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# Associations between clinical and psychosocial factors and metabolic and cardiovascular risk factors in overweight patients with schizophrenia spectrum disorders – Baseline and two-years findings from the CHANGE trial

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ABSTRACT

*Objectives:* People with severe mental disorders die averagely 15 years earlier than people in the Western background population, cardiovascular disease being the most frequent cause of death with unhealthy eating habits and lower levels of physical activity as major contributing risk factors. Understanding possible associations and predictors of the specific cardiovascular risk may permit more targeted and effective prevention. The aim of this study was to investigate the associations between clinical and psychosocial factors and several separate cardiovascular risk factors in a cohort of 428 persons with schizophrenia and abdominal obesity enrolled in the CHANGE trial.

*Methods:* We used data from baseline and two-year follow-up of 428 individuals with schizophrenia spectrum disorders and abdominal overweight enrolled in the CHANGE trial. By linear regressions we explored the relationships between clinical and psychosocial factors and established cardiovascular risk factors: Dependent variables were baseline and follow-up values of the following: $VO_2$max, waist circumference, high density lipoprotein (HDL), systolic blood pressure and HbA1c. Independent variables were baseline values of the following: negative symptoms, positive symptoms, cognition, level of functioning, antipsychotic medication, duration of illness, employment situation and whether the participants had any friend.

*Results:* Negative symptoms were associated with most baseline- as well as two-years-outcome; negatively with cardiorespiratory fitness and with dietary quality and with HDL, and with increasing values of the variables waist circumference, BMI and HbA1c. Negative symptoms were seen also to predict poorer cardiorespiratory fitness and larger waist circumference, higher HbA1c and lower HDL at two year follow-up. Level of functioning and Cognitive function correlated positively with cardiorespiratory fitness and HDL, and correlated negatively with waist circumference and HbA1c. Both parameters also predicted a better fitness, higher HDL and lower HbA1c at two year follow-up. Isolating the antipsychotic drugs known to give the worst metabolic adverse effects (olanzapine, clozapine, quetiapine), the dosage was positively associated with cholesterol, but not with any other outcome. Psychotic symptoms and duration of illness were not significantly associated with any outcome. Employment of any kind was significantly associated with cardiorespiratory fitness and negatively associated with waist circumference, BMI and systolic blood pressure. At two year follow-up associations were significant for the two year outcomes cardiorespiratory fitness and waist circumference. Friendship relations were negatively associated with waist circumference and positively with HDL cholesterol. None of the two year outcomes were predicted by friendship.

*Conclusions:* We found various clinical and psychosocial factors to be associated with less healthy lifestyle factors and higher risk of cardiovascular disease, with negative symptoms building the strongest associations, although a possible bidirectional causality needs to be regarded. Reduction of negative symptoms should be investigated further in order to reduce the increased cardiovascular morbidity and mortality in people with schizophrenia spectrum disorders.



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## 1. Introduction

Individuals with schizophrenia die on average 15 years before the general population (Hjorthøj et al., 2017), cardiovascular disease being the most common cause of death with an approximately 2- to 3-fold increased risk, compared to the general population (DE Hert et al., 2011; Correll et al., 2017). Contributing to the higher cardiovascular risk are elevated rates of overweight, hypertension, and diabetes (McEvoy et al., 2005). This overrepresentation of cardiovascular risk factors can partly be explained by unhealthy lifestyle factors: People with schizophrenia and schizoaffective disorder have been shown to engage in markedly less physical activity and have more sedentary behavior (Janney et al., 2015), smoke more tobacco and have unhealthier eating habits with a diet high in caloric intake, richer in saturated fats and poorer in fiber and fruit (Dipasquale et al., 2013).

Negative symptoms and cognitive deficits often seen in schizophrenia spectrum disorders are known to be more challenging to treat than psychotic symptoms (Remington et al., 2016). At the same time cognition and negative symptoms are known to substantially influence the functional and metabolic outcome of the disease (Bowie et al., 2006; Vancampfort et al., 2012), although their interrelationship and respective contributions are debated (Austin et al., 2013; Vancampfort et al., 2013). Previous research has demonstrated that negative symptoms result in motivational deficits towards physical activity and effort to maintain healthy eating habits (Vancampfort et al., 2015a), possibly mediated through the lack of autonomous motivation (Vancampfort et al., 2015b). The associations between cognitive ability and longevity is debated (Gottfredson and Deary, 2004), with some studies showing sign of this relation being mainly genetic (Arden et al., 2016), while others suggest that higher cognitive ability enhances individuals' care of their own health by learning, reasoning and problem-solving skills useful in preventing chronic diseases (Gottfredson and Deary, 2004).

Understanding possible associations and predictors of the specific cardiovascular risk factors in schizophrenia spectrum disorders may permit more targeted and effective prevention. The aim of this study was to investigate the associations between clinical and psychosocial factors and several separate cardiovascular risk factors in a cohort of 428 persons with schizophrenia and abdominal obesity enrolled in the CHANGE trial (Speyer et al., 2016).

We hypothesized that a higher baseline level of negative symptoms, poorer cognitive skills, and lower level of functioning and higher doses of certain types of antipsychotic medication would be associated with a worse cardiovascular risk profile in the form of increased body mass index and waist circumference, lower High Density Lipoprotein (HDL) cholesterol and higher glycosylated haemoglobin (HbA1c), poorer cardiovascular fitness and higher systolic blood pressure. We hypothesized that the same clinical and psychosocial parameters would also predict the same outcomes at two years follow up.

## 2. Methods

### 2.1. Subjects and study design

This is a secondary analysis of data from the CHANGE trial, the design and results of which have been described elsewhere (Speyer et al., 2015, 2016). Briefly, CHANGE was an investigator-initiated parallel-group, superiority, multi-center trial. Its original aim was to investigate the effect of a lifestyle coaching intervention on cardiovascular risk. 428 patients were recruited via referrals from primary and secondary health care and hospital admissions. Inclusion criteria were a diagnosis in the schizophrenia spectrum (schizophrenia, delusional disorder or schizoaffective disorder – DF20, DF22 and DF25, respectively, according to the ICD-10 (World Health Organization, 2010)) and a waist circumference above the recommendations from the Danish National Board of Health (Sundhedsstyrelsen, 2013) (88 cm and 102 cm for women and men, respectively). Exclusion criteria were only self-reported pregnancy and inability to give written informed consent. The participants were centrally randomized 1:1:1 to 12 months of either lifestyle coaching plus care coordination (N = 138), care coordination (N = 142) or treatment as usual (N = 148) (Speyer et al., 2015, 2016). Blinded outcome assessment was made at baseline, after one year and after two years.

### 2.2. Outcomes

In this post-hoc analysis of the CHANGE Study, we used data from baseline and two-year follow-up to explore the relationships between clinical and psychosocial factors and established cardiovascular risk factors in the participants.

Weight was measured using a standard calibrated floor scale without requiring the subject to undress and Body Mass Index (BMI, kg/$m^2$) was calculated. We assessed waist circumference midway between the lower rib margin and iliac crest at expiration, systolic blood pressure as average of three values measured on the right upper arm in a sitting position after 10 min of rest, and blood was sampled non-fasting to measure haemoglobin A1c (HbA1c), high density lipoprotein cholesterol (HDL), since HDL is a superior measure of risk for CHD compared with total cholesterol or LDL cholesterol (Wilson et al., 1998; Thomsen, 2005).

As cardiorespiratory fitness has been shown to be a more important cardiovascular risk factor than time spent sedentary or time spent on moderate-to-vigorous physical activity (Knaeps et al., 2016), cardiorespiratory fitness was measured as the participants' maximal oxygen uptake ($VO_2$max) using a bicycle exercise test based on L. B. Andersens cycle exercise protocol (Andersen, 1995). During the initial 5 min of the cycle test (Monark) the workload is 75 W for women, and 100 W for men. The workload is then increased by 25 W/2 min. The participants were continuously verbally encouraged to keep a speed of 100 pedal treads/min until exhaustion.

We assessed cognition using the Brief Assessment of Cognition in Schizophrenia (BACS) (Keefe et al., 2004), and calculated T-scores by comparing with a sample of 50 Danish healthy controls (Dannevang et al., 2016). Level of functioning was evaluated using the Global Assessment of Functioning (GAF) score on a 1-to-100 scale (Pedersen et al., 2007), psychotic and negative symptoms were assessed by SAPS (Andreasen and University of Iowa, 1984) and SANS (Andreasen and University of Iowa, 1983), respectively, both estimated on six point likert scales going from zero (no symptoms) to five (severe symptoms). Global psychotic symptom score was calculated as the average of four psychotic dimensions (hallucinations, delusions, bizarre behaviour and thought disturbances). The global negative symptom score was equally calculated as the average of the four dimensions of negative symptoms on six points likert scales (avolition/apathy, anhedonia, affective flattening and alogia) (Andreasen et al., 1990). We explored life-satisfaction and –quality using the Manchester Short Assessment of Quality of Life (MANSA) (Björkman and Svensson, 2005). Medication history was obtained by oral interview. Dietary habits were evaluated as a Dietary Quality Score (DQS) (Toft et al., 2007) from an 8-item food frequency questionnaire that the participants were asked to complete. DQS was calculated from a three-point scoring system that was developed for each of the four food groups: fish, fruits, vegetables and fats. Summation of the four food variables resulted in a score ranging from 4 to 12 points. All assessments were performed by trained assessors and interrater reliability was frequently controlled by common ratings, which makes interrater subjectivity bias less likely.

### 2.3. Covariates

We included in our analyses as covariates certain factors that are known to potentially influence certain of our outcomes in interest: Age as continuous variable and sex were included as covariate in all analyses. Smoking is known to negatively influence cardiorespiratory

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