Jonas Eberhard, Lennart Lundin, Richard Stenmark, Gunnar Edman, Sven V Eriksson, Erik Jedenius, Pia Rydell, Karin Overgaard, Daniel Abrams, and Urban Ösby planned and conducted the study, carried out the statistical analyses, and drafted the manuscript. The U.K. group, including Fiona P Gaughran, Kathryn Greenwood, Shubulade Smith, Khalida Ismail, and Robin Murray supported the Swedish group during study design and implementation phase and provided important intellectual contributions to the manuscript. In addition to his role in the Swedish group, Jonas Eberhard coordinated the Swedish-British collaboration. All the authors reviewed and approved the final version of the manuscript prior to submission.

5.3 Conflicts of interest

The authors declare that they have no conflicts of interest.

5.4 Acknowledgements

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References

- Affuso, O., Kaiser, K.A., Carson, T.L., Ingram, K.H., Schwierts, M., Robertson, H., Abbas, F., Allison, D.B., 2014. Association of run-in periods with weight loss in obesity randomized controlled trials. *Obesity reviews: an official journal of the International Association for the Study of Obesity* 15(1), 68-73.
- Aldossari, K.K., 2018. Cardiovascular outcomes and safety with antidiabetic drugs. *International journal of health sciences* 12(5), 70-83.
- Aveyard, P., Lewis, A., Tearne, S., Hood, K., Christian-Brown, A., Adab, P., Begh, R., Jolly, K., Daley, A., Farley, A., Lycett, D., Nickless, A., Yu, L.M., Retat, L., Webber, L., Pimpin, L., Jebb, S.A., 2016. Screening and brief intervention for obesity in primary care: a parallel, two-arm, randomised trial. *Lancet* 388(10059), 2492-2500.
- Cabassa, L.J., Ezell, J.M., Lewis-Fernandez, R., 2010. Lifestyle interventions for adults with serious mental illness: a systematic literature review. *Psychiatric services* 61(8), 774-782.
- Cather, C., Pachas, G.N., Cieslak, K.M., Evins, A.E., 2017. Achieving smoking cessation in individuals with schizophrenia: special considerations. *CNS drugs* 31(6), 471-481.
- Cook, B.L., Wayne, G.F., Kafali, E.N., Liu, Z., Shu, C., Flores, M., 2014. Trends in smoking among adults with mental illness and association between mental health treatment and smoking cessation. *Jama* 311(2), 172-182.
- Correll, C.U., Solmi, M., Veronese, N., Bortolato, B., Rosson, S., Santonastaso, P., Thapa-Chhetri, N., Fornaro, M., Gallicchio, D., Collantoni, E., Pigato, G., Favaro, A., Monaco, F., Kohler, C., Vancampfort, D., Ward, P.B., Gaughran, F., Carvalho, A.F., Stubbs, B., 2017. Prevalence, incidence and mortality from cardiovascular disease in patients with pooled and specific severe mental illness: a large-scale meta-analysis of 3,211,768 patients and 113,383,368 controls. *World psychiatry : official journal of the World Psychiatric Association* 16(2), 163-180.
- Crow, R., Gage, H., Hampson, S., Hart, J., Kimber, A., Thomas, H., 1999. The role of expectancies in the placebo effect and their use in the delivery of health care: a systematic review. *Health technology assessment* 3(3), 1-96.
- Endicott, J., Spitzer, R.L., Fleiss, J.L., Cohen, J., 1976. The global assessment scale. A procedure for measuring overall severity of psychiatric disturbance. *Archives of general psychiatry* 33(6), 766-771.
- Gardner-Sood, P., Lally, J., Smith, S., Atakan, Z., Ismail, K., Greenwood, K.E., Keen, A., O'Brien, C., Onagbesan, O., Fung, C., Papanastasiou, E., Eberhard, J., Patel, A., Ohlsen, R., Stahl, D., David, A., Hopkins, D., Murray, R.M., Gaughran, F., team, I.M., 2015. Cardiovascular risk factors and metabolic syndrome in people with established psychotic illnesses: baseline data from the IMPaCT randomized controlled trial. *Psychological medicine* 45(12), 2619-2629.
- Gates, J., Killackey, E., Phillips, L., Alvarez-Jimenez, M., 2015. Mental health starts with physical health: current status and future directions of non-pharmacological interventions to improve physical health in first-episode psychosis. *Lancet Psychiatry* 2(8), 726-742.
- Gaughran, F., Stahl, D., Ismail, K., Atakan, Z., Lally, J., Gardner-Sood, P., Patel, A., David, A., Hopkins, D., Harries, B., Lowe, P., Orr, D., Arbuthnot, M., Murray, R.M., Greenwood, K.E., Smith, S., 2013a. Improving physical health and reducing substance use in psychosis--randomised control trial (IMPACT RCT): study protocol for a cluster randomised controlled trial. *BMC psychiatry* 13, 263.
- Gaughran, F., Stahl, D., Ismail, K., Greenwood, K., Atakan, Z., Gardner-Sood, P., Stubbs, B., Hopkins, D., Patel, A., Lally, J., Lowe, P., Arbuthnot, M., Orr, D., Corlett, S., Eberhard, J., David, A.S., Murray, R., Smith, S., Team, I.M., 2017. Randomised control trial of the effectiveness of an integrated psychosocial health promotion intervention aimed at improving health and reducing substance use in established psychosis (IMPACT). *BMC psychiatry* 17(1), 413.
- Gaughran, F.P., Greenwood, K.E., Smith, S., Ismail, K., Murray, R., on behalf of the IMPACT team, 2013b. *The Better Health Handbook*. King's College, London, U.K.

Goodwin, M.A., Stange, K.C., Zyzanski, S.J., Crabtree, B.F., Borawski, E.A., Flocke, S.A., 2017. The Hawthorne effect in direct observation research with physicians and patients. *Journal of evaluation in clinical practice* 23(6), 1322-1328.

Hjorthoj, C., Sturup, A.E., McGrath, J.J., Nordentoft, M., 2017. Years of potential life lost and life expectancy in schizophrenia: a systematic review and meta-analysis. *Lancet Psychiatry* 4(4), 295-301.

Howes, O.D., Gaughran, F.P., Amiel, S.A., Murray, R.M., Pilowsky, L.S., 2004. The effect of clozapine on factors controlling glucose homeostasis. *The Journal of clinical psychiatry* 65(10), 1352-1355.

International Diabetes Federation., 2006. *The IDF Consensus Worldwide Definition of the Metabolic Syndrome*. IDF Communications, Brussels.

Jakobsen, A.S., Speyer, H., Norgaard, H.C.B., Karlsen, M., Birk, M., Hjorthoj, C., Mors, O., Krogh, J., Gluud, C., Pisinger, C., Nordentoft, M., 2017. Effect of lifestyle coaching versus care coordination versus treatment as usual in people with severe mental illness and overweight: two-years follow-up of the randomized CHANGE trial. *PLoS one* 12(10), e0185881.

Jakobsen, A.S., Speyer, H., Norgaard, H.C.B., Karlsen, M., Hjorthoj, C., Krogh, J., Mors, O., Nordentoft, M., Toft, U., 2018. Dietary patterns and physical activity in people with schizophrenia and increased waist circumference. *Schizophrenia research* 199, 109-115.

Kimhy, D., Vakhrusheva, J., Bartels, M.N., Armstrong, H.F., Ballon, J.S., Khan, S., Chang, R.W., Hansen, M.C., Ayanruoh, L., Lister, A., Castren, E., Smith, E.E., Sloan, R.P., 2015. The impact of aerobic exercise on brain-derived neurotrophic factor and neurocognition in individuals with schizophrenia: a single-blind, randomized clinical trial. *Schizophrenia bulletin* 41(4), 859-868.

Laursen, T.M., Wahlbeck, K., Hallgren, J., Westman, J., Osby, U., Alinaghizadeh, H., Gissler, M., Nordentoft, M., 2013. Life expectancy and death by diseases of the circulatory system in patients with bipolar disorder or schizophrenia in the Nordic countries. *PLoS one* 8(6), e67133.

McGinty, E.E., Baller, J., Azrin, S.T., Juliano-Bult, D., Daumit, G.L., 2016. Interventions to address medical conditions and health-risk behaviors among persons with serious mental illness: a comprehensive review. *Schizophrenia bulletin* 42(1), 96-124.

Mulhern, B., Mukuria, C., Barkham, M., Knapp, M., Byford, S., Soeteman, D., Brazier, J., 2014. Using generic preference-based measures in mental health: psychometric validity of the EQ-5D and SF-6D. *The British journal of psychiatry : the journal of mental science* 205(3), 236-243.

Nordentoft, M., Wahlbeck, K., Hallgren, J., Westman, J., Osby, U., Alinaghizadeh, H., Gissler, M., Laursen, T.M., 2013. Excess mortality, causes of death and life expectancy in 270,770 patients with recent onset of mental disorders in Denmark, Finland and Sweden. *PLoS one* 8(1), e55176.

Olsson, E., Westman, J., Sudic Hukic, D., Eriksson, S.V., Edman, G., Boden, R., Jedenius, E., Reutfors, J., Berntsson, A., Hilding, A., Schalling, M., Ostenson, C.G., Osby, U., 2015. Diabetes and glucose disturbances in patients with psychosis in Sweden. *BMJ open diabetes research & care* 3(1), e000120.

Pajonk, F.G., Wobrock, T., Gruber, O., Scherk, H., Berner, D., Kaizl, I., Kierer, A., Muller, S., Oest, M., Meyer, T., Backens, M., Schneider-Axmann, T., Thornton, A.E., Honer, W.G., Falkai, P., 2010. Hippocampal plasticity in response to exercise in schizophrenia. *Archives of general psychiatry* 67(2), 133-143.

Scheewe, T.W., van Haren, N.E., Sarkisyan, G., Schnack, H.G., Brouwer, R.M., de Glinck, M., Hulshoff Pol, H.E., Backx, F.J., Kahn, R.S., Cahn, W., 2013. Exercise therapy, cardiorespiratory fitness and their effect on brain volumes: a randomised controlled trial in patients with schizophrenia and healthy controls. *European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology* 23(7), 675-685.

Singh, V.K., Karmani, S., Malo, P.K., Virupaksha, H.G., Muralidhar, D., Venkatasubramanian, G., Muralidharan, K., 2018. Impact of lifestyle modification on some components of metabolic syndrome in persons with severe mental disorders: A meta-analysis. *Schizophrenia research* 202, 17-25.

Speyer, H., Christian Brix Norgaard, H., Birk, M., Karlsen, M., Storch Jakobsen, A., Pedersen, K., Hjorthoj, C., Pisinger, C., Gluud, C., Mors, O., Krogh, J., Nordentoft, M., 2016. The CHANGE trial:

no superiority of lifestyle coaching plus care coordination plus treatment as usual compared to treatment as usual alone in reducing risk of cardiovascular disease in adults with schizophrenia spectrum disorders and abdominal obesity. *World psychiatry : official journal of the World Psychiatric Association* 15(2), 155-165.

Stevens, J., Truesdale, K.P., McClain, J.E., Cai, J., 2006. The definition of weight maintenance. *International journal of obesity* 30(3), 391-399.

Stiekema, A.P.M., Looijmans, A., van der Meer, L., Bruggeman, R., Schoevers, R.A., Corpeleijn, E., Jorg, F., 2018. Effects of a lifestyle intervention on psychosocial well-being of severe mentally ill residential patients: ELIPS, a cluster randomized controlled pragmatic trial. *Schizophrenia research* 199, 407-413.

Vancampfort, D., Firth, J., Schuch, F.B., Rosenbaum, S., Mugisha, J., Hallgren, M., Probst, M., Ward, P.B., Gaughran, F., De Hert, M., Carvalho, A.F., Stubbs, B., 2017. Sedentary behavior and physical activity levels in people with schizophrenia, bipolar disorder and major depressive disorder: a global systematic review and meta-analysis. *World psychiatry : official journal of the World Psychiatric Association* 16(3), 308-315.

Ward, M.C., White, D.T., Druss, B.G., 2015. A meta-review of lifestyle interventions for cardiovascular risk factors in the general medical population: lessons for individuals with serious mental illness. *The Journal of clinical psychiatry* 76(4), e477-486.

West, D.S., Harvey-Berino, J., Krukowski, R.A., Skelly, J.M., 2011. Pretreatment weight change is associated with obesity treatment outcomes. *Obesity* 19(9), 1791-1795.

Westman, J., Eriksson, S.V., Gissler, M., Hallgren, J., Prieto, M.L., Bobo, W.V., Frye, M.A., Erlinge, D., Alfredsson, L., Osby, U., 2017. Increased cardiovascular mortality in people with schizophrenia: a 24-year national register study. *Epidemiology and psychiatric sciences* 27(5), 519-527.

Zheng, W., Zhang, Q.E., Cai, D.B., Yang, X.H., Ungvari, G.S., Ng, C.H., Wu, R.R., Xiang, Y.T., 2019. Combination of metformin and lifestyle intervention for antipsychotic-related weight gain: a meta-analysis of randomized controlled trials. *Pharmacopsychiatry* 52(1), 24-31.