

# Metabolic syndrome and physical activity in patients with first-episode schizophrenia

PhD dissertation

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This PhD dissertation is based on the three papers. The papers have not earlier been part of a PhD dissertation or other theses. In the dissertation they are referred to as paper I, II and III.

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**Paper I:** Lene Nyboe, Claus Høstrup Vestergaard, Hans Lund, Marianne Kleis Møller, Poul Videbech  
*Metabolic syndrome in first-time hospitalised patients with depression. A 1 year follow-up study.* Acta Psychiatr Scand 2015: 1–8. DOI: 10.1111/acps.12470.

**Paper II:** Lene Nyboe, Claus Høstrup Vestergaard, Marianne Kleis Møller, Hans Lund, Poul Videbech  
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**Paper III:** Lene Nyboe, Marianne Kleis Møller, Claus Høstrup Vestergaard, Hans Lund, Poul Videbech  
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## Preface

Physical therapy is an evident and integrated part of mental health care in Denmark, including body awareness therapy, supervised physical activity and somatic rehabilitation. Physical therapists are subject to provide evidence-based treatment in line with other health professionals, and there is a growing need for research in this field. In relation to the present PhD thesis, my clinical experience with patients with schizophrenia has inspired the research questions regarding metabolic syndrome, low physical activity and anomalous bodily experiences.

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Aarhus, September 2015

Lene Nyboe

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## Abbreviations

AD:	Anti-depressive medication
AP:	Antipsychotic medication
BMI:	Body Mass Index
BP:	Blood pressure
CPZ:	Chlorpromazine equivalents
CVD:	Cardiovascular disease
DDD:	Defined daily dosages
EASE:	Examination of Anomalous Self-experiences
FES:	First-episode schizophrenia
FEP:	First-episode psychosis
FG:	Fasting-glucose
FGA:	First generation antipsychotics
GAF:	Global Assessment of Function
HR:	Heart rate
IDF:	The International Diabetes Federation
IFG:	Impaired fasting glucose
IGT:	Impaired glucose tolerance
MetS:	Metabolic syndrome
PAS:	Physical Activity Scale
PSQI:	The Pittsburgh Sleeping Quality Index
SANS:	Scale for Assessment of Negative Symptoms
SAPS:	Scale for Assessment of Positive Symptoms

SGA:	Second generation antipsychotics
SSRI:	Selective serotonin reuptake inhibitor
TCA:	Tricyclic antidepressants
T2D:	Type 2 diabetes
WC:	Waist circumference
WHO:	World Health Organization



## 1. Introduction

Schizophrenia is a severe mental illness and one of the most debilitating disorders worldwide. The overall prevalence of schizophrenia is 1 % and the incidence of schizophrenia in Denmark is 500 new patients every year. Approximately 12.000 people with schizophrenia receive treatment from the Danish mental health system. Another 3.000-4.000 patients with schizophrenia receive treatment from their general practitioner, from a specialist in psychiatry, or no treatment at all. Schizophrenia is an episodic illness with a highly various course. Prospective studies of first-episode schizophrenia have found that 25-30 % of all patients have complete remission of symptoms, 50 % have a moderate course with intermittent symptoms, and 20-25 % have a chronic course of the illness<sup>1</sup>. Schizophrenia is often associated with significant impairments in social and vocational functioning and a reduced lifespan.

Patients with schizophrenia have a 15-20 years shorter life-expectancy compared with the general population<sup>2</sup> and the excess mortality in patients with schizophrenia is well-documented<sup>3-9</sup>. Although there is a high risk of suicide among patients with schizophrenia<sup>10</sup>, mounting evidence suggests that the shorter life-expectancy is due to death from natural causes, in particular from increased cardiovascular mortality<sup>5,11,12</sup>. A review from 2012 identified four main reasons for the shorter life-expectancy: 1) an unhealthy lifestyle, including physical inactivity, smoking, poor diet and alcohol; 2) adverse effects of antipsychotic medicine; 3) delayed diagnosis and insufficient treatment of physical illness; and 4) a higher risk of suicide and accidents<sup>13</sup>.

The concept of metabolic syndrome (MetS) is helpful in screening and monitoring the risk of cardiovascular disease (CVD) and has therefore been studied intensively in relation to patients with schizophrenia in the past decades<sup>14</sup>. However, there is limited knowledge about the course and non-pharmacological predictors of MetS in patients with first-episode schizophrenia (FES). Mounting evidence suggests that physical inactivity is strongly correlated with an increased risk of MetS<sup>15,16</sup>. Yet, the correlation of physical activity and MetS in patients with FES has not previously been sufficiently addressed. Likewise, only a few studies have compared the prevalence of MetS in patients with FES and healthy controls; and no studies have compared the prevalence of MetS in patients with FES against patients with other severe mental illness e.g. severe depression. Given the fact that patients with depression have a significant risk of cardiovascular disease<sup>17,18</sup> it is relevant to compare the prevalence of MetS in patients with FES and patients with depression.

In the present PhD dissertation we studied the prevalence and course of MetS in patients with FES compared with both first-time hospitalised patients with depression and healthy controls. Furthermore, we

investigated the impact of physical activity on MetS in patients with FES. Finally we explored the effect of anomalous bodily experiences on physical activity in patients with FES.

## 2. Background

### 2.1 Symptoms and diagnosis of schizophrenia

Schizophrenia is characterized by a variety of symptoms affecting many different domains of mental function, e.g. reasoning, emotion, language, motor activity and perception. The symptoms can include experiencing false perceptions (hallucinations), having false beliefs (delusions), experiencing disorganized speech and behaviour, suffering from lack of initiative (avolition), exhibiting blunted affect, being unable to find pleasure in activities or in social relations (anhedonia), presenting poverty of speech and thought (alogia) and impaired attention. These symptoms vary between patients, resulting in diverse individual profiles of symptoms.

Symptoms are often divided into positive and negative symptoms:

Positive symptoms are characterized by distortion of normal function, e.g. impaired reality testing with an inability to distinguish personal experiences from the reality of the external world, delusions, and hallucinations.

Negative symptoms, on the other hand, are characterized by loss of normal function, e.g. a reduction of emotional responsiveness, motivation, socialization, speech and movement. Negative symptoms can be divided in I) primary negative symptoms, which are hypothesized to be related to the core psychopathology of schizophrenia, or II) secondary negative symptoms derived from psychotic symptoms, i.e. paranoid experiences, social environment, depression or sedative side-effects of psychopharmacological medication<sup>19</sup>.

Disorders of self-experience are emphasized as essential features of schizophrenia in the classic psychiatric literature and phenomenological psychiatry<sup>20,21</sup>. Distorted or anomalous self-experiences have thus been described as being prevalent in the prodromal and/or early phases of schizophrenia<sup>22,23</sup>. Anomalous bodily experiences may occur as part of the distorted self-experiences<sup>24</sup>. A subtype of schizophrenia, "Cenesthetic schizophrenia" characterized by abnormal bodily sensations has been proposed<sup>25</sup>. Cenesthesia is defined as the internal perception of one's own body in contrast to cenesthopathy or cenesthetic disturbances, referring to abnormal bodily sensations.

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)<sup>26</sup> or The International Classification of Diseases (ICD-10)<sup>27</sup> are the most commonly applied when diagnosing and classifying schizophrenia. In a Danish context ICD-10 is most common, and the specific criteria for fulfilling a diagnosis of schizophrenia according hereto are presented in table 1.

**Table 1. ICD-10 diagnostic criteria for schizophrenia**<sup>27</sup>

<p><u>At least one of the following:</u></p> <ul style="list-style-type: none"> <li>• Thought echo, thought insertion or withdrawal, or thought broadcasting.</li> <li>• Delusions of control, influence or passivity, clearly referred to body or limb movements or specific thoughts, actions, or sensations; delusional perception.</li> <li>• Hallucinatory voices giving a running commentary on the patient's behavior, or discussing him between themselves, or other types of hallucinatory voices coming from some part of the body.</li> <li>• Persistent delusions of other kinds that are culturally inappropriate and completely impossible (e.g. being able to control the weather, or being in communication with aliens from another world).</li> </ul>
<p><u>or at least two of the following:</u></p> <ul style="list-style-type: none"> <li>• Persistent hallucinations in any modality, when occurring every day for at least one month, when accompanied by delusions (which may be fleeting or half-formed) without clear affective content, or when accompanied by persistent over-valued ideas.</li> <li>• Neologisms, breaks or interpolations in the train of thought, resulting in incoherence or irrelevant speech.</li> <li>• Catatonic behavior, such as excitement, posturing or waxy flexibility, negativism, mutism and stupor.</li> <li>• "Negative" symptoms such as marked apathy, paucity of speech, and blunting or incongruity of emotional responses.</li> </ul>

## 2.2 Metabolic syndrome and metabolic abnormalities

The increased rates of cardiovascular disease (CVD)<sup>28-30</sup> and mortality in patients with schizophrenia has brought more clinical focus on screening and monitoring CVD risk factors, in which the concept of metabolic syndrome (MetS) is useful. MetS is defined as a number of risk-factors, comprising abdominal obesity, elevated blood pressure (BP), low high-density lipoprotein cholesterol (HDL), increased triglyceride (TG), and increased fasting glucose (FG), which combined increase the risk of CVD, type 2 diabetes (T2D) and mortality<sup>31-34</sup>. The specific criteria for MetS vary in different definitions. Most commonly used are the Adult Treatment Panel III of the National Cholesterol Education program(NCEP-ATP III)<sup>35</sup>, the adapted Adult Treatment Panel (NCEP-ATP III-A) proposed by the American Heart Association<sup>31</sup> and The International Diabetes Federation<sup>32</sup> (Table 2). Both the prevalence of MetS (fulfilling the criteria as defined) as well as the fulfilment of the individual metabolic abnormalities is often reported, as the latter also indicates an increased cardiovascular risk. In some studies metabolic abnormalities also include measures of low-density lipo-protein (LDL), body mass index (BMI), and impaired glucose tolerance (IGT).

**Table 2. Common definitions of metabolic syndrome**

	<b>ATP- NCEP III (3 of 5 required)</b>	<b>ATP NCEP III-a (3 of 5 required)</b>	<b>IDF (waist plus 2 required)</b>
<b>Waist circumference</b>	Male > 102 cm Female > 88 cm	Male > 102 cm Female > 88 cm	Male ≥ 94 cm Female ≥ 80 cm
<b>Blood pressure</b>	≥130 / ≥85 mm HG	≥130 / ≥85 mm HG	≥130 / ≥85 mm HG
<b>HDL cholesterol</b>	Male < 1.04 mmol/L Female > 1.29 mmol/L	Male < 1.04 mmol/L Female > 1.29 mmol/L	Male < 1.04 mmol/L Female > 1.29 mmol/L
<b>Triglycerides</b>	≥ 1.7 mmol/L	≥ 1.7 mmol/L	≥ 1.7 mmol/L
<b>Fasting glucose</b>	≥ 6.1 mmol/L	≥ 5.6 mmol/L	≥ 5.6 mmol/L

ATP: Adult Treatment Panel; IDF: International Diabetes Federation; HDL: high-density-lipoprotein

The development of MetS is attributable to numerous causes, including genetic factors, physical inactivity, smoking, poor diet and sleeping disturbances<sup>15,36-40</sup>.

### Antipsychotic medication

Allison *et al*<sup>41</sup> were among the first to describe weight gain as an adverse metabolic effect to antipsychotic medication (AP) in patients with schizophrenia, and the finding has been confirmed in numerous subsequent studies<sup>42,43</sup>. Especially some second generation antipsychotic (SGA) have a well-known adverse effect on weight gain<sup>44,45</sup> (table 3). Dyslipidaemia and disturbances of glucose metabolism resulting in hypercholesterolemia and T2D are other adverse effects of AP<sup>46-48</sup>. The adverse metabolic effects occur after short-time exposure to antipsychotic medication in patients with FES<sup>47,49,50</sup>.

Patients with depression are often prescribed AP, e.g. because of anxiety, and may therefore be subjective to the adverse metabolic effects, even though AP is prescribed in smaller anxiolytic dosages<sup>51</sup>.

**Table 3. Weight gain in antipsychotics ( The Maudsley prescribing guidelines) <sup>45</sup>**

Drug	Weight gain
Amisulpride	+
Aripiprazole	+/-
Asenapine	+/-
Chlorpromazine	++
Clozapine	+++
Haloperidol	+
Olanzapine	+++
Paliperidone	++
Perphenazine	+
Promazine	++
Quetiapine	++
Risperidone	+
Sertindole	-
Ziprasidone	+
Zuclophenthixol	++

Key: +++ High, ++ Moderate, + Low, - Very low

### *Antidepressants*

Weight gain and dyslipidaemia are well described adverse metabolic effects of tricyclic antidepressants and mirtazapine<sup>52,53</sup>. Patients with schizophrenia are often prescribed antidepressant medication for treatment of depressive symptoms.

### *Life-style habits*

Lifestyle habits with relevance for development of MetS include physical activity, smoking and dietary habits and sleeping disturbances. *Physical activity* will be described independently and in more detail in *section 2.3*.

### **Smoking**

The prevalence of smokers in patients with schizophrenia is significantly higher than age- and gender matched general population subjects and patients who smoke are less physically active and have increased cardiovascular risk compared to non-smokers<sup>54</sup>. A meta-analysis from 2014 found a similarly high prevalence of smokers in patients with FES (58.9%), and patients are much more likely to smoke compared with healthy controls (OR=6.04; 95%CI: 3.03-12.02). Furthermore, patients with FES tend to smoke for some years prior to being diagnosed and have difficulties in smoking cessation, also after adherence to

treatment<sup>55</sup>. People with a current or past depression are twice as likely to be smokers compared with healthy controls (non-depressed)<sup>56</sup>.

### **Diet**

Patients with schizophrenia have poor dietary habits, characterized by a high intake of saturated fat and a low consumption of fruit and fibre<sup>57,58</sup>, increasing the risk for T2D<sup>59</sup>. Similarly, poor dietary habits are also found in patients with FES<sup>60,61</sup>. The dietary habits of patients with depression are characterized by an excessive caloric intake and a low consumption of fish, vegetables and cereals<sup>62</sup>.

### **Sleeping disturbances:**

Sleep deficiencies, including insomnia, short sleep duration, and sleep apnoea are significantly associated with an increased risk of MetS<sup>39,40</sup>. Insomnia is common both in patients with schizophrenia and patients with depression characterized with more nocturnal awakenings and poorer sleep quality compared with healthy controls patients<sup>63-65</sup>. It has not previously been studied how sleeping disturbances are associated with MetS and metabolic abnormalities in patients with FES.

### **2.2.1 Metabolic syndrome and metabolic abnormalities in patients with schizophrenia**

The prevalence of MetS in patients with multi-episode schizophrenia has been thoroughly studied during the past decades and the overall rate of MetS is approximately 30%<sup>14,66</sup>. The duration of illness seems to have the strongest influence on the rate of MetS, whereas age only has a modest influence. The highest rate of MetS is seen in patients prescribed clozapine (52%) while the lowest rate is seen in un-medicated patients (20.2%). There are no significant differences between male and female patients in the prevalence of MetS<sup>14</sup>.

Patients with multi-episode schizophrenia have more than double the risk of MetS compared with age- and gender-matched healthy controls<sup>66</sup>. Regarding the individual metabolic abnormalities, patients with multi-episode schizophrenia have a four times higher risk of increased abdominal obesity, more than double the risk of low HDL, increased triglycerides and fasting -glucose, and an increased risk of hypertension compared with the general population<sup>66</sup>. Both the higher rates of MetS and of the individual metabolic abnormalities indicate a higher cardio-metabolic risk in patients with multi-episode schizophrenia compared with healthy controls.

The prevalence of MetS is significantly lower in patients with first-episode schizophrenia than in patients with multi-episode schizophrenia<sup>66</sup>. Based on two different meta-analyses from 2013, the overall rates of MetS vary from 15.9 %<sup>66</sup> to 9.9 %<sup>67</sup> in patients with first-episode schizophrenia (FES). In subsequent studies the prevalence of MetS varies from 6 %<sup>68</sup> to 13.2 %<sup>69</sup>.

Only few studies have compared the prevalence of MetS in patients with FES and healthy controls; one study included a group of healthy controls (direct comparisons)<sup>70</sup> whereas the remaining studies included data from general population cohorts (in-direct comparisons)<sup>68,69,71</sup>. In the former studies the prevalence of MetS tends to be higher in patients with FES than in healthy controls. However, the few studies suffer from being heterogeneous, e.g. in duration of illness and of antipsychotic exposure, and are therefore difficult to compare. Conclusively, it is still unknown whether the prevalence of MetS differs between patients with FES and healthy controls<sup>66</sup>.

There are no significant differences between the prevalence of MetS in drug-naïve and medicated patients with FES<sup>66,67</sup>. However, drug-naïve patients have significantly lower waist-circumference and blood pressure compared with medicated patients with FES<sup>67</sup>.

Regarding the individual metabolic abnormalities it is noteworthy that patients with FES have a high prevalence of the individual metabolic abnormalities, thus indicating an underlying cardio-metabolic risk<sup>66-69</sup>. *Fleischhacker et al*<sup>68</sup> reported one or more metabolic abnormalities in 58.5 % of patients with FES at baseline: 8.2% had an increased waist circumference (WC); 24.2 % had hypertension; 28.5 % had low HDL; 17.7% had hypertriglyceridemia; and 7.3 % had hyperglycaemia. Similarly, in the study of *Correll et al*<sup>69</sup> 17.5 % of patients with FES had an increased WC, 10.0 % had hypertension, 16.1 % had hypertriglyceridemia, and 15.4 % had pre-diabetes.

In a review from 2011 patients with FES were found to have an increased cardio-metabolic risk after first exposure to any antipsychotic drug<sup>72</sup>. A systematic search for subsequent studies on cardio-metabolic risk in patients with FES or patients with first episode psychosis (FEP) revealing 5 cross-sectional studies(baseline data)<sup>68,69,71,73,74</sup>, 12 prospective studies<sup>50,75-85</sup> and one retrospective study<sup>86</sup> confirm the adverse metabolic effect of AP, especially second generation antipsychotics (SGA).

Several studies have compared the prevalence of metabolic abnormalities (individual criteria of MetS as well as body mass index (BMI), visceral fat, low-density lipoprotein (LDL), and impaired glucose-tolerance) in drug-naïve patients with FES or FEP and healthy controls, which, due to the mounting evidence of an



increased cardio-metabolic risk early in treatment, is highly relevant<sup>74,87-96</sup> (table 4). Special interest was given to the risk of pre-diabetes (impaired glucose tolerance, increased insulin resistance, higher fasting-glucose) in drug-naïve patients with FES/FEP. Apart from findings in one study<sup>90</sup>, an increased risk of pre-diabetes in drug-naïve patients with FES/FEP prior to antipsychotic medication is confirmed<sup>74,87,89,94,95</sup>. These findings correspond to earlier research antedated modern antipsychotic medication hypothesising a possible predisposition for diabetes in patients with schizophrenia<sup>97</sup>.

**Table 4. Comparison of metabolic abnormalities<sup>1</sup> in drug-naïve patients with FES and healthy controls**

Reference	Study-design and study-population	Study findings
Ryan et al, 2003 <sup>87</sup>	<i>Cross-sectional</i> FEP - drug-naïve (N=26) Healthy controls(N=26)	FEP, drug-naïve: ↑ IFG compared with healthy controls
Ryan et al, 2004 <sup>98</sup>	<i>Cross-sectional</i> FES - drug-naïve (N=19) Healthy controls (N=19)	FES- drug-naïve: ↑ levels of visceral fat stores
Spelman et al, 2007 <sup>89</sup>	<i>Cross-sectional</i> FEP - drug-naïve (N= 38) Healthy controls(N= 38) First degree relatives(N=44)	FES – drug-naïve and first degree relatives: ↑ IGT compared with healthy controls
Sengupta et al, 2008 <sup>90</sup>	<i>Cross-sectional</i> FEP - drug-naïve (N= 38) Healthy controls(N=36)	No significant differences in glucose and lipid metabolites, prevalence of diabetes or IFG in FEP and healthy controls
Saddichha et al, 2008 <sup>91</sup>	<i>Prospective study (6 wks.)</i> FES- drug-naïve( N= 99) Healthy controls (N=51)	FES-drug-naïve: ↑ increase in BMI compared with healthy controls
Saddichha et al, 2008 <sup>96</sup>	<i>Prospective study (6 wks.)</i> FES drug-naïve (N=99) Healthy controls (N=51)	FES : ↑ incident of T2D compared with healthy controls
Verma et al, 2009 <sup>99</sup>	<i>Cross-sectional</i> FEP drug-naïve (N=160) Healthy controls (N=200)	Healthy controls: BMI, total and LDL cholesterol compared with FEP FEP: ↑ diabetes compared with healthy controls
Kirkpatrick et al, 2010 <sup>93</sup>	<i>Cross-sectional</i> FEP-drug-naïve (N=87) Healthy controls(N=92)	No significant differences in total cholesterol, HDL, LDL, and TG
Kirkpatrick et al 2012 <sup>94</sup>	<i>Cross-sectional</i> FEP-drug-naïve (N=64) Healthy controls (N=82)	FEP- drug-naïve: have abnormal glucose-tolerance, also when tested for potential confounders: lifestyle, smoking, socio-economic status
Chen et al. 2013 <sup>74</sup>	<i>Cross-sectional</i> FES drug-naïve( N=49) Healthy controls (N=30)	Significantly more frequent insulin-resistance and dyslipidaemia in FES compared with healthy controls
Wu et al. 2013 <sup>95</sup>	<i>Cross-sectional</i> FES(N=70) Healthy controls( N=44)	FES-drug-naïve: ↑ frequent Insulin-resistance, increased TG, and decreased HDL compared with healthy controls

<sup>1</sup>Metabolic abnormalities: individual criteria of MetS as well as body mass index (BMI), visceral fat, low-density lipoprotein (LDL), and impaired glucose-tolerance. IFG: impaired fasting-glucose. IGT: Impaired glucose tolerance. LDL: low-density lipoprotein. BMI: body mass index. HDL: high-density lipo-protein. T2D: type 2 diabetes. TG: triglycerides.

Metabolic abnormalities (comprising the individual criteria of MetS as well as body mass index (BMI), visceral fat, LDL cholesterol, and impaired glucose-tolerance) were also compared in medicated patients with FES/FEP and healthy controls in a limited number of studies. The majority of studies included data from general population cohorts to compare the prevalence metabolic abnormalities in FES /FEP with healthy controls (indirect comparison)<sup>68,69,71,100,101</sup> (table 5). Some studies report no differences in

metabolic abnormalities between patients with FES and healthy controls after shorter periods of antipsychotic medication (< 6 wks.)<sup>68,101,102</sup>. However, after longer periods of antipsychotic treatment (up to 52 wks.) patients with FES have significant increase in metabolic abnormalities compared with healthy controls<sup>69,71,100-103</sup>. Based on the relatively few studies it is inconclusive to which extent the prevalence of metabolic abnormalities in patients with FES differs from that of healthy controls. All studies addressed the adverse metabolic effect of antipsychotic medication, whereas other risk factors e.g. duration and severity of illness, smoking, socio-economic data, and genetics, were only included in some of the studies. No studies included data on physical activity or dietary habits, although these are strongly correlated to an increased risk of MetS and the individual metabolic abnormalities<sup>104-106</sup>.

**Table 5. Comparisons of metabolic abnormalities<sup>1</sup> in patients with FES/ FEP and healthy controls**

Reference	Study-design and study-population	Study findings
<b>Studies including a healthy control group</b>		
Strassnig et al, 2007 <sup>103</sup>	<i>Prospective study (1 year)</i> FEP (N=89) Healthy controls (N=30)	FEP: ↑ weight gain in compared with healthy controls.  Weight gain correlated with young age and negative symptoms
Graham et al, 2008 <sup>102</sup>	<i>Prospective study</i> FEP (N=45) Healthy controls (N=41)	Baseline: No significant differences in metabolic risk factors between FES and healthy controls  24 wks. follow-up: FEP ↑ BMI, glucose, cholesterol
<b>Studies with in-direct comparisons with general population cohorts</b>		
Phutane et al, 2011 <sup>100</sup>	<i>Cross-sectional</i> FEP (N=56) GP Healthy controls (N=145)	FES: ↑ prevalence of hypertension compared with GP healthy controls
Srihari et al, 2013 <sup>101</sup>	<i>Prospective study</i> FEP (N=76) GP Healthy controls (N=156)	Baseline: No significant differences in BMI, BP, total cholesterol, IFG, or HDL between FEP and GP healthy controls  1 year follow-up: FEP had significant ↑ weight, IFG, and MetS
Bensor et al 2012 <sup>71</sup>	<i>Cross sectional</i> FEP (N=82) GP Healthy controls (N=?)	FEP: ↑ hypertension, diabetes compared with GP healthy controls  FEP: ↑ MetS compared with GP healthy controls
Fleischhacker et al, 2013 <sup>68</sup>	<i>Cross sectional</i> FES (N=488) GP healthy controls	FES: no differences in MetS and metabolic abnormalities compared with GP healthy controls
Correll et al, 2014 <sup>69</sup>	<i>Cross-sectional</i> FES (N=394) GP Healthy controls	FES: ↑ dyslipidaemia, prehypertension compared with GP healthy controls  FES: ↑ MetS compared with GP healthy controls

<sup>1</sup>Metabolic abnormalities: individual criteria of MetS as well as body mass index (BMI), visceral fat, low-density lipoprotein (LDL), and impaired glucose-tolerance. IFG: impaired fasting-glucose. LDL: low-density lipoprotein. BMI: body mass index. HDL: high-density lipoprotein. T2D: type 2 diabetes. TG: triglycerides. GP: general population.

### 2.2.2 Metabolic syndrome and metabolic abnormalities in patients with depression

Patients with depression, like other patients with severe mental illness have an increased risk for premature death<sup>107,108</sup>, and CVD is among the most common causes<sup>17,18</sup>. Studies on MetS in relation to patients with depression are therefore highly relevant. Based on data from a meta-analysis performed in 2014<sup>109</sup> patients with severe depression have an average rate of MetS of approximately 30 %, and this is confirmed in subsequent studies<sup>110,111</sup>. The prevalence of MetS in patients with depression is thus found to be 2-3 times higher than in the background population<sup>112</sup>. The majority of studies included middle-aged or older patients (mean age > 45 years) with severe depression<sup>109</sup>. Only few studies have evaluated the prevalence and progression of MetS in younger patients with severe depression, showing that the prevalence of MetS significantly increase during the two first year of treatment<sup>113</sup>. Furthermore, patients with a history of childhood or adolescent severe depression have a higher risk of MetS or other metabolic risk factors later in life compared with non-depressed peers<sup>114-116</sup>.

Epidemiological research indicates a bidirectional association of depression and MetS. Based on meta-analyses of epidemiological studies the odds for depression vary from 1.27 to 1.49 in subjects with metabolic alterations. Conversely, depressed patients have a 1.34 to 1.52 higher risk for developing MetS compared to healthy controls<sup>117</sup>. Different mechanisms have been hypothesized for the associations between MetS and depression. Firstly, metabolic side-effects of psychopharmacological treatment are well-described. The metabolic profile of the serotonin reuptake inhibitors are, however, rather benign<sup>118</sup>, but tricyclic antidepressants (TCA) and mirtazapine have metabolic side-effects, comprising weight gain and dyslipidaemia<sup>52,53</sup>. Likewise, atypical antipsychotics are frequently prescribed for patients with severe depression<sup>119</sup> and have well-described metabolic side-effects<sup>120</sup>. Secondly, as many as 40 % of patients with severe depression have increased HPA-axis activity, resulting in chronically elevated glucocorticoids, impeding insulin's ability to promote glucose uptake and resulting in abdominal obesity, dyslipidaemia, and insulin resistance<sup>62,121</sup>. Thirdly, poor health behaviour, such as sedentary life style, smoking and high-caloric diet increases the risk of MetS and are also prevalent in patients with depression<sup>15,122,123</sup>.

### 2.3. Physical activity

The correlation of low physical activity and an increased risk of MetS is well documented<sup>15,16</sup>. Likewise, physical activity is efficient in reducing overall cardio-metabolic risk<sup>124,125</sup>.

Physical activity can be assessed with various methods which are often divided into direct, objective measures or indirect, subjective measures. The objective measures include actigraphs, pedometer and

observation, whereas subjective measures include diary or log and questionnaires<sup>126,127</sup>. Physical activity is often described in *metabolic equivalents* (MET); 1 MET is defined as the metabolic resting rate obtained during quiet sitting. Other physical activities are defined as multiples of the resting MET-level and range from 0.9 (sleeping) to 18 METs (running at 10.9 mph)<sup>128</sup>.

The physical activity level of a given population is often evaluated in relation to public health recommendations. The World Health Organization (WHO) has the following recommendations for physical activity in adults:

**Textbox 1: WHO recommendation for physical activity in adults (18-64 years)**<sup>129</sup>

- Adults aged 18–64 should do at least 150 minutes of moderate-intensity aerobic physical activity throughout the week or do at least 75 minutes of vigorous-intensity aerobic physical activity throughout the week or an equivalent combination of moderate- and vigorous-intensity activity.
- Aerobic activity should be performed in bouts of at least 10 minutes duration.
- For additional health benefits, adults should increase their moderate-intensity aerobic physical activity to 300 minutes per week, or engage in 150 minutes of vigorous-intensity aerobic physical activity per week, or an equivalent combination of moderate- and vigorous-intensity activity.

### 2.3.1 Physical activity in patients with schizophrenia

Patients with multi-episode or chronic schizophrenia have low levels of physical activity<sup>130-135</sup>, and physical activity is significantly lower than in comparable background populations<sup>136-139</sup>. A systematic search for studies evaluating physical activity in patients with FES/FEP revealed four studies<sup>140-143</sup>. The findings of these few studies suggest that physical activity is lower in patients with FES than in healthy controls, but higher than in patients with multi-episode schizophrenia, indicating that physical activity declines over the course of schizophrenia<sup>143</sup>. Furthermore, patients at risk for psychosis have a lower level of physical activity compared with healthy controls<sup>144,145</sup>, indicating that physical activity might be affected prior to being diagnosed.

Physical activity in patients with schizophrenia has commonly been assessed using questionnaires i.e. The International Physical Activity Questionnaire<sup>130</sup> or the 7-Day Physical Activity Recall Questionnaire<sup>146</sup>. More recently actigraphic monitoring of physical activity has been applied, providing more detailed description of physical activity in patients with schizophrenia<sup>147,148</sup>.

Different causes for low physical activity in patients with schizophrenia have been proposed, including negative symptoms, physical health problems, anxiety, lack of motivation, and lack of social support<sup>149-153</sup>. Experiences from physical therapy in relation to patients with schizophrenia often show that anomalous

bodily experiences can have a negative impact on the person's body awareness and on his or her activities of everyday life, in particular physical activity. Anomalous bodily experiences are also expected to decrease the ability or the wish to be physically active, and even to move at all. It is therefore important for clinical practice to know whether there is a relationship between anomalous bodily experiences or not, as it could help in identifying those most in need of support to improve physical activity. The influence of anomalous bodily experiences on physical activity in patients with FES has not previously been investigated.

### **2.3.2 Physical activity in patients with depression**

The role of physical activity in relation to depression has been investigated in clinical research in several decades. Primarily studies have focused on the anti-depressant effect of physical activity<sup>154</sup>, whereas only few studies present measures of physical activity level in clinically depressed patients. Patients with severe depression have lower levels of physical activity compared with healthy controls<sup>155,156</sup>, yet similar to that of patients with schizophrenia<sup>122</sup>. The physical activity in younger first-time hospitalised patients with severe depression has not previously been studied and presented.

Findings from general population cohort studies suggest that depressive symptoms are associated with excessive amounts of sedentary time and low fulfilment of physical activity guidelines<sup>157</sup>. Furthermore there seems to be a bidirectional association between physical activity and depression: Physical activity may decrease depressive symptoms, and in turn depressive symptoms may be a barrier to being physically active<sup>158</sup>. Among adolescents and younger adults physical activity is associated with a lower risk of depression<sup>159,160</sup>.

### 3. Aim and hypotheses

#### 3.1 Overall aim of the PhD thesis

The overall aim of this PhD project was to study the prevalence and course of metabolic syndrome in patients with first-episode schizophrenia (FES) and compare this with first-time hospitalized patients with depression and healthy controls. Furthermore, to investigate the impact of physical activity on the development of MetS in patients with FES.

#### 3.2 Hypotheses

The following hypotheses were studied:

- Patients with first-episode schizophrenia (FES) have higher baseline prevalence of MetS compared with healthy controls.
- Patients with first-episode schizophrenia (FES) have higher baseline prevalence of metabolic abnormalities compared with healthy controls.
- Patients with first-episode schizophrenia (FES) and first-time hospitalised patients with depression have similar prevalence of MetS and metabolic abnormalities.
- The prevalence of MetS and metabolic abnormalities in patients with FES increase during the first year of treatment.
- Low physical activity is an independent risk factor for MetS and metabolic abnormalities in patients with FES.
- Anomalous body-experiences have a negative impact on physical activity in patients with FES.

## 4. Methods and material

### 4.1 Design and study sample

The study was a controlled, observational, 1 year follow-up study conducted from 2010 to 2014.

The population of interest was patients with an ICD-10 diagnosis of first-episode schizophrenia (F20.0) aged 18-45 years. Patients were recruited from an outpatient-clinic for first-episode schizophrenia (OPUS)<sup>161</sup> in Central Denmark Region. For comparisons we also included gender-and-age-matched I) first-time hospitalized patients with depression (F.32), recruited from psychiatric wards at Aarhus University Hospital, Risskov, and II) healthy controls, recruited by advertisement in a local newspaper.

#### 4.1.1 Inclusion criteria

Patients with schizophrenia were included from the OPUS outpatient clinic for first-episode schizophrenia if fulfilling the following criteria: I) age 18-45 years with legal residence in the catchment area; II) having a diagnosis of schizophrenia or schizophrenia-like psychosis according to the Research Criteria of International Classification of Diseases<sup>27</sup>; III) familiar with the Danish language.

Patients with depression were included if I) they were hospitalized for the first time, and II) if they fulfilled the Research Criteria of International Classification of Diseases<sup>27</sup> for depression (F.32.). All participants were included after written confirmed consent. All participants spoke and understood Danish.

Healthy controls were recruited from advertisement in local newspaper.

#### 4.1.2 Exclusion criteria

Participants were excluded from the study if they were physically disabled, had a somatic illness impairing physical activity, were pregnant, had an intellectual disability, fulfilled ICD-10 criteria for mental and behavioral disorders due to psychoactive substance use (F.10-F.19), or were subject to coercive measures. For the healthy controls, the use of any psychotropic medication led to exclusion.

### 4.2 Procedures and measures

The patients were assessed at baseline and after one year of follow-up; the healthy controls were only assessed at baseline. All assessments, apart from blood samples, Global Assessment of Function (GAF), Scale for Assessment of Negative Symptoms (SANS), and Scale for Assessment of Positive Symptoms (SAPS)

were carried out by the same researcher (LN). All questionnaires were administered as structured interviews to account for possible cognitive deficits in the clinical population. Participants were described as having MetS if they fulfilled the criteria defined by IDF<sup>32</sup> (table 2).

#### 4.2.1 Metabolic measures

Metabolic measures included level of triglycerides (TG), high-density lipo-proteins (HDL), and fasting glucose (FG), blood pressure, waist circumference (WC), weight, height, and body mass index (BMI). Routinely taken blood samples gave data on TG, HDL, and FG, and data was obtained from the patients' electronic medical record. The waist circumference (WC) at umbilical level was measured in all participants using a tape measure. The umbilical level was chosen although WC is often measured at the midpoint between the iliac crest and lower rib. However, experiences from clinical practice show that this measurement site can be difficult, especially in obese patients. Moreover, finding the exact point between iliac crest and lower rib involves thorough palpation, which can be too intimate for many patients. There is no consensus of optimal measurement of WC. There seems to be no significant differences in measures of WC when using different measurements sites<sup>162</sup>.

Blood pressure (BP) was measured after at least ten minutes of resting, using *The UA-852 Digital Blood Pressure Monitor* placed on the left upper arm of the sitting participant. BP was measured twice and the average value calculated and registered.

Participants were weighed on a digital weight wearing light clothes and no shoes. Height was measured on a wall-mounted stand, participants wearing no shoes. BMI was calculated as weight in kilograms divided by the square of height in meters.

#### 4.2.2 Physical activity

The Physical Activity Scale<sup>163,164</sup> was used for measuring physical activity. The scale consists of nine different physical activities with different metabolic equivalents comprising sleep, work and leisure time activities. Responders report the time spent on each specific physical activity on an average weekday. By multiplying the given time spent on an activity with the corresponding metabolic equivalent and thereafter summarizing all the determined metabolic equivalents, the physical activity level of a given responder can be described.



All participants were asked to recall their physical activities during the past week. Physical activity was presented in metabolic equivalents; a higher score reflected a higher level of physical activity.

Aerobic fitness (defined as  $VO_2$ max) served as a proxy for physical activity prior to inclusion and during the follow-up period, and was measured at time of inclusion and at the 1 year follow-up. The Astrand–Rhyming single-stage cycle ergometer test was used to describe aerobic fitness<sup>165</sup>. The test is designed to elicit a steady-state heart rate (HR) over a 6 minute period. All tests were performed on a Monark 827 Ergometer cycle, and HR was measured during the entire test by a Polar HR monitor.

Only patients who had a normal electrocardiogram were allowed to perform the test. The test was interrupted if the patient experienced unusual dizziness, nausea, or other types of discomfort during the test. Based on HR at a specific workload (Watt) the oxygen uptake ( $VO_2$  max) was estimated using the Astrand–Rhyming sex-and-age-sensitive nomogram. The continuous data on aerobic fitness were divided into four categories, from very poor to very high aerobic fitness in accordance with the Astrand–Rhyming test<sup>165</sup>.

#### **4.2.3 Socio-economic data, sleeping, smoking and dietary habits**

Socio-demographic data, smoking and dietary habits were assessed for all participants – the latter using a questionnaire adapted from the Danish Health Examination Survey 2007 – 2008<sup>166</sup>. Smoking habits were categorized as either (I) “non-smoker”, comprising previous and non-smokers, or (II) “smoker”, comprising daily and weekly smokers.

Dietary habits were presented as sum-scores obtained from Likert scales, with a higher sum indicating a healthier diet, defined as having more regular meals, and a more frequent intake of vegetables, fruits, whole-grain products, fish and meat, and a less frequent intake of sweets, cakes, snacks and soft drinks.

Sleeping disturbances were assessed by The Pittsburgh Sleeping Quality Index (PSQI)<sup>167</sup>. The questionnaire includes 19 items assessing a wide variety of factors relating to sleep quality such as sleep duration and latency and frequency and severity of specific sleep-related problems. The scores on the individual items are summed to a global PSQI score with a range from 0-21; higher scores indicate worse sleep quality.

#### 4.2.4 Psychopathological data

Psychopathological data included Global Assessment of Functioning (GAF)<sup>168</sup>, Scale for Assessment of Negative Symptoms (SANS)<sup>169</sup> and Scale for Assessment of Positive Symptoms (SAPS)<sup>170</sup>.

GAF is a numeric scale (1 through 100) used to rate subjectively the social, occupational, and psychological functioning of patients, e.g., how well or adaptively one is meeting various problems-in-living.

SANS is a rating scale for measuring negative symptoms in schizophrenia and the scale includes items covering *affective flattening or blunting, alogia, avolition, anhedonia, and attention*.

SAPS is a rating scale to measuring positive symptoms in schizophrenia, and the scale include items covering *hallucinations, delusions, bizarre behavior and thought disorder*.

Assessments of GAF, SANS and SAPS were carried out by experienced psychiatric health professionals (medical doctors, psychologists, nurses, occupational therapists), and data were obtained from patient-charts.

Anomalous bodily experiences were described by selected items from Examination of Anomalous Self-Experiences (EASE)<sup>171</sup>, comprising “morphological changes” (perceptions of the body or parts of the body becoming thinner, shorter, contracting, enlarging, being pressed down or diminished); “bodily estrangement” (the body or parts of it are perceived as strange, alien, lifeless, isolated, dislocated or not existing); “cenesthetic experiences” (unusual body sensations, e.g. of numbness, pain, dysesthesias, electric bodily sensations, thermal sensations and migrating bodily sensations); “bodily disintegration” (feelings of the body falling into pieces or disappearing); and “motor disturbances” (experiences of pseudo-movements of the body, motor interference, motor blocking, motor paresis or de-automation of movement).

Furthermore, a single item from The Body Awareness Scale (BAS)<sup>172</sup>, “hypochondriasis” was applied. Each item was given a score from 0 to 4, increasing with experienced frequency, intensity and distress of the symptom in concordance with the EASE manual. A score of  $\geq 2$  was defined as an anomalous bodily experience with regard to the specific item in the EASE manual.

#### 4.2.5 Psychotropic medication

Data were obtained from patients' electronic medical records and included medical data from up to 6 months before inclusion and during the study period. Prescribed antipsychotics (AP), antidepressants, and benzodiazepines were registered. On a general level, patients were divided into four groups depending on prescribed antipsychotic medication: a) only first generation AP, b) both first- and second generation AP, c) only second generation AP, d) more than one second generation AP. Furthermore, antipsychotic

medication was described in defined daily dosages (DDD) and chlorpromazine equivalents based on the average doses given prior to and during the study period, respectively. Antidepressant medication such as Tricyclic Antidepressants (TCA) and Selective Serotonin Reuptake Inhibitors (SSRI), as well as use of benzodiazepines was also registered. Medication prescribed as “pro necessitate” was not included due to uncertainty of actual ingestion.

#### 4.4 Ethics

All participants were included in the study after their written, confirmed consent was obtained in accordance with the Declaration of Helsinki. The study protocol was approved by the local ethical committee, and the study was registered with the Danish Data Protection Agency and ClinicalTrials.gov.PRS (NCT00957294).

#### 4.5 Statistical analyses

The number of participants with MetS in each group was calculated, and changes in each of the metabolic components of MetS were analyzed individually. For analyses of differences between the patients and the healthy controls, the chi-squared test or Fischer’s exact test was applied for categorical variables, and the Kruskal-Wallis test was applied for continuous variables. The Mann–Whitney *U*-test for between-group comparisons and Wilcoxon’s Signed Rank Test was applied for paired analyses of patients at baseline vs. follow-up. All tests were two-sided ( $p \leq 0.05$ ).

In *paper I* a stepwise backward elimination in regression analyses was applied starting with all candidate variables and deleting variables one at the time until no further improvement of the model could be found. Due to small sample size data from baseline and follow-up was pooled and adjusted for follow-up effect in all regression analyses. Multivariate logistic regression analyses were performed to examine factors independently correlated with fulfilling the IDF -criteria for MetS. Analyses were presented as odds-ratios (with 95% CI;  $p \leq 0.05$ ). Multiple linear regression analyses were performed to examine factors correlated with the continuous variables on waist circumference (WC), triglycerides (TG), blood pressure (BP), and high-density lipoprotein (HDL).

In *paper II* a forward, stepwise approach in all regression analyses was applied starting with no variables in the model, testing the addition of each variable using a chosen model comparison criterion, adding the variable (if any) that improved the model the most, and repeating this process until none improved the

model further. Logistic regression analyses were performed to examine factors independently correlated with fulfilling the IDF criteria for MetS. Data was presented as odds ratios (with 95% CI); a p-value  $\leq .05$  was considered to be statistically significant. Linear regression analyses were performed to examine the independent factors correlated with WC, TG, (BP), and HDL. For these regression analyses data from baseline and follow-up was pooled, and adjusted for follow-up effect due to small sample size. Furthermore, multiple linear regression analyses were performed to examine factors correlated with the changes from baseline to follow-up (paired data).

In *paper III* scores on anomalous body experiences was categorized into three groups: (I) score  $< 2$ ; (II) score = 2; (III) score  $\geq 3$  in at least one item. Spearman's rho was applied for analyzing correlations between anomalous body experiences and physical activity. Linear regression analyses were performed to examine the independent factors associated with physical activity (pooled data).

In all papers the results from multiple linear regression analyses were presented as regression coefficients (95% CI;  $p \leq .05$ ). All statistical analyses were done with STATA version 13.1 (Stata Corp., College Station, TX, USA).

## 5. Results

Of 182 patients with FES eligible for inclusion during the study period, 101 were included in the study. Two patients were subsequently excluded - one due to not fulfilling the diagnostic criteria for schizophrenia, and one due to fulfilling the criteria for psychoactive substance use (in accordance with exclusion criteria); additional 24 patients were lost to follow (Fig. 1). There were no significant differences in GAF, SANS or SAPS between eligible patients with FES and included patients. Likewise there were no significant differences in patients lost to follow and patients who succeeded in completing the study regarding baseline measures of age, sex, WC, BP, TG, HDL, FG, BMI, antipsychotics, SANS, SAPS, and GAF.

In all, 52 first-time hospitalized patients with depression were included, of which 17 were lost to follow, and 50 healthy controls (Fig.1). There were no significant differences in baseline measures of age, gender, WC, BP, TG, BMI, physical activity and medication between patients lost to follow and patients who succeeded the study (paper I).

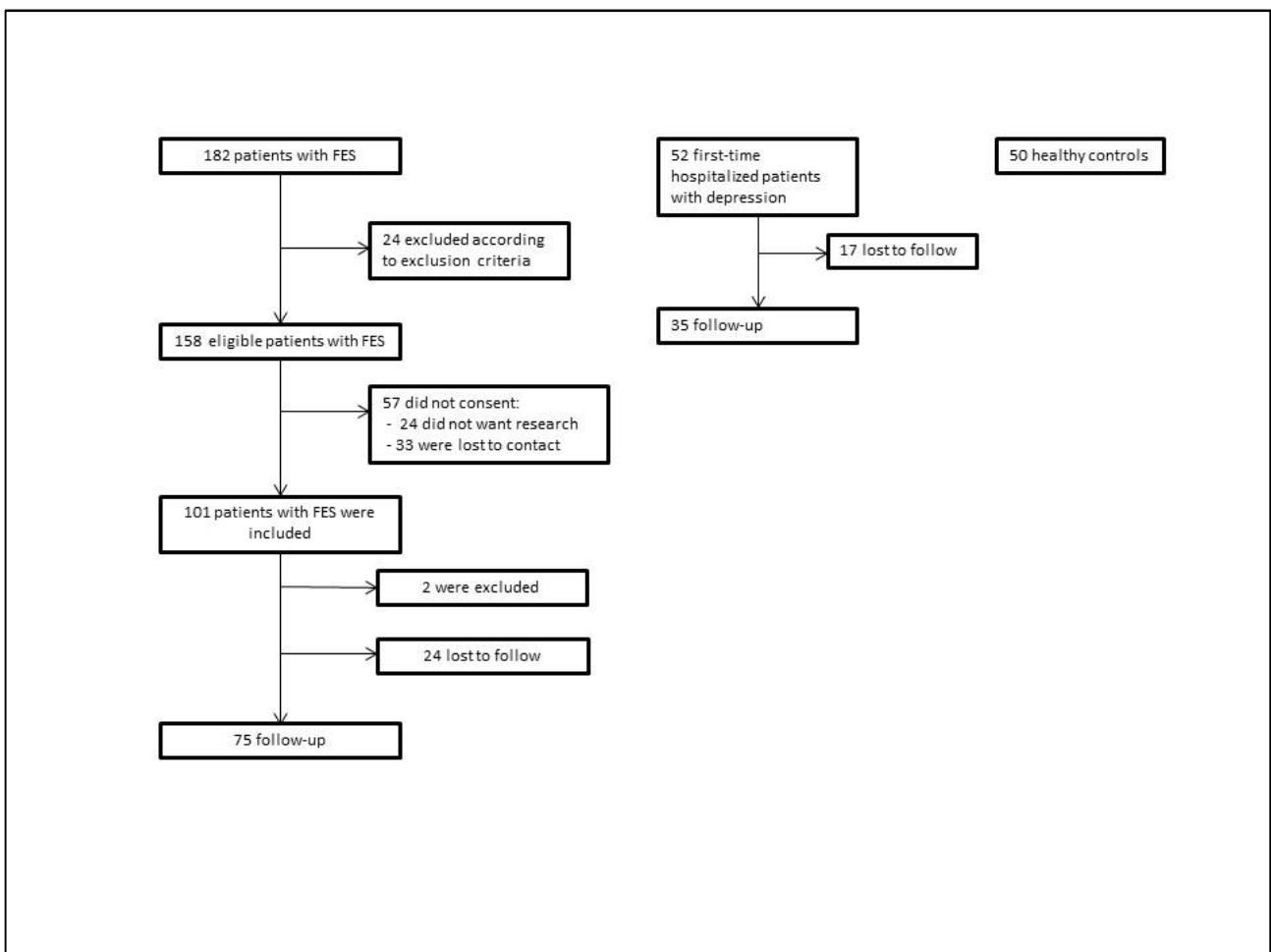


Fig.1 Flowchart of included participants

Patients with FES were significantly less educated, more frequently received social security compared with both healthy controls and first-time hospitalized patients with depression. Compared with healthy controls patients with FES had significantly higher BMI and poorer health habits (were less physically active, were more frequent smokers, and had poorer dietary habits).

At baseline 17/99 patients (17.2 %) with FES were antipsychotic drug-naïve, whereas 6/99 (6.1 %) were prescribed both first-generation antipsychotics (FGA) and second generation antipsychotics (SGA), 44/99 (44.4 %) only one SGA, and 30/99 (30.3 %) were prescribed  $2 \geq$  SGA. At the time of follow-up 2/75 (2.6 %) were AP-drug-naïve, 7/75 (9.3 %) were prescribed both FGA and SGA, 7/75 (9.3 %) only one SGA and 59/75 (78.7 %)  $2 \geq$  SGA. From baseline to follow-up patients with FES had significant increase in AP both described in chlorpromazine equivalents (CPZ) (from 372.6 (313.5) to 647.2 (436.1) (mean (SD)) or in defined daily dosages (DDD) (from 1.18(0.13) to 4.25(0.48) (mean (SD))). The predominately prescribed SGA's were Aripiprazole and Quetiapine. Antidepressants, comprising TCA and SSRI, were prescribed to 30/98 (30.6 %) patients with FES at baseline and to 38/74 (51.3%) at follow-up (paper II).

At baseline, 25/52 (48.1 %) of first-time hospitalized patients with depression were treated with AP, and at time of follow-up 25/35 (71.4 %) were treated with AP; there were, thus, a significant increase in both CPZ from 170.6 (125.7) to 255.1 (213.5) (mean (SD)) and in DDD, from 0.58(0.68) to 0.73(0.46) (mean (SD)). Quetiapine, typically within the range of 22 to 180 mg, was the predominately prescribed AP. All first-time hospitalized patients with depression were treated with antidepressants, comprising TCA, SSRI or Mirtazapine at baseline and at follow-up (paper II).

### 5.1 Prevalence of metabolic syndrome and metabolic abnormalities (paper I and II)

The baseline prevalence of MetS in patients with FES was 10 % compared with 2 % of healthy controls, which was not statistically significant when adjusting for age ( $p = 0.072$ ) (Table 6). However, patients with FES had a significantly higher WC (85.0 cm vs. 70.5cm), higher TG (1.1mmol vs. 0.8mmol), and a higher FG level (5.2mmol vs. 5.0 mmol) compared with healthy controls, and significantly more patients (20.6 % vs. 6.0 %) with FES fulfilled the IDF criteria for low HDL.

In patients with FES there were no significant differences in the prevalence of MetS between men and women at baseline or at follow-up. There were no differences between medicated patients and antipsychotic-naïve patients in prevalence of MetS and metabolic abnormalities when adjusted for age.

**Table 6. Baseline characteristics of patients with FES in comparison with first-time hospitalized patients with depression and healthy controls**

	FES (N=99)	Depression (N=52)	p- value*	Healthy controls (N=50)	p- value*
Mean Age (SD)	24.9 (7.1)	29.1(7.4)	<b>0.013</b>	23.6 (4.6)	0.063
Female (%)	33.3	50.0	0.046	42	0.299
<i>Civil status n (%)</i>					
Living alone	19.2	7.7	0.174	22.0	0.686
Living with parents	52.5	61.5	0.302	40.0	0.184
Married or cohabiting	29.3	30.8	0.803	38.0	0.283
<i>Years of education n (%)</i>					
≤ 10 years	26.3	9.6	<b>0.04</b>	6.0	<b>0.006</b>
>10 and ≤ 12 years	51.5	50.0	0.773	26/50 (52.0)	0.863
> 12 years	23.2	40.4	<b>0.128</b>	21/50 (42.0)	<b>0.018</b>
<i>Income n (%)</i>					
Wages	1.0	3.8	0.264	5/50 (10.0)	<b>0.028</b>
Social security	61.8	19.2	<b>&lt;0.0001</b>	1/50 (2.0)	<b>&lt;0.0001</b>
Educational grants	18.5	30.8	<b>0.021</b>	40/50 (80.0)	<b>&lt;0.0001</b>
Sickness benefit	13.4	36.5	<b>0.047</b>	-	<b>0.018</b>
Unemployment grant	4.1	7.7	0.528	1/50 (2.0)	0.864
No income	1.0	2.0	0.498	3/50 (6.0)	0.214
<i>ICD-10 diagnoses (%)</i>	F.20.0: 74.4	F.32.0: 1.9			
	F.20.3: 18.8	F.32.1: 28.8			
	F.20.6: 2.3	F.32.2: 38.5			
	Other F.20: 4.5	F.32.3: 9.6			
		F.32.9: 3.8			
		F.33.1: 1.9			
		F.33.2: 11.5			
		F.33.3: 3.8			
BMI (median(min;max))	24.8 (17.1;42.6)	24.1 (15.8;39.0)	0.580	22.1(17.9;37.8)	<b>&lt;0.0001</b>
Physical activity ** (Median(min;max))	29.4 (23.3;50.1)	27.9 (22.1;37.8)	<b>0.006</b>	34.2 (28.6;48.8)	<b>&lt;0.0001</b>
Aerobic fitness (ml O <sub>2</sub> /min/kg) (median(min;max))	35.7 (13.0;77.7)	33.9 (10.1;74.7)	0.516	53.5 (23.1;87.1)	<b>&lt; 0.0001</b>
Dietary habits (median(min;max))	101.0 (62.0;128.0)	103.5(76;124)	0.775	110.0 (90;131)	<b>&lt;0.0001</b>
Daily smoking n (%)	50.0	64.7	0.643	30.6	<b>&lt;0.004</b>
Sleeping disturbances (median(min;max))	10.0 (1.0; 16.0)	15,5 (4;19)	<b>&lt;0.0001</b>	10 (4;19)	0.666
Metabolic syndrome (%)	9/90 (10.0)	6/46 (13.0)	0.956	2.0 (1/50)	0.072
WC(cm)(median(min;max))	80.0 (58.0;111.0)	81.0 (58.0;115.0)	0.084	70.5( 59.0;107.0)	<b>&lt;0.0001</b>
IDF-criteria n/N (%)	26/97 (26.8)	16/52 (30.8)	0.714	2/50 (4.0)	<b>&lt;0.0001</b>
TG(mmol/L)(median(min;max))	1.1 (0.4;4.5)	1.1 (0.5; 2.7)	0.958	0.8 (0.4;2.6)	<b>&lt;0.008</b>
IDF-criteria n /N (%)	15/97 (15.5)	9 /34 (25)	0.220	4/50 (8.9)	0.164
HDL (mmol/L)(median(min;max))	1.3 (0.7;2.3)	1.25(0.75;2.7)	0.837	1.4 (0.85;2.6)	0.262
IDF-criteria n/N (%)	20/97 (20.6)	11/34(32.4)	0.267	3/50 (6.0)	<b>0.017</b>
Sys BP (mm HG)(median(min;max))	120.0 (92.0;162.0)	123.0(97.0;158.0)	0.767	119.0(100.0;148.0)	0.665
IDF-criteria n/N (%)	19/97 (19.6)	11/52 (21.2)	0.433	14/50 (28.0)	0.220
Dia BP (mmHG)(median(min;max))	78.0 (55.0;99.0)	78.0 (56.0;99.0)	0.444	75.0 (59.0;98.0)	0.452
IDF-criteria n/N (%)	28/97 (28.9)	10/52 (19.2)	<b>0.044</b>	10/50 (20.0)	0.271
FG (mmol/L)(median(min;max))	5.2 (3.9;7.6)	5.5 (4.2; 5.9)	0.713	5.0 (4.1 ;5.8)	<b>0.045</b>
IDF-criteria n/N (%)	6/33 (15.3)	2/9 (22.2)	0.558	2/50 (4.0)	0.062

\*Age-adjusted p-values by linear or logistic regression analyses; \*\* Described in metabolic equivalents; WC: waist circumference; TG: triglycerides; HDL: high-density-lipoprotein; Sys BP: systolic blood pressure; Dia BP: diastolic blood pressure; FG: fasting glucose

In first-time hospitalized patients with depression the baseline prevalence of MetS was 13 %, which was similar to patients with FES when adjusted for age (p=0.956). Apart from the IDF criteria for diastolic BP

there were no significant age-adjusted differences in the baseline prevalence of the individual metabolic abnormalities (WC, TG, HDL, BP, and FG) between the two patient groups (table 6).

The overall prevalence of MetS in patients with FES increased significantly from 10 % to 22.1 % ( $p = 0.031$ ); in paired analyses MetS increased from 10.2 % to 25 %, however this was not statistically significant ( $p = 0.082$ ). Patients with FES had significant increases of WC (80.0 cm to 88.0cm) and TG (1.1 mmol/L to 1.3 mmol/L) during the study period (paper II).

Similar hereto, first-time hospitalized patients with depression had an increase in MetS during 1 year follow-up from 13 % to 20 % (paper I). There were no significant differences between patients with FES and first-time hospitalized patients with depression in the individual metabolic abnormalities after 1 year follow-up (table 7).

**Table 7. Comparisons of MetS and metabolic abnormalities between patients with FES and first-time hospitalized patients with depression at 1 year follow-up**

	FES (N=77)	Depression (N=37)	p-value*
Metabolic syndrome n/N (%)	15/68 (22.1)	6/24 (25.0%)	0.644
WC (cm) ( <b>median(min;max)</b> )	88.0 (66.0;133.0)	90.5 (62.0;130.0)	0.602
IDF-criteria n/N (%)	32/77 (41.6)	14/34 (44.1)	0.734
TG (mmol/L)( <b>median(min;max)</b> )	1.3 (0.3; 3.8)	1.4 ( 0.7; 4.5)	0.098
IDF-criteria n /N (%)	24/75 (32.0)	23/37 (62.2)	0.726
HDL (mmol/L) ( <b>median(min;max)</b> )	1.3 (0.8; 2.6)	1.2 (0.68; 2.7)	0.322
IDF-criteria n/N (%)	18/74 (24.3)	7/23 8 (30.4)	0.657
Sys BP (mm HG)( <b>median(min;max)</b> )	120,50 (80.0; 150.0)	122.0 (96.0; 153.0)	0.631
IDF-criteria n/N (%)	15/76 (19.7)	9/33 (27.3)	0.827
Dia BP (mm HG) ( <b>median)min;max)</b>	77.0( 62.0; 99.0)	81.0 (55.0; 102.0)	0.657
IDF-criteria n/N (%)	17/76 (22.4)	13/33 (39.4)	0.362
FG	5.35 ( 4.0; 7.0)	5.20 (5.0; 7.0)	0.880
IDF-criteria n/N (%)	9/28 (32.1)	4/12 (33.3)	0.887

WC: waist circumference; TG: triglycerides; HDL: high-density-lipo-protein; Sys BP: systolic blood pressure; Dia BP: diastolic blood pressure.

\* Age adjusted analyses

### Correlates of metabolic syndrome and metabolic abnormalities

Patients with FES had significant increase in defined daily dosages (DDD) ( $p = 0.001$ ) and DDD was significantly correlated with a higher WC ( $p = 0.04$ ), a higher TG level ( $p = 0.01$ ), a lower HDL level ( $p = 0.05$ ), a higher systolic BP ( $p = 0.01$ ), and a higher FG ( $p = 0.05$ ) (paper II). Low physical activity was significantly correlated with a higher WC ( $p = 0.02$ ), a higher TG level ( $p = 0.07$ ), a lower HDL level ( $p = 0.04$ ), and a

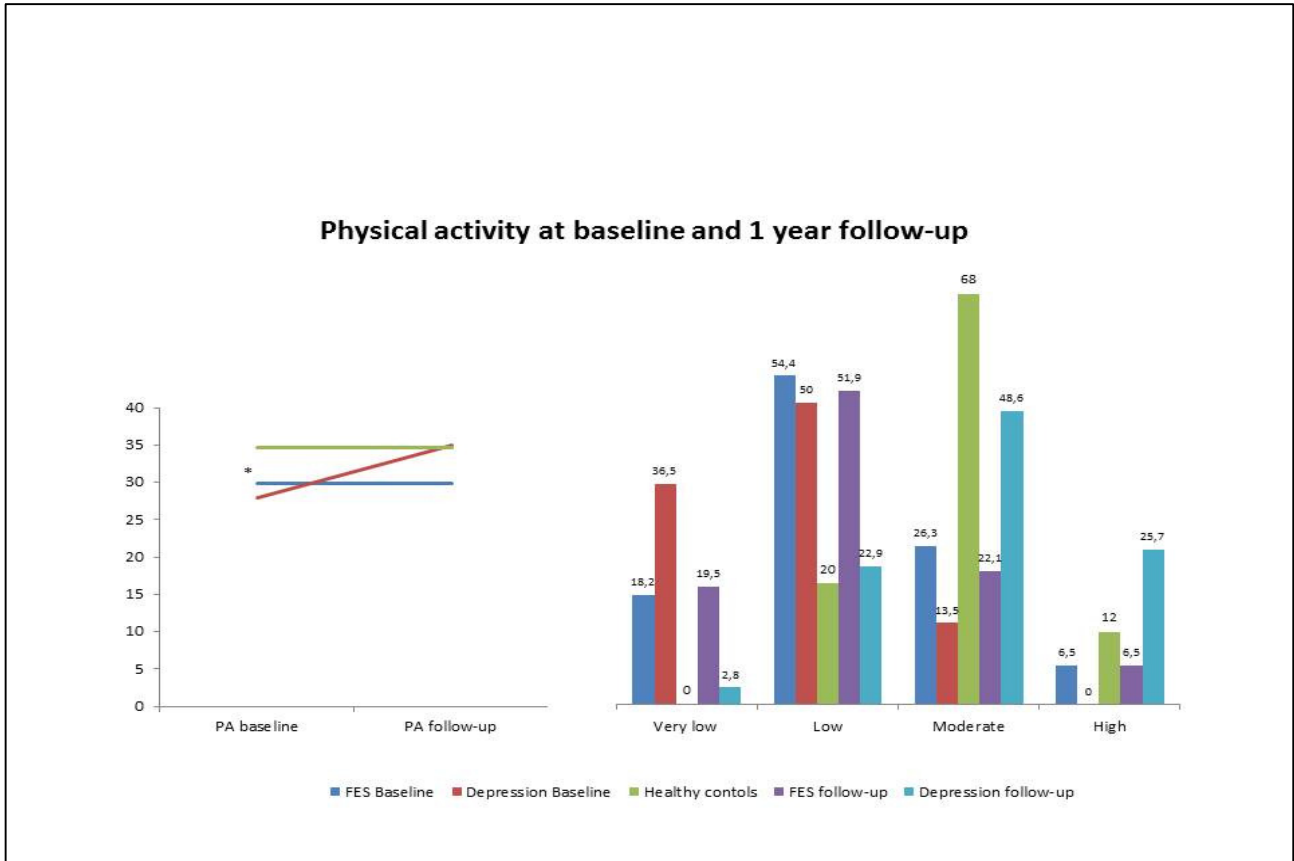


higher systolic ( $p = 0.07$ ) and diastolic BP ( $p = 0.02$ ) (Paper II). However, in stepwise multiple logistic regression analyses only low aerobic fitness was statistically significantly correlated with MetS in FES; a one unit increase in aerobic fitness lowered the odds for MetS by 12 % (95% CI 0.83–0.95;  $p < 0.0001$ ) (paper II). In first-time hospitalized patients with depression both AP and low aerobic fitness were statistically significantly correlated with MetS and metabolic abnormalities (paper me).

Multiple linear regression analyses showed that low aerobic fitness, AP, DDD, age, sex, and low physical activity were correlated with the continuous score of one or more individual, metabolic abnormalities in patients with FES. Only low aerobic fitness was associated with changes in WC in patients with FES (paper II); a one unit increase in aerobic fitness decreases the predicted increase in WC by 0.2 percentage points. Likewise, low aerobic fitness was significantly correlated with increase in WC, TG and systolic and diastolic BP (paper II).

## 5.2 Physical activity (paper III)

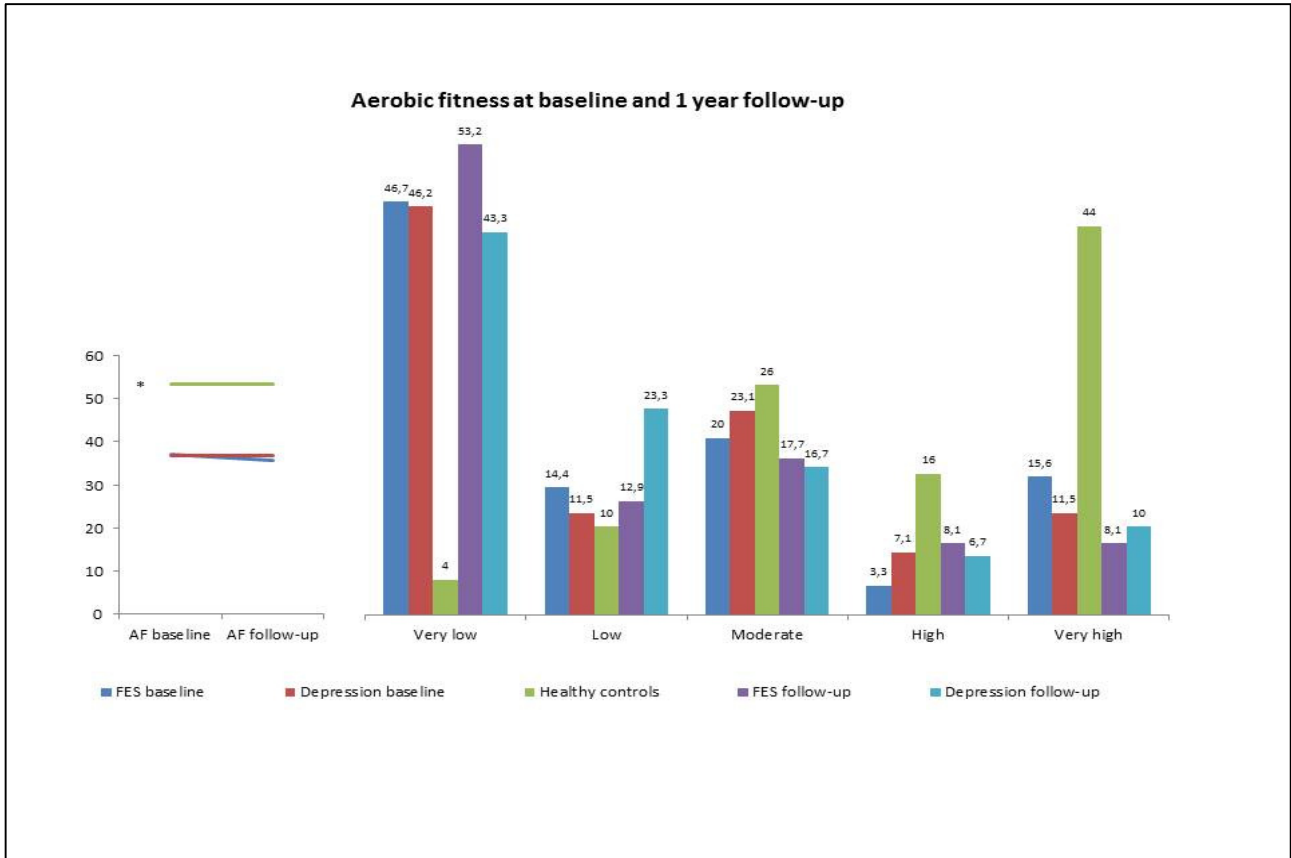
At baseline patients with FES had significantly lower levels of physical activity (measured in metabolic equivalents) compared with healthy controls (29.4 METS vs. 34.2 METS ( $p < 0.0001$ )), yet significantly higher to that of first-time hospitalized patients with depression (29.4 METS vs. 27.9 METS ( $p = 0.006$ )) (age-adjusted analyses) (table 5). At baseline both the majority of patients with FES and patients with depression were predominately engaged in “very low” or “low” physical activities (72.6 % and 86.5 %, respectively) and to a lesser degree in “moderate” and “high” physical activities (27.4 % and 13.5 %, respectively). In patients with FES, physical activity level remained low during 1 year of follow-up opposed to patients with depression, who became significantly more physically active (from 27.9 METS to 34.7 METS). At time of follow-up the physical activity in patients with first-time depression resembled that of healthy controls at baseline (Fig. 2).



**Fig. 2.** Physical activity level (in metabolic equivalents) and physical activity categories (%) in patients with FES, first-time hospitalized patients with depression, and healthy controls at baseline and 1 year follow-up. \* $p < 0.0001$ . Physical activity in healthy controls at follow-up are replicated from baseline data.

Baseline aerobic fitness was significantly lower in patients with FES than in healthy controls (35.5 vs. 53.5 ml O<sub>2</sub>/min/kg ( $p < 0.0001$ )), and similar to that of patients with depression (Table 6). Only 18.9 % of patients had “high” or “very high” aerobic fitness (Fig. 3).

Patients with FES tended to deteriorate aerobic fitness during the study period as the number of patients with very low aerobic fitness increased from 46.7 % to 53.2 % and the number of patients with very high aerobic fitness declined from 15.6 % to 8.1 %. The average change in aerobic fitness was however not statistically significant ( $p = 0.092$ ). Similar hereto, first-time patients with depression had no significant changes in average aerobic fitness, yet significantly more patients had “high” and “very high” aerobic fitness levels (Fig. 3) (95 % CI 0.83–0.95;  $p < 0.0001$ ).



**Fig. 3** Continuous and categorical data (%) of aerobic fitness (AF) in patients with FES, first-time hospitalized patients with depression, and healthy controls at baseline and 1 year follow-up. \* $p < 0.0001$ . Aerobic fitness at follow-up for healthy controls was replicated from baseline data.

### Anomalous bodily experiences

Anomalous bodily experiences defined as a score  $\geq 2$  in one or more of the individual items occurred in 72.2 % of patients with FES. Cenesthetic experiences and motor disturbances were the most frequent anomalous bodily experiences (Table 8).

Patients who scored  $\geq 3$  on anomalous bodily experiences had significantly lower levels of physical activity ( $p = 0.025$ ) than patients with lower scores. Likewise, in correlation analyses (Spearman's rho) a score  $\geq 3$  on anomalous bodily experiences was significantly correlated with a lower physical activity ( $p=0.022$ ;  $r=-0.176$ ).

**Table 8. Anomalous body experience patients with FES (N = 99)**

Items *	Score $\geq$ 2 (%)	Score $\geq$ 3 (%)	Examples of patients' statements
<b>Morphological changes</b>	36.2	16.6	<i>"I feel my knees expanding..sometimes they take up the entire room"</i>  <i>"The entire body bulges..like superman"</i>  <i>"My skeleton enlarges, my inner organs grow"</i>
<b>Bodily estrangement</b>	38.5	23.6	<i>"I feel I have micro-chips inside me. I'm like a robot"</i>  <i>"it feels like I'm being pushed out of my body"</i>
<b>Cenesthetic experiences</b>	<b>67.2</b>	<b>43.1</b>	<i>"I've got electric sensations in my hands coming out through my fingers"</i>  <i>"I have a sense of insects crawling under my skin"</i>  <i>"I can feel a worm inside my body crawling from my anus to my heart"</i>
<b>Hypochondriasis</b>	23.6	10.3	<i>"I'm convinced I suffer from cancer or dementia"</i>  <i>"I feel something is wrong with my brain. I have tis constant tingly feeling inside my head"</i>
<b>Bodily disintegration</b>	21.3	13.7	<i>"I feel like breaking into pieces...like I'm disappearing"</i>  <i>"I feel like I'm breaking into two ...my torso is only attached to the rest of my body with small strings..like girdles"</i>
<b>Motor disturbances</b>	<b>48.3</b>	<b>28.1</b>	<i>"I sometimes doubt I'm controlling my own body ...it does something else than I'd planned"</i>  <i>"Sometimes I forget how to do simple things ...like slicing bread or writing"</i>  <i>"I often feel my movements are blocked...its like being paralyzed"</i>

\*Items from Examination of Anomalous Self-Experience and Body Awareness Scale. The values in bold present the most frequent anomalous bodily disturbances.

In multiple linear regression analyses with physical activity as the dependent variable only negative symptoms (SANS) were significantly correlated with low physical activity ( $\beta = -.88$ ; 95% confidence interval  $-1.48$  to  $-0.29$ ;  $p < 0.001$ ) (Paper III).

### 5.3 Hypotheses outcome

The following hypotheses were studied:

*I. Patients with first-episode schizophrenia (FES) have higher baseline prevalence of MetS compared with healthy controls:*

The hypothesis was rejected (paper II).

*II. Patients with first-episode schizophrenia (FES) have higher baseline prevalence of metabolic abnormalities MetS compared with healthy controls:*

The hypothesis was confirmed (paper II).

*III. Patients with first-episode schizophrenia (FES) and first-time hospitalised patients with depression have similar prevalence of MetS and metabolic abnormalities:*

The hypothesis was confirmed (paper I and II).

*IV. The prevalence of MetS and metabolic abnormalities in patients with FES increase during 1 year of follow-up.*

The hypothesis was confirmed (Paper II).

*V. Low physical activity is an independent risk factor for MetS and metabolic abnormalities in patients with FES:*

The hypothesis was confirmed (Paper II).

However, in multiple regression analyses aerobic fitness proved to be a more significant and consistent risk factor for MetS and metabolic abnormalities (Paper II).

*VI. Anomalous bodily experiences have a negative impact on physical activity in patients with FES.*

The hypothesis was confirmed (Paper III).

However, in regression analyses only negative symptoms was significantly correlated with low physical activity (Paper III).

## 6. Discussion

### 6.1 Prevalence of metabolic syndrome and metabolic abnormalities

The baseline prevalence of MetS in patients with FES was higher compared with healthy controls, although this was not statistically significant when adjusted for age. However, patients with FES had significantly higher prevalence of metabolic abnormalities than healthy controls. Compared with first-time hospitalized patients with depression, patients with FES had similar rates of MetS and metabolic abnormalities at baseline and at 1 year follow-up. The prevalence of MetS increased significantly in patients with FES and in first-time hospitalized patients with depression. Both patients with FES and first-time hospitalized patients with depression had significant increases in WC and TG during the 1 year follow-up period.

Our findings of MetS in both patients with FES and first-time hospitalized patients with depression are in concordance with previous findings<sup>67,69</sup>. The prevalence of MetS in patients with FES found in our study is significantly higher ( $p=0.04$ ) compared with that of healthy controls from a European population-based study<sup>173</sup>. This is opposed to other studies that found no differences in prevalence of MetS between patients with FES and healthy controls<sup>68,100</sup>. Yet in contrast hereto, the majority of patients in our study were exposed to antipsychotic treatment more than 6 weeks prior to inclusion. This could explain a higher baseline prevalence of MetS, as the adverse metabolic effects of antipsychotics are well known and affects patients early in treatment<sup>42,47,48</sup>. There were no significant differences in the prevalence of MetS between drug-naïve and AP-medicated patients with FES, which is in line with previous findings<sup>67</sup>. The numbers are, however, rather small.

In concordance with other studies patients with FES had significantly more metabolic abnormalities compared to healthy controls, thus confirming that the baseline cardio-metabolic risk is significantly higher in patients with FES<sup>66-69</sup>. The prevalence of MetS and metabolic abnormalities increased significantly in patients with FES during 1 year of follow-up, as found in the few previous prospective studies<sup>70,91,96,103</sup>.

The prevalence of MetS and metabolic abnormalities in first-time hospitalized patients with depression was similar to that of patients with FES and are in concordance with previous findings<sup>109,112</sup>, even though patients in our study were younger.

MetS is significantly correlated with an increased risk of cardiovascular disease<sup>34</sup> and recent research suggests that even fulfilling only two of the individual criteria gives a similar cardiovascular risk<sup>174</sup>. Together this outlines the importance of thoroughly monitoring both MetS and the individual metabolic

abnormalities early in treatment of patients with FES, as well as in younger first-time hospitalized patients with depression.

## 6.2 Physical activity

The baseline physical activity in patients with FES was significantly lower than in healthy controls, yet higher than in first-time hospitalized patients with depression. Physical activity was very low in patients with FES and corresponded to mostly lying and sitting activities throughout the day.

The low level of physical activity in patients with FES is in concordance with the few previous findings<sup>141,142</sup>. Only a limited number of patients with FES were engaged in moderate or high level physical activities, and the sedentary lifestyle is potentially associated with deleterious health outcomes<sup>175</sup>. Patients with FES remained physically inactive during the study period. Opposed hereto, first-time hospitalized patients with depression increased their level of physical activity to a level similar to that of healthy controls. This underlines schizophrenia as a mental illness that affects patients' function in everyday life in general and physical activity specifically, and for long periods of time. Furthermore, it points to the importance of systematic interventions for improving physical activity in patients with FES implemented as part of daily clinical practice.

Aerobic fitness served as proxy for the physical activity prior to inclusion and during the study. Patients with FES had low aerobic fitness at baseline, and this tended to decrease during the study period. The low baseline aerobic fitness in patients with FES is in line with previous findings<sup>176,177</sup> and indicates that patients are physically inactive and debilitated in activities of daily life prior to being diagnosed.

Although first-time hospitalized patients with depression increased their physical activity during the study period aerobic fitness remained unchanged, indicating that increase in physical activity had only persisted for a short period of.

The prevalence of MetS and metabolic abnormalities – WC, TG, HDL, BP, and FG – were significantly correlated with antipsychotic medication and low physical activity. However, in all multivariate regression analyses low aerobic fitness was the most consistently and significantly predictor of MetS and metabolic abnormalities.

Other studies have found significant adverse metabolic effect of AP in patients with FES<sup>68,69</sup>. Yet, in our study regression analyses proved aerobic fitness to be most consistently and significantly correlated with

MetS and metabolic abnormalities in both patients with FES and first-time hospitalized patients with depression, and not as hypothesized physical activity. Recent studies have found similar associations between aerobic fitness and metabolic abnormalities in patients with schizophrenia<sup>178</sup>. Interpreting this result one should consider that physical activity is correlated with aerobic fitness<sup>179</sup>. Furthermore, smoking was significantly more prevalent in patients with FES than in healthy controls, and smoking is also strongly correlated with aerobic fitness<sup>180</sup>.

Conclusively, these findings indicate that clinicians should not only focus on the adverse metabolic effects of antipsychotic medication, but also on low aerobic fitness, physical inactivity, and smoking as significant predictors of MetS in patients with FES, as well as in first-time hospitalized patients with depression.

### Anomalous body experiences

In our study 72.2 % (n=73) of patients with FES had score  $\geq 2$  in one or more anomalous bodily experiences. Most frequent were cenesthetic experiences and motor disturbances. The relatively high prevalence of anomalous bodily experiences is in accordance with other studies<sup>181-183</sup>. To our best knowledge no other study has investigated the correlation of anomalous body experiences and physical activity in patients with FES.

Physical activity was significantly lower in patients with severe anomalous body experiences compared with patients with fewer such experiences. However, in multivariate linear regression analyses only negative symptoms proved to be significantly correlated with low physical activity. The presence of negative symptoms has previously been found to be associated with low physical activity in patients with multi-episode schizophrenia<sup>149</sup>.

Several other barriers for physical activity in patients with schizophrenia have been proposed comprising anxiety, somatic health problems and lack of social support<sup>153,184</sup>. Ambivalent feelings and experiences towards physical activity have been described in a qualitative study of patients with FES. Being engaged in few and static activities of every-day life was in contrast to the energy gained from being physically active; being psychotic and feeling disorganized was contradicted by feelings of being bodily more organized and "whole" after physical activity; physical activities involving social interaction could both provoke anxiety and be reassuring; anxiety was a frequent barrier for being physically active and on the other hand physical activity could often reduce anxiety<sup>185</sup>.



### 6.3 Strengths and limitations

This study differed from other studies on MetS in patients with FES in several ways. Firstly, it compared the prevalence of MetS and metabolic abnormalities in patients with FES with both first-time hospitalized patients with depression and healthy controls. Furthermore, it described the course of MetS and metabolic abnormalities in patients with FES compared with first-time hospitalized patients with depression. Finally, to our best knowledge it was the first prospective study investigating putative risk factors for MetS including both AP as well as physical activity, aerobic fitness, dietary, smoking and sleeping habits in patients with FES.

We were able to obtain thorough data on the patients' prescribed medicine prior to and during the study. Moreover, we used validated measures of psychopathology (GAF, SANS, and SAPS), physical activity, aerobic fitness, and smoking, dietary and sleeping habits.

#### Methodological considerations

We chose to use the IDF-definition of MetS in which abdominal obesity must be fulfilled. The significant increases in WC and TG in both patient groups indicate a higher metabolic risk moving towards fulfillment of the criteria for MetS. As weight gain is a significant adverse metabolic effect of antipsychotic medication, some argue that measuring WC is an easy and feasible way to monitor the metabolic risk in patients with FES in daily clinical practice<sup>68</sup>.

For measures of physical activity we used a validated questionnaire PAS, which, compared with other questionnaires, also covers lying/sleeping activities throughout the day. The low physical activity found in our study underpins the importance of recording sedentary behavior thoroughly. PAS has previously been proven applicable to psychiatric populations<sup>186</sup>, yet in spite of this it can be questioned how precisely physical activity is reported. Especially sedentary adults tend to overestimate their physical activity<sup>187</sup>. For this reason, we also measured aerobic fitness, as it might reflect physical activity more precisely than self-reported activity. It is, however, essential to note that aerobic fitness is not only correlated with physical activity, but also with smoking<sup>180</sup>. Smoking is also significantly correlated with MetS and metabolic abnormalities<sup>37</sup> and should be adjusted for in order to avoid confounding.

In the planning phase of the study we also considered using actigraphs as this can provide objective measures of physical activity<sup>148</sup>. Yet, we chose not to for several reasons. Firstly, the available actigraphs

were not sufficiently developed for reliable and valid measures of physical activity. Furthermore, we had some concern regarding compliance in patients, who to some extent suffer from paranoid delusions.

In this study we chose specific selected items from EASE and BAS to describe anomalous bodily experiences. Both scales are validated measures; however, the specific selection of items can be questioned, as both scales cover additional bodily items. Experiences from physical therapy served as argument for the specific selection of items. In EASE the different items in the various subscales are summarized from which means can be calculated. As we had a selected number of variables and also added an item from BAS, we were not able to summarize the scores without the risk of undermining validity. Instead we analyzed data more conservatively, which might have impaired the ability to correlate anomalous bodily experiences with physical activity. Furthermore, it is important to draw attention to the fact that interviewing patients on bodily experiences (and other anomalous self-experiences) requires a more confident relationship with the patient than what could be established in our study setting. Given this, it is likely that the anomalous bodily experiences found in our study are underestimated. The fact that negative symptoms can be seen as a confounder for low physical activity should be taken with some caution, given the fairly small sample size and the explorative nature of multivariate linear regression analyses. Furthermore, there could be some overlap between some the items, i.e. the item "Decreased spontaneous movement and blocking" (from SANS) and the item "Motor disturbances" (from EASE).

### Study design

Although there was a higher prevalence of MetS in FES compared to healthy controls, this was not statistically significant. This is probably due to lack of statistical power of the small sample size. When compared with a data from a larger sample of healthy controls<sup>173</sup> the prevalence of MetS in patients with FES was significantly higher. Likewise, due to the small sample size of drug-naïve (n=17) patients with FES we were not able to find any differences in MetS and metabolic abnormalities between medicated and un-medicated patients.

Due to the naturalistic study design we had insufficient data on metabolic measures from blood samples, especially FG. This might have led to an underestimation of the prevalence of MetS in patients with FES as well as in first-time hospitalized patients with depression. The routinely taken blood samples now include measures of HbC1A from which FG can be calculated, however, these data were not available during this project. Furthermore, the study's naturalistic design might have limited the ability to correlate

antipsychotic medication with metabolic abnormalities. First, the compliance to prescribed medication may be insufficient in the first year of treatment. Additionally, it is likely that clinicians prescribed antipsychotics with fewer metabolic adverse effects for patients who were obese or who gained weight early in treatment. Finally, we were not able to correct for initiated non-pharmacological interventions, such as physical therapy or dietetic counseling, to improve unhealthy lifestyle for the patients. These potential biases, however, only strengthen our findings.

### Generalizability and representativity

Given this study's exclusion criteria the included sample of patients with FES does not represent all patients with first-episode schizophrenia. However, we do believe that our sample is representative of a majority of patients with FES, as there were no significant differences in GAF, SANS or SAPS between patients with FES eligible for inclusion and the included patients. Likewise, there were no differences in baseline data on BMI, age, gender, WC, BP, TG, HDL, use of AP, GAF, SANS or SAPS between patients who were lost to follow and the 72.4 % of patients who succeeded the study. Although there were no significant differences in MetS and metabolic abnormalities between drug-naïve patients and medicated patients at baseline, we believe that our findings of MetS and metabolic abnormalities can only be generalized to AP-medicated patients with FES, who are not subject to coercive measures, are mentally retarded, or have mental disorders due psychoactive substance abuse.

Recruitment of healthy controls from advertisement in local newspaper might have caused a selected group of healthy controls with healthier lifestyle habits, who might not be representative of the general population. If so, one could hypothesize a higher prevalence of MetS in a more representative sample of the general population. However, given the fact that the metabolic syndrome develops slowly in young adults<sup>173</sup>, we believe that the risk of selection bias is limited. Prospective data on both patients with FES and healthy controls would have strengthened the ability to prove a higher cardio-metabolic risk in patients with FES compared with healthy controls.

### Information bias and confounding

The scores on GAF, SANS and SAPS were based on data collected by many different member of the OPUS clinic for first-episode schizophrenia. Although, these were experienced health professionals the inter-rater reliability could be poor. The internal validity of these data could, thus, be hampered.

In self-reported measures of physical activity there is a tendency to overestimate the amount of time being physically active, especially in sedentary adults<sup>187</sup>. Likewise, there can be a tendency to underestimate smoking and poor dietary habits.

Different factors could confound the findings in our study. Firstly, we had no genetic data, and were therefore not able to address a greater vulnerability to adverse metabolic effect of AP found in patients with certain genotypes<sup>188</sup>. Secondly we had no measures of perceived stress, e.g. measures of cortisol, which is also significantly correlated to an increased risk of MetS<sup>61,189</sup>. Finally, we lacked data on severity of depression in our sample of first-time hospitalized patients with depression and were therefore not able to account for this in relation to MetS<sup>52</sup>.

## 7. Conclusion

In this PhD study we found a high prevalence of MetS and metabolic abnormalities in patients with FES. The baseline prevalence of MetS did not differ significantly from healthy controls, yet patients with FES had significantly more metabolic abnormalities and therefore a significantly higher cardio-metabolic risk. During 1 year of follow-up patients with FES had significant increases of MetS and metabolic abnormalities, thus indicating a significant increase in cardio-metabolic risk. The prevalence and course of MetS and metabolic abnormalities in patients with FES did not differ from first-time hospitalized patients with depression, in line with our initial hypotheses.

Although both AP and physical activity were correlated with MetS and metabolic abnormalities, low aerobic fitness was most consistently and significantly correlated hereto in both patients with FES and first-time hospitalized patients with depression. Despite aerobic fitness being a significant risk factor for MetS, it is important to note the low physical activity in patients with FES throughout the study. A sedentary lifestyle is a significant risk for deleterious health outcomes.

Negative symptoms were significantly correlated with low physical activity in patients with FES. Yet, our findings also suggest that anomalous bodily experiences play a role in the low physical activity in patients with FES.

Our findings emphasize that MetS and metabolic abnormalities should be addressed early in treatment of patients with FES as well as in first-time hospitalized patients with depression. Furthermore, systematic assessment of physical activity and aerobic fitness as significant indicators of metabolic risk should be integrated in treatment and rehabilitation of patients with FES as well as in first-time hospitalized patients with depression.

## 8. Perspectives

The prevalence of MetS and metabolic abnormalities has been studied thoroughly in patients with schizophrenia, in patients with depression and in other patients with severe mental illness. However, these patients still have a shorter life expectancy than the general population, mainly due to CVD. The findings in this PhD study confirm the need of interventions to minimize the cardio-metabolic risk in patients with FES as well as in younger patients with depression.

### Clinical practice

Our findings underpin the importance of addressing MetS and metabolic syndrome early in treatment of patients with FES as well first-time hospitalized patients with depression. A systematic review from 2012<sup>190</sup> found that the clinical routine monitoring of metabolic risk in patients prescribed antipsychotic medication is low, resulting in most patients not receiving adequate testing. Although this might have improved in subsequent years, our findings suggest that there is room for further improvement in daily clinical practice.

Increasing evidence, as described in this PhD study and others, confirm the important role of physical activity and aerobic fitness in relation to MetS and metabolic abnormalities. Systematic assessment of physical activity and aerobic fitness should be provided in psychiatric treatment and rehabilitation. Likewise, physical activity interventions should be an integrated part of multidisciplinary rehabilitation programs for minimizing cardio-metabolic risk in patients with schizophrenia and in patients with depression as proposed by the International Organization of Physical Therapy in Mental Health<sup>191</sup>.

### Future research

There is an evident need for studying the efficacy of physical activity in minimizing cardio-metabolic risk in patients with FES and in patients with depression. Likewise, there is a need for exploring the efficiency of physical activity in improving health-related quality of life and reducing psychopathological symptoms e.g. negative symptoms or anomalous bodily experiences in patients with FES.

Although this PhD study found similar prevalence of MetS and metabolic abnormalities in patients with FES and first-time hospitalized patients with depression, there may be significant differences in the underlying pathophysiological risk factors. This is supported by the proposed bi-directional correlation of MetS and depression<sup>117</sup>. Addressing the correlation of severity of depression and prevalence of MetS would thus be relevant in future research.

Different barriers for participation in physical activities have been proposed. Findings from this PhD study indicate that the patient's experiences of own body might play an important role. This should, however, be elucidated further in future research. Likewise, how to motivate and promote patient-participation in physical activities needs further exploration and development.

## English summary

This PhD dissertation was completed at Aarhus University Hospital, Risskov, and Dep. of Affective Disorders Q. My supervisors were Professor Poul Videbech, MD, DMSc, Aarhus University Hospital, Risskov, Hans Lund PT, PhD, Southern University, Odense and Marianne Kleis Møller, MD, PhD, Region Hospital, Horsens.

### Background

Patients with schizophrenia have a 15-20 years shorter life-expectancy compared to the general background population. Death from natural causes, in particular due to cardiovascular disease, is among the most common causes for the premature death. The concept for metabolic syndrome (MetS) is helpful in screening and monitoring the risk of cardiovascular disease (CVD) and has therefore been studied intensively in relation to patients with schizophrenia in the past decades. In patients with multi-episode schizophrenia the prevalence of MetS is 2-4 times higher compared to the general background population. However, little is still known about the prevalence, course and predictors of MetS in patients with first episode schizophrenia (FES), including how this might differ from healthy controls or patients with another severe mental illness, e.g. depression.

### Aim

The aim of this PhD study was to investigate the prevalence and course of MetS in patients with FES aged 18-45 years in comparison with healthy controls and first-time hospitalized patients with depression. Furthermore, we investigated the impact of physical inactivity on MetS. Finally we explored the effect of anomalous bodily experiences on physical activity in patients with FES.

### Methods

We included 101 patients with FES, 52 first-time hospitalized patients with depression and 50 healthy controls (aged 18-45 years). We calculated the prevalence of MetS and the individual metabolic abnormalities as defined by The International Diabetes Federation (IDF) including measures of waist circumference (WC), blood pressure (BP) and data from blood samples on triglyceride (TG), high-density lipoprotein (HDL), and fasting-glucose (FG). We also included measures of physical activity, aerobic fitness, smoking-, dietary-, and sleeping habits, socioeconomic data, psychopathological data, including anomalous bodily experiences, and use of antipsychotics, antidepressants, and benzodiazepines.

All participants were measured at baseline, yet only the two patient groups were examined again after 1 year follow-up.



## Results

Patients with FES had higher, non-significant prevalence of MetS compared with healthy controls. However, the individual metabolic abnormalities WC and TG were significantly higher in patients with FES compared with healthy controls. There were baseline differences of MetS and metabolic abnormalities in patients with FES compared with first-time hospitalized patients with depression. The prevalence of MetS and metabolic abnormalities increased significantly during 1 year follow-up in patients with FES as well as in first-time hospitalized patients with depression.

Both physical activity and aerobic fitness were very low during the entire study period in patients with FES. Although both antipsychotic medication and low physical activity was correlated with MetS aerobic fitness was most consistently and significantly correlated with MetS and the individual metabolic abnormalities. Patients with more severe anomalous bodily experiences had significantly lower physical activity, yet negative symptoms were most significantly correlated with low physical activity in patients with FES.

## Conclusion

Patients with FES have high prevalence of MetS and significant higher prevalence of metabolic abnormalities compared to healthy controls, indicating a higher cardio-metabolic risk. During 1 year of treatment patients with FES have significant increases in MetS and metabolic abnormalities, describing an increase of the cardio-metabolic risk.

Besides of confirming the well-known adverse metabolic effect of antipsychotics, the study proved low physical activity and low aerobic fitness to be significantly correlated with MetS and metabolic abnormalities in patients with FES. Interventions for improving health behaviour, especially increasing physical activity and improving aerobic fitness, are therefore warranted.

## Dansk resumé (Danish Summary)

Dette arbejde blev gennemført på Forskningsenheden, Afd. for Affektive Lidelser, afd. Q, Aarhus Universitetshospital Risskov. Min hovedvejleder var Professor, dr.med. Poul Videbech, Aarhus Universitetshospital, Risskov. Øvrige vejledere var lektor og ph.d. Hans Lund, Syddansk Universitet og Overlæge, ph.d. Marianne Kleis Møller, Regionshospitalet, Horsens.

### Baggrund

Patienter med skizofreni har 15-20 års kortere levetid end baggrundsbeholdningen. Blandt de væsentligste årsager hertil er død af hjertekarsygdom. Metabolisk syndrom (MetS) er nyttigt i forhold til at screene og monitorere de patienter, der er i risiko for at udvikle hjertekarsygdom og forekomst af MetS hos mennesker med skizofreni har derfor været grundigt undersøgt gennem de sidste årtier. Der er dog fortsat begrænset viden om forekomst, udvikling og prædiktorer for MetS hos patienter med ny-diagnosticeret skizofreni, herunder om dette adskiller sig fra raske og fra andre patienter med alvorlig sindslidelse f.eks. depression.

### Formål

Formålet med dette Ph.d. studie var at undersøge forekomst, udvikling og prædiktorer for MetS hos ny-diagnosticerede patienter med skizofreni i sammenligning med raske kontrolpersoner og førstegangs-indlagte patienter med depression. Desuden at undersøge betydningen af fysisk inaktivitet på MetS. Endelig at undersøge hvilken betydning anomale kropslige oplevelser har for fysisk aktivitet.

### Metode

Vi inkluderede 101 patienter med ny-diagnosticeret skizofreni, 52 første gangs-indlagte patienter med depression samt 50 raske kontrolpersoner (alder 18-45 år). MetS og metaboliske forstyrrelser blev beskrevet ud fra kriterier defineret af det internationale diabetes forbund (IDF), omfattende taljemål, blodtryk samt serumværdier af triglycerider (TG) high-density-lipo-protein (HDL) og faste glukose. Desuden registrerede vi deltagernes fysiske aktivitetsniveau, fysiske kondition (kondital), tobaks- og kostvaner, søvn, socioøkonomiske data, forbrug af anti-psykotika, anti-depressiva og benzodiazepiner, samt psykopatologiske symptomer, bl.a. omfattende anormale kropslige oplevelser. Alle deltagere blev undersøgt ved inklusion, og de to grupper af patienter blev tillige undersøgt efter 1 år.

### Resultat

Patienter med ny-diagnosticeret skizofreni havde høj forekomst af MetS, dog ikke signifikant forskelligt fra raske kontrolpersoner. I forhold til raske havde patienter med ny-diagnosticeret skizofreni signifikant højere forekomst af forøget taljemål og TG. Der var ingen signifikant forskel i forekomsten af MetS og metaboliske forstyrrelser mellem patienter med ny-diagnosticeret skizofreni og første gangs indlagte patienter med depression. I løbet af 1 år steg forekomsten af MetS og metaboliske forstyrrelser signifikant hos både patienter med ny-diagnosticeret skizofreni og første gangs indlagte patienter med depression. Både fysisk aktivitetsniveau og kondition var signifikant lavere hos patienter med ny-diagnosticeret skizofreni end hos raske. Selvom både antipsykotisk medicin og fysisk inaktivitet var signifikant korreleret med MetS, var lav kondition mest konsistent og signifikant korreleret med MetS. Patienter med flere og sværere anomale kropslige oplevelser havde signifikant lavere aktivitetsniveau, dog var negative symptomer mere signifikant korreleret til lavt fysisk aktivitetsniveau hos patienter med ny-diagnosticeret skizofreni.

#### Konklusion

Patienter med ny-diagnosticeret skizofreni har høj forekomst af MetS og signifikant flere metaboliske forstyrrelser end raske, hvilket indikerer en højere kardio-metabolisk risiko. I løbet af 1 år steg både forekomsten af MetS og metaboliske forstyrrelser hos patienter med ny-diagnosticeret skizofreni som udtryk for en forøget kardio-metabolisk risiko.

Udover at bekræfte metaboliske bivirkninger af antipsykotisk medicin viser studiet, at både fysisk inaktivitet og i særdeleshed lav fysisk kondition er signifikant korreleret med MetS og metaboliske forstyrrelser hos patienter med ny-diagnosticeret skizofreni. På baggrund heraf er interventioner med henblik på at fremme sundhedsadfærd, særligt at øge fysisk aktivitet og kondition, relevante i behandlingen af patienter med ny-diagnosticeret skizofreni.

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## Appendix I: papers (I-III)

**Paper I:** Lene Nyboe, Claus Høstrup Vestergaard, Marianne Kleis Møller, Hans Lund, Poul Videbech  
*Metabolic syndrome in first-time hospitalised patients with depression. A 1 year follow-up study.* Acta  
Psychiatr Scand 2015: 1–8. DOI: 10.1111/acps.12470.

**Paper II:** Lene Nyboe, Claus Høstrup Vestergaard, Marianne Kleis Møller, Hans Lund, Poul Videbech  
*Prevalence and predictors of metabolic syndrome in patients with first-episode schizophrenia, including a 1-  
year follow-up.* Schizophr. Res. (2015). <http://dx.doi.org/10.1016/j.schres.2015.07.053>.

**Paper III:** Lene Nyboe, Claus Høstrup Vestergaard, Marianne Kleis Møller, Hans Lund, Poul Videbech  
*Physical activity and anomalous body-experiences in patients with first-episode schizophrenia.* Submitted to  
Early Intervention in Psychiatry.

# Metabolic syndrome in first-time hospitalized patients with depression: a 1-year follow-up study

Nyboe L, Vestergaard CH, Lund H, Møller MK, Videbech P.  
Metabolic syndrome in first-time hospitalized patients with depression: a 1-year follow-up study.

**Objective:** Studies on metabolic syndrome (MetS) in younger patients with depression are few. We examined the prevalence and progression of MetS in first-time hospitalized patients with depression during 1 year of follow-up. Furthermore, we explored putative risk factors of MetS.

**Method:** We evaluated MetS and its components in first-time hospitalized patients with depression ( $N = 52$ ) and healthy controls ( $N = 50$ ) (18–45 years). Physical activity, aerobic fitness, sleeping disturbances, smoking and dietary habits, and psychopharmacological treatment were recorded at baseline for all participants and after 1 year for the patients.

**Results:** Patients had significantly higher waist circumference (WC) and lower high-density lipoproteins compared with healthy controls ( $P < 0.05$ ). Patients had higher prevalence of MetS, but this was not significant when adjusted for age. Patients had significant increase in WC and triglycerides and a non-significant increase in the prevalence of MetS. Antipsychotic medication (OR 10.5, 95% CI 1.18–94.14) and low aerobic fitness (OR 0.79, 95% CI 0.68–0.93) were significantly correlated with MetS ( $P < 0.05$ ).

**Conclusion:** Metabolic syndrome is highly prevalent in younger, severely depressed patients and the incidence increases during 1 year of follow-up. Low aerobic fitness and use of atypical antipsychotics are strongly correlated with MetS.

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Key words: depression; metabolic syndrome; aerobic fitness; antipsychotics

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## Significant outcomes

- Metabolic syndrome (MetS) and metabolic abnormalities increases significantly during 1 year of follow-up in younger, first-time hospitalized patients with depression.
- Low aerobic fitness and antipsychotic medication are strongly correlated with the MetS and its individual components in younger, first-time hospitalized patients with depression.

## Limitations

- Due to insufficient data from blood samples, the prevalence of metabolic syndrome in younger first-time hospitalized patients with depression might be underestimated.

## Introduction

In recent years, the prevalence of the metabolic syndrome (MetS) among psychiatric patients has been studied intensively. MetS is a cluster of risk

factors, comprising elevated waist circumference (WC), increased blood pressure (BP), elevated triglycerides (TG), decreased high-density lipoproteins (HDL), and increased fasting glucose (FG), which significantly increase the risk of

cardiovascular disease (CVD) and type 2 diabetes (T2D) (1, 2). Although there has been a growing focus on depression and MetS (3–6), the majority of studies have focused on patients with schizophrenia or bipolar disorder rather than patients with unipolar depression. Yet, like other patients with severe mental illness, patients with depression have an increased risk for premature death (7, 8) and CVD is among the most common causes (9, 10). Studies on MetS in relation to patients with depression are therefore highly relevant.

Different causes have been hypothesized for associations between MetS and depression. First, adverse metabolic effects of psychopharmacological treatment are well described. Contrary to serotonin reuptake inhibitors (11), tricyclic antidepressants (TCA) and mirtazapine have adverse metabolic effects, comprising weight gain and dyslipidemia (12, 13). Likewise, atypical antipsychotics have well-described metabolic side-effects (14, 15) and are frequently prescribed for patients with severe depression (16).

As many as 40% of patients with major depression have increased hypothalamic–pituitary–adrenal axis activity. This results in chronically elevated glucocorticoids, impeding insulin's ability to promote glucose uptake and leading to abdominal obesity, dyslipidemia, and insulin resistance (17, 18).

Furthermore, poor health behaviours, such as sedentary lifestyle, smoking, and high-caloric diet, increase the risk of MetS and are also common in patients with depression (19–22). It is, however, uncertain to which extent low physical activity (PA) increases the risk of MetS in younger patients with depression, independently of other risk factors.

A meta-analysis performed in 2014 found a mean prevalence of MetS of 29.7% in patients with depression (6). Subsequent studies have found similar prevalence rates (23, 24). The prevalence of MetS in patients with depression is thus 2–3 times higher than in the background population (25). The majority of studies included middle-aged or older patients (mean age > 45 years) (6). To the best of our knowledge, only very few studies evaluate the prevalence and progression of MetS in younger patients with depression (26).

#### Aims of the study

The study aimed to describe the prevalence of metabolic syndrome (MetS) in younger (18–45 years of age), first-time hospitalized patients with depression compared with healthy controls;

furthermore, to study the development of MetS and its individual components in patients with depression during 1 year of follow-up; and finally, to study putative risk factors of MetS in patients with depression, hypothesizing that physical inactivity is an independent risk factor.

#### Material and methods

This was a controlled, observational, follow-up study of first-time hospitalized patients with depression fulfilling the ICD-10 criteria (27). The subjects were between 18 and 45 years of age and were consecutively recruited at Aarhus University Hospital, Risskov, during 2010–2013 with 1-year follow-up. For comparison, healthy controls were included from another research project at the site. The healthy controls were recruited through advertisement in a local newspaper and received participation grants.

#### Exclusion criteria

All participants understood and spoke Danish. The participants were excluded from the study if they were physically disabled or had somatic illness impairing PA, were pregnant, mentally retarded, or subject to coercion. For the healthy controls, use of any psychotropic medication led to exclusion.

#### Ethics

All participants were included in the study after written, informed consent in accordance with The Helsinki Declaration. The study protocol was approved by The Local Ethical Committee, Central Region, Denmark, and the study was registered at The Danish Data Protection Agency and ClinicalTrials.gov.PRS (NCT00957294).

#### Procedures

The patients were assessed at baseline and after 1 year of follow-up; the healthy controls were only assessed at baseline. All assessments were carried out by the same researcher (LN). All questionnaires were administered as structured interviews to account for possible cognitive deficits in the clinical population.

#### Measurements

The level of FG, TG, and HDL were measured in blood samples.

*Waist circumference* was measured with the participant standing using a tape measure at umbilical

level (28). *Weight and height* were measured, the former with participants wearing light clothes and no shoes. *The body mass index (BMI)* was calculated as weight in kilograms divided by the square of height in meters.

*Blood pressure* was measured after at least 10 min of resting, with the participant sitting using *The UA-852 Digital Blood Pressure Monitor* placed on left upper arm.

*The level of PA* was assessed by *The Physical Activity Scale* (29, 30). *Aerobic fitness*, defined as (ml O<sub>2</sub>/min)/kg, was measured using *The Astrand-Rhyming submaximal exercise test* (31) and served as a proxy for the PA level prior to inclusion and during the study period.

*Smoking habits* were assessed using a questionnaire, comprising (i) no smoker, (ii) previous smoker, (iii) weekly smoker, (iv) daily smoker < 9 cigarettes, or (v) daily smoker >10 cigarettes. *Dietary habits* were assessed with a questionnaire adapted from *The Danish Health Examination Survey 2007–2008* (32).

*Sleeping disturbances* were assessed by *The Pittsburgh Sleep Quality Index* (33).

*Psychotropic medication* comprising antidepressants, antipsychotics, and sedatives were registered for all patients. Data were obtained from patients' electronic medical records and included medical data from up to half a year before inclusion and during the study period. Antipsychotic medication was described in *defined daily dosages (DDD)* based on the average doses given prior to and during study period respectively.

Furthermore, data on gender, age, level of education, socioeconomic status, and diagnoses were recorded.

#### Statistical analyses

Physical activity was presented in metabolic equivalents; a higher score reflected a higher level of PA. Smoking habits were categorized in (i) 'non-smoker', comprising previous and non-smokers; or (ii) 'smoker', comprising weekly and daily smokers together. The questionnaire of dietary habits presents sum scores from Likert scales; a higher sum indicated a healthier diet, defined as having more regular meals, more frequent intake of vegetables, fruits, whole-grain products, fish and meat and less frequent intake of sweets, cakes, snacks, and soft drinks.

The participants were described as having MetS if fulfilling the criteria defined by *The International Diabetes Federation (IDF)* (1). The number of participants with or without MetS in each group was compared using a chi-squared test. Changes in

the individual metabolic components of MetS were analyzed individually. For analyses of differences between the patients and the healthy controls, the chi-squared test or Fischer's exact test was applied for categorical variables and the Mann–Whitney *U*-test was applied for continuous variables. The Wilcoxon signed rank test was applied for paired analyses of patients at baseline vs. follow-up. All tests were two-sided ( $P \leq 0.05$ ). In regression analyses, we used stepwise backward elimination starting with all candidate variables and deleting variables one at the time until no further improvement of the model could be found. Due to small sample size, we pooled data from baseline and follow-up and adjusted for follow-up effect in all regression analyses. Multivariate logistic regression analyses were performed to examine factors independently correlated with fulfilling the IDF criteria for MetS. Analyses were presented as odds ratios (95% CI;  $P \leq 0.05$ ). Multiple linear regression analyses were performed to examine factors correlated with the continuous variables on WC, TG, BP, and HDL and were presented as regression coefficients (95% CI;  $P \leq 0.05$ ). All statistical analyses were performed using *STATA* version 13.1 (Stata Corp., College Station, TX, USA).

#### Results

In all, 52 first-time hospitalized patients with depression and 50 healthy controls were included in the study. The majority of patients had first-episode depression ( $n = 43$  (82.7%)). Only seven patients had depression with psychotic symptoms. Of the 52 patients with depression, 17 were lost to follow-up; only two patients were hospitalized at time of follow-up, yet none had been hospitalized during the entire study period. There were no significant differences between patients lost to follow-up and patients who succeeded regarding baseline measures of age, gender, WC, BP, TG, BMI, PA, or medication (data not shown). The majority of blood samples from patients were non-fasting resulting in limited data on FG.

The baseline characteristics of the study sample are summarized in Table 1. The depressed patients were 4 years older on the average than the controls ( $P = 0.0017$ ). The patients with depression differed from healthy controls in having higher BMI, lower levels of PA and aerobic fitness, more sleeping disturbances, poorer diet and were more frequent smokers. The prevalence of MetS in patients and healthy controls was 13% and 2%, respectively; however, this was not statistically significant when adjusting for age (95% CI: 0.022–1.971;  $P = 0.171$ ). Yet, in age-adjusted analyses, patients

had statistically significantly higher WCs than the healthy controls: 95% CI: -11.85 to -2.09;  $P = 0.06$ ; likewise statistically more patients fulfilled the IDF criteria for low HDL: 95% CI: 3.41 to -0.50;  $P = 0.008$ .

The patients with depression had no significant changes in smoking or dietary habits, but sleeping disturbances improved significantly from baseline to follow-up (Table 2). There was a significant increase in the percentage of patients receiving antipsychotic medication ( $P = 0.011$ ) and a signifi-

cant increase in the average dosage of TCA ( $P = 0.016$ ) during the study period. Patients with depression became statistically significantly more physically active ( $P < 0.0001$ ), whereas improvements in aerobic fitness were not statistically significant.

During 1-year follow-up, the prevalence of MetS in patients with depression increased from 13% to 20%, but this was not statistically significant (data not shown). The 35 patients able to follow had statistically significantly increases in WC

Table 1. Baseline characteristics of patients with depression and healthy controls

	Depression (N = 52)	Healthy controls (N = 50)	P-value	P-value*
Age, median (min; max)	25.6 (18.7; 45.5)	23.1 (18.3; 42.8)	0.002	0.002
Female, n (%)	26 (52)	21/40 (50)		0.316
Civil status, n (%)				
Living alone	4/5 (7.7)	11/50 (22.0)	0.061	0.061
Living with parents	32/52 (61.5)	20/50 (40.0)	0.009	0.009
Married or cohabiting	16 (30.8)	19/50 (38.0)	0.629	0.629
Years of education, n (%)				
≤10 years	5/52 (9.6)	3/50 (6.0)	0.427	0.427
>10 and ≤12 years	26/52 (50.0)	26/50 (52.0)	0.839	0.839
>12 years	31/52 (40.4)	21/50 (42.0)	0.868	0.868
Income, n (%)				
Wages	2/52 (3.8)	5/50 (10.0)	0.262	0.262
Social security	10/52 (19.2)	1/50 (2.0)	0.003	0.003
Educational grants	16/52 (30.8)	40/50 (80.0)	<0.0001	<0.0001
Sickness benefit	19/52 (36.5)	–	<0.0001	<0.0001
Unemployment grant	4/52 (7.7)	1/50 (2.0)	0.155	0.155
No income	1/52 (2.0)	3/50 (6.0)	0.327	0.327
BMI, median (min; max)	24.1 (15.8; 39.0)	22.1 (17.9; 37.8)	0.006	0.062
Physical activity, median (min; max)†	27.9 (22.1; 37.8)	34.2 (28.6; 48.8)	<0.001	<0.0001
Aerobic fitness (ml O <sub>2</sub> /min/kg), median (min; max)	33.9 (10.1; 74.7)	53.5 (23.1; 87.1)	<0.001	<0.0001
Dietary habits, median (min; max)	103.5 (76; 124)	110 (90; 131)	<0.001	<0.0001
Daily smoking, n (%)	33/52 (64.7)	15/50 (30.6)	0.001	0.001
Sleeping disturbances, median (min; max)	15.5 (4; 19)	10 (4; 19)	0.011	0.015
Diagnoses				
F.32.0	1 (1.9)	–		
F.32.1	15 (28.8)	–		
F.32.2	20 (38.5)	–		
F.32.3	5 (9.6)	–		
F.32.9	2 (3.8)	–		
F.33.1	1 (1.9)	–		
F.33.2	6 (11.5)	–		
F.33.3	2 (3.8)	–		
Metabolic syndrome, IDF criteria, n (%)	6/46 (13.0)	2.0 (1/50)	0.044	0.171
Waist circumference (cm), median (min; max)	81.0 (58.0; 115.0)	70.5 (59.0; 107.0)	<0.0001	0.006
IDF criteria, n/N (%)	16/52 (30.8)	2/50 (4.0)	<0.0001	0.003
Triglycerides (mmol/l), median (min; max)	1.1 (0.5; 2.7)	0.8 (0.4; 2.6)	0.026	0.177
IDF criteria, n/N (%)	9/34 (25)	4/50 (8.9)	0.034	0.105
HDL (mmol/l), median (min; max)	1.25 (0.75; 2.7)	1.4 (0.85; 2.6)	0.05	0.511
IDF criteria, n/N (%)	11/34 (32.4)	3/50 (6.0)	0.002	0.008
Systolic BP (mmHg), median (min; max)	123.0 (97.0; 158.0)	119.0 (100.0; 148.0)	0.467	0.888
IDF criteria, n/N (%)	11/52 (21.2)	14/50 (28.0)	0.388	0.088
Diastolic BP (mmHg), median (min; max)	78.0 (56.0; 99.0)	75.0 (59.0; 98.0)	0.547	0.432
IDF criteria, n/N (%)	10/52 (19.2)	10/50 (20.0)	0.882	0.157
Fasting glucose (mmol/l), median (min; max)	5.5 (4.2; 5.9)	5.0 (4.1; 5.8)	0.004	0.164
IDF criteria, n/N (%)	2/9 (22.2)	2/50 (4.0)	0.106	0.33

IDF, International Diabetes Federation; HDL, high-density lipoprotein; BP, blood pressure.

Mann–Whitney U-test for continuous variables; chi-squared test or Fischer's exact test for categorical variables.

\*Age-adjusted P-values by linear or logistic regression analyses.

†Described in metabolic equivalents.



Table 2. Changes in clinical characteristics of patients with depression during 1-year follow-up (N = 35)

	Depression baseline	Depression follow-up	P-value
BMI, median (min; max)	24.6 (15.9; 39.0)	27.5 (17.5; 44.1)	<0.0001
Physical activity, median (min; max)*	28.0 (22.9; 37.8)	33.7 (25.6; 53.3)	<0.0001
Aerobic fitness (ml O <sub>2</sub> /min/kg), median (min; max)	35.0 (10.1; 74.7)	34.7 (14.7; 74.2)	0.569
Dietary habits, median (min; max)	105.0 (76.0; 124.0)	101.0 (75.0; 122.0)	0.346
Daily smoking (%)	64.7	61.8	0.783
Sleeping disturbances, median (min; max)	13.0 (4.0; 18.0)	6.0 (1.0; 15.0)	<0.0001
Medication (%)			
Patients receiving AP (%)†	45.7	71.4	0.011
Quetiapine (mean ± SD)	104.5 ± 74.0	79.2 ± 57.4	0.711
DD (mean ± SD)	0.58 ± 0.68	0.73 ± 0.46	0.003
CPZ (mg)	170.6 (125.7)	255.1 (213.5)	0.021
SSRI (%)	71.4	60.0	0.237
SSRI dosage (mean ± SD)	56.6 ± 48.3	56.4 ± 53.3	0.862
TCA (%)	8.6	28.6	0.011
TCA dosage (mean ± SD)	66.7 ± 14.4	72.5 ± 36.2	0.016
Mirtazapine (%)	48.6	34.3	0.063
Mirtazapine dosage (mean ± SD)	11.7 ± 6.1	55.0 ± 82.6	0.130
Benzodiazepines (%)	54.3	57.1	0.398

AP, second-generation antipsychotics; DD, daily dosage; TCA, tricyclic antidepressants; SSRI, selective serotonin reuptake inhibitor.

Wilcoxon signed rank test (non-normal distribution) or paired t-test (normal distribution) on continuous variables; chi-squared test for categorical variables (P ≤ 0.05).

\*Described in metabolic equivalents.

†Here mainly Quetiapine (73.1%).

(P < 0.0001) and TG (P = 0.007) during the study period (Table 3). Due to missing data, we were not able to compare changes in FG for these patients.

The stepwise logistic regression analyses showed statistically significant correlations between MetS and low aerobic fitness and antipsychotic medication respectively (Table 4). A one-unit increase [ml/O<sub>2</sub>/kg] in aerobic fitness lowered the odds for MetS by a factor 0.769 (95% CI: 0.68–0.93; P = 0.005). Antipsychotic medication and gender (male) increased the odds of MetS by 10.5

(95% CI: 1.18–94.1; P = 0.035) and 5.16 (95% CI: 0.76–35.1; P = 0.094) respectively. The multiple linear regression analyses showed that low level of aerobic fitness was statistically significantly correlated with increases in WC, TG, and systolic and diastolic BP but not to HDL. Due to insufficient data, it was not possible to detect whether low aerobic fitness was associated with FG (Table 5). A one-unit increase in aerobic fitness lowered WC with 0.42 cm, lowered TG with 0.02 mmol/l, and systolic and diastolic BP with 0.28 and 0.25 mmHg respectively.

Table 3. Changes in metabolic abnormalities in patients with depression during 1-year follow-up (N = 35)

	Depression baseline	Depression follow-up	P-value
Waist circumference (cm), median (min; max)	85.5 (58.0; 105.0)	90.5 (62.0; 130.0)	<0.0001
IDF criteria, n/N (%)	10/34 (29.4)	14/34 (41.2)	0.305
Triglycerides (mmol/l), median (min; max)	0.85 (0.5; 2.7)	1.4 (0.7; 4.5)	0.007
IDF criteria, n/N (%)	4/18 (22.2)	8/18 (44.4)	0.144
HDL (mmol/l), median (min; max)	1.30 (0.75; 2.7)	1.2 (0.68; 2.7)	0.221
IDF criteria, n/N (%)	5/16 (31.3)	6/16 (37.5)	0.500
Systolic BP (mmHg), median (min; max)	123.0 (97.0; 158.0)	122.0 (96.0; 153.0)	0.837
IDF criteria, n/N (%)	6/33 (18.2)	9/33 (27.3)	0.378
Diastolic BP (mmHg), median (min; max)	78.0 (61.0; 95.0)	1.0 (55.0; 102.0)	0.124
IDF criteria, n/N (%)	6/33 (18.2)	13/33 (39.4)	0.057

IDF, International Diabetes federation; HDL, high-density lipoprotein; BP, blood pressure.

Wilcoxon signed rank test (continuous variables), Fischer's exact test (dichotomous variables) (P ≤ 0.05).

Discussion

This follow-up study investigated the prevalence and progression of MetS in a sample of younger, first-time hospitalized patients with depression. The patients with depression had higher prevalence of MetS compared with healthy controls, although this was not statistically significant when adjusted for age. Yet, on the time of inclusion, the patients

Table 4. Logistic regression of odds for metabolic syndrome in first-time hospitalized patients with depression

	OR	95% CI	P-value
Gender	5.16	0.76–35.06	0.096
Aerobic fitness	0.79	0.68–0.93	0.005
Antipsychotic medication	10.54	1.18–94.14	0.035

Stepwise (backward elimination) regression analyses, age, physical inactivity, smoking and dietary habits, tricyclic antidepressants or benzodiazepine, were not included in the model.

Table 5. Correlations between aerobic fitness and metabolic abnormalities in first-time hospitalized patients with depression

	Waist circumference			Triglycerides			Systolic BP			Diastolic BP		
	$\beta$	95% CI	<i>P</i> -value	$\beta$	95% CI	<i>P</i> -value	$\beta$	95% CI	<i>P</i> -value	$\beta$	95% CI	<i>P</i> -value
Aerobic fitness	-0.42	-0.64 to -0.20	<0.0001	-0.02	-0.03 to -0.02	0.03	-0.28	-0.48 to -0.08	0.007	-0.25	-0.43 to -0.07	0.006

BP, blood pressure.

Stepwise (backward elimination) linear regression analyses; age, gender, smoking, dietary habits, sleeping disturbances, physical inactivity, AP, tricyclic antidepressants or benzodiazepines were not included in the model.

had significantly higher WC and lower HDL levels than the healthy controls. Both WC and TG increased significantly in the patients with depression during follow-up; fulfillment of all MetS criteria increased from 13% to 20%. Antipsychotic medication and low levels of aerobic fitness significantly increased the odds ratios for MetS in patients with depression. Low level of aerobic fitness was significantly correlated with increase in WC, TG, and systolic and diastolic BP.

As opposed to the majority of previous studies, we found no significant differences in the age-adjusted prevalence of MetS between depressed patients and healthy controls (6). Interpreting this result, it is important to note that insufficient data on blood samples and a limited samples size could lead to type II error. Compared with the prevalence of MetS in healthy controls described in a large European population study (34), patients with depression in our study had significant higher prevalence of MetS ( $P = 0.035$ ).

A higher prevalence of MetS in patients with depression has previously been reported, yet these results were based on study samples with significantly older patients (6, 23, 24). The majority of previous studies have been cross-sectional (6, 23, 24). In contrast hereto, the prospective design in this clinical study allowed for analyses of progression in MetS in patients with depression. Regarding the progression of MetS in patients with depression, the prevalence increased from 13% at baseline to 20% at 1-year follow-up. It is important to note that four of the six patients who fulfilled criteria for MetS at baseline were lost to follow-up. Additionally, four patients fulfilled criteria for MetS during the study period. If these patients still had MetS at the time of follow-up, it can be estimated that the prevalence of MetS would be up to 25%. The significant increases in both WC and TG found in our study clearly states that metabolic abnormalities worsen over time and notably in a sample of fairly young patients with first-episode depression. In the general population, MetS develops more slowly (34) than that found in our study. The increase in MetS was, however, not statistically significant probably due to missing

data from blood samples. Besides from impairing the research results, it also underlines insufficient clinical procedures, such as monitoring metabolic risk by routinely taken blood samples. Considering the significant increases in individual components of MetS, in particular increase in WC, it is likely that the true prevalence of MetS after 1 year of follow-up is higher than found in this study had all measures been sufficiently recorded. The significant increase in WC is in accordance with other studies (35). Moreover, it is important to note that fewer patients fulfilled the criteria of low levels of HDL at follow-up than at baseline. Taken together, our findings underpin that assessment of metabolic risk is clinically relevant in younger and first-time hospitalized patients with depression.

Low aerobic fitness, and not as hypothesized physical inactivity, was found to be strongly correlated with MetS and metabolic abnormalities, which corresponds to findings in non-depressed populations (36–38). The low aerobic fitness resembled previous findings (39) and is similar to that found in patients with schizophrenia (40, 41). Self-reported level of PA is moderately correlated to aerobic fitness (38), and as such, both measures may be correlated with MetS. Sedentary adults often have a tendency to overestimate their PA (42), whereas aerobic fitness is an objective and more precise measure. The latter should therefore preferably be considered in clinical settings to identify the risk of MetS.

We found antipsychotic medication to be strongly correlated with MetS in accordance with previous findings (6). It is noteworthy that even small dosages of antipsychotics, described in DDD or chlorpromazine equivalents, as prescribed in this sample, are strongly correlated with MetS. The antipsychotic drugs were used as anxiolytics not because the patients were psychotic; only seven patients fulfilled the diagnostic criteria for depression with psychotic symptoms. Our finding of these drugs having a grave influence on the risk of MetS underscores the importance to use these for a short period of time. Moreover, alternative treatment such as benzodiazepines, relaxation therapy, or PA could be considered. As opposed to others, this

study did not find adverse metabolic effects of antidepressant treatment, including TCA (13). In relation to the limited sample size, it is likely that the impact of antipsychotics on metabolic risk drowns the possible metabolic risk of TCA.

In our study, being male also increased the odds for MetS in depressed patients in contrary to findings from population-based studies, in which depressive symptoms in females increase the odds for MetS (43, 44).

A low level of HDL is a significant risk factor for CVD (45). During the study period, HDL increased, reflecting a decrease in this specific metabolic risk factor. HDL is negatively correlated to depressive symptoms (46, 47) and therefore clinically interesting. Although we had no data on severity of depression, it is reasonable to believe that first-time hospitalized patients experienced improvement of their depressive symptoms during the study. This might explain the increase in HDL over time and support the findings of a bidirectional association in metabolic abnormalities and depression (48).

Conclusively, the prevalence and progression of MetS and metabolic risk factors should be monitored thoroughly in patients with depression, in particular patients treated with antipsychotic medication. The strong correlation of aerobic fitness and metabolic abnormalities support the use of physical exercise as a relevant conjunctive treatment of patients with depression (49).

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**Declarations of interest**

None.

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# Metabolic syndrome and aerobic fitness in patients with first-episode schizophrenia, including a 1-year follow-up



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## ABSTRACT

**Objective:** To compare the prevalence of metabolic syndrome (MetS) and metabolic abnormalities in patients with first-episode schizophrenia (FES) with sex- and age-matched healthy controls; to investigate changes in MetS during 1 year of treatment; and to investigate predictors of MetS.

**Methods:** Patients with FES (N = 99) and healthy controls (N = 50) were included in the study. MetS was defined according to IDF based on waist circumference (WC), blood pressure (BP), triglycerides (TG), high-density lipoprotein (HDL), and fasting-glucose. Data on physical activity, aerobic fitness, smoking, and dietary habits, sleeping disturbances, psychopathology and psychotropic medication were also obtained. Patients were assessed at baseline and at 1 year follow-up.

**Results:** Compared with healthy controls patients with FES had a higher baseline prevalence of MetS (p = .07), and metabolic abnormalities: WC (p < .01), TG (p < .01), HDL (p = .017), and fasting glucose (p = .04). Patients with FES had significantly increased prevalence of MetS (p = .03), WC (p = .04), and TG (p = .01) during the study period. Antipsychotics and low physical activity were significantly correlated with the increase in metabolic abnormalities. In multivariate analyses low aerobic fitness was the most consistent and significant predictor of metabolic abnormalities and MetS.

**Conclusion:** MetS and metabolic abnormalities are highly prevalent in patients with FES, and both increase significantly during 1 year of treatment. Apart from confirming the metabolic adverse effects of antipsychotics, our study highlights that low aerobic fitness is a significant risk factor for MetS. Promoting a healthier lifestyle should be part of psychiatric treatment and rehabilitation.

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## 1. Introduction

Patients with schizophrenia have a 15- to 20-year shorter life expectancy than the general population (Laursen, 2011; Laursen et al., 2014). The higher mortality is mainly due to somatic illnesses such as cardiovascular disease (CVD), type 2 diabetes (T2D), and cancer (Brown et al., 2010; De Hert et al., 2009; Jin et al., 2011). Metabolic syndrome (MetS) – comprising abdominal adiposity, insulin resistance, increased blood pressure, elevated triglyceride (TG) levels, and low high-density

lipoprotein (HDL) levels – significantly increases the risk for CVD and T2D (Alberti et al., 2006; Mottillo et al., 2010). The concept of MetS is useful when screening and monitoring cardiovascular risk factors in patients with schizophrenia.

The development of MetS is attributable to multiple factors, including genetic factors, physical inactivity, smoking, a high-calorie diet, and sleeping disturbances (Povel et al., 2011; Huang and Liu, 2014; Sun et al., 2012; Jennings et al., 2007). Moreover, patients with schizophrenia are also exposed to the well-known metabolic adverse effects of antipsychotic medication (Allison and Casey, 2001; De Hert et al., 2011). Weight gain has been given significant attention and both low baseline BMI and specific genetic factors prove to predict weight gain in patients with first-episode schizophrenia (FES) (Saddichha et al., 2008a; Boden et al., 2009; Srisawat et al., 2014).

The prevalence of MetS in multi-episode patients with schizophrenia is 35.3%, which is 2- to 4-fold higher than in the general population (Mitchell et al., 2011; Vancampfort et al., 2013). Patients with schizophrenia have a fourfold increased risk of abdominal obesity, and a

**Abbreviations:** BMI, body mass index; CVD, cardiovascular disease; FES, first-episode schizophrenia; FG, fasting glucose; GAF, Global Assessments of Function; HDL, high-density lipoprotein; MetS, metabolic syndrome; SANS, Scale for Assessment of Negative Symptoms; SAPS, Scale for Assessments of Positive Symptoms; T2D, type 2 diabetes; TG, triglycerides; WC, waist circumference; AP, antipsychotics; AD, antidepressants.

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more than doubled risk of low HDL levels and hypertriglyceridemia (Lamberti et al., 2006; McEvoy et al., 2005; Boke et al., 2008; Cohn et al., 2004; Saari et al., 2005; Vancampfort et al., 2013).

A 2013 meta-analysis found that drug-naïve patients and patients with FES have comparable rates of MetS (~10%), although patients with FES have a significantly higher waist circumference (WC) and blood pressure (BP) (Mitchell et al., 2013). The significant increase of individual metabolic abnormalities early in the treatment of patients with FES have been confirmed in subsequent studies as comprising weight gain (Perez-Iglesias et al., 2014; Chiliza et al., 2015), dyslipidemia (Phutane et al., 2011; Wu et al., 2014), glycometabolism (Nielsen et al., 2010; Graham et al., 2008; Correll et al., 2014; Fleischhacker et al., 2013), and hypertension (Bensenor et al., 2012; Beary et al., 2012). Only a few studies have compared the rates of MetS in patients with FES and healthy controls, with divergent results. Some studies show no differences (Fleischhacker et al., 2013) but others do (Correll et al., 2014; Saddichha et al., 2008b; Bensenor et al., 2012). However, all studies have found a significantly higher prevalence of metabolic abnormalities in patients with FES compared with healthy controls, thereby also confirming a high metabolic risk early in the treatment of patients with FES.

The majority of studies describing an adverse metabolic effect of antipsychotics in patients with FES lack concurrent examination of non-pharmacological risk factors. Therefore, little is still known about how lifestyle factors such as physical inactivity, smoking, and poor diet contribute to the increased metabolic risk in patients with FES.

The aims of this study were to investigate the prevalence of MetS in patients with FES compared with healthy controls; to study how MetS and its individual metabolic abnormalities progress in these patients during the first year of treatment; and to examine predictors of MetS and metabolic abnormalities in patients with FES. We hypothesized that both antipsychotic medication and low physical activity would significantly increase the risk of MetS and metabolic abnormalities.

## 2. Methods and materials

This was a controlled, 1-year follow-up study, ending in 2014, of patients with FES (International Classification of Diseases-10 [ICD-10] diagnoses F.20) aged between 18 and 45 years. Patients were recruited from an outpatient clinic for patients with FES in the Central Region of Denmark. For comparison, we also included sex- and aged-matched healthy controls recruited via an advertisement in a local newspaper.

Only participants who spoke and understood Danish were included. Other exclusion criteria were physical disability or somatic illness impairing physical activity, pregnancy, mental retardation, or substance or alcohol abuse according to ICD-10 criteria, or coercion. For healthy controls, the use of any psychotropic medication or medical condition led to exclusion. All participants were included in the study after written, confirmed consent was obtained in accordance with the Declaration of Helsinki. The study protocol was approved by the local ethical committee and the study was registered with the Danish Data Protection Agency and ClinicalTrials.gov.PRS (NCT00957294).

Patients with FES were assessed at baseline and after 1 year of follow-up; healthy controls were only assessed at baseline. Apart for psychopathological data, all assessments were carried out by the same researcher (LN). All questionnaires were administered as structured interviews to account for cognitive deficits in the clinical population.

### 2.1. Socio-demographic data, smoking, and dietary habits

Socio-demographic data, smoking, and dietary habits were assessed, the latter using questionnaires adapted from the Danish Health Examination Survey 2007–2008 (Eriksen et al., 2011). Smoking habits were categorized as i) “nonsmoker”, comprising previous and nonsmokers, or ii) “smoker”, comprising daily and weekly smokers. Dietary habits were presented in sum scores from Likert-type scales, with a higher

sum indicating a healthier diet, defined as having more regular meals, a more frequent intake of vegetables, fruits, whole-grain products, fish, and meat, and a less frequent intake of sweets, cakes, snacks, and soft drinks.

### 2.2. Metabolic measures

Metabolic measures comprised data from blood samples on level of fasting glucose (FG), TG, and HDL, measures of WC, weight, height, and body mass index (BMI), and BP. Participants were described as having MetS if they fulfilled the criteria defined by the International Diabetes Federation (IDF) (Alberti et al., 2006).

### 2.3. Physical activity

Physical activity was assessed by the Physical Activity Scale (Aadahl and Jorgensen, 2003; Andersen et al., 2010). All participants were asked to recall their activity level during the past week. Physical activity was presented in metabolic equivalents, with a higher score reflecting a higher level of physical activity. Aerobic fitness, defined as oxygen uptake (VO<sub>2</sub> max/kg), served as a proxy for physical activity level prior to inclusion and during the study period, and was measured using the Astrand–Rhyning test, a single-stage cycle ergometer test (Astrand, 1960). The test is designed to elicit a steady-state heart rate (HR) over a 6-min period. All tests were performed on a Monark 827 Ergometer cycle, and HR was measured during the entire test by a Polar HR monitor. Only patients who had a normal electrocardiogram were allowed to perform the test. Based on HR at a specific workload (Watt) the oxygen uptake (VO<sub>2</sub> max) was estimated using the Astrand–Rhyning sex- and age-sensitive nomogram. A recent study has proved The Aastrand–Rhyning test as valid and applicable for patients with schizophrenia (Vancampfort et al., 2014).

### 2.4. Sleeping disturbances

Sleeping disturbances were assessed by the Pittsburgh Sleep Quality Index (Buysse et al., 1989).

### 2.5. Psychopathological data

Psychopathological data included Global Assessment of Function (GAF), Scale for Assessment of Negative Symptoms (SANS) (Andreasen, 1984a), and Scale for Assessment for Positive Symptoms (SAPS) (Andreasen, 1984b). Data were assessed by trained psychiatric staff members.

### 2.6. Psychopharmacological data

Psychopharmacological data comprised names and dosages of prescribed antipsychotics (AP), antidepressants (AD), and benzodiazepines, and were registered for all patients. Data were obtained from patient's electronic medical records and included medical data from up to 6 months before inclusion and during the study period. Antipsychotic medication was described in defined daily dosages (DDD) and chlorpromazine equivalents based on the average doses given prior to and during study period, respectively.

### 2.7. Statistical analyses

For analyses of differences between the patients and the healthy controls a chi-squared test or Fischer's exact test was applied for categorical variables, and the Kruskal–Wallis test applied for continuous variables. The number of participants with MetS in each group was compared using the chi-squared test. The progression of the individual metabolic components of MetS was analyzed individually. For paired

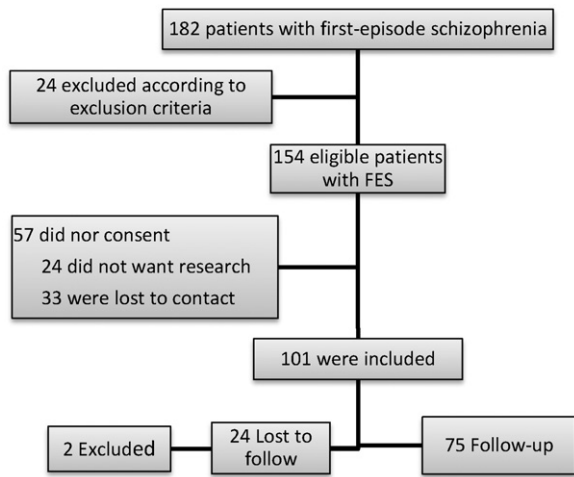


Fig. 1. Flowchart of included patients with first-episode schizophrenia (FES).

comparisons of differences at baseline and follow-up, the Wilcoxon Signed Ranks test was applied.

Because of non-normal distribution of physical activity and use of antipsychotic medication (DDD), respectively, Spearman's rho was

used to assess correlations between these variables and continuous MetS variables (providing more power than categorical variables).

In all regression analyses, a forward, stepwise approach was applied, starting with no variables in the model, testing the addition of each variable using a chosen model comparison criterion, adding the variable (if any) that improves the model the most, and repeating this process until none improved the model. Logistic regression analyses were performed to examine factors independently correlated with fulfilling the IDF criteria for MetS. Data were presented as odds ratios (95% confidence intervals [CIs]); a  $p$ -value  $\leq .05$  was considered to be statistically significant. Linear regression analyses were performed to examine the independent factors correlated with WC, TG, (BP), and HDL. For these regression analyses we pooled data from baseline and follow-up, and adjusted for follow-up effect due to small sample size. Furthermore, we performed multiple linear regression analyses to examine factors correlated with the changes from baseline to follow-up. Data were presented as regression coefficients (95% CI;  $p \leq .05$ ). All tests were two-sided with ( $p \leq .05$ ). All statistical analyses were done with Stata version 13.1 (Stata Corp., College Station, TX, USA).

### 3. Results

Of 182 patients with FES eligible for inclusion during the study period, 101 were included in the study. Two patients were subsequently

Table 1

Baseline characteristics of patients with first-episode schizophrenia (FES) and healthy controls.

	Patients with FES (N = 99)	Healthy controls (N = 50)	p-Value
Age, years (mean $\pm$ SD)	24.9 $\pm$ 7.1	23.6 $\pm$ 4.6	0.063
Female (%)	33	42	0.299
Civil status (%)			
Living alone	19.2	22.0	0.686
Living with parents	51.5	40.0	0.184
Married or cohabiting	29.3	38.0	0.283
Years of education (%)			
$\leq 10$	26.3	6.0	<0.006
$> 10$ and $\leq 12$	51.5	52.0	0.863
$> 12$	23.2	42.0	0.018
Income (%)			
Wages	3.8	10.0	<b>0.028</b>
Social security	61.9	2.0	<0.0001
Educational grants	18.5	80.0	<0.0001
Sickness benefit	13.4	–	0.018
Unemployment grant	4.1	2.0	0.864
No income	1.0	6.0	0.214
BMI (median (min; max))	24.8 (17.1; 42.6)	22.1 (17.9; 37.9)	<0.0001
Physical activity (median (min; max))	29.4 (23.3; 50.1)	34.3 (28.6; 48.4)	<0.0001
Aerobic fitness (median (min; max))	35.7 (13.0; 77.7)	53.5 (23.1; 87.1)	<0.0001
Dietary habits (median (min; max))	101.0 (62.0; 128.0)	111.0 (90.0; 131.0)	<0.0001
Daily smokers (%)	50.0	30.6	<0.004
Sleeping disturbances (median (min; max))	10.0 (1.0; 16.0)	10.0 (9.0; 11.0)	0.666
ICD-10 diagnoses			
F.20.0	74.4	–	
F.20.3	18.8	–	
F.20.6	2.3	–	
Other F.20	4.5	–	
Metabolic syndrome IDF criteria n/N (%)	9/90 (10.0)	1/50 (2.0)	0.072
Waist circumference (cm) (median (min; max))	85.0 (58.0; 111.0)	70.5 (59.0; 107.0)	<0.0001
IDF criteria n/N (%)	26/97 (26.8)	2/50 (4.0)	<0.0001
Triglycerides (mmol/L) (median (min; max))	1.1 (0.4; 4.5)	0.8 (0.4; 2.6)	<0.008
IDF criteria n/N (%)	15/97 (15.5)	4/49 (8.2)	0.164
HDL (mmol/L) (median (min; max))	1.3 (0.7; 2.3)	1.4 (0.85; 2.6)	0.262
IDF criteria n/N (%)	20/97 (20.6)	3/49 (6.1)	<b>0.017</b>
Systolic BP (mm HG) (median (min; max))	120.0 (92.0; 162.0)	119.0 (100.0; 148.0)	0.665
IDF criteria n/N (%)	19/97 (19.6)	14/49 (28.0)	0.220
Diastolic BP (mmHG) (median (min; max))	78.0 (55.0; 99.0)	75.0 (59.0; 98.0)	0.452
IDF criteria n/N (%)	28/97 (28.9)	10/49 (20.4)	0.271
Fasting glucose (mmol/L) (median (min; max))	5.2 (3.9; 7.6)	5.0 (4.1; 5.8)	<b>0.045</b>
IDF criteria n/N (%)	6/33 (15.3)	2/50 (4.0)	0.062

BMI, body mass index; ICD-10, International Classification of Diseases-10; IDF, International Diabetes Federation; HDL, high-density lipoprotein; BP, blood pressure. Kruskal-Wallis test for comparison. Physical activity measured in metabolic equivalents; aerobic fitness: ml O<sub>2</sub>/min/kg. p-value (bold): <0.01.

excluded (in accordance with exclusion criteria) and 24 patients were lost to follow-up (Fig. 1). In addition, 50 healthy controls were included. There were no significant differences between patients lost to follow-up and patients who succeeded in completing the study regarding baseline measures of age, sex, WC, BP, TG, HDL, FG, BMI, antipsychotics, SANS, SAPS, and GAF (data not shown).

Physical activity and aerobic fitness was significantly lower in patients with FES compared with healthy controls ( $p < 0.0001$ ). Significantly more patients were smokers ( $p < 0.004$ ) and had significantly poorer dietary habits ( $p < 0.0001$ ) compared with healthy controls. The majority of patients (82.8%) had received antipsychotic medication (mean  $\pm$  SD: 8.13  $\pm$  5.9 weeks) prior to inclusion in the study.

### 3.1. Baseline

The baseline prevalence of Mets in patients with FES was 10% compared with 2% of healthy controls ( $p = 0.072$ ; age-adjusted  $p = 0.129$ ) (Table 1). In age-adjusted analyses patients with FES had a significantly higher WC ( $p < 0.005$ ), higher TGs ( $p = 0.033$ ), and a higher FG level ( $p = 0.056$ ) compared with healthy controls. Significantly more patients with FES had a low HDL level according to IDF criteria ( $p = 0.032$ ).

There were no significant differences in the prevalence of MetS between men and women at baseline. Medicated patients and antipsychotic-naïve patients had no significant differences in MetS and its individual components when adjusted for sex and age (data not shown).

### 3.2. Follow-up

Apart from poorer dietary habits ( $p = 0.004$ ) patients had no significant changes in health behavior (Table 2). There was a significant increase in DDD of antipsychotic medication ( $p < 0.0001$ ) during the study period.

In patients with FES the prevalence of MetS increased significantly from 10.0% to 22.1% ( $p = 0.031$ ) (data not shown). Paired analyses of patients at baseline and at follow-up, the prevalence of MetS increased from 10.2% to 25%, yet this was not statistically significant ( $p = 0.082$ ). However, patients had a significant increase in both WC ( $p < 0.0001$ ) and TG ( $p = 0.0006$ ) (Table 3). There were no significant differences in the prevalence of MetS between men and women at follow-up. Yet significantly more women than men fulfilled MetS criteria for WC at follow-up.

Significant increase in WC (cm) was observed in patients treated with aripiprazole ( $n = 52$ , mean change: 6.33 cm,  $Z = -4.51$ ,  $p < 0.0001$ ), quetiapine ( $n = 20$ , mean change 8.8 cm,  $Z = -3.26$ ,  $p = 0.006$ ), risperidone ( $n = 17$ , mean change: 3.66 cm,  $Z = -1.89$ ,  $p = 0.06$ ), paliperidone ( $n = 39$ , mean change: 5.64 cm,  $Z = -3.37$ ,  $p = 0.001$ ); patients treated with olanzapine had a non-significant increase in WC ( $n = 14$ , mean change: 2.93 cm,  $Z = -1.16$ ,  $p = 0.245$ ).

Higher DDDs of antipsychotic medication was significantly correlated with a higher WC ( $p = 0.04$ ), a higher TG level ( $p = 0.01$ ), a lower HDL level ( $p = 0.05$ ), a higher systolic BP ( $p = 0.01$ ), and a higher FG ( $p = 0.05$ ). Correspondingly, low physical activity was significantly correlated with a higher WC ( $p = 0.02$ ), a higher TG level ( $p = 0.07$ ), a lower HDL level ( $p = 0.04$ ), and a higher systolic ( $p = 0.07$ ) and diastolic BP ( $p = 0.02$ ).

A stepwise multiple logistic regression analysis with MetS as the dependent variable was performed with age, sex, antipsychotic medication (DDD), physical activity, aerobic fitness, smoking, eating habits, sleeping disturbances, SANS, SAPS, antidepressant medication, and the use of benzodiazepines as covariates. Only low aerobic fitness was statistically significantly correlated with MetS: a one-unit increase in aerobic fitness lowered the odds for MetS by 12% (95% CI 0.83–0.95;  $p < 0.0001$ ).

In multiple linear regression analyses low aerobic fitness, AP, DDD, age, sex, and low physical activity were associated with one or more of the individual (continuous) components of MetS (Table 4).

**Table 2**

Changes in clinical characteristics in patients with first-episode schizophrenia (FES) during one year follow-up.

	Patients with FES baseline (N = 99)	Patients with FES follow-up (N = 75)	p-Value <sup>b</sup>
BMI (median (min; max))	24.8 (17.1; 42.61)	25.2 (17.7; 44.4)	<0.0001
Physical activity <sup>a</sup> (median (min; max))	29.4 (23.3; 50.1)	29.11 (23.0; 44.31)	0.780
Aerobic fitness (median (min; max))	35.7 (13.0; 87.1)	33.2 (17.2; 69.7)	0.227
Dietary habits (median (min; max))	101.0 (62.0; 128.0)	97.0 (68.0; 124.0)	0.004
Daily smokers (%)	53.4	54.7	0.99
Sleeping disturbances (median (min; max))	10.0 (1.0; 16.0)	10.0 (0; 17.0)	0.398
Psychopathological data			
GAF_ symptom (median (min; max))	39.0 (19.0; 75.0)	48.0 (0.0; 95.9)	<0.0001
GAF_ function (median (min; max))	45.0 (8.0; 77.0)	49.0 (0.75; 75.0)	0.002
SANS (median (min; max))	2.0 (0.0; 4.5)	1.5 (0.0; 4.76)	0.006
SAPS (median (min; max))	2.0 (0.0; 5.5)	1.0 (0.0; 4.0)	<0.0001
Antipsychotic medication			
CPZ-equivalents (mean $\pm$ SD)	372.6 $\pm$ 313.5	647.2 $\pm$ 436.1	<0.0001
DDD (mean $\pm$ SD)	1.18 $\pm$ 0.13	4.25 $\pm$ .48	0.001
Olanzapine (%)	17.3	11.8	0.480
Clozapine (%)	0.0	5.2	0.046
Aripiprazole (%)	39.8	64.9	<0.0001
Quetiapine (%)	33.7	42.9	0.275
Risperidone (%)	16.2	16.9	1.00
Paliperidone (%)	19.6	53.4	<0.0001
Ziprasidone (%)	3.1	0.0	0.157
Amisulpride (%)	1.0	5.7	0.157
None (%)	17.2	2.6	<0.0001
Comedication (%)			
Antidepressants	30.6	51.3	0.001
Benzodiazepines	24.5	26.3	0.353

BMI, body mass index; GAF, Global Assessments of Function; SANS, Scale for Assessment of Negative Symptoms; SAPS, Scale for Assessment of Positive Symptoms; CPZ, chlorpromazine equivalents; DDD, defined daily dose.

<sup>a</sup> Measured in metabolic equivalents; aerobic fitness (ml O<sub>2</sub>/min/kg).

<sup>b</sup> Differences between baseline and follow-up Wilcoxon signed rank test (paired data (n = 75)).



**Table 3**

Changes in metabolic syndrome and metabolic abnormalities in patients with first-episode schizophrenia (FES) during 1 year of follow-up (N = 75).

	FES baseline			FES follow-up			p-Value <sup>a</sup>
	Total	Male	Female	Total	Male	Female	
MetS n/N (%)	6/59 (10.2)	5/(57) (8.8)	4/24 (16.7)	13/52 (25.0)	12/34 (35.3)	3/19 (15.7)	0.082
WC (median (min; max))	80 (58; 108)	82.0 (67; 108)	77.5 (58; 105)	88.0 (68.0; 133.0)	89.0 (69.0; 114.0)	84.5 (68.0; 133)	<0.0001
IDF-criteria n/N (%)	20/75 (26.6)			31/75 (41.3)			0.058
TG (mmol/L) (median (min; max))	1.1 (0.4; 4.5)	1.1 (0.4; 4.5)	0.9 (0.4; 3.0)	1.3 (0.3; 3.8)	1.5 (0.5; 3.8)	0.2 (0.3; 2.2)	<0.0001
IDF-criteria n/N (%)	11/74 (14.8)			24/74 (32.4)			0.012
HDL (mmol/L) (median (min; max))	1.3 (0.7; 2.3)	1.2 (0.7; 7.7)	1.6 (0.93; 2.3)	1.3 (0.8; 2.6)	1.2 (0.8; 2.0)	1.55 (0.89; 2.6)	0.334
IDF-criteria n/N (%)	14/73 (19.2)			17/73 (23.3)			0.544
Systolic BP (median (min; max))	121.0 (92.0; 162.0)	123.0 (99.0; 162.0)	117 (92.0; 138.0)	120.0 (80.0; 150.0)	123.0 (99.0; 150.0)	114.0 (80.0; 138.0)	0.747
IDF-criteria n/N (%)	16/74 (21.6)			15/74 (20.3)			0.840
Diastolic BP (mean ± SD)	78.0 (55.0; 99.0)	77.0 (55.0; 99.0)	78.0 (60.0; 93.0)	77.0 (66.0; 99.0)	77.0 (62.0; 99.0)	76.0 (60.0; 93.0)	0.726
IDF-criteria n/N (%)	23/74 (31.1)			16/74 (21.6)			0.192
FG (median (min; max))	5.2 (3.9; 6.4)	5.4 (3.9; 6.4)	5.2 (5.1; 6.4)	5.4 (4.7; 6.19)	5.5 (4.7; 6.1)	5.25 (4.8, 6.0)	0.834
IDF-criteria n/N (%)	3/13 (23.1)			4/13 (30.8)			.0500

MetS, metabolic syndrome; WC, waist circumference; IDF, International Diabetes Federation; TG, triglycerides; HDL, high-density lipoprotein; BP, blood pressure; FG, fasting glucose.

<sup>a</sup> Differences between baseline and follow-up Wilcoxon signed rank test (paired data (n = 75)). p-value(bold): <0.01

Additionally, linear regression analyses examined factors related to the significant changes in WC and TG. For changes in WC the adjusted R<sup>2</sup> was 0.09 and the only included factor was aerobic fitness (coefficient –0.003, 95% CI –0.0049 to –0.00043; p = 0.020). A one-unit increase in aerobic fitness decreases the predicted gain in WC by 0.2 percentage points.

#### 4. Discussion

We found a higher prevalence of metabolic abnormalities in patients with FES than in healthy controls. The prevalence of MetS increased significantly in patients with FES, as did WC and TG, during the follow-up period. The prevalence of MetS and the individual components – WC, TG, HDL, BP, and FG – were significantly correlated with antipsychotic medication and low physical activity. However, in all multivariate regression analyses low aerobic fitness was the most consistent and significant predictor of MetS and metabolic abnormalities.

The baseline prevalence of MetS in patients with FES in our study is in accordance with previous findings (Correll et al., 2014; Mitchell et al., 2013). We found no statistically significant baseline differences in MetS between patients with FES and healthy controls. However, compared with a European population-based study (Vishram et al., 2014), the prevalence of MetS in patients with FES found in our study is significantly higher (p = 0.04).

Others have found similar rates of MetS in patients with FES and healthy controls (Fleischhacker et al., 2013; Phutane et al., 2011). In contrast to the EUFEST study (Fleischhacker et al., 2013), the majority of patients in our study were exposed to antipsychotic medication more than 6 weeks prior to inclusion. This could explain a higher baseline prevalence of MetS compared with that found in the EUFEST study as the adverse metabolic effects of antipsychotics are well known and affects patients early in treatment (De Hert et al., 2011; Nielsen et al., 2010; Graham et al., 2008; Tarricone et al., 2010; Leucht et al., 2013). As expected patients treated with antipsychotic medication had significant increase in WC during 1 year of treatment. Yet, this was not found for patients treated with olanzapine, which is known as an antipsychotic agent with significant adverse metabolic effects (Taylor et al., 2012). This finding is possibly due to a small sample size as only 14 patients were treated with olanzapine. The increase of MetS from 10% to 25%, as well as the significant increases in WC and TG, over 1 year of treatment clearly states that metabolic abnormalities should be monitored carefully early in treatment of patients with FES.

Opposed to previous studies low baseline BMI was not correlated with increases in WC (Saddichha et al., 2008a). Aerobic fitness, and not as hypothesized physical activity, was most significantly correlated with MetS and its individual components and aerobic fitness was the only significant predictor for increases in WC. Aerobic fitness is

moderately correlated with self-reported physical activity (Minder et al., 2014); as such, both physical activity and aerobic fitness may be correlated with MetS. Furthermore, patients with FES were significantly more frequent smokers compared with healthy controls (p < .01), and smoking is also strongly correlated to aerobic fitness (Leyk et al., 2012). Our results resemble those found of a recent study of first-time hospitalized patients with depression (in press (Nyboe et al., submitted for publication)). As in patients with FES, aerobic fitness was found to be significantly correlated with MetS and metabolic abnormalities. To improve aerobic fitness one can either increase maximum oxygen uptake or lose weight. Taken together, the findings suggest that clinicians should not only focus on the adverse metabolic effects of antipsychotic medication, but also on aerobic fitness, physical activity, weight gain and smoking as significant predictors of MetS. Clinicians should thus encourage patients treated with antipsychotics to try to counteract the sedentary lifestyle often observed.

Our study differs mainly from others by investigating non-pharmacological risk factors for MetS in patients with FES. We believe that our results from this study of MetS in patients with FES are generalizable. The drop-out rate was fairly small, as 77.8% of the patients were followed. Furthermore, there were no baseline differences between patients who fulfilled the study and those who were lost to follow-up. We used validated measures of MetS, psychopathology (GAF, SANS, SAPS), physical activity, aerobic fitness, smoking, and dietary habits.

We were also able to obtain valid data on prescribed medication. In addition, we presented both simple and more advanced statistical analyses of associates of MetS. In all, the results of this study may contribute to a better understanding of MetS in patients with FES.

However, several limitations must be addressed. The fact that patients had significantly lower physical activity, were more frequent smokers, and had poorer dietary habits compared to healthy controls might be confounded by patients also being less educated and having lower income. The sample of 99 patients at baseline and 77 at follow-up is fairly small. In particular, this could affect the results of multivariate analyses. We had limited data on FG, and given the significant increase in WC it is likely that the number of patients who fulfilled the IDF criteria for FG is underestimated. Only 17 patients were antipsychotic naïve, and the comparisons with previously exposed patients should therefore be taken with some caution. The study's naturalistic design limits the ability to correlate antipsychotic medication with metabolic abnormalities. Firstly, a patient's compliance to prescribed medication may be insufficient in the first year of treatment. Furthermore, it is likely that clinicians selected antipsychotics with fewer metabolic adverse effects for patients who were obese or who gained weight early in treatment. Finally, clinicians might have initiated non-pharmacological interventions, such as physical therapy or dietetic counseling, to improve unhealthy lifestyle for these

**Table 4**  
Logistic regression analyses of risk factors for metabolic abnormalities in patients with first-episode schizophrenia.

	WC (n = 151)			Triglycerides (n = 148)			HDL (n = 136)			Systolic BP (n = 149)			Diastolic BP (n = 149)			Fasting glucose (n = 61)		
	$\beta$	95% CI	p-Value	$\beta$	95% CI	p-Value	$\beta$	95% CI	p-Value	$\beta$	95% CI	p-Value	$\beta$	95% CI	p-Value	$\beta$	95% CI	p-Value
Age	0.71	0.40 to 1.02	<0.01															
Gender (male)				0.21	-0.01 to 0.43	0.06	-0.39	-0.49 to -0.28	<0.01	7.59	3.62 to 11.57	<.01	0.22	-0.031 to 0.47	0.08			
Gender	-0.46	0.59 to -0.33	<0.01	-0.01	-0.2 to -0.005	0.01	0.005	0.001 to 0.009	0.01	-0.17	-0.31 to -0.02	0.03	-0.19	-0.31 to -0.09	<0.01			
AP										6.33	0.54 to 12.1	0.03						
DDD																0.18	0.08 to 0.28	<0.01
Low PA							-0.03	-0.05 to -0.007	<0.01				-0.52	-0.85 to -0.19	0.02			

WC, waist circumference; HDL, high-density lipoprotein; BP, blood pressure; AP, antipsychotics; DDD, defined daily dose; PA, physical activity; CI, confidence interval. Stepwise (backward estimation) regression analyses. Global Assessments of Function, Scale for Assessment of Negative Symptoms and Scale for Assessment of Positive Symptoms were not included in the model.

patients. These potential biases may, however, only strengthen our findings.

In conclusion, MetS and metabolic abnormalities are highly prevalent in patients with FES and both increase significantly during one year of treatment. Apart from confirming the well-known metabolic adverse effects of antipsychotics, our study highlights that aerobic fitness is a significant risk factor for MetS. As patients with FES can have motivational barriers to physical activity interventions for improving aerobic fitness should also encounter dietary counseling for weight loss and smoking cessation and interventions should be part of psychiatric treatment and rehabilitation.

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There are no agreements and policies specified as conditions for the grant awards received for this study.

### Contributors

Author Lene Nyboe designed the study and wrote the protocol. This was supervised by author Poul Videbech, author Hans Lund, and author Marianne K. Moeller. Author Lene Nyboe and author Claus H. Vestergaard undertook the statistical analyses. Author Lene Nyboe wrote the first draft of the manuscript. All authors contributed to and approved the final manuscript.

### Conflict of interest

The authors report no conflict of interest.

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**Title:****Physical activity and anomalous body experiences in patients with first-episode schizophrenia****Authors:**

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## Abstract

### Aim

The purpose of this study was to compare physical activity in patients with first-episode schizophrenia (FES) with healthy controls; to investigate changes in physical activity over 1 year of follow-up; and to explore the correlations of physical activity and anomalous body experiences reported by patients with FES.

### Methods

The Physical Activity Scale was used to measure physical activity. Aerobic fitness served as a proxy for physical activity before and during the study period, and was measured by the Astrand–Rhyning test. Anomalous body experiences were measured by selected items from the Examination of Anomalous Self-Experience and The Body Awareness Scale. Psychopathological data comprising negative and positive symptoms and data on psychotropic medication were obtained from the medical records of all patients.

### Results

Physical activity and aerobic fitness was significantly lower in patients with FES compared with healthy controls ( $p < .01$ ). Physical activity in patients with FES corresponded mostly to lying or sitting activities throughout the day. Over 1 year of follow-up patients had unaltered physical activity and aerobic fitness. Patients with more severe anomalous body experiences had significantly lower physical activity compared with patients with fewer such experiences ( $p = 0.030$ ). In linear regression analyses only negative symptoms were significantly correlated with low physical activity ( $\beta = -.88$ ; 95% confidence interval  $-1.48$  to  $-0.29$ ;  $p < 0.001$ ).

## **Conclusion**

Physical activity and aerobic fitness is low in patients with FES. Although anomalous body experiences may reduce physical activity, negative symptoms are more significantly correlated with low physical activity.

## **Keywords**

First-episode schizophrenia, physical activity, aerobic fitness, anomalous body experience

## Introduction

Physical activity is effective in preventing and treating numerous somatic illnesses,<sup>1-3</sup> and physical inactivity is an independent risk factor for both type 2 diabetes (T2D) and cardiovascular disease (CVD).<sup>4,5</sup> Compared with the general population, the life expectancy of patients with schizophrenia is shortened by 15-20 years, owing primarily to somatic illness and CVD, in particular.<sup>6,7</sup>

The relationship between physical activity and somatic illness in patients with schizophrenia is therefore highly relevant.

In patients with multiepisode or chronic schizophrenia, physical activity is significantly lower than in the background population.<sup>8,9</sup> Low physical activity is associated with more frequent occurrence of T2D, more metabolic disturbances, reduced global functioning and lower quality of life.<sup>10-12</sup> A systematic search for all studies evaluating physical activity in patients with first-episode schizophrenia (FES) revealed four studies.<sup>13-16</sup> Preliminary findings suggest that physical activity is lower in patients with FES than in healthy controls but higher than in patients with multiepisode schizophrenia, indicating that physical activity declines over the course of schizophrenia<sup>16</sup>. In previous studies physical activity was measured only at the time of inclusion. As reduced physical activity could be a marker of deterioration in the course of schizophrenia it is relevant to study how physical activity develops during the progression and treatment of patients with FES.

Different causes for low physical activity in patients with schizophrenia have been proposed, including negative symptoms, physical health problems, anxiety, lack of social support and lack of motivation.<sup>17-20</sup> The occurrence of anomalous self-experiences is common in patients with schizophrenia.<sup>21</sup> A validated measure of this is presented in the Examination of Anomalous Self-Experience (EASE),<sup>22</sup> which also includes a number of body-related items (“anomalous bodily experiences”), for example motor disturbances and morphological changes. Motor disturbances comprise experiences of interference with the intended movements (or speech), of impediment



or complete blockage of intended movements, sudden feeling of paresis of the arm or leg, or de-automation of everyday movements that have previously been performed automatically.

Morphological changes comprise experiences of the body becoming thinner, shorter, contracting, enlarging or diminishing.<sup>22</sup> Having these kinds of experiences could be expected to decrease the ability to be physical active, and even to move at all. It is therefore of importance for clinical practice to know whether there is a relationship between anomalous body experiences or not, as it could help in identifying those most in need of support to improve physical activity. The influence of anomalous body experiences on physical activity has not previously been investigated.

Thus, in this study we aimed to (i) describe baseline physical activity in patients with FES compared with healthy controls; (ii) describe and investigate changes in physical activity in patients with FES over a 1-year follow-up period; and (iii) explore the correlations of physical activity and anomalous body experiences in patients with FES.

## Method

### Study design and sample

This was a controlled, observational, follow-up study conducted from 2012 to 2014 on patients with FES (F.20; according to the International Classification of Diseases 10th revision [ICD-10]),<sup>23</sup> aged between 18 and 45 years. Patients were recruited from an outpatient clinic for patients with FES in Central Region, Denmark. For comparison, sex- and age-matched healthy controls were included. The healthy controls were recruited via advertisement in a local newspaper. All participants spoke and understood Danish. Participants were excluded from the study if they were otherwise physically disabled, had a somatic illness impairing physical activity, were pregnant, had an intellectual disability, fulfilled ICD-10 criteria for abuse or were subject to coercive measures. For the healthy controls, the use of any psychotropic medication led to exclusion.



Patients were assessed at baseline and after 1 year of follow-up; healthy controls were only assessed at baseline. Apart from psychopathological data, all assessments were carried out by the same researcher (LN). All questionnaires were administered as structured interviews to account for possible cognitive deficits in the clinical population.

### Physical activity

Physical activity was measured using the Physical Activity Scale (PAS).<sup>24,25</sup> Participants were asked to recall their physical activities during the previous week, and the researcher filled out the PAS. Physical activity was calculated in metabolic equivalents (METs), in accordance with the PAS. Based on average METs scores, physical activity was divided into four categories, from very low to high physical activity.

### Aerobic fitness

Aerobic fitness (defined as  $VO_2\text{max}$ ) served as a proxy for physical activity prior to inclusion and during the follow-up period, and was measured at time of inclusion and at the 1-year follow-up. The Astrand-Rhyming single-stage cycle ergometer test was used to describe aerobic fitness.<sup>26</sup> The test is designed to elicit a steady-state heart rate (HR) over a 6-min period. All tests were performed on a Monark 827 Ergometer cycle, and HR was measured during the entire test by a Polar HR monitor. Only patients who had a normal electrocardiogram were allowed to perform the test. Based on HR at a specific workload (Watt) the oxygen uptake ( $VO_2\text{ max}$ ) was estimated using the Astrand-Rhyming sex-and-age-sensitive nomogram. The continuous data on aerobic fitness were divided into four categories, from very poor to very high aerobic fitness in accordance with the Astrand-Rhyming test.<sup>26</sup>

### Anomalous body experiences

Anomalous body experiences were described by selected items from EASE,<sup>22</sup> comprising “morphological changes” (perceptions of the body or parts of the body becoming thinner, shorter, contracting, enlarging, being pressed down or diminished); “bodily estrangement” (the

body or parts of it are perceived as strange, alien, lifeless, isolated, dislocated or not existing); “cenesthetic experiences” (unusual body sensations, e.g. of numbness, pain, dysesthesias, electric bodily sensations, thermal sensations and migrating bodily sensations); “bodily disintegration” (feelings of the body falling into pieces or disappearing); and “motor disturbances” (experiences of pseudo-movements of the body, motor interference, motor blocking, motor paresis or de-automation of movement). Furthermore, a single item from the Body Awareness Scale (BAS),<sup>27</sup> “hypochondriasis” (exaggerated preoccupation or worrying about ill health or disease), was used. Each item was given a score from 0 to 4, increasing with experienced frequency, intensity and distress of the symptom, in accordance with the EASE manual. A score of  $\geq 2$  was defined as an anomalous body experience with regard to the specific item in the EASE manual.

### Psychopathological data

Psychopathological data included Global Assessment of Function (GAF),<sup>28</sup> Scale for Assessment of Negative Symptoms (SANS) and Scale for Assessment of Positive Symptoms (SAPS).<sup>29,30</sup>

### Psychotropic medication

Psychotropic medication (names and dosages of prescribed antipsychotics, antidepressants and benzodiazepines) was registered for all patients. Antipsychotic medication was described in defined daily dosages based on the average doses given prior to and during study period. Data were obtained from patients’ electronic medical records and included medical data from up to 6 months before inclusion and during the study period.

### Sociodemographic data, smoking and dietary habits

Sociodemographic data, smoking and dietary habits were assessed for all participants - the latter using a questionnaire adapted from the Danish Health Examination Survey 2007-2008.<sup>31</sup>

Smoking habits were categorized as either (i) “non-smoker”, comprising previous and non-smokers, or (ii) “smoker”, comprising daily and weekly smokers. Dietary habits were presented as sum-scores obtained from Likert scales, with a higher sum indicating a healthier diet, defined as having more regular meals, and a more frequent intake of vegetables, fruits, whole-grain products, fish and meat, and a less frequent intake of sweets, cakes, snacks and soft drinks.

## Ethics

All participants were included in the study after written, confirmed consent was obtained in accordance with the Declaration of Helsinki. The study protocol was approved by the local ethics committee, Central Region, Denmark, and the study was registered with the Danish Data Protection Agency and at ClinicalTrials.gov. (NCT00957294).

## Statistical analyses

Scores for anomalous body experiences were categorized into three groups: (i) score < 2; (ii) score = 2; (iii) score  $\geq 3$  in at least one item. Owing to non-normal distribution The Mann-Whitney *U*-test was applied for between-group comparisons and Wilcoxon’s Signed Rank Test for in-group comparisons (paired test). Linear regression analyses were performed to examine the independent factors associated with physical activity. All statistical analyses were two-sided ( $p \leq 0.05$ ). All analyses were performed in STATA version 13.1.

## Results

Of the 101 patients with FES initially included, two were excluded (in accordance with the exclusion criteria) and 25 were lost to follow-up. In total, 50 healthy controls were included in the study. It was not possible to complete the Astrands-Rhyming test for all participants; therefore, full data sets were obtained for 62 patients with schizophrenia and 50 healthy controls (Fig. 1). With regard to baseline measures of age, sex, physical activity, physical

fitness, antipsychotic medication, SANS, SAPS and GAF, there were no significant differences between patients lost to follow-up and patients who completed the study (data not shown). Significantly more patients were smokers ( $p < .0001$ ) and had significantly poorer dietary habits ( $p < .0001$ ) compared with healthy controls (Table 1). The majority of patients (82.8%) had received antipsychotic medication, on average 8.1 weeks ( $SD \pm 5.9$  weeks) prior to inclusion in the study.

### **Baseline**

Physical activity was significantly higher in healthy controls compared with patients with FES ( $p < 0.0001$ ). The majority of patients were predominately engaged in “very low” or “low” physical activities (72.6%) and to a lesser degree in “moderate” and “high” physical activities (27.4%) (Fig. 2). Likewise, aerobic fitness was significantly lower in patients with FES than in healthy controls ( $p < 0.0001$ ). Only 18.9% of patients had “high” or “very high” aerobic fitness (Fig. 3).

### **Follow-up**

Patients had no significant changes in physical activity ( $p = 0.781$ ) (Fig.2). However, the patients tended to deteriorate with respect to aerobic fitness during the study period as the number of patients with very low aerobic fitness increased from 46.7% to 53.2% and the number of patients with very high aerobic fitness declined from 15.6% to 8.1%. The average change in aerobic fitness was however not statistically significant ( $p = 0.092$ ) (Fig.3).

Anomalous body experiences were very frequent in patients with FES (Table 2), with cenesthetic experiences and motor disturbances being the most frequent. Physical activity was significantly lower ( $p = .03$ ) in patients who had more severe anomalous body experiences (score  $\geq 3$  in any one item) (Table 3). In linear regression analyses with physical activity as the dependent

variable and age, sex, SANS and SAPS, anomalous body experiences and antipsychotics as covariates, only negative symptoms (SANS) were significantly correlated with low physical activity ( $B = -.88$ ; 95% confidence interval  $-1.48$  to  $-0.29$ ;  $p < 0.001$ ).

## Discussion

Physical activity and aerobic fitness in patients with FES was significantly lower compared with healthy controls. The baseline physical activity for patients was very low and corresponded to mostly lying and sitting activities throughout the day. Patients had unaltered physical activity and tended to have decreased aerobic fitness during the study period, that is, 1 year after baseline. Physical activity was significantly lower in patients with severe anomalous body experiences compared with patients with fewer such experiences. However, in multivariate linear regression analyses only negative symptoms proved to be significantly correlated with low physical activity.

Physical activity in patients with FES was very low, and only a limited number of patients were engaged in moderate- or high-level physical activities. Our findings are in accordance with previous findings.<sup>14,15</sup> We used the PAS, which, compared with other questionnaires, also covers lying/sleeping activities throughout the day. PAS has previously been proven applicable to psychiatric populations.<sup>32</sup> The low physical activity found in our study underpins the importance of thoroughly recording sedentary behavior in patients with FES. The sedentary lifestyle found in the patients in our study is associated with deleterious health outcomes,<sup>33</sup> and is a significant risk factor in patients with FES.

Patients with FES remained physically inactive and had a small decrease in aerobic fitness during the study period. This outlines schizophrenia as a mental illness that affects patients' function in everyday life in general and physical activity specifically, and for longer periods of time. Furthermore, it might reflect the fact that interventions for improving physical activity in patients with FES are not implemented as part of daily clinical practice.

As a proxy for physical activity we measured aerobic fitness as it might reflect physical activity more precisely than self-reported physical activity.<sup>34</sup> The low baseline aerobic fitness in patients with FES compared with healthy controls is in accordance with previous studies,<sup>35,36</sup> and indicates that patients are physically inactive and debilitated in activities of daily life prior to being diagnosed. Additionally, significantly more patients were smokers, and thus both very low physical activity and smoking contribute to poor aerobic fitness.<sup>37</sup> Low aerobic fitness is a significant risk factor for metabolic syndrome and CVD,<sup>38-40</sup> and has therefore been given more attention in recent years in patients with schizophrenia.<sup>41-43</sup> In a recent study, low aerobic fitness was significantly correlated with metabolic syndrome and metabolic abnormalities in patients with FES.<sup>44</sup>

Taken together, both a sedentary lifestyle and low aerobic fitness in patients with FES warrants clinicians to focus more on these hazardous health behaviors early in treatment and on the importance of providing lifestyle interventions as part of psychiatric treatment and rehabilitation.

It is noteworthy that low physical activity was not correlated with the dose of antipsychotic medication, as described previously.<sup>44</sup> Patients with more severe anomalous experiences were less physically active. However, in multivariate logistic regression analyses only negative symptoms were significantly correlated with low physical activity, which is in line with previous studies.<sup>17</sup> It is reasonable to believe that negative symptoms are a confounder for low physical activity. However, there could be some overlap between the items “decreased spontaneous movement and blocking” (from SANS) and “motor disturbances” (from EASE).

### Strengths and limitations

We used valid measures of physical activity and aerobic fitness. In relation to patients with FES it is essential that data on physical activity comprise thorough descriptions of sedentary behavior as covered by the PAS. The Astrand-Rhyming test was recently found to be a reliable measure of aerobic fitness in a sample of patients with schizophrenia.<sup>45</sup> In our study, only two patients

refused to participate in the test, whereas the remaining missing data was owing to investigation in the patient's own home or patients lost to follow-up. Furthermore, the dropout rate was fairly low (22.2%). Therefore, we believe that our findings on physical activity and aerobic fitness in patients with FES are generalizable.

We had no follow-up data for healthy controls, and were therefore unable to clarify if the unaltered physical activity and decline in aerobic fitness over a 1-year follow-up period is common. However, in a similar study, first-time hospitalized patients with depression had a significant increase in physical activity over 1 year of follow-up.<sup>45</sup>

Selected items from EASE and the BAS were used to describe anomalous body experiences. Both EASE and the BAS are validated measures; however, the specific selection of items can be questioned, as both scales cover additional bodily items. Selection was primarily argued by experiences from physical therapy with patients with schizophrenia. Interviewing patients on bodily experiences (and other anomalous self-experiences) can be difficult and often requires a closer relationship with the patient than could be established in our study setting.<sup>22</sup> It is therefore likely that the occurrence of anomalous body experiences found in our study is underestimated.

In conclusion, patients with FES have a low level of physical activity and aerobic fitness, which did not improve over 1 year of follow-up. Anomalous body experiences are frequent in patients with FES and, for some patients, influence physical activity negatively. However, negative symptoms are strongly correlated with low physical activity and should be considered when promoting a more physically active lifestyle in patients with FES.

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The authors report no conflict of interest.



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Table 1 Characteristics of the included participants

	Schizophrenia (N = 99)	Healthy controls (N = 50)	p-value
Age, years $\pm$ (SD)	24.9 $\pm$ 7.1	23.6 $\pm$ 4.6	0.062
Female (%)	33.0	42.0	0.299
Civil status (%)			
Living with parents	19.2	22.0	0.184
Living alone	51.5	40.0	0.686
Married or cohabiting	29.3	38.0	0.283
Years of education (%)			
$\leq$ 10 years	26.3	6.0	<b>&lt;0.006</b>
> 10 and $\leq$ 12 years	51.5	52.0	0.863
> 12 years	23.2	42.0	<b>0.018</b>
Income (%)			
Wages	3.8	10.0	<b>0.028</b>
Social security	61.9	2.0	<b>&lt; 0.0001</b>
Educational grants	18.5	80.0	<b>&lt; 0.0001</b>
Sickness benefit	13.4	–	<b>0.018</b>
Unemployment grant	4.1	2.0	0.864
No income	1.0	6.0	0.214
Physical activity (median (min; max)) <sup>†</sup>	29.4 (23.3;50.1)	34.2 (28.6; 48.8)	<b>&lt;0.0001</b>
Aerobic fitness (median (min; max))	36.99(13.0)	53.26 (13.2)	<b>&lt;0.0001</b>
Dietary habits (mean $\pm$ SD)	100.1 $\pm$ 13.8	110.3 $\pm$ 7.8	<b>&lt; 0.0001</b>
Daily smokers (%)	50.0	30.6	<b>&lt; 0.0001</b>
Psychopathological data (mean $\pm$ SD)			
GAF symptom	40.8 $\pm$ 10.3		
GAF function	52.3 $\pm$ 76.1		
SANS	2.06 $\pm$ 1.08		
SAPS	2.01 $\pm$ 0.11		
Antipsychotic medication			
CPZ-equivalents (mean $\pm$ SD)	372.6 $\pm$ 313.5 1.18 $\pm$ 0.13		
DDD (mean $\pm$ SD)	17.3		
Olanzapine (%)	0.0		
Clozapine (%)	39.8		
Apripiprazole (%)	33.7		
Quetiapine (%)	16.2		
Risperidone (%)	19.6		
Paliperidone (%)	3.1		
Ziprasidone (%)	1.0		
Amisulprid (%)	17.2		
None (%)	6.1		
FGA			

<sup>†</sup>Physical activity measured in metabolic equivalents. <sup>‡</sup>Values in bold indicate statistical significance.

GAF: Global Assessment of Function; SANS: Scale for Assessment of Negative Symptoms; SAP: Scale for Assessment of Positive Symptoms; CPZ: chlorpromazine equivalent; DDD: defined daily dosages; FGA: first-generation antipsychotics.

Table 2. Anomalous body experience in first-episode schizophrenia (N = 99)

Items <sup>†</sup>	Score $\geq$ 2 (%)	Score $\geq$ 3 (%)
Morphological changes	36.2	16.6
Bodily estrangement	38.5	23.6
Cenesthetic experiences	<b>67.2</b>	<b>43.1</b>
Hypochondriasis	23.6	10.3
Bodily disintegration	21.3	13.7
Motor disturbances	<b>48.3</b>	<b>28.1</b>

<sup>†</sup>Items from Examination of Anomalous Self-Experience and Body Awareness Scale.

<sup>‡</sup>Values in bold present the most frequent anomalous disturbances.

Table 3. Differences in physical activity in patients with first-episode schizophrenia in relation to anomalous body experiences†

	Anomalous body experience < 2 (n =36)	Anomalous body experience =2 (n=43)	p-value	Anomalous body experience ≤ 3 (n=79)	Anomalous body experience ≥ 3 (n=95)	p-value
Physical activity (Median(min;max.))	34.2 (28.7; 48.8)	32.3 (28.6; 36.0)	.197	30.1 (23.5; 44.3)	28.7 (23.0; 50.1)	<b>.030</b>

† Selected items from Examination of Anomalous Self-Experience and Body Awareness Scale. Values in bold indicate statistical significance. Pooled data from baseline and follow-up.



Fig. 1. Flowchart of included participants

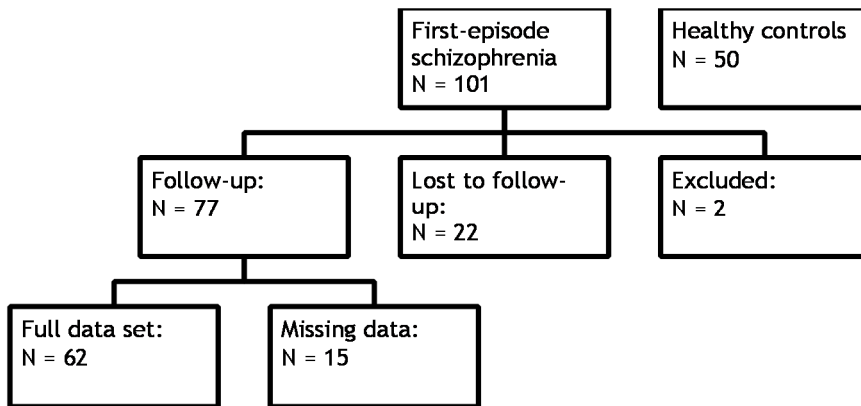


Fig. 2. Physical activity level in metabolic equivalents (METS) and physical activity categories (%) in patients with first-episode schizophrenia (FES) and healthy controls at baseline and 1 year follow-up.

\* $p < 0.0001$ .

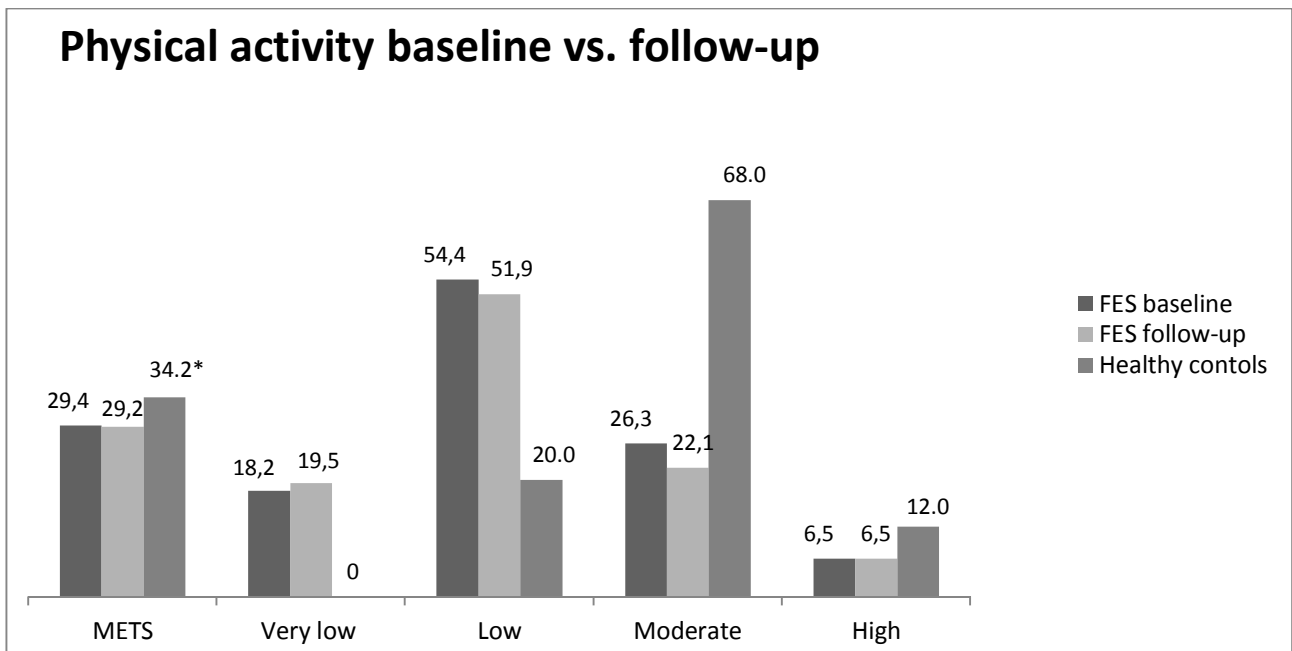


Fig. 3. Continuous and categorical data (%) of aerobic fitness in patients with first-episode schizophrenia (FES) and healthy controls at baseline and 1 year follow-up. \* $p < 0.0001$ .

