Individualised lifestyle interventions to reduce cardiovascular risk factors in patients with schizophrenia

PhD Dissertation

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Content

Preface

Outline of thesis papers

The work included in this PhD thesis was conducted at the Copenhagen University Hospital, Mental Health Centre Copenhagen and the Psychosis Research Unit, Aarhus University Hospital, under the supervision of Professor Merete Nordentoft and Professor Ole Mors.

The aim is to investigate whether lifestyle interventions is a feasible method to reduce excess mortality due to cardiovascular disease in schizophrenia in a real-world setting. The topic is explored in a clinical study and a review of the literature.

The clinical trial, CHANGE, is a pragmatic randomized clinical trial aiming to reduce the risk of cardiovascular disease in patients with schizophrenia and abdominal obesity. Two interventions were investigated; lifestyle coaching and care-coordination. Results were obtained after 12 months of intervention and after 24 months. The focus of this thesis is the effect of lifestyle coaching after 12 months on quantitative outcomes assessing risk of cardiovascular disease. Care coordination, qualitative results and 24 months' results are covered by other theses by Hans Christian Nørgaard Brix, Ane Moltke and Ane Storch Jakobsen.

The thesis is based on three manuscripts I was involved in during my fellowship. Paper I describes the design of the CHANGE trial, initiated by Professor Merete Nordentoft. I participated in the finalization of the protocol, including power decisions on outcomes and power calculation.

Paper II presents the main results from the CHANGE trial. I had the responsibility for recruitment and examination of 278 participants from Copenhagen. When follow-up examinations were terminated after one year, I performed the statistical analyses and drafted the manuscript.

Paper III is a review and a meta-analysis of the effect of lifestyle interventions on weight reduction and other cardiovascular risk factors. I designed the search strategy, performed the statistical analyses and drafted the manuscript.

This thesis is written in three parts: 1) A common introduction to the field; 2) Methods and Results section including a distinct presentation of methods and results from first paper I and II followed by methods and results from paper III; 3) A common discussion and conclusion.

Abbreviations

ANCOVA: Analysis of covariance

BACS: Brief assessment of Cognition in Schizophrenia

BMI: Body mass index

BP: Blood pressure

CI: Confidence interval

CVD: Cardiovascular disease

CRS: Copenhagen Risk Score

FEV1: Forced expiratory volume

GAF: Global assessment of functioning

GP: General practitioner

GRADE: Grading of Recommendations Assessments, Development and Evaluation

HbA1c: Haemoglobin A1c

HDL: High density lipoprotein

hsCRP: High sensitivity C-reactive protein

ICD-10: International classification of disease, 10^{th} revision

IHD: Ischaemic Heart Disease

LDL: Low density lipoprotein

MANSA: Manchester Short Assessment of quality of life

MI: Motivational interviewing

N: Number

RCT: Randomised clinical trial

RR: Risk Ratio

SANS: Scale for assessment of negative symptoms

SAPS: Scale of assessment of positive symptoms

SD: Standard deviation

SMD: Standardised mean difference

SMI: Severe mental illness

TAU: Treatment as usual

TSA: Trial Sequential Analysis

English summary

Schizophrenia is associated with an increased medical burden and shortened life expectancy. The excess mortality seems largely driven by natural causes like cardiovascular disease. Risk factors like obesity, hypertension and glucose intolerance are highly prevalent in schizophrenia. Unhealthy lifestyle and harmful side effects of medication directly contributes to elevated metabolic risk factors. Factors relating to schizophrenia (cognitive, negative and psychotic symptoms) and societal factors (social isolation, homelessness, lack of education, poverty) might play a substantial role as determinants of lifestyle pattern. Another contributor to cardiovascular disease is the lack of medical screening and treatment of somatic morbidity in patients with schizophrenia. The somatic treatment is compromised on all level of preventive care: From primary prevention (lack of screening), secondary prevention (lack of treatment of elevated risk factors) to tertiary prevention (lack of treatment of manifest cardiovascular disease).

The aim of this thesis is to investigate if lifestyle interventions are a feasible and effective method to reduce mortality from cardiovascular disease in patients with schizophrenia.

Paper I describes the rationale and design of the CHANGE trial. We hypothesized that risk of cardiovascular disease could be decreased by improving lifestyle and medical treatment. The primary outcome was risk of cardiovascular disease, estimated with the Copenhagen Risk Score. By designing a three-armed randomized clinical trial, we could compare the effect of care coordination and care coordination plus lifestyle coaching to treatment as usual. The rationale for this was to evaluate if care coordination, being a cheap intervention, would be enough, or if lifestyle coaching, demanding more resources, would add to the potential effect. To increase the relevance of the trial to real world clinical population, we created a pragmatic design with few exclusion criteria and flexible interventions. The target population was patients with schizophrenia spectrum disorders and increased waist circumference, recruited with an active strategy to minimize healthy volunteer bias.

Both interventions lasted for 12 months. The care coordinators were experienced nurses with a caseload of 40 participants. Their duty was to secure guideline concordant monitoring and treatment of somatic disease by facilitating contact to a general practitioner. The lifestyle coaches were health professionals with a case load of 10-12 participants. In addition to care coordination, they offered weekly individual meetings and group sessions focusing on physical activity, healthy dieting and smoking cessation. Each process was individually tailored to the specific wishes and possibilities of

the participant. The theoretical framework was motivational interviewing, an assertive outreach and stages of change.

Paper II presents the main results of the CHANGE trial. We recruited 428 participants. After the interventions were completed, we evaluated the effect on three categories of outcome measures: Metabolic risk factors, lifestyle pattern and indicators of mental health. There was no detectable improvement in metabolic risk factors, including weight, lipids, glucose, waist circumference, blood pressure and the composite measure of cardiovascular risk (Copenhagen Risk Score). Regarding lifestyle, including dietary pattern, physical activity, cardiorespiratory fitness and smoking rates, we could not measure any improvements. Likewise, the mental health, measured as quality of life, positive and negative symptoms, cognition and self-perceived health remained the same between the three groups. Exploratory analyses of the frequency of contacts between coach and participants suggested moderate acceptability of the intervention, as 40% of the participants attended less than half of the intended meetings. Sensitivity analyses including only the 60% attending more than half of the intended sessions did not change the results. Thus, we conclude that patients with schizophrenia were willing to be included in the study, the intervention had a moderate acceptability but lifestyle patterns were not improved sufficiently to affect metabolic health.

In paper III, we integrated the results from the CHANGE trial in a systematic review with a meta-analysis. The aim was to evaluate the effect of lifestyle interventions in patients with severe mental illness. Weight reduction, as continuous outcome and as proportion achieving clinically relevant weight were primary outcomes. We applied a novel statistical approach for sample size calculation in meta-analyses, Trial Sequential Analyses, to allow for differentiation between inconclusive and neutral results, as well as random errors. We demonstrated a small effect of lifestyle interventions on reduction in BMI, 0.60 kg/m^2, which had vanished at long-term follow up. This observed reduction is doubtfully clinical relevant, and statistical significance could have occurred due to overpowering. Adverse events were only reported sporadically. No effect could be found for lipids, blood pressure and glucose regulation. However, we did not have sufficient power to rule out that the neutral findings were type II errors, and thus should be categorized as inconclusive. We explored heterogeneity using a range of predefined potential moderators and mediators. Interestingly, trials with pragmatic design had lower effect, suggesting that lifestyle interventions might be effective in explanatory trial, but less so in a real-world setting.

The experimental work conducted during my fellowship shows that the effect of lifestyle interventions on physical health in populations with severe mental illness is questionable. This is in line with trials in the general population, finding that individually based lifestyle interventions have

limited effect in reducing mortality. Thus, even though the quality of the evidence is heterogeneous, it is unlikely that further research based on an individual approach will substantially change the conclusion.

However, our conclusion should not be interpreted as a recommendation to abandon the issue of premature mortality in the severe mentally ill. Quite the contrary. As the obvious and easy strategy has been proven ineffective, increased effort should be put into alternative strategies. We have two suggestions: 1) Recognition that the capability of the individual to change lifestyle, even in the general population, is limited, a structural approach should be considered, based on principles of nudging (making the healthy choices easy) 2) Based on a comprehensive understanding of determinants of health, up-stream socioeconomic factors like social isolation, employment and stigma should be targeted and evaluated as means of improving unhealthy lifestyle.

We acknowledge that our suggestions are not easy, cheap or fast. However, improving this inequity in health is an obligation for society, even though it demands substantial resources.

Dansk resume

Skizofreni er associeret til somatisk sygdom og forkortet levetid. Den øgede dødelighed skyldes primært naturlige dødsårsager som hjertekarsygdom. Mange mennesker med skizofreni udvikler risikofaktorer som fedme, hypertension og glukose intolerance. En usund livsstil og bivirkninger til den antipsykotiske medicin påvirker de metaboliske risikofaktorer. Faktorer der er direkte relateret til skizofreni (kognitive, negative og psykotiske symptomer) samt samfundsrelaterede faktorer (hjemløshed, manglende uddannelse og fattigdom) kan spille en central rolle som determinanter for livsstil. En anden bidragsyder er somatisk underbehandling. Den somatiske behandling er forringet på alle niveauer af forebyggelse: Primær forebyggelse (manglende screening), sekundær forebyggelse (manglende behandling af risikofaktorer) og tertiær forebyggelse (manglende behandling af manifest sygdom).

Formålet med denne afhandling var at undersøge om livsstilsinterventioner er en gennemførlig og effektiv metode til at reducere dødeligheden af hjertekarsygdom hos patienter med skizofreni.

Artikel I beskriver rationalet og design af CHANGE. Vores hypotese var at risikoen for hjertekarsygdom kunne nedsættes ved at forbedre livsstil og somatisk behandling. Det primære endepunkt var Copenhagen Risk Score, et sammensat mål for risiko for hjertekarsygdom. Ved at designe et tre-armet lodtrækningsforsøg, kunne vi sammenligne effekten af care coordination med care coordination plus livsstil coaching med standardbehandling. Rationalet for dette var at evaluere om den billige care coordinator intervention var nok, eller om den mere omkostningstunge livsstil coaching var signifikant bedre. For at optimere forsøgets relevans i den virkelige verden, valgte vi et pragmatisk design med få ekslusionskriterier og fleksible interventioner. Målgruppen var patienter med skizofreni og et forøget talje omfang, rekrutteret med en aktiv strategi for at undgå selektionsbias.

Begge interventioner varede i 12 måneder. Care coordinatorene var erfarne sygeplejersker med 40 patienter tilknyttet ad gangen. Deres opgave var at sikre at undersøgelse og behandling var i overensstemmelse med gældende kliniske retningslinjer, ved at understøtte kontakten til egen læge. Livsstilscoachene var sundhedsfagligt uddannede med 12-15 patienter tilknyttet ad gangen. I tillæg til care coordination, tilbød de ugentlige møder samt grupper med fokus på fysisk aktivitet, sund kost og rygestop. Interventionen var tilpasset den enkeltes særlige ønsker og muligheder. Den teoretiske ramme var baseret på ”den motiverende samtale”, forandrings-cirkelen og den assertive tilgang.

Artikel II præsenterer hovedresultaterne fra CHANGE. Vi rekrutterede 428 deltagere. Da interventionen var færdig, evaluerede vi effekten på tre kategorier af endemål: Metaboliske risikofaktorer, livsstil og mental sundhed. Der var ingen målbare forbedringer i metaboliske parametre, inklusive vægt, lipider, glukose, talje omfang, blodtryk og Copenhagen Risk Score. Med hensyn til livsstil, kunne i ikke se nogen forbedringer i hverken kost, fysisk aktivitet, cardiorespiratorisk fitness eller rygestop. Tilsvarende vare der ingen forbedringer i den mentale sundhed, målt som livskvalitet, psykotiske og negative symptomer, kognition og selv-vurderet helbred. Eksplorative analyser af kontakten mellem coach og deltager indikerede en moderat accept af interventionen, da kun 60% benyttede halvdelen eller mere af de tilbudte møder med coachen. Sensitivitetsanalyser der kun medtog de 60% viste heller ingen effekt. Vi konkluderede at patienterne var villige til at deltage i forsøget, interventionen var moderat acceptabel, men livsstilsmønsteret blev ikke ændret tilstrækkeligt til at påvirke den metaboliske sundhed.

Artikel II integrerer resultaterne fra CHANGE i et systematisk review med en meta-analyse. Formålet var at evaluere effekten af livsstilsinterventioner på fysisk sundhed hos patienter med alvorlig psykisk sygdom. De primære endepunkter var vægt, klinisk relevant vægtændring både på kort og lang sigt samt potentielle skadelige virkninger. Vi benyttede en ny statistisk model til at beregne sample size,

Trial Sequential analyses, der muliggjorde en differentiering mellem inkonklusive resultater, neutrale resultater samt tilfældige fejl. Vi fandt en lille reduktion i BMI på 0.60 kg/m^2, der forsvandt ved opfølgning. Det er tvivlsomt om denne reduktion er klinisk relevant. Den statistiske signifikans kan være resultatet af "overpowering". Skadelige virkninger var kun sporadisk rapporteret. Der var ingen effekt på lipider, glukose, blodtryk eller talje omfang. Vi havde dog ikke styrke til at afvise at de neutrale fund var type II fejl, og kategoriserede dem derfor som inkonklusive. Vi undersøgte heterogeniteten med en række præ-definerede variabler, og fandt at studier med mere pragmatisk design havde lavere effekt. Dette indikerer at livsstilsinterventioner kan være effektive i eksplanatoriske forsøg, men virkningsløse i den virkelige verden.

Det eksperimentelle arbejde der indgår i denne afhandling, viser samlet set at for populationer med alvorlig psykisk sygdom, er effekten af individuelle livsstilsinterventioner er tvivlsom. Dette er i overensstemmelse med tilsvarende forsøg i baggrundsbefolkningen, der ligeledes finder begrænset effekt af individuelle interventioner. På trods af en betydelig heterogenitet i evidensen, er det derfor usandsynligt at flere studier af individuelle livsstilsinterventioner vil ændre konklusionen.

Vores konklusion skal dog ikke fortolkes som en opfordring til at opgive at forebygge præmatur dødelighed hos patienter med alvorlig psykisk sygdom. Tvært i mod bør vores resultater føre til øget opmærksomhed på alternative strategier, da der de mest oplagte interventioner er fundet uvirksomme.

Vi har to forslag: 1) I erkendelse af at individets evne til at ændre vaner, selv i baggrundsbefolkningen, er begrænsede bør strukturelle interventioner baseret på nudging overvejes. 2) Baseret på en omfattende model for forståelse af determinanter for livsstil og sundhed, bør interventioner der fokuserer på distale determinanter som social isolation, arbejde og stigma evalueres med henblik på effekt på fysisk sundhed.

Vi erkender at ovenstående forslag hverken er nemme, hurtige eller billige. Det er dog en moralsk forpligtelse for samfundet at fortsætte arbejdet med at opnå social lighed i sundhed, også for psykisk syge, selv om det kræver en omfattende indsats.

Part 1: Background

Schizophrenia

"The schizophrenic disorders are characterized in general by fundamental and characteristic distortions of thinking and perception, and affects that are inappropriate or blunted. Clear consciousness and intellectual capacity are usually maintained although certain cognitive deficits may evolve in the course of time".[1] As schizophrenia is a syndrome, the diagnosis is made by comparing the symptoms to a list of criteria, thus resulting in a broad range of clinical pictures. Schizophrenia was first conceptualized in the late nineteenth century by the German psychiatrist Emil Kraepelin, suggesting that severe mental disorders could be dichotomized into manic-depressive illness and dementia praecox. The current prevailing view in genetic research, is that schizophrenia is a polygenic disorder and that gene-environment interactions play an important role.[2] However, as some genetic studies find shared risk genes for schizophrenia and bipolar disorder,[3] the validity of schizophrenia as a diagnostic entity has been questioned and the categorical system of mental illness is now being re-evaluated in favour of a dimensional approach.[4] At the same time, the concept of schizophrenia as a brain disorder is challenged by hypothesis suggesting that schizophrenia is a systemic disorder.[5,6] This concept regards somatic disorders as another manifestation of common underlying pathophysiological mechanisms rather than comorbidities. Increased inflammation[7] and increased oxidative stress[8] have been suggested as shared mechanisms.

A Danish register-based study estimates the incidence rate of schizophrenia for adolescents between 15 and 34 years to be approximately 37 per 100, 000 person-years.[9] While Kraepelin once perceived a chronic course as a pathognomonic feature of schizophrenia, there is now consensus that the course can vary from a single episode to severe impairment.[10] However, schizophrenia will, for the majority, lead to impaired functional outcome, reducing the ability to achieve milestones such as regular employment, marriage and independent living.[11]

Mortality

The association between mental illness and excess mortality has been consistently reported over the last decade. A study published in 1937[12] reported 6 times greater mortality rate for psychiatric inpatients in New York: This was followed by a Scandinavian study, likewise from the pre-neuroleptic era, also reporting elevated mortality rates.[13] Recent research even indicates that the mortality gap might still be widening.[14,15] Excess mortality occurs if a person dies before the average life expectancy for a person of a particular demographic category.[16] Excess mortality for schizophrenia is based on calculations using the general population as a reference group, and can be reported as mortality rate ratios (observed mortality rates divided by mortality rates in the general population) or as years potentially lost to schizophrenia, by comparing life expectancy at a given age to the life expectancy in

the general population. Currently, the mortality rate ratios for patients with schizophrenia is 2 to 3, and life expectancy is shortened by 15-20 years.[16,17] Some studies have estimated that as much as 60% of the excess mortality is due to natural causes, as opposed to accidents and suicide.[18] Natural causes of death are the major driver for the premature mortality,[19] with cardiovascular disease being the single cause accounting for most cases.[20] In Denmark, the mortality from CVD in the general population has decreased, but no equal decrease can be seen in patients with schizophrenia.[21] This could be explained by several factors: Unhealthy lifestyle, insufficient treatment of somatic morbidity, adverse effects of antipsychotics, genetic vulnerability, psychological stress and socioeconomic deprivation, as briefly reviewed below.

Unhealthy lifestyle

Lack of physical activity, smoking and unhealthy dieting are highly prevalent factors in patients with schizophrenia and is likely to contribute to the development of cardiovascular disease. Cigarette smoking approximately triples the risk for cardiac disease; the other risk factors approximately double the risk.[22] The relationship between cigarette smoking and schizophrenia is complex and potentially bidirectional. Smoking prevalence is three-fold increased in schizophrenia compared to the general population,[23] the smoking intensity is higher and the quitting rates very low.[24] The traditional understanding of this pattern has been an hypothesis of self-medication, as smoking can increase the metabolism of antipsychotics[25] and thus alleviate medication adverse effects or improve cognitive deficits. However, a recent meta-analysis found that daily tobacco use was associated with earlier onset of psychosis, suggesting that the causality might be the other way around.[26]

Few studies have reported dietary pattern in schizophrenia. A meta-analysis[27] from 2013 found schizophrenia to be associated to a higher intake of saturated fat and lower intake of fruit and fibre. However, this was not confirmed by a recent study, finding no differences between patients with schizophrenia and controls.[28] In the general population, the current obesity pandemic has been linked to energy dense food and sugary beverages.[29] It could be speculated, that the craving for sugar is even more pronounced in psychotic subjects, due to potential alterations in the reward system[30] or harmful effects of antipsychotics.[31]

Sedentary behaviour is associated with an increased risk of cardiovascular disease in the general population.[32]A recent meta-analysis found the self-reported time being sedentary was 11 hours a day for patients with psychosis, or 12.6 hours when using objective measurements, which was estimated to be 2.8 hours more than healthy controls.[33]

Cardiorespiratory fitness is way to estimate physical performance, as a measure of the ability of the circulatory and respiratory systems to supply oxygen during physical activity (ml/O_2/kg). Cardiorespiratory fitness is independently associated to cardiovascular risk, and an increase of 3.5 ml/o2/kg is associated to a 13% reduced risk of all-cause mortality in the general population. [34] The level of fitness in patients with schizophrenia is consistently reported low, even in first episode patients.[35] Several barriers are described to understand the reasons for physical inactivity, including mental health symptoms, tiredness and insufficient social support.[36]

Insufficient treatment of somatic comorbidity

All Danish citizens have access to cost free health care. Despite this effort to avoid inequality in health care, studies report that patients with schizophrenia receive suboptimal care.[20] All levels of prophylactic care seem to be affected. Primary prophylaxes, the screening for cardiovascular risk factors, does not meet the current guidelines,[16] in spite of both The European Psychiatric Association[37] and the National Institute for Health Care and Excellence (NICE) recommending annual screening for patients with schizophrenia. Secondary prevention, understood as guideline-recommended concurrent treatment once elevated risk factors have been identified, does not seem to happen.[38,39] Finally, patients with schizophrenia are less likely to receive treatment of manifest cardiovascular disease,[40] meaning that even the tertiary prophylaxis is compromised. Furthermore, there might even be safety issues, as mentally ill individuals have a higher risk of hazards and harms, such as prescribing errors during non-psychiatric hospitalisations.[41]

Several mechanisms have been suggested to explain the under-treatment. These can be divided in factors relating to the patient (patient`s delay), to the health professionals (doctors` delay) and to the system.[42] Factors relating to the patients include a different pattern of help seeking compared to the general population. This pattern can be affected by negative symptoms (lack of motivation, self-neglect), cognitive symptoms (disability to communicate needs), positive symptoms (suspiciousness, fearfulness) or pain insensitivity.[43] Issues relating to health professionals can be driven both by the physician and by the psychiatrist. Stigma is important: The physician may experience fear or insecurity about the communication with psychotic patients.[44] On the other hand, the psychiatrist could lack relevant knowledge and experience to suspect and diagnose medical conditions.[45] On system level, separation of mental and medical health care systems, both geographically and culturally, as well as lack of clarity about treatment responsibilities are important issues.[42]

Adverse effects of antipsychotics

Even though observations of premature mortality predate the introduction of psychotropic drugs, antipsychotics have been blamed for the majority of weight gain. This attitude has been challenged though, by recent large-scale studies finding a protective effect of moderate doses of antipsychotic on cardiovascular mortality.[46,47] The curve illustrating the association between antipsychotic dose and mortality is U-shaped, with patients receiving either no medication or high doses showing the highest mortality. However, as studies elucidating these issues are observational of nature, causality remains unknown, and it could be speculated that proper treatment of positive symptoms improves the pattern of lifestyle and somatic care. It is evident, beyond discussion, that antipsychotics cause weight gain. Even though some of the drugs are worse than others,[48,49] none are completely weight neutral.[50] The mechanism underlying weight gain is not fully understood and involves both peripheral and central mechanisms. Of suggested peripheral mechanism, histamine H_1 receptor[51] and serotonin$_{2A}$ receptor[52] blockade might induce appetite, while interference with the dopaminergic system might affect the reward system leading to abnormal craving and overeating.[53]

Genetic vulnerability

Increasing evidence suggests that schizophrenia is a multisystem disease, indicating that cardiovascular disease is not a comorbidity, but rather another manifestation of the common underlying disease process. Several studies have supported this theory using different methodology: The association existed already in the pre-neuroleptic era,[54] cardiovascular risk factors are elevated in antipsychotic-naive people with schizophrenia [55,56] and in first degree relatives[57] register based studies find an association,[58] and genetic linkage studies find shared genes.[59]

Psychological stress

Psychological stress is involved in both schizophrenia and cardiovascular disease. The association between stress and schizophrenia has been observed on several levels: Prenatal stress increase the risk of psychosis[60] and psychotic symptoms increase with stress.[61] It has even been suggested that exposure to stress induces psychological and physiological changes that lead to altered cognition in schizophrenia.[62] Psychological stress leads to biological alterations. Oxidative stress and altered immunological responses have been proposed as markers of psychological stress, linking metabolic disease and psychosis.[63] In the general population, psychological stress has been found to be an important predictor of cardiovascular disease.[64] The potential pathways are not fully understood, but among suggested mechanisms are enhanced platelet reactivity, lower heart rate variability, increased

inflammation, and endothelial dysfunction. All of these are affected by schizophrenia,[65–67] enhancing the potential understanding of stress as a common pathway between psychosis and cardiovascular disease.

Socioeconomic determinants

The 2016 European Society of Cardiology guidelines (SCORE) state that "*low socio-economic status, defined as low educational level, low income, holding a low-status job or living in a poor residential area, confer an increased risk of CAD; the relative risk (RR) of CAD mortality risk is 1.3–2.0*"[68] and the risk is further increased by isolation and lack of social connectedness.[69] Indeed, a meta-analysis from 2010 found an substantial increased likelihood of survival for participants with stronger social relationships, and the risk associated with loneliness exceeded the risk of hypertension or obesity.[70] Two general explanations have been proposed: The buffering hypothesis and the main effects model. The buffering model suggests that resources achieved through relationships have protective effects against stressors. The main effect suggest that ability of self-care in the form of health behaviour improves.[70] As schizophrenia has a major impact of social and economic functioning,[71–73] it is reasonable to assume that these factors play a crucial role in the development of cardiovascular disease.

The contributors mentioned above may act in a complex interaction which it is currently not fully understood. Some factors obviously mediate or moderate each other, while others might be additive or even synergistically. A model could be constructed of proximal determinants (causes), medial determinants (causes of the causes) and distal determinants (causes of the causes of the causes) (Figure 1). The distal determinants are also termed up-streams factors. For schizophrenia, the causes of the causes could be lack of education and employment, low income, lack of proper housing and lack of social support. Going upstream, the lack of education might be caused by the first psychotic episode typically occurring in the late adolescence or the society`s increased demands concerning education. Equally, work possibilities could be affected both by symptoms like cognitive deficits and by the lack of flexibility in the job market. Lack of social support and friendship could be caused by stigma of mental disease and social anxiety. A major upstream factor for all citizens is the multinational companies promoting unhealthy lifestyle choices. The corporations have commercial interests in making unhealthy choices, like sugary beverage, easy and attractive. As they have substantial economic resources to develop their sales strategies, they have a tremendous power to influence lifestyle choices by their strategic campaigns. It could even be speculated that vulnerable subgroups such as the mentally ill, are easy victims.

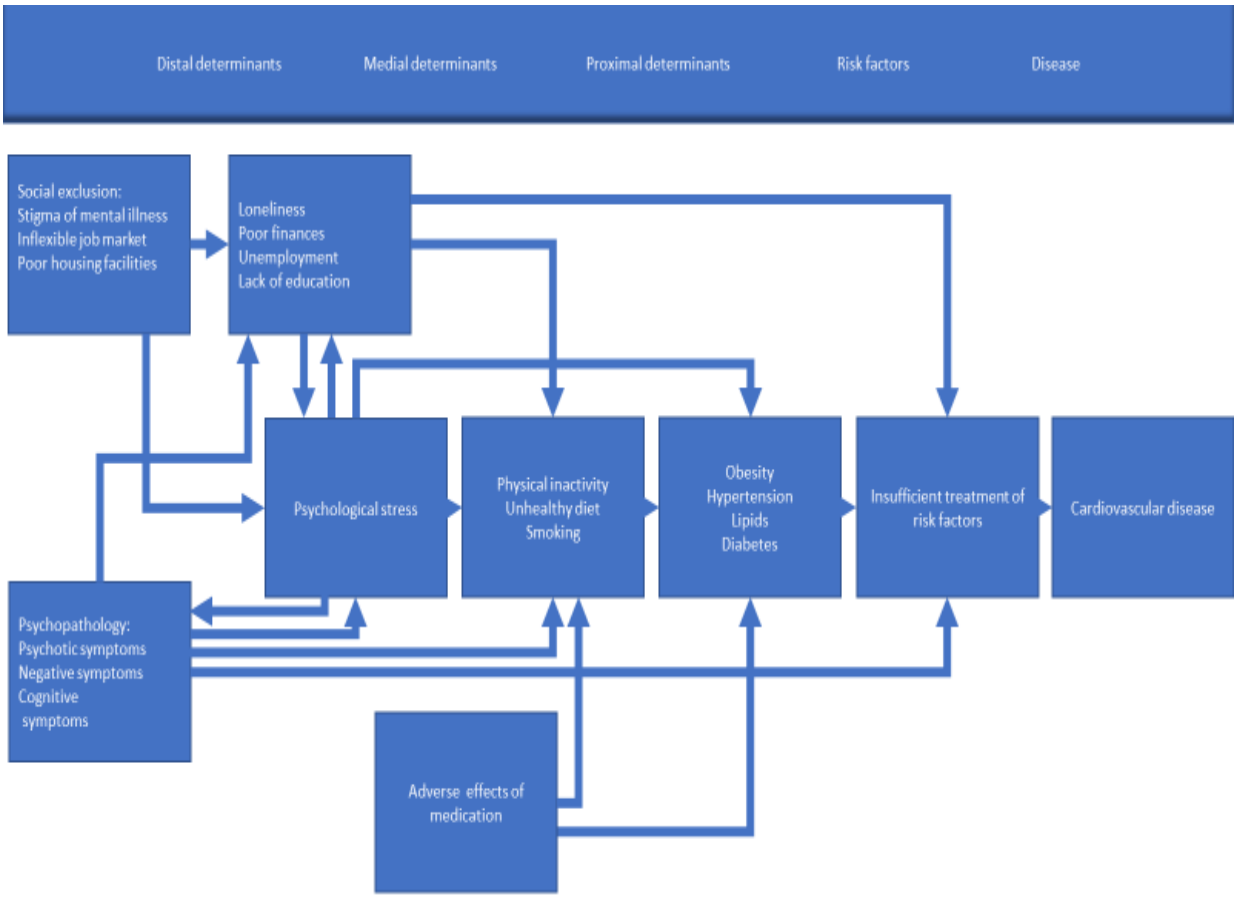

Figure 1: Suggested interaction between determinants of cardiovascular disease in schizophrenia

Interventions to reduce cardiovascular disease in schizophrenia

Preventive interventions can be classified according to stage into primary, secondary and tertiary or according to strategy into individual, environmental or political interventions. In the case of cardiovascular disease in schizophrenia, several mechanisms can be targeted, in accordance with the factors described above, using one or more strategies and stages. Recent recommendations for the general population emphasises the importance of a structural approach. Proposed tools include nudging,[74] a soft paternalistic way of structuring the environment in order to make the healthy choices the "default" and the unhealthy choices difficult. However, addressing what Rose called upstream-factors, such as poverty and low education, receives little attention when developing interventions to reduce excess mortality in schizophrenia. Three major focus areas for preventing cardiovascular disease: 1) individual lifestyle modification, 2) improved medical treatment, and 3) switching antipsychotic medication.

Lifestyle

Looking back in history to the days of psychiatric asylums, inhumanity characterised life of the insane, with a complete lack of autonomy and contact to community. However, there were some good intentions that might inspire modern psychiatry. In some psychiatric asylums, "moral management" with focus on diet, exercise and gainful occupation was an integrated part of the treatment. The Irish psychiatrist Dr. Hallaran, born in 1765, mentioned the problem of premature mortality among the insane, and suggested "removing the convalescent, and incurable insane, to convenient distances from large cities and towns, to well enclosed farms, properly adapted to the purposes of employing them with effect, in the different branches of husbandry and horticulture".[75] With the introduction of neuroleptic treatment, the integrated approach was abandoned in favour of a biological model. However, focus on healthy lifestyle has regained attention as a research area during the last few years.

Lifestyle interventions are a branch of the concept of health promotion. There are several attempts to define health and health promotion. In the Ottawa Charter for Health promotion (WHO 1986), health promotion is defined as "…the process of enabling people to take exert control over the determinants of health and thereby improve their health". Individual lifestyle interventions are any interventions designed to affect the action taken by the individual regarding health. This could be nutrition, smoking or physical activity.

Smokers with schizophrenia are just as likely to want to quit as smokers in the general population but the cessation rate is less than half of smokers without schizophrenia.[76] Explanations for this might obviously be factors related to schizophrenia (negative symptoms, heavy addiction pattern). An alternative explanation could be an attitude that smoking cessation might harm patients with severe mental illness.[77] The harm could be directly by increasing depressive symptoms or anxiety, or indirectly if smoking cessation medication is used. However, the largest RCT to date, investigating safety and efficacy of varenicline, bupropion and nicotine patch has just been published.[78] They did not find that varenicline or bupropion increased the risk of neuropsychiatric adverse effects compared to placebo. The positive findings are further confirmed in a recent meta-analysis[79] of varenicline to smokers with severe mental illness, finding a fourfold increased chance of smoking abstinence compared to placebo. However, advice or psychosocial interventions have not been found effective in promoting smoking cessation.[80]

Most the published lifestyle studies in severe mental illness aiming to improve physical health, reported body weight as the primary outcome. Details on published studies are provided in table 1 as a part of paper III.

The results from clinical trials evaluating the effect of lifestyle interventions have been consecutively summarized in reviews and meta-analyses, generally reporting pooled effect for weight, lipids, glucose and hypertension. Caemmerer et al.[81] included 17 trials of patients taking antipsychotics, and reported mean reduction in weight of −3.12 kg (95% CI −4.03 to −2.21; P<0.0001), with significant reductions in glucose, lipids and waist circumference. Bruins et al,[82] confirmed the positive findings, now including 25 trials. Gierisch et al.[83] including 11 trials with patients with serious mental illness only found significant effect on weigh, but insufficient evidence on other metabolic risk factors.

Five lifestyle interventions of reasonable size have been reported since 2013.[84–88] The methodology and primary results will be described here:

The ACHIEVE study

Results from the ACHIEVE behavioural intervention have been reported in a quantitative study[84] and a qualitative study.[89] 291 patients with serious mental illness were recruited from an outpatient rehabilitation setting. The program consisted of 6 months of intensive interventions, followed by 12 months maintenance phase. There were three contact types: Group weight-management sessions (once a week), individual weight-management sessions (once a month), and group exercise sessions (three times a week). Healthy breakfast and lunch were included. After 18 months a significantly larger proportion had achieved a clinically significant weight loss of 5% or more (37.8 vs 22.7, p=0.009). Semi structured interviews with 20 participants reported that increased self-efficacy and improved ability to perform activities of daily living were commonly cited.[89]

The STRIDE study

200 patients taking antipsychotics were recruited from an outpatient clinic. The intervention consisted of 6 months of weekly group meetings including 20-30 minutes of exercise and nutritional counselling, followed by 6 months of monthly maintenance meetings, also with exercise. After 12 months, there was a weight loss of 2.6 kg,[85] but the effect had vanished at follow-up after 24 months.[90]

The InShape studies

The In Shape intervention was investigated in two clinical trials. The intervention consisted of a free fitness club membership and a health mentor. The mentor met with participants once a week for 45–60 minutes at a local fitness club. Apart from fitness coaching, nutrition counselling was offered consisting of discussions with the mentor, individual meetings with a dietitian, group cooking classes or grocery store tours. The first trial from 2013[91] recruited 133 patients with serious mental illness and BMI>25. They did not find any effect on weight loss, but a small improvement in

cardiorespiratory fitness. The second trial from 2015[92] aimed to replicate the finding in a real life setting with an ethnically diverse population. 210 patients were recruited. After 12 months, 51% had either lost >5% of baseline weight or improved cardiorespiratory fitness, compared to 38% in the control group.

The Capicor study

332 participants with severe mental illness were recruited from outpatient clinics.[87] The 3 month`s intervention consisted of 24 sessions with physical activity and 16 sessions on dietary education. Preliminary results after 3 months found a significant increase in BMI in the interventions group compared to controls.

The Life Goal Collaborative Care study

287 patients with chronic mental disorders (schizophrenia, bipolar, major depressive disorder) were recruited from a Veterans Affairs outpatient clinic.[88] The intervention consisted of five group sessions during 1-2 months with education on cardiovascular risk factors and setting up of personal goals. A care management had subsequent contacts up to 6 months after the group sessions ended. No clinically relevant changes were found on cardiovascular risk factors after 12 months

Care coordination

The European Psychiatric Association[37] and the National Institute for Health and Care Excellence (NICE) guidelines[93] recommend annual screening of cardiovascular risk factors in patients with schizophrenia, followed by guideline concordant treatment, but this does not appear to happen.[94] In order to fill this treatment gap, several approaches have been suggested: An expanded role for the psychiatrist, an integrative care model with a general practitioner allocated to supported housings or care coordination providing contact to primary care. Care coordination is not a well-defined concept and only a few trials have tested the effectiveness. Osborne et al. developed an intervention aiming to increase rates of screening, and found that screening increased with approximately 30%. For others, care coordination have been integrated in a behavioural interventions, McKibbin et al.[95] targeted patients with schizophrenia and diabetes, and provided education on diabetes and tools to keep track of laboratory values. *The Life Goal Collaborative Care* were evaluated in three trials.[88,96,97] The intervention combined behavioural counselling with care coordination. The care manager used registries to track cardiovascular risk factors and contacted primary care provider when action was needed. In the largest study,[88] where patients with schizophrenia were included, no effect were found on cardiovascular risk factors.

Aims of the thesis

The primary aim of this thesis was to evaluate the effect of lifestyle interventions to reduce the risk of cardiovascular disease in patients with schizophrenia. This was done in two steps; by designing and executing a clinical trial and by integrating these results in the current literature by conducting a meta-analysis.

Part 2: Methods and results

Paper I and II: The CHANGE trial

When the CHANGE trial was initiated, no large-scale trials had been published of lifestyle trials in patients with schizophrenia. From a review of counselling and education aimed at behaviour change, we knew that mortality in the general population was not reduced, but it could be effective in certain high-risk populations.[98] We hypothesised that patients with schizophrenia were such a population. The concept was developed by the primary investigators Professor Merete Nordentoft in cooperation with an interdisciplinary working group. The CHANGE study aimed to answer some research questions rising from the gaps in the knowledge on that time about lifestyle, cardiovascular disease and schizophrenia:

1. Can we create sustainable lifestyle changes?
2. Can create lifestyle changes in a real-world setting?
3. Is a complex intervention feasible?
4. Is somatic treatment enough or will lifestyle coaching add to the effect?

CHANGE was registered on Clinical.Trials.gov (NCT 01585493) the 27th of March 2012.

Ethical approval: Approval from the Danish Ethical Committee: H-4-2012-051

Approval from the Danish Data Protection Agency referral number: 01689 RHP-2012-007

Methods

The objective of the CHANGE trial was to evaluate the effectiveness of 1) affiliation to the CHANGE team, offering a tailored, manual-based intervention targeting physical inactivity, unhealthy dietary habits, smoking cessation, and facilitating contact to their general practitioner to secure medical treatment of somatic comorbidity; versus 2) affiliation to a care coordinator securing guideline-concordant monitoring and treatment of somatic comorbidity by facilitating contact to their general practitioner, versus 3) treatment as usual (TAU).

Hypotheses of the study

The trial was based on the following hypotheses that were tested:

1. CHANGE is more effective than care coordination and TAU in reducing risk of cardiovascular disease

2. CHANGE is more effective than care coordination and TAU in reducing unhealthy lifestyle (improving diet, increase physical activity, decrease smoking)
3. Care coordination is more effective than TAU in reducing risk of cardiovascular disease

Participants

Patients were recruited from well-defined catchment areas in two major Danish cities (Aarhus and Copenhagen). Information about the trial was provided in meetings arranged by the research staff in relevant in- and outpatient`s clinics, in supported housing and community centres, where patients as well as care takers were invited. Referrals came from usual caretakers or directly from interested patients. Eligible participants were invited to a meeting at the research centre, the outpatient clinic, or at the patient's home according to their own wish. Verbal and written information was provided. If the patient accepted participation in the trial, an informed consent was signed and an appointment for collection of baseline data was made. Data collection started in December 2012 and the 12 months follow up was completed in May 2015.

Inclusion criteria:

1. >17 years
2. Fulfilling the ICD-10 diagnostic criteria for schizophrenia, persistent delusional disorders, or schizoaffective disorders using the Schedule for Clinical Assessment in Neuropsychiatry (SCAN);
3. Waist circumference ≥ 88 cm for females and > 102 cm for males
4. Written informed consent.

Exclusion criteria:

1. Current self-reported pregnancy
2. Inability to consent.

Participants were randomized with a 1:1:1 ratio to either the CHANGE intervention, care coordination versus treatment as usual by Copenhagen Trial Unit. All investigators were blinded, including

outcome assessors and statisticians. Analyses and drafting of the manuscript were conducted blinded to participant allocation.

Outcome assessments

Primary outcome

The primary outcome was the 10 years risk of ischemic heart disease at 12 months, assessed by the Copenhagen risk score.[99]A risk assessment computer program (PRECARD®) combines the Copenhagen risk score with data from randomised clinical trials. This composite measure includes: Sex, family history of CVD (defined as parents suffering fatal or non-fatal cardiovascular event before the age of 55 (father) or 60 (mother); prior heart disease (defined as myocardial infarction or verified atherosclerosis of coronary arteries); +/- smoking; +/- diabetes mellitus (HbA1c-based or receiving anti glycaemic drugs); total cholesterol, high density lipoprotein cholesterol; systolic blood pressure; and body mass index. Risk was defined as the probability of a clinical event (ischemic heart disease, myocardial infarction, stroke, death) happening to a person within 10 years. Ischemic heart disease was defined as hospitalization for myocardial infarction or angina pectoris. Age was simulated to be 60 years. [100]

Secondary outcomes

Cardiorespiratory fitness was originally defined as an exploratory outcome, due to insecurity of the acceptability and feasibility of the test procedure among the recruited participants. After completed data collection at baseline, we found an acceptable level of satisfying tests, and redefined fitness to key secondary outcome.

Other secondary outcomes included waist circumference, blood pressure, resting heart rate, HDL, non-HDL-cholesterol, high sensitivity CRP and HbA1c.

Exploratory outcomes

Anthropometric measures: Weight in kg and body mass index (weight/height^2), Forced expiratory volume (FEV1).

Psychometric measures: Positive and negative symptoms (SANS and SAPS)[101], cognition (BACS) [102], quality of life (MANSA and eq-5d),[103] Global Assessment of Functioning (GAF) [104], perceived health, [105] and perceived stress. [106]

Biomedical status measures: Triglycerides, high sensitive CRP (hsCRP), low-density lipoprotein cholesterol (LDL).

Life styles measures: Food Frequency Questionnaire,[107] 24 hour recall, Physical Activity Scale[108] (PAS2), self-reported point abstinence from smoking (Nicotine Dependence Questionnaire[109]);

Interventions

Overview of the interventions

1. The CHANGE intervention

   Affiliation to the CHANGE team, offering a tailored, manual-based intervention targeting one or more of these four tracks: physical inactivity, unhealthy dietary habits, smoking cessation, and care coordination (see below)

2. The care coordination group

   Affiliation to a care coordinator who will secure guideline-concordant monitoring and treatment of somatic comorbidity by facilitating contact to their general practitioner,

3. Treatment as usual

   In Denmark, all persons have a personal general practitioner and can consult her/him for free when needed. Patients stayed affiliated with their local outpatient clinics in secondary mental health services and they had access to their own general practitioner, which should include the mandatory yearly screening of metabolic risk factors.

Theoretical framework for the CHANGE intervention

Motivational interviewing

Low adherence with prescribed regimens is more the rule than an exception. According to the World Health Organization less than 60% of patients fully comply with their medication for diabetes, less than 40% fully comply with medications for hypertension, and not even 30% fully comply with the behavioural regimens. [110] To understand this apparent paradox, a model of barriers has been proposed. Barriers could be lack of knowledge, emotional distress or high costs. These models assume an underlying urge to choose the healthy life, anticipating that individuals would adhere to health recommendations if the barriers were properly addressed. However, being motivated to change is a complex process. Motivational interviewing (MI) offers a framework to understand motivation and strengthening a person's own motivation to change.

MI was introduced in 1983 by Miller and Rollnick, who based the theory on their own experience with problem drinkers and was further evolved over the last three decades into the concept known as MI today.[111] MI is goal-oriented and client centred. A specific goal characterised as a behaviour change is the core, and the motivation for choosing this specific goal must originate from the client and not from the interviewer.

According to the theory behind MI, motivation is determined by at least two components; first, the change in behaviour must be important to the client, and second, the client has to feel confident that the change is possible. If the change does not carry the necessary importance for the patient, confidence alone is not enough. On the other hand, importance alone is never sufficient, if the patient, based on earlier experience or global lack of own abilities, has lost the faith.[112] Even though both determinants are fulfilled, motivation cannot be dichotomized into either motivated or non-motivated. As described below, motivation can be understood as a dynamic process, where ambivalence determines the degree of motivation.

Ambivalence is inherent in all efforts to change behaviour. There will be pros and cons, and the balance between these will predict the probability for change. Verbalising the pros and cons is the heart of MI. A core assumption is that health professionals can influence the balance between pros and cons, and that this balance turns into subsequent change.[113]

Stages of change

The trans-theoretical model has been used as an integrated part of MI.[114] This model proposes a circular series of stages of change, explaining the hypothesised process individuals go through when

changing behaviour. "Pre-contemplation" is the first step, where the considerations about a change has not yet evolved. The next step is "contemplation" where ambivalence is exaggerated, and pros and cons balance. If the scale tips in the direction of pros, individuals move to stage of "preparation", resulting in "action" and "maintenance". However, maintenance will often be followed by relapse and the circle starts over again.

MI exploits the interviewing skills to facilitate a person's movement through these stages of change. This is done by determining whether the change is important to the individual by listening to pros and cons, and by reinforcing the confidence that change is possible. Thus, empathic listening can evoke and strengthen the commitment to change.[115]

Stages of change were incorporated in the CHANGE intervention. A first step was to clarify possibilities for changes that seem achievable and realistic according to the stages of change, supporting the patient in setting up goals in accordance with the patient's values and life conditions.

Assertive community treatment

Drop-out rate in lifestyle interventions is high, and probably even higher when including patients with schizophrenia. To minimize this, we adopted the tools from the "assertive community model" (ACT). Originally developed to counteract the effect of de-institutionalization, ACT has been found effective in treating patients that are difficult to reach. In this case, adopting the outreaching principles of ACT, allowed us to be persistent, yet respectfully active and flexible in time and place.[116] Thus, apart from weekly meetings with the patients, further support was offered by phone calls, e-mails, and text messages.

Training and supervision

Lifestyle coaches were health professionals (occupational therapists, physiotherapists or dieticians) with clinical experience in psychiatry. They received a 5-day course in motivational interviewing, a 5-day course in smoking cessation, a 1-day course in examination and treatment of lifestyle disorders, and a 2-day course in healthy dieting, all based on the Danish Health Authority guidelines. During the trial, lifestyle coaches had weekly sessions with supervision to ensure program fidelity. Coaches had a case load of 12-15. The care coordinators were certified nurses with clinical experience in psychiatry. They had a caseload of 40 participants. Both coaches and care coordinators were full time project employed during the study.

The four tracks

There are multiple risk factors underlying development of cardiovascular disease. The individuals in our target population have different risk profiles and different motivations and unmet needs. Therefore, to be able to improve health conditions for a broad sample, the intervention had to be multifactorial, with the possibility to tailor the treatment to the individual needs. One or more of the following four tracks, diet, physical activity, smoking cessation and care coordination could be chosen as focus areas by the patient. A manual was provided for each track and are available as supplementary material from paper I.

1. *Diet*

Dietary changes require specific examination of the patient's dietary habits, food purchases and cooking practices. A dietitian offered individual and group counselling, aimed at identifying attractive and realistic alternatives. Individual foci could be on consuming artificially sweetened beverages instead of sugary soda or choosing wholegrain products instead of white bread. The groups had weekly meetings. Before each meeting, the participants chose a favourite dish that was converted to a healthy meal by the dietician. The group then shopped, cooked and ate together.

2. *Physical activity*

During home visits, the coach took part in the activities if requested by the patient, to support lifestyle changes. Personal and professional networks and patient network could be part of individual plans. Parallel to the cooking groups, there were physical activity groups playing games or running together.

3. *Smoking cessation*

The smoking cessation program was adopted from the program published by The National Cancer Organization[117,118] and tailored to the patient population to enhance motivation and maintain smoking cessation. Support was provided for motivation, including prevention of relapses by weekly meetings, phone calls and text messages. Apart from the groups, the first line treatment was nicotine substitution followed by bupropion if requested.

4. *Care coordination*

The care coordinators were experienced nurses, with a caseload of 40 participants at a time. They were provided with a manual including a decision tree and criteria for when the regular general practitioner should be contacted. The aim of this function was to support the patient in timely reaction to symptoms as well as to assist the health care system in guideline concurrent monitoring and treatment. The frequency of contact was flexible and based on agreements between care coordinator and patient, allowing high intensity in periods of serious physical illness.

Statistical methods

A detailed plan of the statistical analyses is provided in appendix I.

Power calculation

We expected that the active interventions reduced the cardiovascular risk score by 2.5% compared with the cardiovascular risk score in patients allocated to treatment as usual. We planned to compare all three groups and accordingly reduce our alpha level to 0.05/3 = 0.0166. Allowing a power of 80% we needed to recruit 150 patients to each arm for a total of 450 participants. This calculation was based on an SD of 5.9 as found in the Inter99-investigation.[100]

Analysis of the outcomes

The primary outcome analysis was an intention-to-treat (ITT) analysis. For continuous outcomes, analysis of covariance (ancova) was calculated for end scores from the three groups, using the three stratification variables to preserve power. For dichotomous outcomes, logistic regression was applied, with two dummy variables with the control group as reference and stratification variables as covariates. Multiplicity was handled as described in the detailed analysis plan. Missing data was handled with multiple imputation.

Post-hoc exploratory analysis

Based on registrations from the CHANGE coaches, descriptive analyses were performed on frequencies and types of contacts. Univariate and multivariate regressions were performed to explore contact pattern in subgroups and to evaluate contributions of contacts (number and type) on outcome. These analyses were considered hypothesis-generating.

Results

Baseline data

Baseline data for participants in the three experimental groups can be seen in paper II. This is a more detailed description of the complete sample to provide details enabling the generalizability to a clinical population.

Patients were recruited from Copenhagen or Aarhus over 18 months. 513 patients were screened for eligibility and 428 were included and randomized to the CHANGE intervention (N=138), or care coordination plus treatment as usual (N=142), or treatment as usual alone (N=148). Retention proportion was 86.0% with no difference in the dropout rates among the three groups (p=0.68). Dropouts did not differ from completers regarding baseline characteristics.

Sociodemographic variables

The mean age of the sample was 38 years, ranging from 18 to 68 years old. There were more females (n=236) than males (n=192). More than a third had not finished other education than primary school, only 2% of the females and 4% of the males had a regular employment and the majority was early retired. About 80% lived independently, but only 19% were in a relationship, and 30% reported that they did not have at least one close friend.

	Females n=236	Males N=192
Age (years)	37.6 (13.3)	39.7 (11.0)
Only finished primary school	40%	36%
Employment	2%	4%
Under education	11%	8%
Living independently	83%	75%
Living in a relationship	9%	18%
Early retirement	55%	70%
Having a close friend	74%	63%

Table 1: Socioeconomic characteristics

Metabolic variables

Three quarters of the participants had a BMI exceeding 30, which is the cut off for obesity. More than half had lipids above the recommendations, and 13% had diabetes, while another 10% had prediabetes (defined as hbA1c>42<48).

Body composition		Females n=236	Males N=192
	BMI kg/m^2 (mean (SD))	37.9 (10.3)	38.5 (7.8)
	% with BMI>30 kg/m^2	72%	79%
	Waist circumference, cm, (mean (SD))	109.6 (13.9)	120.4 (17.1)
Lipid metabolism			
	Non-HDL-C mg/dl (mean (SD))	140.4 (41.8)	152.7 (42.5)
	% with >130 mg/dL	55%	56%
Carbohydrate metabolism			
	HbA1c mmol/mol mean (SD)	5.6 (1.9)	5.7 (1.7)
	Prediabetes	9%	10%
	Diabetes	13.5%	13.6%
Hypertension			
	Systolic BP mm/Hg mean (SD)	124 (13.3)	131.8 (14)
	%>140 mmHg	8.9%	24.0%
	Diastolic BP mm/Hg mean (SD)	80.7 (9.6)	82.8 (10.0)
	%>90 mmHg	16.9%	20.3%

Table 2: Metabolic characteristics

Lifestyle variables

The dietary pattern, based on 24 hours recall, showed that females consumed 1738 kcal/day and males consumed 2240 kcal/day, and the distribution of energy from fat, carbohydrates and protein were within the recommendations for both genders. About half of the sample was daily smokers, consuming a mean of 23 cigarettes daily. There was reported a mean of 2.2 hours of moderate/vigorous activity per week. However, cardiorespiratory fitness was as low as 16.5 for females and 18.3 for males. These values correspond to "very low" for individuals above 60 years.

		Females n=236	Males N=192
Diet			
	Energy/day kcal	1738 (710)	2240 (924)
	Fat E%	34%	34%
	Carbs E%	49%	49%
	Protein E%	16%	16%
	Alcohol	1%	1%
Smoking	Daily smokers	47.6%	58.9%
	Numbers of cigarettes	22	24
	Former smokers	20%	22%
Physical activity			
	Moderate/vigorous hrs/week	2.2 (4.3)	2.2 (4)
	Sedentary hrs/day	9.6 (3.7)	10.7 (3.5)
	Fitness (mlO_2/min/kg)	16.5 (5.5)	18.3 (5.4)

Table 3: Lifestyle pattern

Medication

About 5% did not receive antipsychotic medication, and 60% received one type. The last third received antipsychotic polypharmacy. Close to half were treated with antidepressants and 25 % received benzodiazepines.

		Females n=236	Males N=192
Antipsychotics			
	One	65.3%	58.3%
	Two	29.2%	34.6%
	Three	1.3%	1.6%
	None	4.2%	5.2%
Antidepressants			
		49.2%	38%
Benzodiazepines			
		25.8%	24%
Mood stabilisers			
		13.6%	6.8%

Table 4: Medication pattern

Psychometric variables

According to GAF scores, the majority were between 41 and 60, corresponding to *"moderate to serious impairment in social, occupational, or school functioning (e.g., no friends, unable to keep a job)"* and 18% were below 41, corresponding to at least *"major impairment in several areas, such as work or school, family relations, judgment, thinking, or mood (e.g., depressed man avoids friends, neglects family, and is unable to work; child frequently beats up younger children, is defiant at home, and is failing at school)."*

For positive and negative symptoms, about half exceeded the cut-off value of two on the global scores. 20% were in remission, defined as both negative and positive symptom scores were at 2 or below.

		Females n=236	Males N=192
GAF score			
	>60	12.3%	7.3%

	41-60	55.5%	59.4%
	<41	17.4%	18.2%
Psychotic symptoms		3.4 (1.6)	3.0 (1.6)
	>2	53%	42.2%
Negative symptoms		3.4 (1.1)	3.7 (1.7)
	>2	58.1%	67.2%
Remission			
		19.1%	20.8%

Table 5: Psychometric characteristics

Main outcomes

Primary and secondary outcomes

After the 12 month interventions were completed, the 10 year risk of cardiovascular disease was 8.4% (SD 6.7) in the CHANGE group, 8.5% (SD 7.5) in the care coordination group, and 8.0% (SD 6.5) in the treatment as usual group ($F_{2,}428=1.4$, p=0.41) based on intention-to-treat analysis, using multiple imputation to handle missing data. The sensitivity analyses of the primary outcome using complete cases, or removing outliers, did not change the results. Two per-protocol analyses were performed, one including CHANGE participants who had more than half of the intended 42 sessions and one excluding CHANGE participants with no contact to their coach. Neither of these changed the results. There were no differences between the three groups for any of the secondary outcomes. The means for cardiorespiratory fitness, our key secondary outcome, were 18.1 (SD 5.5) ml O_2/min/kg in the CHANGE group, 18.0 (SD 6.8) ml O_2/min/Kg in the care coordination group, and 18.2 (SD 6.7) ml O_2/min/Kg in the treatment as usual group. There was no effect on any of the exploratory outcomes. Five patients died during the trial. The distribution can be seen in the flow diagram (Figure 1). The causes of death were cancer (N=2), suicide (N=1), and unexplained (N=2). Psychiatric hospitalizations amounted to 18.8% in the CHANGE group, 33.8% in the care coordination group and 24.3% in the treatment as usual group; the difference between the care coordination and the CHANGE group was statistically significant (p=0.004). Somatic hospitalizations amounted to 12.3% in the CHANGE group, 17.6% in the care coordination group and 16.2% in the control group (p=0.40).

Post-hoc exploratory analysis of intervention

Post hoc, we performed some exploratory analyses to understand how the intervention had been delivered and exploited. Based on feedback from coaches and participants, we hypothesized that age, GAF, cognition, level of positive and negative symptoms predicted how many meetings they had with the coach. Based on the literature on social equity in health, we hypothesized that gender, years of education, having at least one friend and living in a relationship predicted how many meetings they had with the coach.

The participants in the CHANGE intervention group had a mean of 24 personal meetings with their coach. Of these, diet was the topic of 16 session, physical activity of 19 and care coordination of 6 (table 6). One session could have more than one focus. 10% had less than 5 meetings with their coach. Exercising took place a mean of 11 times during the 12 months. There were no differences between males and females. Of the above-mentioned predictors, higher age and more severe cognitive deficits correlated with more personal meetings with coach. When both were added in the same model, only age remained significant. Patients over the age of 40 years had a mean of 29 meetings, while the young group under the age of 40 years had a mean of 21 meetings. The topics on the excess meetings in the older group were equally distributed on diet, physical activity and care coordination, but not on smoking.

		Personal meetings	MI focusing on diet	MI focus on exercise	Focus on care coordination	Exercising
Females	N=78					
	Mean	24.5	15.1	19.0	6.0	10.7
	Std. Deviation	16.2	11.4	13.8	6.2	10.6
Males	N=60					
	Mean	24.8	16.8	20.2	6.7	9.2
	Std. Deviation	12.1	11.0	12.3	7.0	10.0

Table 6: Distributions of topics for sessions with coach

For the smokers (table 7), 11 meetings focused on smoking cessation, while the pattern regarding diet, exercise and care coordination was largely similar to the non-smokers. About half of the smokers reported that they were motivated to quit ("much" or "very much") (52%), but they had no more sessions on smoking cessation than those not being ready to quit. (13vs. 10). Neither gender nor age predicted motivation to quit.

	Personal meetings	Smoking cessation	Diet	MI focus on exercise	Focus on care coordination	Exercising
N =73						
Mean	23.8	11.2	13.8	17.5	5.3	9.1
Std. Deviation	15.4	9.3	10.6	12.8	5.7	10.6

Table 7: Distributions of topics for smokers

42.8% of the sample answered that they found it very important to eat healthier. However, they did not have more contacts focusing on diet than the rest of the group. When looking for predictors in change in either 10 year risk of CVD or BMI, none of the variables describing the CHANGE intervention (number of meetings and different topics) were significantly associated to a better outcome.

Paper III: The meta-analysis

Lifestyle influences weight and other metabolic risk factors. What remains to be clarified, is whether individualised lifestyle interventions can affect metabolic risk factors in a real-world setting. That gap in knowledge is crucial for guideline developers. Basing clinical recommendations on evidence drawn from efficacy studies is hazardous, as implementation of intervention without evidence of effectiveness might lead to waste of resources and move attention away from potential better alternatives

Randomised clinical trials can be categorized as explanatory (exploring efficacy) or pragmatic (exploring effectiveness). The explanatory trial investigates a potential causality mechanism under

controlled settings, answering the question “Can this work?” and the pragmatic trial investigates whether an intervention is feasible in a real-world setting, answering the question “Will this work?”.[119]

To assess real life effectiveness and not just efficacy, special considerations are demanded when designing lifestyle trials for patients with severe mental illness (SMI). The composition of the sample included in a clinical trial reflects 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. Even though formal inclusion criteria might be flexible, a strict program (exercise 3 times weekly) is likely to produce selection bias.

The field was rapidly growing while the CHANGE study was underway, and consequently we chose to update the evidence with a meta-analysis, asking similar questions to the literature as we did in the CHANGE trial, aiming to investigate the real-world effectiveness:

1. Can lifestyle interventions reduce cardiovascular risk factors?
2. Is the effect sustainable?
3. Is the effect clinical relevant?
4. Does it work in a real-life setting?
5. Are there any adverse effects?

Methods

The objective of the meta-analysis was to evaluate the effectiveness of lifestyle interventions to reduce metabolic risk factors in patients with severe mental illness.

The following hypotheses were tested in the study:

1. Lifestyle interventions are more effective than control conditions in reducing weight.
2. Lifestyle interventions are more effective than control conditions in reducing waist circumference, systolic blood pressure, cholesterol and fasting glucose.
3. Lifestyle interventions have potential adverse effects measured as quality of life, hospital admissions, weight gain and deaths.

The meta-analysis was registered in PROSPERO (International prospective register for systematic reviews) (CRD42016049093) 10.10.2016.

Eligibility criteria

1) Participants should be diagnosed with major depression, schizophrenia, schizoaffective disorder or bipolar disorder.

2) Participants aged >17 years of both sexes.

3) The trials had to allocate participants to a lifestyle intervention *versus* a concurrent control group or allocate participants to a lifestyle intervention as an add-on to treatment as usual *versus treatment as usual*.

4) 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.

5) Randomized clinical trials. Allocation was perceived as randomized when terms including 'randomly', 'random', and 'randomization' was used.

Outcomes

Primary outcomes were body weight measured as i) BMI measured as continuous outcome and ii) proportion achieving clinically relevant weight loss (≥5%).

Secondary outcomes were i) maintenance effect on weight ii) weight measured in kg iii) adverse events (quality of life, weight gain, hospitalisations, death) and iv) metabolic risk factors (fasting glucose, cholesterol, blood pressure, waist circumference).

Exploratory outcomes were an evaluation of predefined moderators and mediators of effect: Four categories of predictors were defined in the protocol: 1) Internal validity (risk of bias, drop out); 2) external validity (aspect-R); 3) population characteristics (age, sex, diagnoses, weight, Illness duration, global assessment functioning, negative symptoms, cognitive functions, supported housings, illegal drugs, inpatient/outpatient, medication; and 4) intervention characteristics

(prevention/intervention, duration, intensity, modality (exercise, diet or both), and setting (individual, group, or both).

Statistical analysis

Mean difference, standardized mean difference (SMD) or risk ratio (RR) with 95% confidence interval (CI) were reported using a random effects model. Heterogeneity was quantified using the I-squared statistic. Publication bias was assessed by visual inspection of a funnel plot and by Egger's test.

Multiplicity in this analysis was handled as suggested by Jakobsen et al.[120] accepting a p-value of 0.02 for primary outcomes and 0.01 for secondary outcomes. As suggested by Jakobsen et al.,[120] we used Trial Sequential Analysis[121] to calculate the diversity-adjusted required information size and the Trial Sequential Analysis-adjusted confidence intervals. The potential breach of the cumulative z-curves of the pre-defined trial sequential monitoring boundaries, allows us to control the risks of random errors. Hereby we can differentiate significant results into "spuriously significant" (type I error) and "true significance" and neutral results into "true neutral" or type II errors caused by lack of power.

Exploration of heterogeneity was performed with meta-regression. Univariate linear regression was followed by multivariate regressions with backward elimination.

Main outcome

Primary outcomes

Results are presented in table 2. Thirty-seven trials provided data on BMI (n=2,863). The effect of lifestyle intervention was a mean difference in BMI of -0.60 kg/m^2 (95% CI -1.02 to -0.18; P = .005; I^2:72.3%) versus control (figure 1). Eight trials[84,85,91,122–126] (n=1060) reported proportion of participants with clinically significant weight loss, defined as losing ≥5% of baseline bodyweight. The RR for clinically significant weight loss was 1.41 (95%CI 1.13 to 1.77; P = .003) in favor of the intervention. The corresponding NNT was 11 participants.

The diversity-adjusted required information size was reached for BMI but not for the RR for clinically relevant weight loss. Thus, it is unlikely that the observed difference in BMI was a type I error, while this cannot be ruled out for the risk ratio

Secondary outcomes

There were statistically significant improvements for weight in kg and waist circumference. Weight in kg were reported in 32 trials[84,85,91,92,122–148] with a mean difference of -2.4 kg (95%CI -3.15 to -1.65;

P< .0001; I^2=28.7%). Waist circumference was reported in 21 trials, with a mean difference of -2.1 cm (95%CI -3.02 to -1.13; P < .001; I^2=33.0%).

Adverse events were sporadically reported and, none of the included weight loss studies reported on the proportion of participants gaining ≥5% of baseline weight. Twelve trials[88,96,123,126,132,135,141,142,144,146,149,150] (n=1309) reported on quality of life after the intervention. No difference could be found SMD = 0.03 (95% CI -0.15 to 0.21, P = 0.16) with I^2 = 63. Only five studies[84,85,126,133,142] reported other adverse effects such as hospitalizations or death. There were 48 somatic hospitalizations in the intervention group vs 60 in the control group. The numbers for psychiatric hospitalizations were 60 vs 77, and for deaths the numbers were 4 vs 7.

Tables and figures included as supplementary files in paper III and in appendix II.

Exploratory analyses

The heterogeneity was moderate to high, and was explored using the predefined potential mediators and moderators. Four variables explained a significant proportion of the variance: 1) Asian trials were more effective than trials from USA, which were better than European trials; 2) Trials with broader inclusion criteria were less effective than trials with restricted criteria; 3) Trials with flexible interventions that could be tailored to individual needs were less effective than rigid programs; 4) individual sessions were more effective than groups. In a combined model, only geographical origin remained significant after backward elimination, with trials from Asia reporting better effect (-1.69 kg/m^2 (95% CI -2.44 to 0.94)) than USA (-0.68 kg/m^2 (95% CI -1.2 to 0.17) which was better than trials from Europe (0.09 (95% CI -0.65 to 0.83)).

Part 3: Discussion and perspectives

Discussion

Summary of results

The CHANGE trial was a sufficiently powered trial aiming to evaluate if a lifestyle coach or a care coordinator could reduce the risk of cardiovascular disease via a change in lifestyle and optimized medical treatment of risk factors. After 12 months of intervention, there were no significant differences on any measured outcomes between the three groups. In spite of an intensive intervention, the participants did not change lifestyle to a degree that affected the metabolic risk factors, and thus we do not believe the interventions decreased the risk of cardiovascular disease/mortality. We consider these results to be robust, as they were confirmed by sensitivity analyses and per-protocol analyses. It should be stressed though, that we do not conclude that changing unhealthy lifestyle does not affect the human organism.

The coaches registered all contacts with their participants. Based on these registrations, we tried to explore why the intervention did not work by performing post-hoc analyses. We had two hypothesizes: 1) the participants did not use their coach; 2) what happened between coach and participant did not work. The intervention offered 42 individual weekly meetings with a coach. About half of the participants had 24 or more meetings, suggesting a moderate acceptability. We could not identify any subgroups that had more meetings with their coach than others. Neither total number of meetings, nor number of meetings focusing on any of the four possible tracks (smoking, diet, physical activity and care coordination) predicted change in metabolic risk factors. Thus, we conclude that the intervention, despite being delivered as intentioned, did not work.

No previously published studies have reported risk of cardiovascular disease as a composite outcome. Weight management trials are by far the most numerous. Therefore, the further discussion will focus on weight, which was a major modifiable risk factor in the Copenhagen Risk Score. Our neutral results regarding weight were not in line with previously published meta-analyses.[81,82,151,152] This could be explained by 1) CHANGE was designed as a pragmatic study evaluating real world effectiveness; 2) CHANGE had a strict methodology limiting the risk of bias as much as possible; 3) The complexity of the intervention might have diluted the effect on weight; 4) Motivation was not an inclusion criteria. As described in the introduction, a series of large scale trials have been published after the initiation of the CHANGE trial, equally finding no or moderate effect on weight.[88,90,92] This tendency for a research field to find smaller effects when trials grow larger, more pragmatic and more robust in design is observed as a general trend,[153] and will be discussed further in the next chapter.

Reasons for the unexpected neutral effect of care coordination might be explained by two factors; 1) The Danish health care system works 2) The participants had little somatic comorbidity. At baseline, we noted that very few of the participants came out with unexpected elevated risk factors, and most of them received guideline concordant medical treatment. If the external validity is as good as we believe there is no reason to introduce another care person. However, we cannot exclude the possibility that subgroups with more somatic morbidity might benefit from a care coordinator. Indeed, a recent Danish study found a markedly reduced mortality after 19 years for participants with psychiatric illness who had received 6 years of structured diabetes care compared to treatment as usual.[154]

The sociodemographic characteristics describing the sample included in the CHANGE trial, might point to an alternative approach to the excess mortality. Very few of the participants, were educated, had a regular employment and were living in a relationship. The observed social depletion in the CHANGE sample is consistent with the pattern described among mentally ill in Denmark in general. [155] Social inequality is, in itself, linked to reduced life expectancy in people without severe mental illness.[156] Interestingly, a recent study has found that "vital exhaustion", a form of psychosocial stress defined as *"excessive fatigue, feelings of demoralization and increased irritability,*[64] is an independent and important risk factor for cardiovascular disease, ranking first for men and second for women. Based on descriptions of living conditions for mentally ill in Denmark, it could be hypothesised that "vital exhaustion" is a common phenomenon contributing to the elevated risk of cardiovascular disease.

The field has been rapidly growing and we chose to include CHANGE in an up-to-date meta-analysis evaluating effect on weight management. Aiming to guide clinical guideline developers, we focused on clinical relevant outcomes like proportion achieving clinical relevant weight loss. Merely presenting a mean difference with attached p-value can be hard to translate into clinical meaningfulness. Therefore, we reported number needed to treat, maintenance effect and potential harmful effects. In addition, we predefined exploratory analyses aiming to explore moderators and mediators of effect. Among these, we hypothesized that higher risk of bias and lower degree of pragmatism would predict lower effect.

The findings from the meta-analysis were disappointing, as very few papers report on the clinical relevant outcome (weight loss (≥5%). The main finding was a mean difference in BMI of -0.60 kg/m^2 which is statistically significant but unlikely to be clinically relevant. Number needed to treat to achieve a clinically relevant weight loss (≥5%) was 11 participants. This was based on results from eight trials. When pooled mean difference was calculated for this subgroup as continues outcome, a difference of 0 kg/m^2 was found. A possible explanation could be that number needed to harm

(gaining ≥5%) is significant as well, favouring control conditions. However, unintentional weight gain as possible side effect was systematically not reported.

Two features of pragmatism explained a significant proportion of variance, the generalizability of the sample and the flexibility of the intervention. A sample with high generalizability and a flexible intervention lead to greater effect than tightly selected sample and a rigorous program. These two domains might be partly overlapping, as it is likely that unintended selection bias will occur in the a sample accepting a rigorous program with, for instance, regular exercise twice weekly.[157] Indeed, a recent paper has problematized that interventions tested under explanatory conditions turn out to be ineffective when tested in real-world settings.[153] Lower risk of bias did not predict lower effect.

Our meta-analysis found a smaller effect on weight than earlier publications.[81–83,151] This might reflect that the added trials were larger and more pragmatic, and thus decreased the pooled effect. This is in line with the fact that degree of pragmatism is negatively associated with effect. Indeed, the pattern for meta-analyses in all fields show decreasing effects with time.[120]

Even though we were unable to identify a subgroup achieving clinically relevant weight loss, we cannot rule out that some will benefit. Reporting of proportions with ≥5% weight loss is indeed relevant to report in future trials, but will need to be accompanied by the corresponding proportion gaining clinical relevant weight (≥5%) and a mean change to ease the clinical interpretation.

Inter99, one of the largest pragmatic studies[158] to date, using a similar approach to CHANGE found no effect on mortality after 10 years follow-up. Earlier randomized studies are summarized in a Cochrane review,[98,159] confirming the negative results. The first review, Ebrahim et al. included 55 trials investigating the effect of counselling and education aimed at behaviour change and found no reduction in cardiovascular mortality or clinical events in general populations. The second review, Krogsboll et al. included 16 trials investigating the effect of general health checks, and found no reduction in morbidity or mortality.

Strengths and limitations

The CHANGE trial and the meta-analysis share some strengths. Both are based on pre-published protocols, limiting the risk of data driven type I errors. These protocols provided a detailed hierarchy of outcomes, with relevant precautions being taken to reduce the risk of type I errors resulting from

multiple testing. Furthermore, both studies included a power calculation, enabling us to distinguish between neutral and inconclusive results.

The major strengths of the CHANGE trial are the pragmatic design and methodological rigor. Pragmatic components are the limited exclusion criteria together with active recruitment, the assertive and flexible intervention and broad range of outcomes including patient-centred outcomes (quality of life) Methodological strengths include centralized randomization, allocation concealment, blinded outcome assessments, data management and analyses, and independent funding. Thus, CHANGE had high external and internal validity.

The major limitations of the CHANGE trial are the difficulties in evaluating effect of complex interventions. This includes the use of surrogate outcome as primary end-point, and the use of self-reported measurements on lifestyle, instead of objectively measured outcomes, the lack of assessment of harmful effects and lack of power to detect potential effects on exploratory outcomes.

For the systematic review the strengths include the clinical relevance of outcomes (like quality of life, minimal clinical important differences, reported number needed to treat.) and the integration of a formal evaluation of strength of evidence using the GRADE tool. Limitations of our analyses include the fact that all trials were at high risk of bias, lack of power on secondary outcomes, and a high degree of unexplained heterogeneity.

Methodological considerations: Evaluating a complex trial

The neutral findings of the CHANGE trial are far from alone. A succession of complex phase III trials in psychiatry have presented negative results, and it has been questioned if the negative findings are a cause of concern or just good clinical practice.[153] To approach an answer to that question regarding CHANGE, an in-depth discussion of the evaluation is required, both regarding the quantitative data that were collected and the qualitative data that should have been collected.

In contrast to simple drug interventions, most health promotion interventions are complex, as they contain several interacting components.[160] In 2000, the Medical Research Council published a framework as an aid to design and evaluate complex interventions.[161] The framework was revisited and updated in 2008,[162] and a supplementary guide was published in 2015.[163] The latter providing detailed guidance on process evaluation, not as a substitution for outcome evaluations, but supplementing the evidence. The qualitative data collected from the CHANGE trial were not a process

evaluation, but rather an ethnographic description of the perception of health among patients with schizophrenia, and has not yet been published.

The overall aim of the CHANGE trial was to create value in form of increased life expectancy and increased quality of life. This is, indeed, a complex matter to measure. The CHANGE trial was fuelled by incentives to reduce the number of excess deaths in schizophrenia due to somatic morbidity. As cardiovascular disease accounts for the largest number of excess deaths, the incidence of cardiovascular disease and death was the ultimate clinical endpoint of interest. While designing a trial with these hard endpoints would be optimal, the required time frame and financial resources made it necessary to look at surrogate outcomes.

To be faithful to the randomised design, we sought for *one* primary outcome, and a few secondary outcomes (blood pressure, pulse, VO_2 max, HbA1c, HDL, FEV1 and waist circumference). The interventions in CHANGE were highly complex. Three features of the intervention that especially contributed to the complexity: 1) The four different tracks 2) The participants were at different stages of change (some not being motivated at all) 3) The manuals encouraged tailoring of the treatment. It is unknown whether there were synergistic or antagonistic working elements. For instance, smoking cessation could lead to weight gain (antagonistic) or diet-induced weight loss could lead to more physical activity (synergistic). The high degree of complexity comprises a special challenge for the chosen outcome, as simple measures like smoking cessation or waist circumference might not capture the effect for all participants. Thus, the primary outcome had to capture a range of potential effects, as well as being a good surrogate outcome for cardiovascular disease. To handle the risk of multiplicity, a clear outcome hierarchy should be presented a priori, and adjustment of threshold for significance should be made accordingly. If we had chosen a range of outcomes to be primary, the proper adjustment could be Bonferroni-adjustment, simply derived by dividing the p-value by the number of outcomes. In CHANGE, this was handled by defining outcomes after 12 months as primary, comparing the three groups pairwise. Thus, 0,05/3 gave us a p-value of 0,017, however, this approach is too conservative if outcomes are correlated.

A surrogate outcome is a measurement that can predict a treatment response on the clinical outcome of interest. *A clinical outcome measure is an outcome that is relevant and noticeable to the patient's quality of life. It detects how a patient feels, functions, or fails in the fight for survival.*[164] The link between these two outcomes needs validation, to ensure the clinical relevance of a trial. The intervention must affect the surrogate outcome and the change in surrogate outcome must predict a change in the clinical outcome of interest. There are several laboratory measures linking risk of cardiovascular disease, both as single risk factors and as composite measures as risk equations.

However, there is limited evidence on the ability of interventions to influence these factors as well as the precision by which these risk equations can predict CVD. Despite these limitations, we chose to look for a composite outcome predicting cardiovascular risk. As most of the well-known scores exclude diabetics and those with previous cardiovascular disease, we ended up with Copenhagen Risk Score (CRS) as primary outcome. The Copenhagen risk score is based on age, sex, family history of CVD (defined as parents suffering fatal or non-fatal cardiovascular event before the age of 55 years (father) or 60 years (mother); prior heart disease (defined as myocardial infarction (MI) or verified atherosclerosis of coronary arteries); +/- daily smoking; +/- diabetes mellitus (HbA1c-based or receiving anti glycaemic drugs); total cholesterol, high density lipoprotein cholesterol (HDL); systolic blood pressure; and body mass index (weight/height^2). Absolute risk is defined as the probability of a clinical event (IHD, MI, stroke, death) happening to a person within 10 years.

The strengths of CRS include that it was developed in the Danish population and incorporating data from intervention studies, meaning it was sensitive to changes in risk. Furthermore, unlike other risk equations, the model applied to patients with diabetes and a history of CVD, making it possible for us to use the same model for all participants. By choosing a composite outcome, we could potentially measure change in the multiple risk factors, without increasing the risk of multiplicity.

While it is intuitively easy to understand mortality risk ratios and number needed to treat, reduction in weight or cholesterol is harder to evaluate. The weaknesses include that no prospective studies have evaluated the effect of lifestyle counselling on CRS and accordingly on the clinical endpoint of interest. Thus, the validity of CRS as a surrogate marker is not well described. A general problem with risk equations is the relatively low risk for young individuals, despite having a high-risk lifestyle. To increase our ability to detect a change, we extrapolated the age of all participants to 60. Thus, the results are not a true risk, but a measurement of cluster of risk factors. An obvious limitation of this is the difficulties in translating a change into clinical meaningful effect.

Other approaches could have been applied. It could be argued that narrowing the intervention down to cover for instance only physical activity could strengthen the design. However, this would also limit potential number of participants and potential risk behaviours to target, thus affecting the real-world effectiveness. Furthermore, the potential synergistic effect when improving more than one risk behaviour would be lost. Therefore, we decided to keep the multifaceted intervention, acknowledging that there are multiple intertwined pathways to cardiovascular disease. Another approach could be to increase the number of primary outcomes, recognizing that an intervention modifying multiple targets needs multiple outcomes, and several risk factors have been linked to increased risk of CVD. This is a way to evaluate the intervention as if it was a series of simpler interventions. This approach

leads to two methodological problems: High risk of type I errors (falsely rejecting the 0-hypothesis increases with number of outcomes) and high risk of type II errors (falsely accepting the 0-hypothesis due to lack of power). If we expected subgroups to responds to certain elements in the intervention, it compares to designing small, exploratory trials with too small sample sizes to detect a clinical meaningful difference.

The latest published guidance from the Medical Research Counselling[163] suggests that process evaluation is crucial. Process evaluation can assess fidelity, clarify causal mechanisms and suggest unexpected beneficial and harmful effects. The method can be a combination of quantitative and qualitative data collection, but in-depth qualitative data is suggested to understand how the intervention works. We did not conduct a formal process evaluation in CHANGE. This is a major limitation that could have provided valuable insight in why the intervention failed and explore potential unexpected beneficial or harmful effects.

Apart from assessing feasibility and acceptance, exploration of possible mechanisms is important when building an evidence base, as further research should build on core mechanisms that are found to be effective. In complex behavioural interventions, several assumptions are made regarding causality, and each of them might be wrong, and thereby lead to failed studies. Assumptions might be based on current evidence, existing theories, common sense or experience.[163] Some of the core assumptions in CHANGE were that 1) motivational interviewing would increase motivation to change lifestyle habits in the direction we suggested and 2) social support and education would help defeating the barriers the participants had that kept them from healthy living.

Complex interventions are unpredictable of nature. Informal interviews with lifestyle coaches and former participants revealed both positive and negative effects at a level that we could not measure. The positive effects included increased self-esteem, faith that changing habits is possible or gratefulness for the time and attention received from the coaches. On the negative side, were feelings of fiasco, stress or anger with the coaches being too pushy. Indeed, very few of the published trials reported measurable adverse effects. Historically, there have been few official demands on reporting adverse effects of lifestyle interventions. However, the presumptions that complex psychosocial interventions are free of adverse effects are being challenged. The Danish Health Authorities have proposed a framework[165] to evaluate potentially harmful ethical aspects, and recently, the Ethical advisory board have published a checklist[166] for the same purpose. Among the suggested harms are 1) increased level of worrying, 2) pathologising, 3) increased stigma, and 4) medicalisation,

A process evaluation could have provided insight into the 1) acceptability: Were the lifestyle coaches acceptable to the target population 2) feasibility: Was it possible to deliver the intended intervention? 3) Causality: Which assumptions regarding causality were wrong 4) effectiveness: Did the beneficial effects outweigh the harms?

Conclusion

The individual approach in CHANGE failed in reducing cardiovascular risk factors in patients with schizophrenia. Probably because the participants failed to make significant changes of their lifestyle habits. The effect of similar behavioural trials targeting cardiovascular risk factors like weight, lipids, glucose metabolism and hypertension in patients with severe mental illness have found limited effect. In the background population, two large scale studies[158,167] and a systematic review[159] have evaluated the effect of general health checks and counselling on mortality, and found no effect.

Implications for practice

Our results from the CHANGE trial cannot be used as argument for systematically offering lifestyle coaches or care coordinators to patients with schizophrenia and abdominal obesity. While the result from the CHANGE study was neutral, a statistically significant effect was found on weight reduction in our meta-analysis. The clinical relevance of the weight loss was questionable, and was not maintained at follow-up and did not translate into improved lipids, blood pressure or glucose metabolism. The effect size was negatively associated to degree of pragmatism, indicating low real world effectiveness.

Most of the studies, including CHANGE, did not properly assess and report harmful effects. The lack of knowledge of potential adverse effects compromises the possibility for clinical guideline developers to weigh benefits and harms.

Our results do not imply that clinicians should stop the annual screening of cardiovascular risk factors or advising motivated patients about healthy lifestyle. We do however, question if a systematic approach to risk behaviour is meaningful. In Denmark, regular screening (KRAM)[168] for unhealthy lifestyle is mandatory for in- and out patients in psychiatric units. A cardinal concept of screening is that the results lead to a consequence that can change the prognosis. If this is not the case, screening is a waste of resources and potentially harmful.

Implications for research

We suggest that future research is not limited to proximal determinants of health, but develops multilevel interventions addressing the whole range of determinants as shown in figure 1.

As both the CHANGE trial and the meta-analyse were sufficiently powered, we find it unlikely that similar future studies, investigating the effect of individualised interventions, will lead to major shift in evidence. However, there are some open questions regarding 1) could less complex interventions be more effective 2) Are interventions offered to motivated patients more effective, and is there a valid way to assess motivation? 3) Could interventions be effective if offered in an early phase? 3) Are there harmful effects of lifestyle interventions and do they outweigh positive effects? 4) Are the interventions cost-effective?

Our primary suggestion is that researchers follow the trend in the general population, moving away from an individualised approach to structural interventions targeting environmental factors and up-stream determinants for cardiovascular disease. Environmental interventions could be to remove obesogenic elements like snacks and sugary drinks and cakes from hospitals and community centres, to prohibit smoking in mental wards or to provide free and healthy meals for patients with severe mental illness. Up-stream interventions could be to improve the living conditions, including a more flexible labour market, anti-stigma campaigns and increased possibilities for co-habituating. At policy level, the effect of regulation of industries promoting unhealthy food and drinks should be considered.

Finally, any future interventions should be well powered with long-term follow up, both to escape the hazardous use of surrogate outcomes and to investigate a sustained effect. The high costs of these trials should be weighed against human and economic costs of the currently observed excess mortality as well as the costs of implementing ineffective programs at a preliminary level.

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Papers

Paper I

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Protocol for CHANGE: a randomized clinical trial

assessing lifestyle coaching plus care coordination versus care coordination alone versus treatment as usual to reduce risks of cardiovascular disease in adults with schizophrenia and abdominal obesity

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Abstract

Background: *Life expectancy in patients with schizophrenia is reduced by 20 years for males and 15 years for females compared to the general population. About 60% of the excess mortality is due to physical illnesses, with cardiovascular disease being the single largest cause of death.*

Methods/design: *The CHANGE trial is an investigator-initiated, independently funded, randomized, parallel-group, superiority, multi-centre trial with blinded outcome assessment. 450 patients aged 18 years or above, diagnosed with schizophrenia spectrum disorders and increased waist circumference, will be recruited and randomized 1:1:1 to 12-months interventions. We will compare the effects of 1) affiliation to the CHANGE team, offering a tailored, manual-based intervention targeting physical inactivity, unhealthy dietary habits, and smoking, and facilitating contact to their general practitioner to secure medical treatment of somatic comorbidity; versus 2) affiliation to a care coordinator who will secure guideline-concordant monitoring and treatment of somatic comorbidity by facilitating contact to their general practitioner; versus 3) treatment as usual to evaluate the potential add-on effects of lifestyle coaching plus care coordination or care coordination alone to treatment as usual. The primary outcome is the 10-year risks of cardiovascular disease assessed at 12 months after randomization.*

Discussion: *The premature mortality observed in this vulnerable population has not formerly been addressed specifically by using composite surrogate outcomes for mortality. The CHANGE trial expands the evidence for interventions aiming to reduce the burden of metabolic disturbances with a view to increase life expectancy. Here, we present the trial design, describe the methodological concepts in detail, and discuss the rationale and challenges of the intermediate outcomes.*

Trial registration: *Clinical Trials.gov NCT01585493. Date of registration 27th of March 2012.*

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Background

Schizophrenia is a life shortening disease, with life expectancy being reduced by 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]. While the general population has benefitted from a steady decline in ischemic heart disease since the 1980s, this is not the case for patients with schizophrenia [3-5].

Death due to cardiovascular disease is closely related to metabolic syndrome [6]. It has been estimated that the prevalence of metabolic syndrome in patients with schizophrenia may be as high as one in three [7]. The high mortality due to cardiovascular disease can be explained by unhealthy lifestyle [8], disparities in quality of health care [9], metabolic adverse effects of antipsychotics [10],

and probably genetic vulnerability [11]. Of these, lifestyle and use of primary health care might be considered modifiable factors and thus accessible to intervention.

Sedentary lifestyle, smoking, and unhealthy dietary habits are highly prevalent among patients with schizophrenia. A recent study found that patients with schizophrenia spend more than 12 hours on sedentary activities on a daily basis [12], and make unhealthy dietary choices, consuming more sugar and saturated fats than the background population [8]. The combination of pronounced sedentary behaviour and a diet rich in sugar and fat, highly contributes to the reported proportion of obesity of 42% to 60% among patients with schizophrenia [13]. A significant association between low aerobic fitness and metabolic syndrome has been found in patients with schizophrenia [14]. Furthermore, patients with schizophrenia have more than five times the odds of being smoker, and smoking cessation is lower than compared to the general population [15]. Thus, the high prevalence of cardiovascular disease is multifactorial, and likely requires a multifaceted intervention.

Several studies have examined the effect of behavioural and pharmacological interventions targeting single cardiovascular risk factors like obesity, smoking, glucose intolerance, and dyslipidaemia in patients with schizophrenia [16-24]. Weight loss or prevention of weight gain has been studied in trials aiming to improve unhealthy diet, physical inactivity, or a combination. Two recent systematic reviews of randomized clinical trials of lifestyle interventions conclude that there is significant reduction of 0.94 kg/m^2 [25] and 0.98 kg/m^2 [26] in body mass index (BMI), the latter review finding a superior effect of combined nutritional counselling and exercise. This is supported by our own work [27], where exercise as a single intervention does not seem to affect BMI or other cardiovascular risk factors [28]. Further support for the effect of interventions combining exercise and nutrition has been found recently, in a randomized clinical trial for weight loss in patients with schizophrenia resulting in a net difference in BMI of 1.1 kg/m^2 between patients in the intervention group and controls [29]. There is evidence that bupropion and varenicline increase the chance for smoking cessation in patients with schizophrenia [24,30,31], but no randomized clinical trial has combined smoking cessation with an exercise and nutritional interventions, to maximize the possibility to reduce cardiovascular disease.

Disparity in quality of primary health care is another major issue explaining the high mortality. The European Psychiatric Association [32] and the National Institute for Health and Care Excellence (NICE) guidelines both recommend that patients with schizophrenia are annually screened for obesity and cardiovascular risk factors, and receive guideline concordant prophylactic treatment of these factors, but this does not appear to happen [33]. Acknowledging the unmet need for primary health care among patients with schizophrenia, several approaches have been proposed to fill the gap; an expanded role for the psychiatrist, an integrative care model with a general practitioner allocated to supported housings or care coordination providing contact to primary care. Reviewing the literature in the electronic databases (PubMed, EMBASE, and
Clinical Trials.gov) for studies related to the terms “shared care, collaborative care and care coordination” and “SMI
(severe mental illnesses) and/or schizophrenia” resulted in no published studies that have examined the effect of care coordination on schizophrenia patients in a randomized clinical trial. We found one ongoing trial assessing the effect of care management with quality of life as the primary outcome and cardiovascular risk factors as the secondary outcome [34]. No results from that trial have yet been published [34].

Our systematic search revealed no trials or studies investigating the add-on effect of lifestyle interventions compared with care coordination alone in a randomized clinical trial.

Aim and hypothesis

We will compare in a randomized clinical trial the benefits and harms of 1) lifestyle coaching defined as affiliation to a CHANGE team member, offering a tailored, manual-based intervention targeting physical inactivity, unhealthy dietary habits, smoking, and facilitate contact to their general practitioner to secure medical treatment of somatic comorbidity; versus 2) affiliation to a care coordinator who will secure guideline-concordant monitoring and treatment of somatic comorbidity

by facilitating contact to their general practitioner; versus 3) treatment as usual for obese patients with schizophrenia. The primary outcome of the CHANGE trial is the estimated 10-years risk of cardiovascular at 12 months post-randomization. Our alternative hypotheses are that there will be a reduction in the estimated 10-years risk of cardiovascular disease in the two experimental intervention groups compared with the control group, and that the lifestyle coaching will be more effective than the care-coordination.

The duration of all interventions is 12 months. Assessment of outcomes will take place 12 months and 24 months after randomization.

Method

Design

The CHANGE trial is an investigator-initiated, independently funded, randomized, parallel-group, superiority, multicentre trial with blinded outcome assessment.

Patients

Patients were recruited from well-defined catchment areas in two major Danish cities (Aarhus and Copenhagen). Eligible patients were verbally informed by the usual caretaker, and referred to CHANGE research staff by phone or e-mail, if accepting. The patients were contacted by phone, and a meeting was arranged at the research centre, the outpatient clinic, or at the patient's home. Verbal and written information was provided. If the patient accepted participation in the trial, an informed consent was signed and an appointment for collection of baseline data was made. Baseline data were collected between 1st of December 2012 and 1st of May 2014.

Patient inclusion criteria

1) Adults, ≥18 years, fulfilling the ICD-10 diagnostic criteria for schizophrenia, persistent delusional disorders, or schizoaffective disorders [35] using the Schedule for Clinical Assessment in Neuropsychiatry (SCAN) [36]; 2) Waist circumference ≥88 cm for females and ≥102 cm for males [37] measured between the crista iliac and lowest rib); and 3) Written informed consent.

Patient exclusion criteria

1) Current self-reported pregnancy 2) Inability to consent.

Randomization and blinding

Patients were randomized with a 1:1:1 ratio to either the lifestyle coaching versus care coordination versus treatment as usual. Randomization was stratified according to the two psychiatric centres, sex, and a high/low risk of cardiovascular disease. High risk was defined according to cut-off points from a Danish population study using the Copenhagen risk score, aiming to identify the quintile at highest risk. Each person was - in the computer program - simulated as 60 years old, to reach a substantial level of risk [38]. This approach is was recommended by the European cardiovascular risk factor management guidelines to asses risk in young individuals [39].

The randomization was centralized and carried out by the Copenhagen Trial Unit using a computerized randomization sequence with alternating block sizes unknown to the investigators. After inclusion in the trial, a health care provider contacted the Copenhagen Trial Unit with a unique patient identifier plus stratification variables and in return received the patient allocation.

Blinding

Outcome assessors, statisticians, and all investigators involved in the trial are blinded to patient allocation. Patients and the health professionals providing the interventions are not blinded to patient allocation. The statistical analysis of the 12 months post randomization follow up and the drafting of the first result manuscript will be carried out blinded to patient allocation.

Interventions

Lifestyle coaching

The theoretical framework of the lifestyle coaching was based on the theory of stages of change [40], motivational interviewing (MI), and an assertive approach adapted from the assertive community treatment [41]. MI is a method to help patients elicit their own wishes to change, and it has been shown effective in patients with schizophrenia and comorbid alcohol abuse [42]. The assertive approach allows the staff to be respectfully active and still persistent in follow-up; be flexible in time; and conduct short message services, phone calls, home visits or meetings in the local area.

Manuals (see Additional file 1: care coordinator manual, Additional file 2: diet manual and Additional file 3: physical activity manual (Danish)): The three methods mentioned above, were incorporated in four manuals with detailed descriptions of the intervention addressing care coordination, smoking cessation, healthy diet, and increased physical activity, based on the official Danish guidelines [43,44]. An important first step was to clarify possibilities for changes that seem achievable and realistic according to the stages of change. The aim of the lifestyle coach was to support the patient in setting up individual goals that pay attention to the patient's values, life conditions, and priorities. The coach offered home visits with systematic exploration of possibilities for physical activity in daily life, which were realistic and attractive to the patient. Dietary changes require concrete examination of the patient's dietary habits, food purchases and cooking practices, and identification of economically realistic, easy and attractive possibilities for change. During home visits, the coach took part in the activities (ex. physical activity or food purchases) if requested by the patient, to support lifestyle changes. Personal and professional networks and patient network could be part of individual plans. The smoking cessation program was adapted from the program published by The National Cancer Organization [45,46], and tailored to the patient population in order to elicit and enhance motivation and maintain smoking cessation. Support was provided for motivation, including prevention of relapses, and smoking cessation medication. First line treatment was nicotine substitution and second line was bupropion.

The staff had access to anthropometric measures and blood samples collected at baseline and used these in their first consultation with patients to plan the further course. Weight was monitored every third month.

Patients commenced the lifestyle coaching as soon as possible after collection of baseline data, even if they were in-patients. The coach:patient ratio was 1:15. To allow sufficient time to implement changes in habits, each patient was offered affiliation with the team member for one year and we offered a follow-up after 24 months, to investigate whether changes in lifestyle and treatment of physical disorders were maintained one year after the intervention ended. The lifestyle coach aimed to have individual meetings or activities with their patients weekly. Further support was provided by phone calls, e-mails, and text messages.

The lifestyle coaches and care coordinators performed written registration of all contact with patients including cancellations and classification of the focus area of each consultation, enabling the researchers to evaluate adherence and program fidelity.

Training and supervision: Lifestyle coaches were health professionals (e.g., occupational therapist, physiotherapists, or dieticians) with clinical training in psychiatry. They received a 5-days course in motivational interviewing, a 5-days course in smoking cessation, a 1-day course in examination and treatment of lifestyle disorders and a 2-days course on healthy dieting, based on the official Danish guidelines. During the intervention, supervision of the team took place weekly. In addition to the

intervention described above, the patients were offered care coordination (see below) and treatment as usual.

Care coordinator function

The care coordinator function was incorporated in the lifestyle intervention as well as the add on treatment in the second intervention group (see Figure 1). The care coordinator facilitated contact to primary care in order to ensure treatment of physical health problems. The care coordinator was nurse with a nurse:patient ratio of 1:25. Affiliation to the care-coordinator was offered for one year. The intervention was manual-based, and the aim was to ensure that the patients in this group were monitored and received guideline-concordant medical treatment. Their contact with patients comprised personal

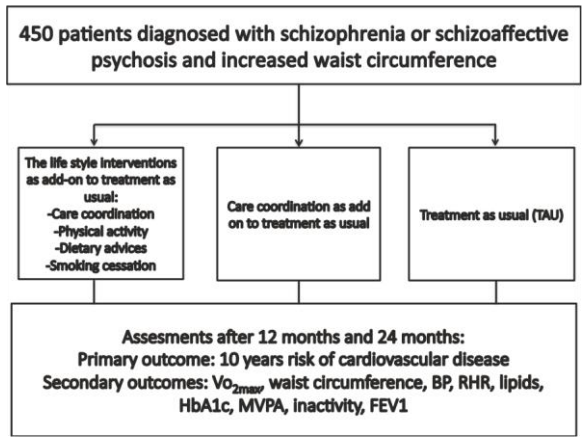

Figure 1 10 years risk of CVD estimated with Copenhagen Risk Score, Vo2max = max. oxygen uptake, BP = blood pressure, RHR = resting heart rate, HbA1c = glycosylated haemoglobin, MVPA = moderate/vigorous activity, inactivity = sedentary activity, FEV1 = forced expiratory volume.

meetings, phone calls and text messages, and the frequency of contact was adjusted according to the individual need. The first meeting with the patient consisted of a general health talk about the physical well-being and test results from physical examination performed at baseline. Special awareness was paid to symptoms of obstructive pulmonary disease, diabetes and cardiovascular disease. The care coordinator used the decision tree (Figure 2) to plan the further course. In addition to the care coordinator intervention described above, the patients continued treatment as usual.

Treatment as usual

In Denmark all persons have a personal general practitioner and can consult her/him for free when needed. Patients in secondary mental health services stay affiliated with their general practitioner, who is responsible for treating abnormal results from the mandatory yearly screening of metabolic risk factors. No formalized extra effort was made regarding lifestyle counselling or treatment of physical disorders. Results from the baseline assessment were available if requested by the patient or usual caretakers, and if any of the results was a matter of urgent consideration, the CHANGE research staff contacted the usual caretaker.

Outcomes

Research staff blinded to patient allocation assesses outcomes. All patients will be assessed at the following time points: baseline (T0), 12 months post-randomization (T1-at completion of intervention), and 24 months post randomization (T2).

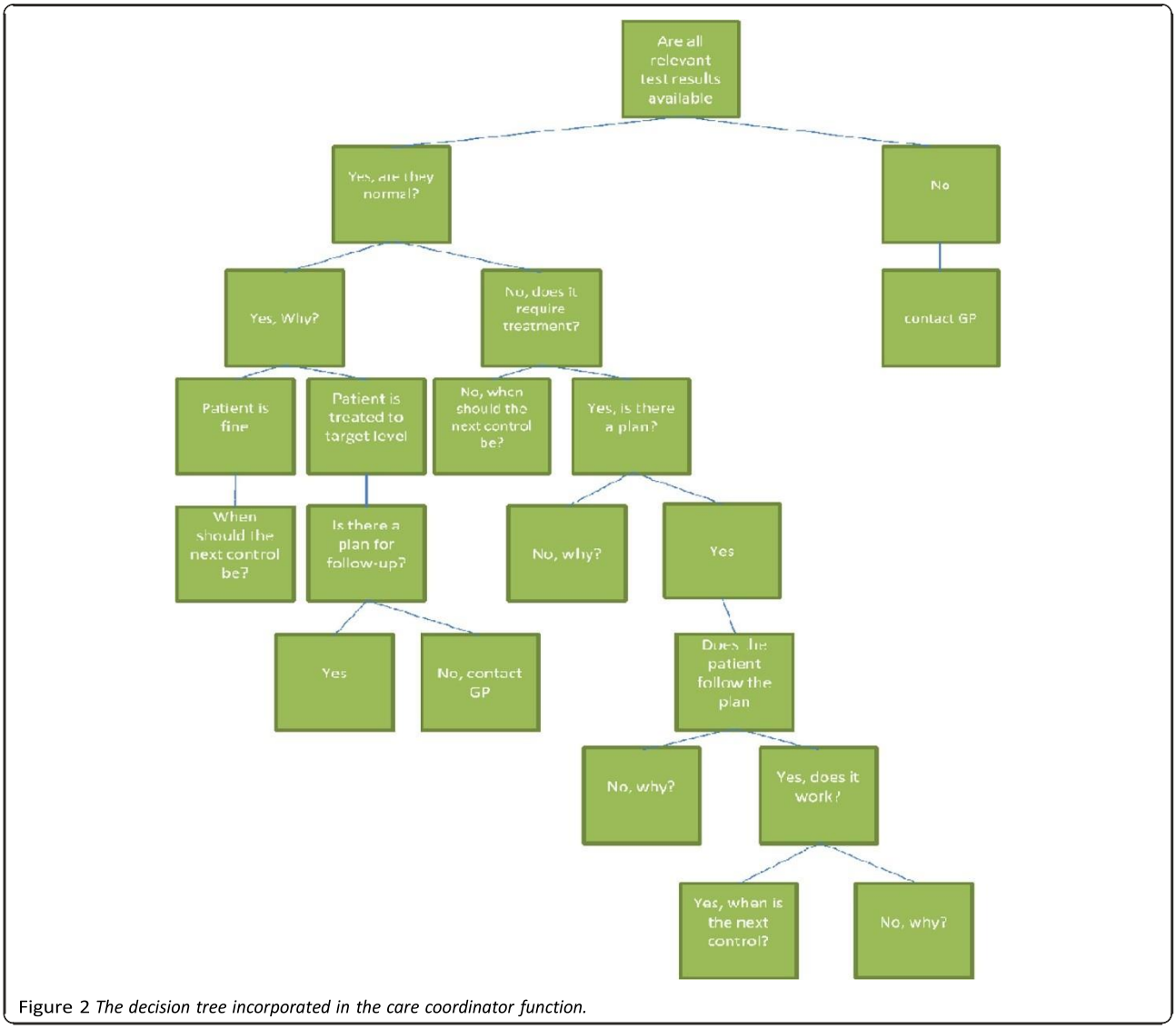

Figure 2 *The decision tree incorporated in the care coordinator function.*

Study objectives

The CHANGE trial aims to answer the questions set out below under primary objectives, secondary objectives and exploratory objectives.

Primary objectives

1. Is lifestyle coaching plus care coordination more effective than treatment as usual in reducing risk of cardiovascular disease 12 months from randomisation?
2. Is lifestyle coaching plus care coordination more effective than care coordination alone in reducing risk of cardiovascular disease 12 months from randomisation?
3. Is care coordination alone more effective than treatment as usual in reducing risk of cardiovascular disease 12 months from randomisation?

Primary outcome

The primary outcome is the risk of cardiovascular disease at 12 months, assessed by the Copenhagen risk score. The Copenhagen risk score is based on data from two large epidemiological studies in the Copenhagen area [47].

A risk assessment computer program (PRECARD®) combines the Copenhagen risk score with data from randomized clinical trials [47]. This composite measure includes: sex, family history of CVD (defined as parents suffering fatal or non-fatal cardiovascular event before the age of 55 years (father)

or 60 years (mother); prior heart disease (defined as myocardial infarction (MI) or verified atherosclerosis of coronary arteries); +/- smoking; +/- diabetes mellitus (HbA1c-based or receiving anti glycaemic drugs); total cholesterol, high density lipoprotein cholesterol (HDL); systolic blood pressure; and body mass index (weight/height^2). Absolute risk is defined as the probability of a clinical event (IHD, MI, stroke, death) happening to a person within 10 years. Age is simulated to be 60 years, to reach a substantial level of risk [38], aiming to estimate life time risk.

Secondary outcomes

Cardiorespiratory fitness was originally defined as an exploratory outcome, due to insecurity of the acceptability and feasibility of the test procedure among the recruited patients. After completed data collection at baseline, we found an acceptable level of satisfying tests, and redefined fitness to a key secondary outcome. The patient's maximal oxygen uptake ($V \cdot O_{2max}$) ml oxygen/kg/min was measured using a bicycle cardiopulmonary exercise test. The test was based on L. B. Andersens cycle exercise protocol where the initial 5 min of the cycle test (Monark) the workload is 75 W for women, and 100 W for men (L. B. [48]). Then the workload is increased by 25 W/2 min till exhaustion. All patients were continuously verbally encouraged. The maximum pulse at VO_{2max} was recorded. Forced expiratory volume (FEV1) measured with Easyone® spirometer.

Physical Activity Scale was used to determine time spent on moderate and vigorous and sedentary activity a day [49]. Waist circumference measured between the crista iliac and lowest rib, blood pressure measured on the right upper arm after 10 minutes of rest in a sitting position the average of the two last consecutive measurements will be reported, resting heart rate after 10 minutes of rest, HDL, non-HDL-cholesterol and HbA1c.

Exploratory outcomes

Anthropometric measures: weight in kg and body mass index, skinfolds measured at four sites (biceps, triceps, subscapular, suprailiac), and body fat percentage calculated from skinfold measures [50].

Psychometric measures: positive and negative symptoms (SAPS and SANS) [51], cognition (BACS) [52], quality of life (MANSA and EQ-5D) [53], global assessment of functioning (GAF) [54], perceived health [55], and perceived stress [56].

Biomedical status measures: triglycerides, high sensitive CRP (hsCRP), low-density lipoprotein cholesterol (LDL).

Lifestyle measures: food frequency questionnaire [57], 24 hour recall, self-reported point abstinence from smoking (nicotine dependence questionnaire [58]).

Baseline measures

At baseline, the following was assessed: socio-demographic data; age, sex, self-reported ethnicity, marital status, economic status, work situation, and educational level. Health care: medical history of diabetes, cardiovascular disease, cerebrovascular disease, and other past medical history. Current medication.

Data regarding vital status, causes of death, use of health services, institutional stay, use of medication and use of services from general practice will be extracted from longitudinal Danish registers [59-62]; The Danish National Health Insurance Service Registry (NHSR) which holds information on all contacts to general practice and all services provided [63]; and The Danish Civil Registration System (CRS), which has updated information on vital status, e.g. day of death, on all Danish citizens. The register is a key tool in Danish epidemiologic research [64].

Statistical analyses Sample size

We expect the experimental interventions to reduce the Copenhagen risk score during 12 months from baseline by 2.5% 10-year risk for coronary heart disease in patients allocated to lifestyle

coaching compared with the score in patients allocated to care coordination alone, and a similar reduction of 2.5% in care coordination compared to treatment as usual as presented in Table 1. We plan to compare all three groups and accordingly we reduced our alpha level to 0.05/3 = 0.0166 [65]. Allowing a power of 90% we need to recruit 150 patients to each intervention group for a total of 450 patients. This calculation is based on an SD of 5.9% of the Copenhagen risk score as found in the Inter99investigation [38].

Data analysis

Analysis of data will be based on the intention-to-treat principle. I.e., all patients randomized will be included in the analysis regardless of adherence to the allocated intervention. The primary outcome and other continuous outcomes will be analysed using a repeated measurement, likelihood-based, mixed-effects model with an unstructured covariance matrix. This analysis will include measurement at baseline and 12 months for the primary outcome, and all measurements (baseline, 12 months, and 24 months post-intervention) for the follow-up results, and is an appropriate approach to handling missing data. Dichotomous outcomes will be analysed using logistic regression. In case more than 5% of data is missing at follow up we will use multiple imputation to handle missing data. The imputations will be based on a linear regression model with 100 imputations and 20 iterations. The pooled analysis will subsequently be used for our analysis.

All statistical analysis will be conducted in SPSS. All tests will be two-tailed and unless otherwise mentioned the alpha level will be set at 0.01666.

Approval

ApprovalfromtheDanishEthicalCommittee:H-4-2012-051.

Approval from the Danish Data Protection Agency referral number: 01689 RHP-2012-007.

Table 1 10 years risk of CVD calculated with Copenhagen risk score, WC = waist circumference, BP = blood pressure, RHR = resting heart rate, HDL = high density lipoprotein, non-HDL = total cholesterol-HDL, HbA1c = glycosylated haemoglobin, FEV1 = forced expiratory volume, VO_{2max} = maximal oxygen uptake, sedentary = hours of physical activity during leisure time spending ≤1.5 metabolic equivalents, MVPA = hours of moderate or vigorous activity

	Variables	Expected difference, mean	Expected standard deviation	α	Power %
Primary outcome	*years risk of CVD (%)*	*2.5*	*5.9*	*0.0166*	*0.90*
Secondary outcomes	*WC (cm)*	*5*	*14*	*0.0166*	*0.75*
	BP (mm Hg)	*5*	*12*	*0.0166*	*0.88*
	RHR (per minutes)	*10*	*20*	*0.0166*	*0.97*
	HDL (mmol/l)	*0.2*	*0.4*	*0.0166*	*0.97*
	Non-HDL (mmol/l)	*0.45*	*1.1*	*0.0166*	*0.87*
	HbA1c (mmol/mol)	*0.5*	*1.1*	*0.0166*	*0.94*
	FEV1 (L)	*-0.36*	*0.92*	*00166*	*0.84*
	VO_{2max}	*3.5*	*9*	*0.0166*	*0.73*
	Sedentary (minutes/day)	*60*	*140*	*0.0166*	*0.90*
	MVPA (Minutes/day)	*20*	*40*	*0.0166*	*0.97*

Discussion

Legitimacy of the study

Based on the growing mortality gap between schizophrenic patients and people without schizophrenia, there is an urgent need to improve the physical health in patients with schizophrenia, allowing them to benefit from the decline in cardiovascular disease that has been seen in the general population in developed countries. A recent Cochrane systematic review concluded that lifestyle counselling is ineffective to prevent cardiovascular disease in the general population, but recommends further research in subgroups with high risk of cardiovascular disease, as they find a modest effect on patients with diabetes or hypertension [66]. As the mortality from cardiovascular disease is twice as high in patients with schizophrenia compared to the general population, we find that the former comprises such a subgroup. Furthermore, we selected patients with increased waist circumference, due to the correlations between central obesity and metabolic disturbances [67]. Daumit et al. confirmed that weight loss is possible in this subgroup, by offering group exercise on a regular basis (three times a week) and free, healthy meals. However, this is a costly intervention demanding a reorganization of the outpatient care. With CHANGE we have developed an alternative intervention, hoping that an individualized approach integrated in the local area can be effective and sustainable, as well as reaching out for those with the most severe psychiatric and medical disabilities that might not be ready to attain regular group exercise.

Statistical considerations

In line with current recommendations, our approach to handling missing data has been described in the study protocol [4]. Several methods have been used, including complete analysis, which excludes participants with missing outcomes or simple imputation where missing values are substituted by 'last observation carried forward' or mean of the sample. These methods assume that variables are missing completely at random, which is usually not the case [68], and underestimate the precision (standard error and confidence interval) [69]. Data are missing at random, given all we have observed about a person, the risk of missing a specific observation is independent of the actual value of that observation. Following this assumption, attempts can be made to substitute missing values by using multiple imputation, where a prediction model is used, and therefore accounts for the uncertainty surrounding missing data values. As this assumption of missing at are random is impossible to verify, multiple imputation will be accompanied by a sensitivity analysis, as recommended by the CONSORT guidelines [70]. In our trial, this is especially crucial, as one might speculate that participants lost to follow up had none or even harmful effects of the lifestyle intervention, which could be weight gain as a result of attempts to stop smoking.

The problem of multiplicity arises in this trial due to multiple interventions, multiple outcomes, and multiple measurements (follow-up at both 12 and 24 months after randomization), increasing the risk of type 1 error (falsely rejecting the 0-hypothesis). To account for this, analysis of primary and secondary outcomes will use a Bonferroni-corrected alpha (0.05/3), hypothesising that the lifestyle intervention will be superior to the care coordination that will be superior to the treatment a usual. This approach might be too conservative, due to a high probability of correlation between the outcomes [65]. We therefore decided to calculate unadjusted p-values, but interpret the results in accordance with values described below:

$P \geq 0.05$: The trial results could not demonstrate an effect of the experimental intervention on the secondary outcome.

$0.01 < P < 0.05$: The trial results indicate that there may be a positive effect of the experimental intervention on the secondary outcome. However, the indication is not strong.

$0.001 < P < 0.01$: The trial results indicate that there may be a positive effect of the experimental intervention on the secondary outcome.

P <0.001: The trial results strongly indicate that there may be a positive effect of the experimental intervention on the secondary outcome.

Outcomes

It is obvious that fatal and non-fatal cardiovascular outcomes would be the optimal outcome for interventions aiming to reduce mortality from cardiovascular disease. Facing limited time and resources though, we chose to focus on cardiovascular risk, and thus searched for the most suitable risk score model, estimating 10-years risk. The Copenhagen risk score is the best suitable in a Danish population, and has incorporated data from randomized clinical trials, thus making it the best model to estimate changes in risk [71]. Furthermore, the Copenhagen risk score can be used to estimate risk in patients with diabetes and patients with a history of cardiovascular disease. As was done in the population based study Inter99 [38], we extrapolated the age at 60 years, to reach a substantial level of risk, as no young persons have a high risk in spite of unhealthy lifestyle habits and values highly above the recommended. Additionally, by choosing a composite outcome, we reduce the risk of multiplicity, without adjusting the alpha-level.

A priori, we defined cardiorespiratory fitness as an exploratory outcome, due to insecurity about the patients' ability and acceptance of the 'watt max test'. After completing data collection, it was redefined to key secondary outcome. In a young high-risk population and in patients with schizophrenia, traditional risk equations tend to underestimate the risk, while cardiorespiratory fitness has consistently been shown to correlate closely to cardiovascular as well as all-cause mortality [72]. A major modifiable risk factor in the Copenhagen risk score is weight. However, recent research has questioned relevance of weight as outcome in lifestyle studies, as most patients regain weight soon after a terminated intervention, and solely focusing on weight reduction might have unhealthy implications. Our sample has a low mean age and very low cardiorespiratory fitness, and it might be just as clinically relevant for these patients to improve cardiorespiratory fitness than to lowering traditional risk factors for cardiovascular disease.

Strengths and limitations

The CHANGE trial has several strengths. First, the design has central randomization, blinded outcome assessments, data management, data analysis, and independent funding [73-79]. Second, we planned our sample size to avoid substantial type 2 errors. Third, we use a manual-based, well described, and evidence-based theoretical framework. Fourth, the approach has a high intensity intervention, offering an assertive approach with at least weekly personal contact. Fifth, we have a multifaceted method, allowing the staff to work on all the known risk factors. Sixth, our composite outcome integrates the results even though they might be heterogeneous. Seventh, by comparing care-coordination with the lifestyle coaching, we will be able to differentiate between the effect of sufficient monitoring and treatment of somatic comorbidity and the effect of lifestyle changes, so a significant difference between the two intervention groups will point at an add-on effect of lifestyle coaching. Eighth, all contacts, and the focus of the contact, with patients are registered. Ninth, the intervention is developed to be sustainable, using low-budget possibilities in the neighbourhood to enable the patients to create long lasting changes. Ninth, we will be able to follow patients through Danish publish register to assess any long-term effects [80].

There are also limitations. Regarding some of the secondary outcomes, we will not have power to detect a clinically relevant difference, for example smoking cessation, why this important outcome has been categorized as an exploratory outcome. The thorough examination at baseline might initialize some lifestyle changes in patients randomized to the control group. The external validity is directed by the selection of patients with abdominal obesity; hence our results will only be valid for this group of patients. Moreover, an unavoidably limitation is also the selection bias created by a heightened motivation to change lifestyle habits, just by accepting participation in the CHANGE trial. Choosing a surrogate outcome like the Copenhagen risk score is a limitation due to the risk scores possible

inaccuracy in predicting actual morbidity and mortality [81]. Furthermore, even though an individualized approach is necessary in order to implement lifestyle changes in daily life, it makes the trial vulnerable regarding its external validity, as not all patients will have the same interventions.

Conclusion

This paper describes the study protocol for a randomized clinical trial to investigate the effectiveness of a tailored, multifaceted health promotion intervention versus care coordination versus treatment as usual in patients with schizophrenia in outpatient care. The primary outcome is the risk of cardiovascular disease assessed at 12 months.

Secondary outcomes are physical health parameters, health related behaviours, and psychometric measures.

The lifestyle coaching is developed to adapt to real life, exploiting the possibilities of individual patients to create long lasting lifestyle changes. There is limited evidence to support the role of lifestyle interventions and care coordination in improving weight loss and reducing metabolic risk in schizophrenia. Several smaller studies have evaluated the effect of either physical activity or diet or smoking cessation programs. However, larger sample sizes and longer follow-up time are needed.

CHANGE will increase the evidence regarding physical health in this vulnerable population, and enable clinicians to provide treatment that will reduce the mortality gap.

Additional files

Additional file 1: Care coordinator manual.
Additional file 2: Diet manual.
Additional file 3: Physical activity manual.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
MN, OM, CP and JK conceived the trial. JK and MN wrote the first draft of the protocol. CG participated in the design of the trial, writing the manuscript, and critical revision of the work. HS and HCBN participated in the design of the trial, writing the manuscript, and critical revision of the work and were involved in the data collection. CH contributed with expertise in smoking cessation. SD and TAM contributed with expertise in physical activity and the design of the intervention, writing the manuscript, and critical revision of the work. CRH contributed with statistical expertise, writing the manuscript, and critical revision of the work. All authors read, improved, and approved the final manuscript.

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Paper II

RESEARCH REPORT

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

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Life expectancy in patients with schizophrenia is reduced by 20 years for men and 15 years for women compared to the general population. About 60% of the excess mortality is due to physical illnesses, with cardiovascular disease being dominant. CHANGE was a randomized, parallel-group, superiority, multi-centre trial with blinded outcome assessment, testing the efficacy of an intervention aimed to improve cardiovascular risk profile and hereby potentially reduce mortality. A total of 428 patients with schizophrenia spectrum disorders and abdominal obesity were recruited and centrally randomized 1:1:1 to 12 months of lifestyle coaching plus care coordination plus treatment as usual (N=138), or care coordination plus treatment as usual (N=142), or treatment as usual alone (N=148). The primary outcome was 10-year risk of cardiovascular disease assessed post-treatment and standardized to age 60. At follow-up, the mean 10-year risk of cardiovascular disease was 8.4±6.7% in the group receiving lifestyle coaching, 8.5±7.5% in the care coordination group, and 8.0±6.5% in the treatment as usual group (p=0.41). We found no intervention effects for any secondary or exploratory outcomes, including cardiorespiratory fitness, physical activity, weight, diet and smoking. In conclusion, the CHANGE trial did not support superiority of individual lifestyle coaching or care coordination compared to treatment as usual in reducing cardiovascular risk in patients with schizophrenia spectrum disorders and abdominal obesity.

Key words: Schizophrenia, abdominal obesity, CHANGE trial, lifestyle coaching, care coordination, cardiovascular risk, cardiorespiratory fit-

ness, physical activity

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The gap in life expectancy between patients with schizophrenia and the general population – twenty years shorter for men and fifteen years shorter for women[1,2] – is a major challenge to public health. About 60% of the premature mortality in schizophrenia is due to physical diseases[3], with cardiovascular disease explaining the majority[4].

Several factors contribute to the early and frequent development of cardiovascular disease in this population, including genetic vulnerability[5], metabolic adverse effects of antipsychotics[6,7], insufficient treatment of somatic comorbidity[8], and unhealthy lifestyle[9]. Of these risk factors, medication with antipsychotic drugs can be considered partly modifiable, as reducing doses or switching prescriptions only leads to moderate improvement of metabolic risk factors[10,11]. Insufficient treatment of somatic comorbidity and unhealthy lifestyle are potentially fully modifiable and, if they are properly targeted, life expectancy for patients with schizophrenia might improve.

Several clinical trials[12-14] have reported an effect of lifestyle modification in this population, indicating that weight reduction and smoking cessation are possible. However, there are still gaps in the current knowledge. Selecting the optimal outcome for trials aiming to reduce cardiovascular risk remains a challenge: weight reduction or weight gain prevention is the most used outcome, but the correlation between weight loss and mortality remains questionable[15]. To overcome this, composite surrogate outcomes assessing the risk of cardiovascular disease have been proposed[16]. Moreover, since the pathogenesis of cardiovascular disease is multifactorial, strategies to reduce multiple, concurrent risk behaviours are needed[17]. Interventions with long-term follow-up are also warranted, since there are no reasons to believe that changes in metabolic risk factors occur faster in patients with severe mental disorders than the general population[18]. Equally important are follow-ups after the intervention has ended, as the effect of lifestyle modification tends to vanish, and an intentional weight loss may be followed by an unhealthy weight gain in the majority of participants in behavioural trials[19]. Finally, it is crucial to evaluate the external validity of trials, which might be compromised by the recruitment of patients with a higher readiness to change and a lower degree of barriers to lifestyle modifications – such as cognitive impairment, anxiety or substance abuse – than the clinical population with severe mental illness as a whole. This can be minimized by pragmatic designs, with few exclusion criteria[20].

The CHANGE trial was designed to address the above-mentioned gaps. We conducted a randomized, pragmatic trial exploring if 12-month lifestyle coaching plus care coordination plus treatment as usual, compared to care coordination plus treatment as usual and to treatment as usual alone, could reduce the 10-year risk of cardiovascular disease in patients with schizophrenia spectrum disorders and abdominal obesity.

METHODS

Study design and participants

CHANGE was an investigator-initiated, independently funded, randomized, parallel-group, superiority, multi-centre trial with blinded outcome assessment. Patients were recruited from well-defined catchment areas in two major Danish cities (Aarhus and Copenhagen). The trial protocol was published in 2015 with no changes made to the original version[21].

Patients were eligible if aged 18 or older, receiving a diagnosis of schizophrenia (F20), schizoaffective disorder (F25) or persistent delusional disorder (F22) according to ICD-10 – as ascertained by the Schedules for Clinical Assessment in Neuropsychiatry (SCAN)[22] – and

having a waist circumference (measured between the iliac crest and the lowest rib) above 88 cm for women and 102 cm for men[23].
Eligible patients were verbally informed by the usual carer and, if accepting, referred to CHANGE research staff by phone or e-mail. An initial meeting was arranged at the research centre, the outpatient clinic, or patient's home. Verbal and written information on the trial was provided to all patients. Patients reporting current pregnancy or unable to provide informed consent were excluded. If the patient accepted participation in the trial, an informed consent form was signed and an appointment for collection of baseline data was made.
The Danish Ethical Committee (H-4-2012-051) and the Danish Data Protection Agency (referral number 01689 RHP2012-007) approved the trial.
Recruited patients were randomized with a 1:1:1 ratio to lifestyle coaching plus care coordination plus treatment as usual (CHANGE intervention), or care coordination plus treatment as usual, or treatment as usual alone. Randomization was stratified according to site (Copenhagen/Aarhus), gender, and a baseline high/low risk of cardiovascular disease. High risk was defined according to cut-off points from a Danish population study[24], using the Copenhagen risk score[16] with age standardized to 60 years.
The randomization was centralized and carried out by the Copenhagen Trial Unit using a computerized sequence with alternating block sizes (9, 12 and 15) unknown to the investigators. After the inclusion of a patient in the trial, one of the lifestyle coaches (see below) contacted the Copenhagen Trial Unit with a unique patient identifier plus stratification variables and in return received the patient allocation. Outcome assessors, statisticians and all investigators involved in the trial were blinded to patient allocation, but patients and the health professionals providing the interventions were not.

Lifestyle coaching

Lifestyle coaching was defined as affiliation to a CHANGE team member, offering a tailored, manual-based intervention targeting physical inactivity, unhealthy dietary habits and smoking, and facilitating contact to the patient's general practitioner to secure medical treatment of somatic comorbidities. The theoretical framework of the lifestyle coaching was based on the theory of stages of change[25], motivational interviewing[26] and an assertive approach adapted from the assertive community treatment[27]. Motivational interviewing is a method to help patients elicit their own wishes to change; the assertive approach allows the staff to be respectfully active and persistent in follow-up, and implement short message services, phone calls, home visits and meetings in the local area. These methods were incorporated into four manuals with detailed descriptions of the interventions addressing four tracks: care coordination, smoking cessation, healthy diet, and physical activity. Manuals are provided in the paper describing the trial protocol[21].
The coach offered home visits with systematic exploration of possibilities for physical activity in daily life, which were realistic and attractive to the patient. Dietary changes involved concrete examination of the patient's dietary habits, food purchases and cooking practices, and identification of economically realistic, easy and attractive possibilities for change. During home visits, the coach took part in the activities (e.g., physical activity or food purchases), if requested by the patient, to support lifestyle changes. Personal and professional networks were included if possible in individual plans. The smoking cessation program was adapted from that published by the Danish Cancer Society[28], and tailored to each patient in order to elicit and enhance motivation and maintain smoking cessation.

The patients were offered affiliation with the team member for one year, with at least one weekly personal meeting of variable duration, often one hour. Further support could be provided by text messages, phone calls and e-mail messages. The coach to participant ratio was 1:15.
Each participant was encouraged to choose if focus should be on one or more of the four possible tracks, and the lifestyle coach supported the patient in setting individual goals. The staff had access to baseline results regarding cardiorespiratory fitness, forced expiratory volume, anthropometric measures and metabolic variables, and used these in their first consultation with each patient to plan the further course.
The lifestyle coaches performed written registration of all contacts with patients including cancellations. All coaching sessions were classified, according to the focus area of each consultation, into care coordination, smoking cessation, healthy diet or physical activity.
Lifestyle coaches were health professionals (occupational therapists, physiotherapists or dieticians) with clinical experience in psychiatry. They received a 5-day course in motivational interviewing, a 5-day course in smoking cessation, a 1-day course in examination and treatment of lifestyle disorders, and a 2-day course in healthy dieting, all based on the Danish Health Authority guidelines. During the trial, lifestyle coaches had weekly sessions with supervision to ensure program fidelity. In addition to the intervention described above, the patients in the CHANGE group were offered care coordination (see below) and continued treatment as usual.

Care coordination

Care coordination was incorporated in the CHANGE group and implemented as add-on to treatment as usual in the care coordination group. The intervention was manual-based. The care coordinator, a trained psychiatric nurse, facilitated contact to primary care in order to ensure that the patients received optimal treatment of physical health problems. Each care coordinator had 30-40 participants assigned at a time. Affiliation to the care coordinator was offered for one year.
The care coordinators' contact with patients comprised personal meetings, phone calls and text messages. The frequency of contact was adjusted according to the individual need. The first meeting with the patient consisted of a general health talk about physical well-being and an evaluation of test results from the physical examination performed at baseline. Special attention was paid to symptoms of obstructive pulmonary disease, diabetes and cardiovascular disease. The care coordinator used a decision tree to plan the further course. In addition to the care coordination described above, the patients in this group continued treatment as usual.

Treatment as usual

All three groups of patients received treatment as usual for obese patients with schizophrenia. In Denmark all persons have a general practitioner and can consult her/him for free when needed. Patients in secondary mental health services stay affiliated with their general practitioner, who is responsible for treating abnormal results from the mandatory yearly screening of metabolic risk factors. No formalized extra effort was made regarding lifestyle counselling or treatment of physical disorders in the treatment as usual group. Results from the baseline assessment were available if requested by the patient or the usual carer and, if any of the results was a matter of urgent consideration, the CHANGE research team contacted staff at the psychiatric outpatient clinic.

Outcome assessments

The primary outcome was the 10-year risk of cardiovascular disease, evaluated post-treatment and standardized to age 60 years. We used the Copenhagen risk score, which is based on data from two large epidemiological studies in the Copenhagen area[16] and is recommended by the European Society of Cardiology for screening of cardiovascular risk[29]. This composite measure incorporates non-modifiable and modifiable factors. The non-modifiable factors include: gender, family history of cardiovascular disease (defined as parents suffering from a fatal or non-fatal cardiovascular event before the age of 55 years for fathers or 60 years for mothers), and prior heart disease (defined as myocardial infarction or verified atherosclerosis of coronary arteries). The modifiable factors include: smoking (defined as daily smoking, yes/no), diabetes mellitus (defined as either haemoglobin A1c >48 mmol/mol or receiving antiglycaemic drugs due to earlier confirmed diagnosis, yes/no), total cholesterol, high density lipoprotein (HDL) cholesterol, systolic blood pressure, and body mass index. Absolute risk was defined as the probability of a clinical event (ischaemic heart disease, myocardial infarction, stroke or death) happening to a person within 10 years. We calculated the risk for each patient, independent of age, as if age was 60, an approach recommended by the European Guidelines on Cardiovascular Disease Prevention in Clinical Practice[29] to assess risk in young individuals.

The key secondary outcome was cardiorespiratory fitness (the patient's maximal oxygen uptake was measured using a bicycle cardiopulmonary exercise test). Further secondary outcomes included: forced expiratory volume (measured with Easy-one® spirometer), waist circumference, systolic blood pressure (average of three values measured on the right upper arm in a sitting position after 10 minutes of rest, and before the bicycle test), resting heart rate, haemoglobin A1c, HDL and non-HDL cholesterol, and self-reported moderate and vigorous physical activity (using the Physical Activity Scale[30]).

The exploratory outcomes included: weight, body mass index, triglycerides, high sensitivity C-reactive protein, self-reported time spent sedentary[30], daily smoking (using the Fagerstrom Test for Nicotine Dependence€ [31]), diet (using the Dietary Quality Score[32]), positive and negative symptoms (assessed using the Scale for the Assessment of Positive Symptoms[33] and the Scale for the Assessment of Negative Symptoms[34]), cognition (assessed by the Brief Assessment of Cognition in Schizophrenia[35]), quality of life (evaluated by the Manchester Short Assessment of Quality of Life[36] and the EuroQOL Five Dimensions Questionnaire[37]), psychosocial functioning (explored by the Global Assessment of Functioning[38]), perceived health[39], and perceived stress[40].

Statistical analysis

We expected the experimental interventions to reduce the Copenhagen risk score by 2.5% in the CHANGE group compared with the care coordination group, and by 2.5% in the care coordination group compared with the treatment as usual group. As we planned to compare all three groups, we reduced our alpha level to 0.05/3=0.0167. Allowing a power of 90%, we estimated to recruit 150 participants to each intervention group, a total of 450 participants. This calculation was based on a standard deviation of 5.9% of the Copenhagen risk score as found in the Inter99-trial[24].

The primary outcome analysis was an intention-to-treat one. Multiple imputation was used to handle missing data. The imputations were

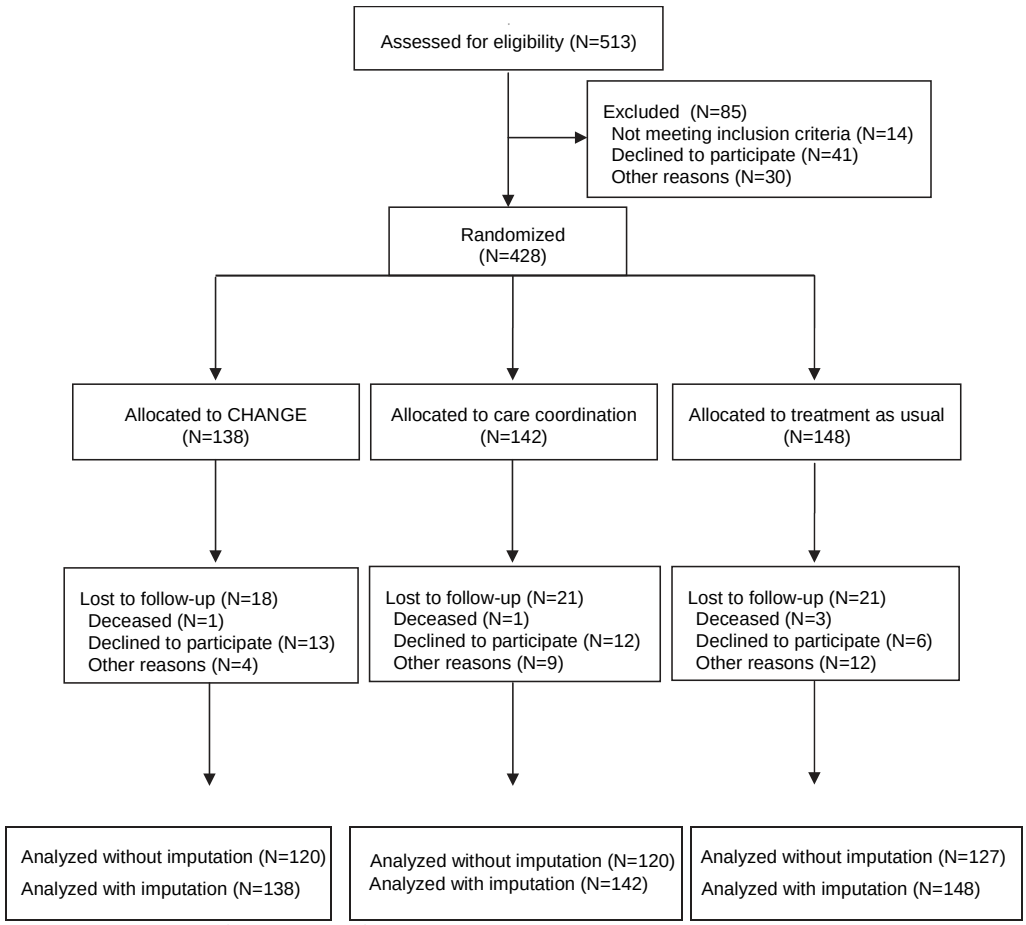

Figure 1 Flow diagram showing the process of recruiting and follow-up

based on a linear regression model with 100 imputations and 20 iterations. As predictors in the imputation model, we selected variables from a predefined list (age, gender, Global Assessment of Functioning score, duration of illness, daily dose of antipsychotic medication in chlorpromazine equivalents, and research centre) if they were significant predictors of the outcome variable or predictors of dropout ($p<0.05$ in a univariable model). These variables were, together with the baseline value of the variable and the randomization group, used as predictors for all imputations, if they had less than 5% missing values. Predictor variables with missing values were then simultaneously imputed along with the outcome variables. For the primary outcome, the composite values were imputed.

Analysis of covariance (ANCOVA) was used to calculate any significant differences between the three intervention groups, using the baseline value of each measure and the three stratification variables (gender, research centre and baseline risk of cardiovascular disease) as covariates. All distributions were assessed for normality using visual inspection of histograms and Q-Q plots. If not normally distributed, variables were log transformed, and if unsuccessful, a non-parametric test was used. For dichotomous outcomes, we performed multiple logistic regressions with treatment as usual as reference and stratification variables as covariates after having imputed missing values using a logistic regression model.

All tests were two-tailed. For the primary outcome, the p values were Bonferroni-adjusted (alpha level50.05/350.0167). We had several secondary and exploratory outcomes, and further Bonferroni correction would have been

too conservative, as this approach demands an assumption of independency between outcomes, which was not reasonable in our study. Therefore, p values for secondary and exploratory outcomes are presented unadjusted, and interpreted as follows: no effect of the experimental intervention if p0.05; a possible positive effect if p<0.05 but >0.001; a strong indication of a positive effect if p<0.001. Sensitivity analyses included an analysis of complete cases, removal of outliers (defined as standardized residuals greater than three standard deviations), a per-protocol analysis defining participants not having a single contact as violating the protocol, and a second per-protocol analysis including participants with at least 50% of intended personal meetings in the CHANGE group. This second per-protocol analysis is likely to cause severe selection bias, as the CHANGE group would include the participants with the highest level of motivation.

Table 1 Baseline socio-demographic and clinical characteristics

	CHANGE (N =138)	CARE (N=142)	TAU (N=148)	Total (N=428)
Age (years, mean ±SD)	37.8±12.6	39.5±12.8	38.5±11.8	38.6±12.4
Gender (female, %)	55.1	57.7	54.7	56.1
Work status (unemployed, %)	86.9	95.0	94.6	92.0
Living in supported housing (%)	8.7	15.5	16.9	13.8
Global Assessment of Functioning (mean ±SD)	44.5±11.3	42.9±9.8	43.7±9.1	43.7±7.5
Risk of cardiovascular disease (high, %)	5.8	7.0	5.9	6.3
Waist circumference (cm, mean ±SD)	113.7±15.8	115.3±14.6	114.8±14.2	114.6±14.8
Body mass index (mean ±SD)	34.1±6.0	34.2±5.9	34.2±6.1	34.2±6.0
Systolic blood pressure (mm Hg, mean ±SD)	126.5±12.8	128.0±13.4	128.3±16.0	127.6±14.2
HDL cholesterol (mmol/l, mean ±SD)	1.2±0.4	1.2±0.4	1.2±0.4	1.2±0.4
Non-HDL cholesterol (mmol/l, mean ±SD)	3.8±1.1	3.4±1.2	3.8±1.1	3.8±1.1
Haemoglobin A1c (mmol/mol, mean ±SD)	39.1±8.7	38.3±9.1	37.7±9.5	38.3±9.1
Diabetes (%)	18.6	17.0	9.5	15.0
Hypercholesterolemia (>5 mmol/l, %)	46.4	52.1	47.3	48.6
Hypertension (>140 mm Hg, %)	14.5	16.9	15.5	15.7
Cardiorespiratory fitness (ml O_2/kg/min, mean± (SD)	17.3±4.6	17.4±5.8	17.4±6.1	17.4±5.5
Daily smoking (%)	52.9	52.1	50.7	52.1
Substance dependence (ICD-10, %)	5.8	2.8	3.4	4.0
High alcohol consumption (%)	8.0	8.5	4.1	6.8
Schizophrenia (ICD-10, %)	90.6	91.5	83.1	88.0
Duration of illness (years, mean ±SD)	17.2±11.3	18.6±11.0	16.7±10.4	17.5±10.9
Antipsychotic daily dose in chlorpromazine equivalents (mg, mean ±SD)	453.4±398.8	502.3±389.5	464.7±406.0	473.5±397.9
Antidepressant use (%)	46.4	42.2	39.2	44.2
Mood stabilizers use (%)	8.7	13.4	9.5	10.5
Positive symptoms (SAPS global score, mean ±SD)	2.2±1.6	2.3±1.6	2.0±1.7	2.2±1.6
Negative symptoms (SANS global score, mean ±SD)	2.5±1.1	2.6±1.1	2.5±1.3	2.6±1.2
Cognition (BACS composite score, mean ±SD)	231.3±51.3	221.5±45.5	222.7±51.5	225.1±49.6

CARE – care coordination, TAU – treatment as usual, HDL – high density lipoprotein, HbA1c – haemoglobin A1c, SAPS – Scale for the Assessment of Positive Symptoms, SANS – Scale for the Assessment of Negative Symptoms, BACS – Brief Assessment of Cognition in Schizophrenia

High alcohol consumption was defined as >14 weekly alcohol units for men and >7 for women

Therefore, it was only considered meaningful to report negative results from this analysis.

RESULTS

Figure 1 illustrates the flow of patients through the trial. Between December 2012 and May 2014, 428 participants were assigned to receive the CHANGE intervention (N=138), or care coordination plus treatment as usual (N=142), or treatment as usual alone (N=148). According to the protocol, we ought to include 450 participants, but had to stop before, due to lack of referrals.

Retention proportion was 86.0% for the sample as a whole. There was no difference in the dropout rates among the three groups (p=0.68). 365 participants (85.3%) provided information enabling a calculation of the primary outcome at follow-up. The dropouts did not differ from completers regarding baseline metabolic or psychometric characteristics or pattern of medication, except for a smaller proportion of the former receiving antidepressant treatment (30.0% vs. 46.0%).

Table 1 shows the baseline socio-demographic and clinical characteristics of the patients. We included slightly more women, and the average age was 38.6 ±12.4 years. Most patients were diagnosed with schizophrenia (88.0%). The majority were unemployed (92.0%), and a small proportion

Table 2 Results for primary and secondary outcomes

	CHANGE	CARE	TAU	F	p
Primary outcome					
10-year risk of cardiovascular disease (%)					
Mean±SD[a]	8.4±±.7	8.5±7.5	8.0±±.5	1.04	0.41
Adjusted mean±SE[b]	8.3±0.3	8.±±0.3	8.1±0.3		
Secondary outcomes					
Cardiorespiratory fitness (ml O_2/min/Kg)					
Mean±SD[a]	18.1±5.5	18.0±±.8	18.2±±.7	0.8±	0.54
Adjusted mean±SE[b]	18.1±0.4	17.9±0.4	18.3±0.4		
Forced expiratory volume (l/sec)					
Mean±SD[a]	3.1±0.8	3.1±0.8	3.0±1.0	0.23	0.2±
Adjusted mean±SE[b]	3.0±0.04	3.1±0.04	3.1±0.04		
Waist circumference (cm)					
Mean±SD[a]	113.9±1±.8	115.8±1±.3	115.0±15.0	0.2±	0.79
Adjusted mean±SE[b]	114.8±0.7	115.1±0.7	114.8±0.±		
Systolic blood pressure (mm Hg))					
Mean±SD[a]	128.7±13.9	127.±±13.8	129.1±14.1	1.12	0.39
Adjusted mean±SE[b]	129.3±1.1	127.4±1.0	128.7±1.0		
Resting heart rate (beats/min)					
Mean±SD[a]	8±.4±14.9	87.5±15.5	8±.0±14.1	0.5±	0.±1
Adjusted mean±SE[b]	8±.9±1.0	8±.9±1.0	85.9±1.0		
HbA1c (mmol/mol)					
Mean±SD[a]	38.4±9.7	38.7±10.±	3±.7±±.9	3.±5	0.07
Adjusted mean±SE[b]	37.8±0.5	38.7±0.5	37.2±0.4		
HDL cholesterol (mmol/l)					
Mean±SD[a]	1.2±0.4	1.2±0.4	1.2±0.4	1.24	0.34
Adjusted mean±SE[b]	1.2±0.02	1.2±0.02	1.2±0.02		
Non-HDL cholesterol (mmol/l)					
Mean±SD[a]	3.8±1.1	3.9±1.2	3.8±1.1	0.29	0.77
Adjusted mean±SE[b]	3.8±0.1	3.8±0.1	3.8±0.1		
Moderate-vigorous physical activity (hours/week)					
Mean±SD[a]	2.5±4.0	3.1±4.4	2.5±4.0	0.99	0.43
Adjusted mean±SE[b]	2.±±0.4	3.0±0.4	2.4±0.3		

CARE – Care coordination, TAU – treatment as usual, HDL – high density lipoprotein, HbA1c – haemoglobin A1c

[b] after multiple imputation; adjusted for gender, research center and baseline risk of cardiovascular disease

lived in supported housings (13.8%). There were 52.1% daily smokers and 15.0% had a diagnosis of diabetes. There were no differences between the intervention groups, apart from a higher proportion of participants living in supported housings (16.9% vs. 8.7%) and a smaller proportion having diabetes (9.5% vs. 18.6%) in the treatment as usual group compared with the CHANGE group.

In the CHANGE group, the mean number of personal meetings was 24.6614.5; 60.0% of the participants attended 21 or more of the intended 42 personal meetings; 97.8% had at least one personal meeting with their coach. The 73 daily smokers allocated to the CHANGE group received a mean of 11.269.3 sessions focusing on smoking cessation. For the group as a whole, there was a mean of 19.5613.1 meetings focused on physical activity, 6.366.6 on care coordination and 15.8611.2 on healthy dieting.

Results for primary and secondary outcomes are shown in Table 2. The mean age-standardized 10-year risk of

Table 3 Results for exploratory outcomes

	CHANGE	CARE	TAU	F	p
Weight (Kg)					
Mean±SD[a]	103.1±23.8	103.7±21.2	102.9±21.7	1.91	0.18
Adjusted mean±SE[b]	102.2±0.7	103.8±0.7	103.±±0.7		
Body mass index					
Mean (SD[a]	33.9±5.9	34.5±±.3	34.4±±.3	1.88	0.19
Adjusted mean±SE[b]	33.9±0.2	34.4±0.2	34.4±0.2		
Triglycerides (mmol/l)					
Mean±SD[a]	2.0±1.2	2.2±1.5	2.2±1.5	1.25	0.34
Adjusted mean±SE[b]	2.0±0.1	2.1±0.1	2.2±0.1		
Hs-CRP (mg/l)					
Mean±SD[a]	3.1±2.7	3.4±2.8	3.1±2.9	0.73	0.59
Adjusted mean±SE[b]	3.2±0.3	3.3±0.3	3.1±0.3		
Time spent sedentary (hours/day)					
Mean±SD[a]	9.9±3.6	10.5±3.4	9.9±3.5	1.23	0.36
Adjusted mean±SE[b]	10.1±0.3	10.4±0.3	9.9±0.3		
Daily smoking (yes/no)					0.65 (CHANGE vs. TAU);
%[a]	49.0	49.0	50.0		0.79 (CARE vs. TAU)
% (adjusted)[b]	49.0	49.0	50.0		
Intake of fruit (g/week)					
Mean±SD[a]	393.1±268.5	439.8±270.7	421.4±258.1	1.39	0.31
Adjusted mean±SE[b]	394.8±20.0	428.6±20.3	430.5±20.0		
Intake of vegetables (g/week)					
Mean±SD[a]	507.5±338.8	475.7±325.1	479.3±307.7	1.25	0.34

Adjusted mean±SE[b]	518.2±28.0	477.2±27.3	467.9±27.1		
Intake of fish (g/week)					
Mean±SD[a]	138.1±14.5	145.0±13.9	140.8±14.4	0.35	0.73
Adjusted mean±SE[b]	136.2±12.3	144.9±12.3	142.6±12.2		
Intake of saturated fat (yes/no)					0.08 (CHANGE vs. TAU);
%[a]	52.0	62.0	66.0		0.33 (CARE vs. TAU)
% (adjusted)[b]	55.0	59.0	65.0		
Positive symptoms (SAPS global score)					
Mean±SD[a]	1.7±1.6	1.7±1.6	1.8±1.6	1.44	0.29
Adjusted mean±SE[b]	1.±±0.1	1.6±0.1	1.8±0.1		
Negative symptoms (SANS global score)					
Mean±SD[a]	2.1±1.2	2.0±1.2	2.0±1.2	0.74	0.52
Adjusted mean±SE[b]	2.1±0.1	2.0±0.1	2.0±0.1		
Cognition (BACS composite score)					
Mean±SD[a]	244.3±50.1	235.8±50.2	242.0±49.5	2.54	0.12
Adjusted mean±SE[b]	238.8±2.2	239.0±2.2	244.1±2.1		
Quality of life (MANSA score)					
Mean±SD[a]	4.7±0.8	4.7±0.8	4.7±0.8	0.74	0.52
Adjusted mean±SE[b]	4.7±0.07	4.8±0.07	4.7±0.07		

Table 3 Results for exploratory outcomes (continued)

	CHANGE	CARE	TAU	F	p
Quality of life (EuroQOL score)					
Mean±SD[a]	1.4±0.3	1.4±0.3	1.3±0.3	1.14	0.36
Adjusted mean±SE[b]	1.4±0.03	1.4±0.03	1.3±0.03		
GAF total score					
Mean±SD[a]	49.4±11.2	47.6±9.8	47.8±9.4	1.19	0.35
Adjusted mean±SE[b]	49.0±0.8	48.1±0.8	47.6±0.8		
Perceived health					
Mean±SD[a]	2.8±1.0	2.8±0.9	2.7±0.8	0.33	0.74
Adjusted mean±SE[b]	2.7±0.1	2.8±0.1	2.7±0.1		
Perceived stress					
Mean±SD[a]	26.8±7.8	27.0±7.4	25.5±7.4	1.68	0.26

Adjusted mean±SE[b]	27.1±0.6	26.5±0.6	25.7±0.6

CARE – care coordination, TAU – treatment as usual, Hs-CRP – high sensitivity C-reactive protein, SAPS – Scale for the Assessment of Positive Symptoms, SANS – Scale for the Assessment of Negative Symptoms, BACS – Brief Assessment of Cognition in Schizophrenia, MANSA – Manchester Short Assessment of Quality of Life, GAF – Global Assessment of Functioning

[a] after multiple imputation; [b] adjusted for gender, research center and baseline risk of cardiovascular disease

For dichotomous outcomes, a mean difference in risk ratios was calculated using the risk ratio in the TAU group as reference

cardiovascular disease was 8.4±6.7% in the CHANGE group, 8.567.5% in the care coordination group, and 8.0±6.5% in the treatment as usual group ($F_{2,428}$51.04, p50.41).
The sensitivity analyses of the primary outcome using complete cases, or removing outliers, did not change the results. When analyzing complete cases, we found that the mean agestandardized 10-yearrisk of cardiovasculardiseasewas8.5±7.0% in the CHANGE group, 8.667.8 in the care coordination group and 7.4±5.3% in the treatment as usual group (p=0.46). After removing outliers, we found that it was 7.9±5.2% intheCHANGE group, 7.6±4.9% in the care coordination group and 7.1±4.1% in the treatment as usual group (p=0.18). After removing CHANGE participants who had less than half of the intended 42 sessions, we found that the mean risk was 8.6±7.7% in the CHANGE group, 8.6±7.8% in the care coordination group and 7.4±5.3% in the treatment as usual group (p=0.65). Equally, the per-protocol analysis removing the three participants with no contact at all to the coach did not change the results.
There were no differences between the three groups for any of the secondary outcomes. The means for cardiorespiratory fitness, our key secondary outcome, were 18.1±5.5 ml O_2/ min/Kg in the CHANGE group, 18.0±6.8 ml O_2/min/Kg in the care coordination group, and 18.2±6.7 ml O_2/min/Kg in the treatment as usual group ($F_{2,428}$=0.86, p=0.54).

The analyses revealed no significant differences between the three groups on any exploratory outcomes (Table 3). For weight, the means were 103.1±23.8 Kg in the CHANGE group, 103.7± 21.2 Kg in the care coordination group, and 102.9±21.7 Kg in the treatment as usual group ($F_{2,428}$1.91, p50.18). The proportion of daily smokers was 49.0% in the CHANGE group,

49.0% in the care coordination group, and 50.0% in the treatment as usual group (CHANGE group vs. treatment as usual group: p=0.65; care coordination group vs. treatment as usual group: p=0.79). Five patients died during the trial. The distribution can be seen in the flow diagram (Figure 1). The causes of death were cancer (N=2), suicide (N=1), and unexplained (N=2). Psychiatric hospitalizations amounted to 18.8% in the CHANGE group, 33.8% in the care coordination group and 24.3% in the treatment as usual group; the difference between the care coordination and the CHANGE group was statistically significant (p=0.004). Somatic hospitalizations amounted to 12.3% in the CHANGE group, 17.6% in the care coordination group and 16.2% in the control group
(p=0.40).

DISCUSSION

We hypothesized that a tailored, multi-domain intervention, delivered by personal coaching in a community setting, would lead to a meaningfully reduced risk of cardiovascular disease in patients with schizophrenic spectrum disorders and abdominal obesity. However, the findings of this trial suggest that neither the CHANGE intervention nor care coordination were superior to standard treatment in reducing the 10-year risk of cardiovascular disease.
CHANGE is the first trial, to our knowledge, to evaluate the effect of lifestyle interventions on a composite score estimating the risk of cardiovascular disease in patients with schizophrenic spectrum disorders. One U.S. study had explored the impact of care coordination in patients with severe mental illness, using a composite cardiovascular risk score, finding a significant effect[41]. Our negative results might be explained by better access to primary care in Denmark. Few of our participants had baseline values of lipids or blood pressure indicating a need for change in medication, according to the current guidelines for cardiovascular prevention[42], and only two had haemoglobin A1c values above the cut-off for diabetes without having being diagnosed and treated beforehand. This might be the result of a successful mandatory examination of blood lipids in the Danish Schizophrenia database, encouraging all clinicians across the three intervention groups to treat risk factors. Thus, the generalizability of results of care coordination might be limited to countries with similar health care systems. Also, we

cannot exclude that selecting a subgroup with more severe somatic comorbidities might have changed our results in favour of care coordination or CHANGE intervention.
For our key secondary outcome, cardiorespiratory fitness, few studies have evaluated the effect of lifestyle interventions in patients with schizophrenia, but they reported promising findings[43-45]. Trials evaluating the effect of behavioural interventions in reducing metabolic risk factors have shown mixed results[17]. Weight reduction is the most used outcome[46-55] and the evidence is reported to be favourable[17], although long-term trials are missing[18]. Trials exploring the effect of behavioural interventions frequently use dyslipidaemia[46,47,49,52], haemoglobin A1c[46,56] and blood pressure[46,49,52,56,57] as secondary outcomes, and the evidence is currently low or inadequate[17]. Thus, our results are not in line with previous trials regarding weight reduction and cardiorespiratory fitness, which might be explained by the clinical characteristics of our sample and the type of intervention.
The clinical characteristics of the sample we recruited reflect our inclusion and exclusion criteria. Our sample might differ from previous trials, as we aimed to optimize the external validity by having as few exclusion criteria as possible, being assertive in the process of recruitment, and offering an intervention without mandatory elements, in order to avoid exclusion of the severely ill (many trials exclude patients with somatic comorbidity, substance abuse or suicidal ideation) and volunteer bias.
The methods used to intervene reflect the chosen outcome variables. As cardiovascular disease is multifactorial, we thought that complex interventions should be the right approach. However, a majority of earlier trials have focused on single risk behaviours, such as diet or smoking or physical inactivity. Our intervention was heterogeneous, as every patient was free to choose the focus area for the intervention in dialogue with the coach. This might have limited our possibility to show an effect on single metabolic outcomes, thus reducing our power.
In spite of a high retention proportion (86.0%), the perprotocol analysis showed that only 60.0% of patients randomized to the CHANGE group attended at least half of the intended weekly meetings, indicating that offering a higher frequency of sessions or a lower caseload would doubtfully have led to different results.
The CHANGE trial had several strengths. First, the design had central randomization; blinded outcome assessments, data management and data analysis; and independent funding. Second, we planned our sample size to avoid substantial type II errors. Third, we used a manual-based, well-described and evidence-based theoretical framework. Fourth, we implemented a high-intensity intervention, offering an assertive approach with at least weekly personal contact. Fifth, we had a multifaceted method, allowing the staff to work on all the known risk factors. Sixth, our composite outcome measure integrated the results even though they might be heterogeneous. Seventh, by comparing lifestyle coaching with care coordination, we were able to differentiate between the effect of lifestyle changes and that of sufficient monitoring and treatment of somatic comorbidities. Eighth, all contacts with patients were registered. Ninth, the intervention was developed to be sustainable, using low-budget possibilities in the neighbourhood.
The ideal outcome measures for trials aiming to reduce mortality from cardiovascular disease are obviously hard ones like death. However, waiting for survival analyses is too time consuming and expensive for most studies, leaving surrogate outcomes as the second best choice. Currently there is no gold standard for surrogate outcomes in trials aiming to improve cardiovascular health, and the outcomes we chose for this trial have strengths and limitations. Strengths are that we used a composite score including several well-known risk factors. The score consisted of both modifiable and non-modifiable risk factors. This may be seen as a weakness, since it means that an intervention could affect all the modifiable risk factors, yet not affect the composite outcome measure. This was not an issue in the CHANGE trial, as there were no indications of significant reductions even in the separate modifiable risk factors. Conversely, we view our choice of primary outcome measure as a strength, as constructing a risk score without non-modifiable risk factors would not yield an accurate estimate of risk. A weakness, though, is the lack of validation of the surrogate measure in a population with

schizophrenia. In fact, research published after the initiation of this trial has questioned the generalizability of cardiovascular risk scores to people with severe mental illness[58].

As we did not succeed in recruiting the planned number of participants (we recruited 428 patients, while 450 were expected), we cannot exclude a risk of being underpowered, increasing the risk for type II errors. However, we find it unlikely that including22further participants would have changed our results substantially, and we still have a power of 87.2% regarding our primary outcome, which seems an acceptable one compared to most trials.

The lack of effect on individual risk behaviours should be interpreted with caution, due to insufficient power. Furthermore, existing tools measuring lifestyle changes have not been validated in a population with schizophrenia, where cognitive impairment and psychotic symptoms might compromise the validity. As self-reporting might be subject to both recall problems (introducing random errors and thus increasing the risk of type II errors) and social desirability bias (leading to systematic errors), more direct measurements like actigraphs would have been preferable, but they were not considered in this study due to logistic reasons.

In conclusion, the CHANGE trial provides evidence that a manual-based individual lifestyle coaching intervention does not reduce the 10-year risk of cardiovascular disease, compared with treatment as usual, in patients with schizophrenia spectrum disorders and abdominal obesity. Offering lifestyle interventions to this group might seem like a moral imperative, but, seen in the light of the lack of beneficial results and moderate compliance with weekly meetings with the coaches, it is just as imperative to ask whether this is the right approach to improve life for patients with schizophrenia. The general population, and even more, a vulnerable population like this one, is facing major barriers to making healthy choices and powerful pressures to select the unhealthy. We suggest that future research should focus on environmental/structural changes rather than individually anchored health interventions, taking into account the special needs of patients with schizophrenia.

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Paper III

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

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Key points

Question

Do lifestyle interventions work to manage weight, and are the effects clinically significant and sustainable in patients with severe mental illness?

Findings

In this meta-analysis of randomized controlled trials investigating lifestyle interventions to manage weight, we demonstrated a statistical significant reduction of weight compared to control groups. Number needed to treat to achieve clinical relevant weight loss (≥5%) was 11. The effect was not sustained and no improvement could be found for other metabolic risk factors. Adverse events were only sporadically reported.

Meaning

We found evidence supporting that individual lifestyle intervention is ineffective to manage weight gain in patients with severe mental illness. Evaluation of Interventions targeting environment and socioeconomic factors are needed to improve lifestyle in this population.

Abstract

Objectives

The objectives of this systematic review were to assess the benefits and harms of lifestyle interventions for weight reduction in patients diagnosed with serious mental illness.

Design

A systematic review with meta-analysis, meta-regression analysis, Trial Sequential Analysis, and Grades of Recommendations, Assessments, Developments and Evaluation (GRADE) to evaluate the quality of evidence.

Data sources

Searches for eligible trials were conducted in CENTRAL, MEDLINE, EMBASE, and Science Citation Index until 09/14/2016.

Eligibility criteria and outcomes

Randomized clinical trials assessing the effect of lifestyle interventions on physical health in patients diagnosed with schizophrenia, schizoaffective disorder, bipolar disorder or major depression were included. Primary outcomes were body mass index (BMI) and proportion achieving clinically relevant

weight loss (≥5%). Secondary outcomes included maintenance effect of weight change at follow-up, adverse effects (quality of life, hospitalization and deaths) and metabolic factors (blood pressure, cholesterol, fasting glucose, weight (kg), waist circumference).

Results

Thirty-eight randomized controlled trials enrolling 3306 patients were included. Three trials targeted diet, five exercise, and 30 a combination of both, all versus a control condition. The mean difference for BMI was -0.60 kg/m^2 (95% confidence interval (CI) -1.02 to -0.18; p= .005; I^2:72.3%) favoring the experimental intervention. The risk ratio for achieving clinically significant weight loss (≥5%) was 1.74 (95% CI 1.13 to 2.69; p= .012) in favor of the intervention, corresponding to a number needed to treat of 11 participants. Regarding the secondary outcomes, only waist circumference was significantly reduced in the intervention group compared to control group: -2.07 cm (95% CI -3.02 to 1.13; p= < .001). Trial Sequential Analysis excluded random error for the effect on BMI, but not for other outcomes. In the fully adjusted multivariate meta-regression model, only the geographical origin of the trial predicted efficacy. GRADE assessments showed very low and low quality of evidence.

Conclusions

We found a statistically significant, but questionable clinically relevant effect of lifestyle interventions on BMI with a NNT of 11 to achieve clinically relevant weight loss. There were no group differences regarding maintenance effect.

Systematic review registration

The protocol was registered at PROSPERO (CRD42016049093).

Introduction

Serious mental illness (SMI) reduces life expectancy, primarily due to somatic morbidity. [169–171] Failure to develop antipsychotics and mood stabilizing medications without obesogenic effects that are often used for SMI,[172] has led to an increased focus on individualized lifestyle interventions to prevent or counter obesity and related morbidity. Recent meta-analyses[81,82,151,173,83] have found beneficial effects of lifestyle interventions on weight and concluded that such interventions should be implemented to manage obesity in patients with SMI.[174] Indeed, the National Institute for Health and Care excellence (NICE) guidelines[175] recommend that "*People with psychosis or schizophrenia, especially those taking antipsychotics, should be offered a combined healthy eating and physical activity program by their mental healthcare provider"* and in case of rapid weight gain, lifestyle weight

management programs are first-line treatment.[175] However, evidence supporting these recommendations is unclear, and concerns have been raised regarding effectiveness in a real world setting, as well as regarding possible adverse effects.[176]

Randomized controlled trials (RCTs) can be categorized as explanatory (exploring efficacy) or pragmatic (exploring effectiveness), neither being superior to the other, but answering different research questions.[119] Behavioral interventions that address unhealthy lifestyle by targeting actions people take regarding their physical health warrant special considerations for people with SMI. Exclusion criteria based on practical and ethical concerns might limit the external validity, as patients with severe symptoms of SMI, substance abuse, or comorbid medical disorders are often excluded from RCTs. Furthermore, individuals volunteering to participate in behavioral trials are likely to be more motivated and well-functioning than the clinical population as a whole. Financial resources and human engagement in clinical trials will often exceed possibilities in clinical settings, evaluating interventions that are not transferable to real world. Based on these considerations, explanatory trials could be more likely to report positive results.

Furthermore, adverse effects of an intervention influence the chance to implement and for the patients to adhere to them. The possibility that behavioral interventions are potentially harmful is counter-intuitive, and therefore an assessment of their adverse effects is often neglected.[177] However, before implementation, evaluation of potential trade-offs are needed.

In order to evaluate the real-world effectiveness of behavioral interventions in SMI populations and provide recommendations for further research, we conducted a systematic review to answer the following questions: i) Do lifestyle interventions work to manage weight, and are the effects clinically significant and sustainable in patients with SMI?; ii) Are there any adverse effects?; and iii) What are the potential mediators and moderators of an observed effect?

Methods/design

The protocol for this review is available on PROSPERO (CRD42016049093).

Search strategy

The following electronical databases were searched until the 09/14/2016: CENTRAL, MEDLINE, EMBASE, Science Citation Index (Web of Science) using medical subject headings (MeSH or similar) when possible or text word terms: (schizophrenia, schizophrenic, psychosis, affective disorder, major depression, major depressive disorder, bipolar disorder, bipolar, schizoaffective, serious mental illness, severe mental illness, severe mental illnesses, seriously mentally ill, severely mentally , major

depressive disorder, antipsychotic) AND (nutrition, diet, exercise, physical activity, counselling, counseling, coaching, health education, health promotion) AND (weight loss program, weight reduction program obesity, weight, abdominal obesity, weight management, BMI, body mass index, overweight) AND (random, randomly, randomized). An example of bibliographic search is available as supplementary material.

Trial selection

Two investigators (KBJ + HS) examined titles and abstracts to remove obviously irrelevant reports. Three investigators (KBJ + ASJ + HS) independently examined full text reports and abstracts determining compliance with our inclusion criteria. Any disagreement was resolved by consensus with CH. Excluded trials were categorized per reason.

Inclusions criteria were:

1) Diagnosis of major depression, schizophrenia, schizoaffective disorder, or bipolar disorder.

2) Males and females aged > 17 years.

3) Allocation of participants to a lifestyle intervention *versus* a concurrent control group or allocate participants to a lifestyle intervention as an add-on to treatment as usual *versus treatment as usual*.

4) Individual lifestyle interventions, defined as interventions designed to affect the action a person takes regarding physical health at an individual level. Such interventions include body weight management aimed at modifying energy balance through improved diet, increased physical activity or both. These approaches may include techniques to modify behavior, like psychoeducation, psychological counseling, motivational interviewing, stages of change, or cognitive therapy. Studies of lifestyle interventions for weight loss could be delivered across any type of setting.

5) Randomized clinical trials (i.e., description of 'randomly', 'random', and 'randomization') without restriction with regards to language or type of publication.

Outcomes

Primary outcomes were 1) Weight measured as BMI and as number needed to treat (NNT) to reach clinically significant effect on weight (≥ 5% weight loss). Secondary outcomes were 1) Adverse effects (weight gain, quality of life, hospitalization, and death), 2) Maintenance effect of weight change 3) Metabolic risk factors (fasting glucose, cholesterol, blood pressure, and waist circumference)

Data extraction

ASJ and HS independently extracted data using a piloted form. Discrepancies in the data extraction were resolved by referring to the original papers. CG or JK assisted as adjudicator in cases of disagreements. Data extraction included, in addition to outcomes, information regarding hypothesized mediators and moderators listed in the published protocol. HS, ASJ and HCBN independently assessed risk of bias,[178] and KBJ assessed risk of bias for the CHANGE trial. HS and ASJ independently performed the assessment of ASPECT-R domains.[179] In case several methods of reporting outcomes were presented, we preferred in the following order: Post-intervention estimates > change from baseline>mean differences between groups.

Risk of bias assessment

Assessment of the risk of bias was conducted according to The Cochrane Handbook for Systematic Reviews of Interventions.[180] The following bias domains were assessed as high risk, low risk, or unclear: allocation sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and other bias. To be categorized as trials at "low risk", all domains had to be assessed as low risk, except for blinding of *participants*, which is practically impossible in behavioral trials. If allocation concealment domain, blinded *outcome assessment* domain and incomplete outcome data domain were assessed as low risk, trials were categorized as "lower risk".

Aspect-R

The ASPECT-R tool (A Study Pragmatic-Explanatory Characterization Tool-Rating; ©2014 Janssen Pharmaceuticals, Inc.),[179] which assesses six domains that are specifically related to the explanatory-pragmatic trial design spectrum, was developed to permit post-hoc evaluation of already published RCTs. The six domains covered by the ASPECT-R are i) eligibility criteria; ii) intervention flexibility; iii) practice setting/practitioner experience; iv) follow up intensity/duration; v) outcome(s); and vi) participant compliance assessment. We abstained from rating domain v and domain vi. Domain v, the relevance of the outcome is weight in all trials. Domain vi, monitoring of compliance, were insufficiently reported and did not allow for valid ratings.

Data synthesis and analysis

Mean difference, standardized mean difference (SMD), or risk ratio (RR) with 95% confidence intervals (CI) were pooled across trials using a random-effects model.[181] Heterogeneity was quantified

using the I-squared statistic, with I-squared ≥50% indicating significant heterogeneity.[182] Publication bias was assessed by visual inspection of a funnel plot and by Egger's test.[183] Multiplicity in this analysis was handled as suggested by Jakobsen et al.[184] accepting a P-value of .02 for primary outcomes and .01 for secondary outcomes. Trial Sequential Analysis[121] (TSA) were applied to calculate the diversity-adjusted required information size. The potential breach of the cumulative z-curves of the pre-defined trial sequential monitoring boundaries allowed us to control for the risks of random errors. This approach allows to differentiate significant results into "spuriously significant" (type I error) and "truly significant" and neutral results into "true neutral" or "spuriously insignificant" (type II errors) caused by lack of power. The models for all outcomes were based on alpha of 2% as described above, and a beta of 10%. The minimally clinically important differences set by consensus in the author group was 1 kg/m^2 for BMI, a relative risk reduction of 15% on the RR for achieving ≥5% reduction of baseline weight, or an effect size of 0.3 points, corresponding to small effect, for quality of life.

Exploration of heterogeneity

Exploration of heterogeneity was performed with meta-regression. Four categories of predictors were defined in the protocol: 1) Internal validity (risk of bias, drop out); 2) external validity (aspect-R); 3) population characteristics (age, sex, diagnoses, baseline-weight, illness duration, global assessment of functioning, negative symptoms, cognitive functions, supported housing, illegal drugs, inpatient/outpatient, medication); and 4) intervention characteristics (prevention/intervention, duration, intensity, modality (exercise/diet/both), and setting (individual/group/both)). Variables that predicted variance ($P < .05$) were included in a multi-regression model and backwards elimination was performed. To reduce the risk of type II errors, we abstained from performing regression with predictors that were available for less than 10 of the included trials. To reduce the risk of type I errors, we categorized results from the meta-regression as exploratory.

Grades of Recommendations, Assessment, Development and Evaluation (GRADE)

Five domains (risk of bias, imprecision, indirectness, heterogeneity and publication bias) were scored[185] and transformed into four possible grades of evidence for the outcome: 1. High quality. 2. Moderate quality. 3. Low quality. 4. Very low quality.

Deviations from our protocol

1) We removed the inclusion criteria stating that only trials reporting any measures of weight as outcome would be included, as we realized that keeping this criteria would have introduced outcome reporting bias into our review. 2) To restrict the number of primary outcomes, we chose to report BMI and NNT to achieve clinical relevant weight loss. All other outcomes were downgraded to secondary. 3) End scores were preferred above change scores, in line with recommendations[178] and to increase homogeneity 3) The decision to use TSA was made post hoc.

Results

Bibliographical search and trial characteristics

The bibliographical search was conducted the 14th of September 2016. Thirty-eight randomized controlled trials enrolling 3306 patients were included (eFigure 1). Characteristics of included trials are provided in table 1. The mean age in the intervention groups was 41.3 years versus 40.2 years in the control groups. Mean baseline BMI in intervention and control groups were 31.2 (SD 3.9) kg/m^2 vs. 30.8 (SD 4.3) kg/m^2. Treatment duration ranged from five to 104 weeks (mean=21.1, median=16). The number of intervention sessions ranged from five to 104 (mean=25.8, median=16). The follow-up duration after cessation of the intervention ranged from eight to 84 weeks (mean=32.1, median=24).

Bias risk assessments

Sequence generation was adequate in 25/38 (66%) trials, allocation concealment was adequate in 17/38 (45%) trials, blinded outcome assessment was performed in 21/38 (57%) trials, low risk of bias in the "incomplete outcome data" domain was found in 22/37 (58%) trials, selective outcome reporting domain was adequate in 16/38 (42%) trials. All 38 trials were at high risk of bias. According to our a priori defined criteria, 10/38 (26%) trials potentially had lower risk of bias.[133,134,92,84,85,141,146,126,144,150] Eighteen (47%) of the trials analyzed their results according to principles of intention-to treat, using a valid method (last observation carried forward was not accepted) (eTable 1).

ASPECT-R

Results for the ASPECT-R scores can be seen in table eTable 2. Given the range from 0-6 on the 4 scored ASPECT-R items, with 0 being entirely explanatory and 6 being entirely pragmatic, the average and median total scores (mean=13.3, median=14) and individual item scores mean=3.1-3.5, median=3-4) indicated that trials were somewhere in the middle on the continuum. Seven trials had total scores <10, and only 4 trials had total scores >16 (i.e., an average of >4 on each item).

Primary outcomes

Results are presented in table 2. Thirty-seven trials provided data on BMI (n=2,863). The effect of lifestyle intervention was a mean difference in BMI of -0.60 kg/m^2 (95% CI -1.02 to -0.18; P = .005; I^2:72.3%) versus control (figure 1). The diversity-adjusted required information size was 1,846, which was reached already after seven trials in the TSA analysis (eFigure 2), suggesting that the result is not a type I error. Eight trials[84,85,126,122–124,91,125] (n=1060) reported proportion of participants with clinically significant weight loss, defined as losing ≥5% of baseline bodyweight. The RR for clinically significant weight loss was 1.41 (95%CI 1.13 to 1.77; P = .003) in favor of the intervention. The corresponding NNT was 11 participants. The I^2 was 48.0%, suggesting moderate heterogeneity. As the required information size was not reached, type I error cannot be ruled out.

Secondary outcomes

Two of the secondary outcomes were significantly different in intervention group and control group. Weight in kg were reported in 32 trials[133,134,92,84,85,141,146,126,144,122–124,91,125,127–132,135–140,142,143,145,147,148] with a mean difference of -2.4 kg (95%CI -3.15 to -1.65; P< .0001; I^2=28.7%) favoring the intervention group compared with the control group. Waist circumference was reported in 21 trials,[176,133,92,146,128,130,132,135,138,142,186,187,87,188,96,97,88,189,190,95,191] with a mean difference of -2.1 (95%CI -3.02 to -1.13; P < .001; I^2=33.0%) cm compared with the control group.

Regarding adverse events, none of the included weight loss studies reported on the proportion of participants gaining ≥5% of baseline weight. Only five studies[133,84,85,126,142] reported other adverse effects, such as hospitalizations or death. There were 48 somatic hospitalizations in the experimental intervention group vs 60 in the control group. The numbers for psychiatric hospitalizations were 60 vs 77, and for deaths the numbers were 4 vs 7.

Publication bias

Funnels plots were inspected for all outcomes, without signs of publication bias, and Eggers tests were non-significant.

Meta-regression and subgroups

Across 10 different univariate meta-regression and 8 subgroup analyses (table 3), four significant moderators of treatment effects on BMI emerged: 1. Asian trials were more effective than trials from the USA, which were better than European trials; 2. Trials with broader inclusion criteria were less effective than trials with restricted inclusion criteria; 3. Trials with flexible interventions that could be

tailored to individual needs were less effective than rigid programs; and 4. Individual sessions were more effective than group sessions. However, after backward elimination, only the origin of the trial remained significant. Indeed, post-hoc comparisons of ASPECT-R ratings suggested more pragmatic features in the trials from Asia (eTable 4).

GRADE

GRADE scores were very low/ low (eTable 3) due to high risk of bias (lack of allocation concealment and blinding), inconsistency (high levels of heterogeneity), imprecision (required information size not reached) and indirectness (study sample differ from that of interest).

Discussion

Thirty-eight randomized controlled trials enrolling 3306 patients were included in this meta-analysis. All trials had a high risk of bias. The meta-analyzed estimates demonstrated a small effect of lifestyle interventions on BMI i.e. a reduction of less than two thirds of a BMI point in the context of a mean baseline BMI of 31.2 kg/m^2 across all included studies. Moreover, there was effect on BMI after the weight loss intervention was stopped. The probability of achieving clinically relevant weight loss, defined as ≥5% weight reduction, seemed higher in the intervention group (NNT=11 participants), but the risk of gaining weight was not reported, thus limiting the interpretability of this outcome. Only geographical place of study origin remained significant in predicting treatment effect in the multivariable model, with Asian trials being more effective than trials from USA, exceeding the efficacy of those from European studies. One explanation of this finding could be that Asian trials were more exploratory in the design (etable 4). Another explanation could be that the Asian culture is more authoritative, so that patients may adhere more stringently to the interventions, or it could be the result of different degrees of pressure to publish positive results. Finally, this finding might reflect a better "treatment as usual" condition in the USA and, especially, in Europe.

Strengths and limitations

This systematic review has several methodological strengths. We published our protocol a priori, and utilized a thorough search strategy. We considered relevant adjustment for multiplicity. Calculating required information sizes and conducting Trial Sequential Analysis enabled us to examine the potential presence of random type I and type II errors. The clinical relevance of the intervention effects was emphasized, as we also included patient-centered outcomes like quality of life, minimal clinically important differences, reported NNT and finally evaluated evidence according to GRADE. Limitations of our analyses included that all trials had a high risk of bias, lack of power on one of our

co-primary outcomes as well as on secondary outcomes, and a moderate degree of unexplained heterogeneity. Furthermore, very few reported adverse events, making it impossible to evaluate a potential beneficial effect.

The effect of lifestyle interventions on weight and metabolic risk factors

The first large meta-analysis in this area, Caemmerer et al.[81] reported that lifestyle intervention reduced weight by 3.12 kg or 0.94 kg/m^2 measured as BMI (n=404). Similarly, Bonfioli et al.[151] found a reduction of 0.98 kg/m^2 (n=311). Bruins et al.[82] reported a reduction in weight corresponding to an effect size of 0.63 and Gierisch et al.[83] reported a reduction of 3.14 kg (n=735) compared to the control group. Our finding of a reduction in BMI of -0.64 kg/m^2 (n=2,863) represents a reduction of experimental intervention effect compared to those of previous analyses. As we reached the required information size and as the cumulative z-curve breached the confidence boundary, we do not believe the observed effect is due to random error. Rather, it likely represents a true effect with limited clinical relevance, or may even be due to bias, which was found to be high across trials. Our neutral findings regarding the maintenance effect on BMI (-0.54 kg/m^2, n=1,410) is in line with the results previously reported by Caemmerer et al. finding no effect (-0.72 kg/m^2 (n=109), but contrasting Bruins et al.'s finding a significant effect (effect size -0.62; (n=474). For the maintenance effect, the required information size was not reached, and the confidence intervals were wider. This result might be a true neutral effect or inconclusive due to lack of power. However, seen in the light of the small reduction in BMI post intervention, it seems unlikely that the contribution of further randomized clinical trials will result in clinically significant effects.

Our results are therefore less convincing in supporting current guideline recommendations of employing behavioral healthy lifestyle interventions for antipsychotic-related weight gain and/or overweight or obesity[175] than former systematic reviews. We included recent large-scale trials with more pragmatic designs. Small trial bias in earlier analyses or the increasing focus on strict methodology (decreasing the risk of bias) and pragmatic designs could explain our more modest findings compared to former meta-analyses. It seems that by focusing on lifestyle interventions for obtaining weight loss for patients with SMI, we are faced with another example of intervention effects that goes from initial optimism into a more realistic and less costly skepticism.[192]

For quality of life, our results were convincingly neutral. The point estimate was close to zero, and the confidence interval (SMD = 0.03; 95%CI -0.15 to 0.21; P = .16)) neither included clinical beneficial nor harmful effects. However, based on the distance from our sample size to the required sample size, a type II error cannot be excluded.

However, clinicians are clearly left with the need to improve the patients` body weight and cardiometabolic abnormalities. Since behavioral weight loss interventions did not yield convincing benefits, add-on medications, such as metformin[193] or topiramate,[193] as well as antipsychotic switching[194] should be considered as treatment options. However, these interventions have yielded effects regarding BMI and body weight change that are in line with the prior meta-analyses for behavioral weight loss interventions[81,82,151,83] and have not been examined with TSA to rule out type I error. These findings underscore the need to prevent inordinate weight gain and metabolic side effect burden in the first place by choosing the lowest risk agents possible.[195]

Conclusions

We have little confidence that the initial mean reduction of 0.60 kg/m^2 will contribute to substantially better physical health in patients with SMI, as the effect was not maintained and had no significant effect on other cardio-metabolic risk factors. The number needed to treat for clinical significant weight loss was 11 participants, but none reported data enabling calculation of a number-needed-to-harm. Moreover, the low quality of the evidence most likely overestimates the effect. Thus, we find little support for implementing lifestyle intervention to counteract weight gain in patients with schizophrenia. We will, however, warn against a nihilistic attitude, as the burden of somatic morbidity among these patients remains a great concern.[196] We have two suggestions for further research: 1) A structural approach should be considered, based on principles of 'nudging' (making the healthy choices easy);[197,198] and 2) Based on a comprehensive model of determinants of health, up-stream socioeconomic factors like social isolation, employment, and stigma should be targeted, as these play a crucial role as moderators of lifestyle.

Competing interests

HS, JK, ASJ, HCBN, CP, CH, CG and MN have previously published a trial on this topic, which could introduce an academic bias in the current systematic review

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Contributors

HS conceived the project, collected data, did the statistical analysis, drafted and revised the manuscript. ASJ collected the data, revised the manuscript. HCBN and KBJ assessed bias and revised the manuscript. CG, MN, CP and CC assisted in design and revised manuscript. CH, JK, and CW assisted in collection of data and revised the manuscript

Transparency declaration

HS affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the protocol has been explained.

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Table 1: Trial, Population and Treatment Characteristics

	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	Prev
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	Prev
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	Prev
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	Prev
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	Prev
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 lifestyl	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	Prev
		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			
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 USA	71	52	81	Schizophrenia: 37% Major depression: 14% Bipolar: 25 %	AP: 100 %	26	22	84.1 kg	Behavior therapy Diet and exercise Group and individual	Written information on helathhealth subjects	OP	WL
Green et al. 2015 USA	200	47.2	28	Schizophrenia: 29% Bipolar: 69 %	AP: 91 % AD: 16.5% MS: 48.5%	24	24	38.3	Behavior therapy Diet and exercise Group	Treatment as usual	OP	WL
Iglesias-Garcia et al. 2010 Europe	15	39.9	68.8	Schizophrenia: 100%	AP: 100 %	12	12	32	Structured education Diet and exercise Group	Weekly weighings	OP	WL
Khazaahl et al. 2007 Europe	61	40.7	45.9	Schizophrenia: 73.8% Bipolar: 8.3%	AP: 100 % MS: 23%	12	12	30	Cognitive behavioral therapy Diet and exercise Group	Brief nutritional information	OP	WL
Kilbourne et al. 2012 USA	68	45.3	39	Bipolar: 100%	AP: 11 % MS: 26%	24	9	35.2	Tailored psychotherapy and caremanagement Diet and exercise Group and individual	Quarterly wellness newsletters	OP	WL
Kilbourne et al. 2013 USA	118	52.8	83	Bipolar: 97.5 % Schizoaffective: 2.5%	AP: 50 % MS: 77.1%	52	16	33.2	Tailored psychotherapy and caremanagement Diet and exercise Group and individual	Quarterly wellness newsletters	OP	WL
Kilbourne et al. 2016 USA	45	55.3	84.6	Schizophrenia: 7.3% Major depression: 57.1% Bipolar: 24%	AP: 38 % AD: 83.5% MS: 52.1	24	9	33.3	Tailored psychotherapy and caremanagement Diet and exercise Group and individual	Quarterly wellness newsletters	OP	WL

Kwon et al. 2006 Asia	48	30.9	31	Schizophrenia: 100%	AP: 100 %	12	10	26.81	Cognitive behavioral therapy Diet and exercise Individual	Routine care with verbal recommendations	OP	WL
Lee et al. 2014 USA	1622	44.1	54.5		AP: 100 %	8	8	33.4	Pedometers and eight weekly phone calls Exercise Individual	Written information on physical activity	OP	WL
Littrell et al. 2003 USA	70	33.7 34.5	61.4	Schizophrenia: 77% Schizoaffective: 33%		16	16	26.3	Psychoeducation Diet and exercise Group	Usual care	OP	Prev
Lovell et al. 2014 Europe	89	25.7	60	Schizophrenia: 83% Schizoaffective: 2%		24	8	32.7	Motivational and behavioral therapy Diet and exercise Group and individual	Usual care	OP	Prev
Marzolini et al. 2009 canada	13	44.6	61	Schizophrenia: 100%	AP: 100 AD: 15 MS: 53	12	24	27.2	Exercise twice weekly Exercise Group	Usual care	OP	
Mauri et al. 2008 Europe	33	38.9	42.8	Schizoaffective: 10.2 % Major depression 2% Bipolar: 87.7 %	AP: 100 %	12	12	30	Psychoeducation Diet Individual	Usual care	OP	WL
McKibbin et al. 2006 USA	57	I:53.1 C:54.8	64.9	Schizophrenia: 84.2% Schizoaffective: 15.8%	AP: 100 %	24	24	33.6	Health education classes Diet and exercise Group and individual	Written material on healthy lifestyle	OP	WL
Methapatara et al. 2011 Asia	64	40.4	64	Schizophrenia: 100%		12	5	28.4	Group education. Pedometer walking Diet and exercise Group and individual	Written material on healthy lifestyle	OP	WL

Milano et al. 2007 Europe	36	45 (N/A)	44		AP: 100	12	27	27.2	Calorie restriction and exercise three times a week Diet and exercise Group and individual	Usual care	OP	Both
Scheewe et al. 2013 Europe	54	I:29.2 30.1	73	Schizophrenia: 76% Schizoaffective: 24%	AP: 100 %	24	48	26.6	Strict protocol physical exercise twice weekly Exercise Group	Occupational therapy	IP/OP	WL
Scocco et al. 2006 Europe	18	46.4	55	Schizophrenia: 75% Schizoaffective: 25%	AP: 100 %	8		29	Weight control education Diet Individual	Usual care	OP	Both
Skrinar et al. 2005 USA	20	I:39.7 C:36.3	33	Schizophrenia: 100%	AP: 100	12	48	32.9	Four weekly training sessions. Diet and exercise Group and individual	Recordkeeping on physical activity	IP/OP	Both
Speyer et al. 2016 Europe	280	38.6	44	Schizophrenia: 90% Schizoaffective: 10%		52	42	34.2	Tailored healthcoach. MI Diet and exercise Group and individual	Care coordination	OP	WL
Ratliff et al. 2012 USA	30	50.1	35	Schizophrenia 60%		8	8	41.6	Financial reimbursment Diet and exercise Group	Wait list	OP	WL
Usher et al. 2013 Australia	101		54.5	Schizophrenia: 84.2% Major depression: 6.9% Bipolar: 6.9%	AP: 100 %	12	12	33.3	Weekly health education Diet and exercise Group	Usual care	OP	WL
Weber et al. 2006 USA	157		29	Schizophrenia: 100%	AP: 100 %	16	16	33	Cognitive behavioral therapy Diet and exercise	Usual care	OP	WL

									Group			
Wu et al. 2007 Asia	53	I:42.2 C:39	41.51	Schizophrenia: 100%	AP: 100 %	12	11	30.3	Psychoeducation Diet and exercise Group and individual	Monthly treadmill test and weighing	IP	WL
Wu et al. 2008 Asia	64	26.3	64	Schizophrenia: 100%	AP: 100 %	24	72	24.5	Dietary and training program Diet and exercise Individual	Usual care	IP	WL

Legend: Trial characteristics. AP: Antipsychotics; AD: Antidepressants; ANX: Anxiolyticsa; MS: Mood Stabilisers; OP: Outpatients; IP: Inpatients; WL: Weight loss; Prev.: Prevention;

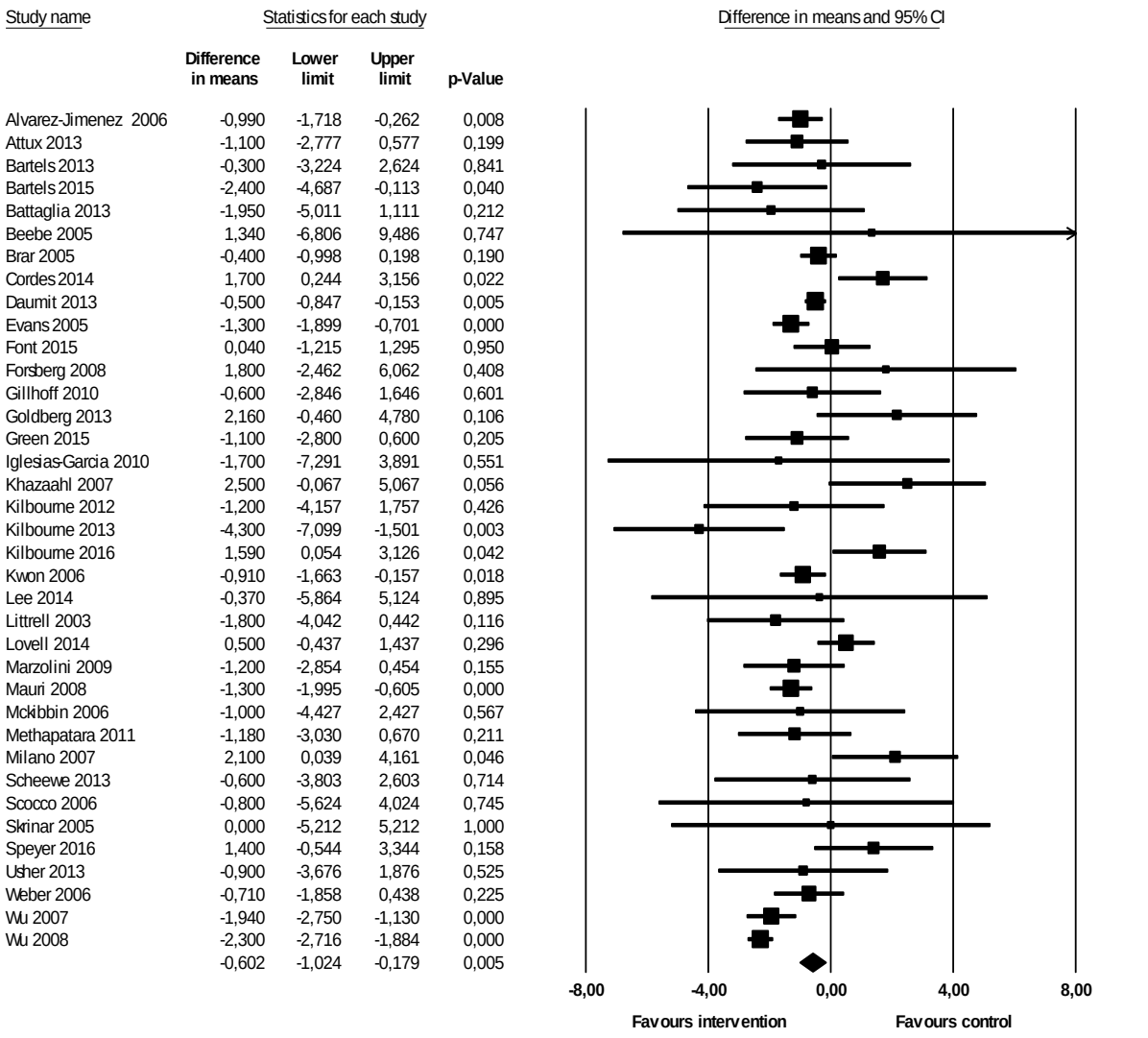
Table 2: Results of uUnivariate meta-reagression analyses

		Coefficient	Standard Error	95% Confidence Interval		2-sided P-value	R^2
Continuous variables							
	Age (years)	0.04	0.03	-0.01	0.09	0.17	0.18
	Baseline BMI	0.05	0.052	-0.05	0.17	0.31	0.18
	Gender (% males)	0.00	0.01	-0.03	0.03	0.87	0.00
	Duration of intervention	0.01	0.01	0.00	0.02	0.15	0.00
	Sessions offered	0.00	0.00	-0.01	0.01	0.75	0.00
	Program fidelity	-0.03	0.03	-0.09	0.02	0.25	0.06
	Drop-out rate	0.01	0.07	-0.12	0.15	0.83	0.00
	Duration of illness	0.05	0.08	-0.11	0.20	0.53	0.13
	Eligibility (Aspect)	0.31	0.12	0.08	0.54	0.01	0.45
	Flexibility (Aspect)	0.25	0.13	0.00	0.50	0.05	0.18
	Expertise (Aspect)	0.08	0.24	-0.39	0.55	0.74	0.00
	Intensity (Aspect)	0.16	0.24	-0.31	0.62	0.51	0.00
	Total score (Aspect)	0.05	0.02	0.01	0.09	0.01	0.14
		Point estimate					
Categorical variables							
Setting	Inpatients (n=2)	-1.17	0.72	-2.58	0.24	0.52	0.11
	Mixed (n=4)	-0.55	1.21	-2.92	1.83		
	Outpatients (n=31)	-0.54	0.21	-0.95	-0.13		
Diagnoses	Affective (n=5)	-0.96	0.84	-2.61	0.69	0.99	0.00
	Mixed (n=12)	-0.21	0.36	-0.91	0.49		
	Schizophrenia (n=20)	-0.84	0.29	-1.41	-0.27		
Modality	Both (n=29)	-0.50	0.25	-1.00	0.00	0.07	0.09
	Diet (n=3)	-1.30	0.24	-1.76	-0.83		
	Exercise (n=5)	-1.13	0.65	-2.40	0.14		
Origin	Asia (n=4)	-1.69	0.38	-2.44	-0.94	0.0011	0.41
	Europe (n=14)	0.09	0.38	-0.65	0.83		
	Other (n=3)	-1.11	0.55	-2.20	-0.03		
	Usa (n=16)	-0.68	0.26	-1.20	-0.17		
Method	Combination (n=15	-0.43	0.31	-1.05	0.18	0.0003	0.18
	Groups (n=14)	-0.31	0.37	-1.03	0.42		
	Individual (n=8)	-1.36	0.28	-1.90	-0.81		
Aim	Prevention (n=8)	-0.69	0.38	-1.43	0.05	0.6931	0
	Intervention (n=29)	-0.61	0.26	-1.11	-0.11		
Risk of bias	Lower (n=10)	-0.53	0.42	-1.36	0.31	0.82	0
	High (n=37)	-0.71	0.23	-1.17	-0.49		
Missing data	Intention to treat (13)	-0.38	0.36	-1.09	0.34	0.39	0.00
	Observed cases (24)	-0.80	0.26	-1.31	-0.29		

Table 3: Result for primary and secondary outcomes

Variables	No. of trials	Pooled effect	95% CI	p	I^2 (%)
BMI kg/m^2	37	-0.6	1.02 to -0.18	.005	72.3
BMI (maintenance) kg/m^2	15	-0.48	-1.17 to 0.20	.16	45.1
Weight. kg	31	-2.4	-3.15 to -1.65	<.001	28.7
Clinical relevant weight loss ≥5%	8	1.5	1.07 to 2.13	.02	48
Clinical relevant weight loss ≥5% (maintenance)	6	1.16	0.90 to 1.15	.25	43.5
Quality of life (SMD)	12	0.03	-0.15 to 0.21	.72	64.4
Waist circumference cm	21	-2.07	-3.02 to 1.13	<.001	33
Glucose mmol/l	10	-0.07	-0.24 to 0.1	.42	49
Cholesterole mmol/l	13	-0.08	-0.17 to 0.01	.09	0
Systolic blood pressure mm/Hg	15	-0.65	-1.98 to 0.67	.33	0

Body mass index



Meta Analysis

Fig 1: Forest plot of body mass index change during the intervention phase. BMI: body mass index, SMD: standradised mean difference,

Appendix

Appendix I

Detailed plan of analyses

Trial overview
In the CHANGE trial, patients from Aarhus and Copenhagen were randomized to standard treatment plus care coordination and life style coaching (experimental group 1) versus standard treatment plus care coordination (experimental group 2) versus standard treatment (the control group). Inclusion criteria were a) schizophrenia, schizoaffective disorder or prolonged delusional disorder b) 18 years or older, c) waist circumference above 88 cm (F)/102 cm (M). Patients who were eligible according to inclusion criteria and who consented to participate after written and verbal information were included. Data were collected at baseline, after 12 and after 24 months. The primary outcome is a reduction in estimated 10 years risk of cardiovascular disease. This protocol was accepted by the Danish Ethical Committee: H-4-2012-051 and the Danish Data Protection Agency referral number: 01689 RHP-2012-007 and is registered on Clinical.Trials.gov (NCT 01585493) the 27th of March 2012.

The primary outcome and sample size
The primary outcome is the difference in 10 years risk of cardiovascular disease, between the three groups after 12 months. We want to be able to detect a minimum difference of 2.5% reduction between each of the experimental arms compared to the control group. Equally, a difference of 2.5% will be necessary for the CHANGE arm to be clinically significant superior to the care coordination arm.

As we plan to compare all three groups and accordingly we reduced our alpha level to 0.05/3 = 0.0166, to account for the type I error induced by multiple testing. Allowing a power of 90% we need to recruit 150 patients to each intervention group for a total of 450 patients. This calculation is based on an SD of 5.9% of the Copenhagen risk score as found in the Inter99-investigation.
Secondary outcomes and power

The power calculations for all secondary outcomes can be seen in the original design paper, hand is based on a sample size of 450 participants (150 in each group) and a power of at least 80%.
Cardiorespiratory fitness is defined as key secondary outcome, and viewed as an alternative measure of cardiovascular mortality, as there is an association between increase in fitness and decrease in mortality.

The mean cardiovascular risk score after 24 months will be presented in a subsequent publication, and will be treated as a secondary outcome.

Further secondary outcomes
Time spent on moderate, vigorous and sedentary activity a day. Waist circumference measured between the crista iliac and lowest rib. Blood pressure measured on the right upper arm after 10 minutes of rest in a sitting position - the average of the two last consecutive measurements will be reported. Resting heart rate after 10 minutes of rest. Forced expiratory volume (FEV1) measured with Easyone® spirometer. HDL, non-HDL cholesterol and HbA1c measurements.
The power calculations for all secondary outcomes can be seen in the original design paper, and is based on a sample size of 450 participants (150 in each group) and a power of at least 80%.
The secondary outcomes will be presented in the primary publication.

Exploratory outcomes

Anthropometric measures: weight in kg and body mass index.
Psychometric measures: positive and negative symptoms (SAPS and SANS), cognition (BACS), quality of life (MANSA and EQ-5D), global assessment of functioning (GAF), perceived health, and perceived stress.
Biomedical status measures: triglycerides, high sensitive CRP (hs-CRP), low-density lipoprotein cholesterol (LDL).
Lifestyle measures: food frequency questionnaire, 24 hours diet recall, self-reported point abstinence from smoking.

Serious adverse events are defined as hospitalizations and deaths from the time of randomization to the 12 months follow-up. Serious advents will be reported and a possible connection to the interventions will be evaluated.

All exploratory outcomes except 24-hour recall will be reported in the primary publication. The results from the recall interviews will be presented in a later publication.

Descriptive variables
For background variables, we will report age, sex, diagnosis, GAF, years of education, type and dose of antipsychotic medication, cognition, symptom severity and duration of illness. The distribution of these variables will be reported for all three groups, but the potential difference between groups will not be significance tested, as the potential difference has happened by coincidence if the randomization is correct.

We also collect detailed data on the pattern of the experimental groups contact with the coach and care coordinator: telephone contacts, home visits, focus of each contact, theoretical methods used and cancellations of appointments consultations. Except from a brief description of the contact patterns, these data will not be part of the primary publication.

Plan of statistical analysis

Significance levels
All tests will be two-tailed. For the primary outcome, the p-value will be Bonferroni adjusted, (0,05/3=0,0166). We have several secondary and exploratory outcomes, and further Bonferroni correction is too conservative, as this approach demands an assumption of independency between each case, which is not reasonable for our outcomes. Therefore, p-values for secondary and exploratory outcomes including outcomes after 24 months, will be presented unadjusted, and interpreted according to the following:

 $P \geq 0.05$: The trial results could not demonstrate an effect of the experimental intervention on the secondary outcome.

 $0.01 < P < 0.05$: The trial results indicate that there may be a positive effect of the experimental intervention on the secondary outcome. However, the indication is not strong.

 $0.001 < P < 0.01$: The trial results indicate that there may be a positive effect of the experimental intervention on the secondary outcome.

 $P < 0.001$: The trial results strongly indicate that there may be a positive effect of the experimental intervention on the secondary outcome.

Furthermore, it will be made clear that we did not expect to have power to detect an effect of the exploratory outcomes, and significant p-values should be interpreted with caution to avoid type I errors.

Analysis of the outcomes
The primary outcome analysis will be an intention-to-treat (ITT) analysis. In case more than 5% of data is missing at follow up multiple imputation will be used to handle missing data. The imputations will be based on a linear regression model with 100 imputations and 20 iterations. The pooled analysis will subsequently be used for our analysis.

As predictors in the imputation model, we will select the variables if they are predictors of the outcome or of having a missing answer (P<0.05 in a univariate model and less than 5% missing on the variable in question): the baseline value, randomization group, age, sex, GAF, duration of illness, dose of antipsychotic and city. We used this approach to avoid noise that would increase the risk of type II errors. We will report the extent and distribution of missing data in the primary publication.

For the primary outcome, analysis of covariance (ancova) will be used to calculate any significant results between the three groups, using the three stratification variables to preserve power. If significance level indicates a difference between two or more groups, further post hoc linear regressions will be performed with the stratification variables as covariates, and a post hoc including covariates that with prognostic value (univariate regression with correlation to dependent variable, p<0,10): baseline value, age, sex, GAF, symptoms severity, cognition, duration of illness and type and dose of antipsychotic drug.

The same methods will be used for continuous secondary and exploratory outcomes.

All distributions will be assessed for normality using visual inspection of histograms and Q-Q plots. If not normally distributed, variables will be log transformed, and if unsuccessful, a non-parametric test will be used.

For dichotomous outcomes, logistic regression will be the method of choice, including two dummy variables with the control group as reference and stratification variables as covariates. If none of the experimental groups are significantly correlated to the outcome (p>0,05), no further analysis will be performed. If one or both are significant, a model adjusted for important prognostic covariates will be done.

For outcomes after 24 months, continuous variables will be analysed using a repeated measurement, likelihood-based, mixed-effects model with an unstructured covariance matrix. This analysis will include measurement at baseline, 12 months, and 24 months follow up.

Sensitivity and explorative analyses of the primary outcome

We plan to make the following sensitivity analyses, to test the robustness of the findings from the primary analyses. The sensitivity analyses will be perceived as exploratory, and will not change our primary conclusion. The pre-planned sensitivity analyses includes an analysis of complete cases, a per protocol analyses defining participants not having a single contact as violating the protocol, and a second per protocol including participants with at least 50% of the intended personal meetings in the CHANGE group. The second per protocol will lead to serious selection bias, and only negative results will be presented as meaningful, as this will be a highly robust finding supporting negative results of the intervention.

Data-management and analyses
HS and HC will do the data management, and major decisions will be discussed with CH and JK. The results will be presented blinded for the rest of the group.

Changes from the design paper

We stated in the design paper, that we would use a mixed model with repeated measurement design to calculate the primary outcome. However, we failed to identify that we do not have a within-subject factor after only 2 measurements, why an ancova would be the method of choice. The mixed model will still be used for the long-term follow up after 24 months.
We have added a description of the pre-planned sensitivity analyses.

We have defined covariates for regressions and imputation models.

Appendix II

Supplementary material

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])) 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])))**

eTable 1: Risk of bias assessments.

Studies	Year	Random sequence generation			Allocation concealment			Blinding of outcome assessments			Blinding of outcome assessment			Incomplete outcome data			Selective reporting			Others bias		
		low	high	unclear	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			X		
Wu	2007			X			X			X		X			X			X		X		
Skrinar	2005			X			X			X		X				X		X		X		
Methapatara	2011	X			X			X				X			X		X					X
Bartels	2015	X			X			X				X		X			X		x	X		
Bartels	2013			X			X		X			X		X			X			X		
Green	2015	X			X					X		X		X				X		X		
Littrell	2003	X		X			X	X				X			X				X	X		
Khazaal	2007			X			X	X				X			X			X		X		
Evans	2005			X			X			X		X			X			X				X
Wu	2008	X			X			X				X		X			X			X		
Alvarez-Jimenez	2006	X			X			X				X	X				X			X		
Attux	2013			X			X	X				X			X				X	X		X
Battaglia	2013	X					X	X				X		X				x	X			X
Cordes	2014	X					X	X				X				X	X			X		
Daumit	2013	X			X					X		X		X			X			X		
Forsberg	2008	X					X			X		X			X			X		X		
Gillhoff	2010			X			X			X		X			X		X			X		
Green	2015	X			X				X			X		X			X			X		
Iglesias-Garcia	2010	X					X			X		X		X			X			X		
Kilbourne	2012			X			X	X				X		X				X				X
Kwon	2006			X			X		X			X			X				X	X		
Lee	2014	X					X			X		X		X				X				X
Lovell	2014	X			X			X				X		X			X			X		
Marzolini	2009	X			X					X		X			X		x		X	X		
Mauri	2008			X			X			X		X			X		x		X			X
Mckibbin	2006			X			X			X		X		X			X			X		
Scheewe	2013	X			X					X		X		X				X		X		
Scocco	2006			X			X			X		X			X			X		X		
Uscher	2013	X			X					X		X		X			X			X		
Weber	2006			X			X			X		X		X			X			X		
Milano	2007		X				X			X		X			X		x		X	X		
Speyer	2016	X			X				X			X		X			X			X		

Kilbourne	2013	X			X					X		X		X				X				X
kilbourne	2016	X			X			X				X		X				X		X		
Goldberg	2013	X			X		O	X				X		X				X		X		
Font	2015	X			X			X				X		X				X		X		
Brar	2005			X			X	X				X				X		X				X
Ratliff	2012	X			X				X			X			X				X			X

eTable 1: Risk of bias assessments.

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
Total mean (median)	13.3 (14)	3.2 (3)	3.2 (3)	3.5 (4)	3.1 (3)

eTable 2: ASPECT-R scores.

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 0.64 kg/m2 lower (1.06 lower to 0.224 lower)	-	2863 (37 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 0.54 kg/m2 lower (1.23 lower to 0.15 higher)	-	1412 (15 RCTs)	⨁◯◯◯ VERY LOW [a,d]	
Clinically significant weightloss	21.708 per 100.000	27819 per 100.000 (17.782 to 40.746)	**OR 1.39** (0.78 to 2.48)	1121 (9 RCTs)	⨁⨁◯◯ 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 (0.15 lower to 0.21 higher)	-	1309 (12 RCTs)	⨁⨁◯◯ LOW [a]	
Waist circumference	The mean waist circumference was 0 cm	The mean waist circumference in the intervention group was 2.13 cm lower (3.05 lower to 1.2 lower)	-	2128 (21 RCTs)	⨁◯◯◯ VERY LOW [a,b]	
Fasting glucose	The mean fasting glucose was 0 mg/dl	The mean fasting glucose in the intervention group was 0.07 mg/dl lower (0.24 lower to 0.1 higher)	-	1056 (10 RCTs)	⨁◯◯◯ VERY LOW [a,b]	
Cholesterole	The mean cholesterole was 0	The mean cholesterole in the intervention group was 0,08 lower (0.168 lower to 0.013 higher)	-	1658 (13 RCTs)	⨁◯◯◯ VERY LOW [a,b]	

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**				
Systolic bloodpressure	The mean systolic bloodpressure was 0 mmHg	The mean systolic bloodpressure in the intervention group was 0,66 mmHg lower (1.98 lower to 0.67 higher)	-	1733 (15 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

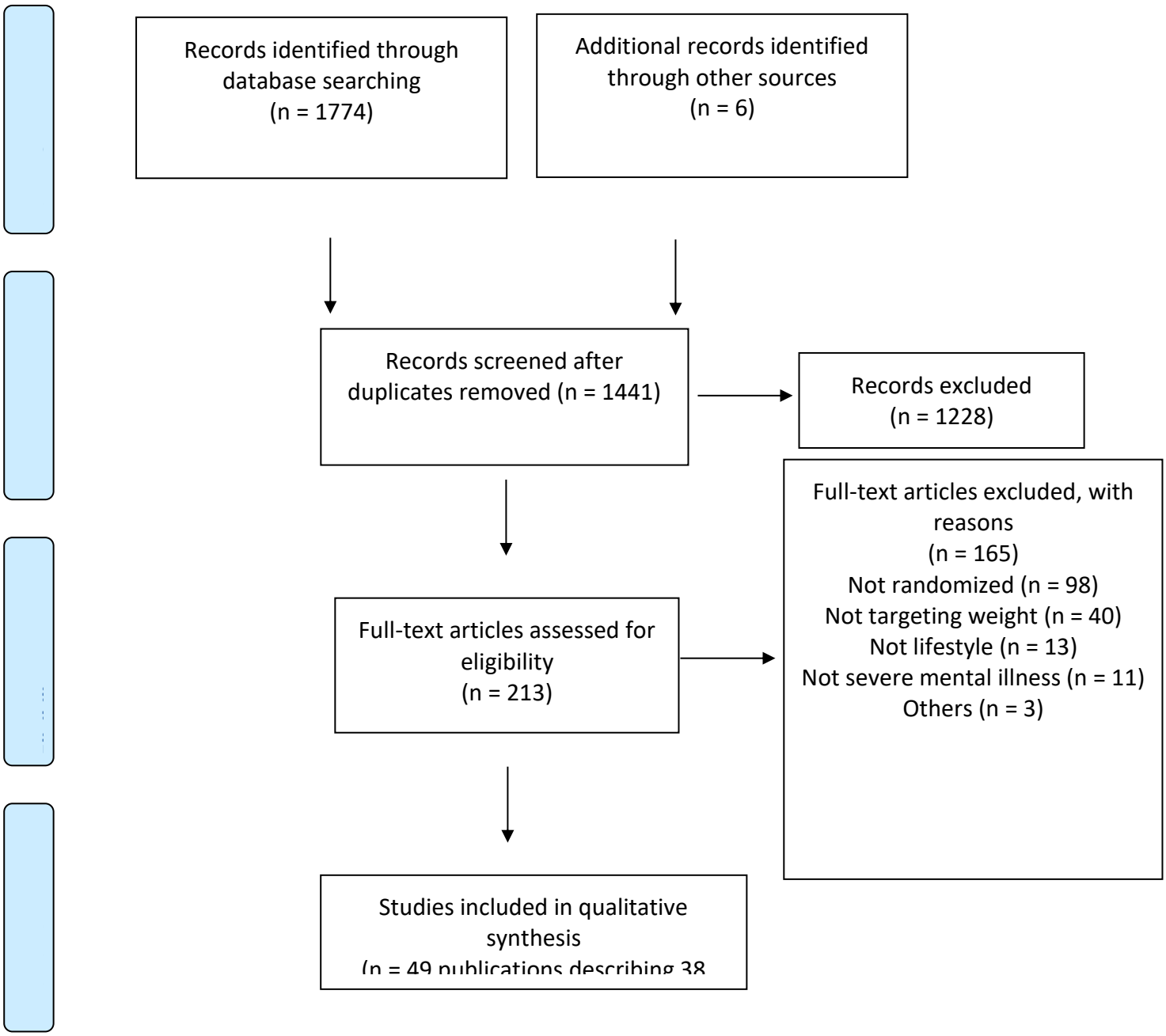
GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility 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

eTable 3: Grades of Recommendation, Assessment, Development and Evaluation (GRADE): Summary of findings

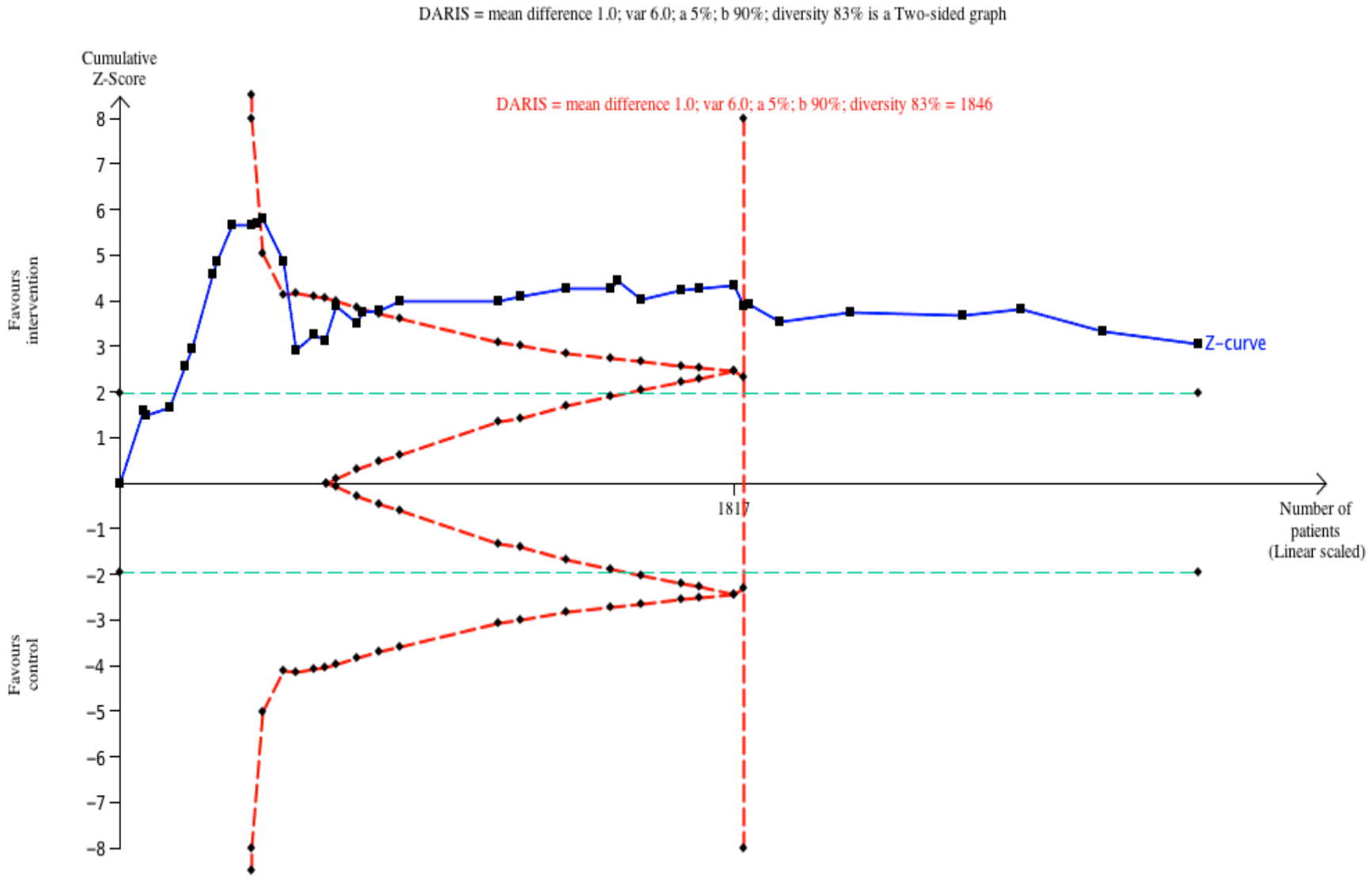
	Europe	USA	Asia	Europe vs. USA	Europe vs. Asia	USA vs Asia
				P	P	P
BMI change	0.09	-0.68	-1.69			
ASPECT total score	13.5	13.9	8	.64	.01	.004
ASPECT eligibility	3.1	3.8	1.2	.14	.02	.002
ASPECT flexibility	3.6	3.1	1.7	.43	.04	.09
ASPECT expertise	3.3	3.8	2.7	.11	.22	.02
ASPECT duration	3.3	3.1	2.2	.55	.05	.09

eTable 4: Aspect scores as a function of origin. BMI: Body mass index

eFigure 1: CONSORT flowdiagram



eFigure 2: Trial Sequential Analysis



DARIS = diversity-adjusted required information size

[Skriv tekst]