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The incidence of metabolic syndrome and its reversal in a cohort of schizophrenic patients followed for one year

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ABSTRACT

Cross-sectional studies showed a high prevalence of metabolic syndrome in patients with schizophrenia. This study aimed to identify the incidence of metabolic syndrome and its reversal in a non-preselected cohort of chronic psychotic patients in routine practice in one year follow-up and to find variables to describe development and reversal of metabolic syndrome. This cohort study was conducted as part of a disease management program and patients were included if they had two complete assessments in a one year follow-up. We conducted two logistic regressions to find variables to describe the development of metabolic syndrome and the reversal of metabolic syndrome. At the time of the first assessment 35% ($n = 92$) of the 260 included patients had metabolic syndrome. Within one year 21 patients developed metabolic syndrome and 30 patients had it reversed. This was an incidence of 13% (21/168) and a reversal of 33% (30/92). Smoking, family history of cardiovascular diseases, and duration of disease >6 years was associated with a higher risk of developing metabolic syndrome as well as abdominal obesity and dyslipidemia. Patients with abdominal obesity had a smaller chance of reversing metabolic syndrome. Other variables included in the logistic regression such as receiving cardiovascular/antidiabetic drug treatment or duration of disease >6 years did not alter the risk of reversing the metabolic syndrome. Our study showed that the natural course of metabolic syndrome is dynamic. A considerable number of patients developed or reversed the metabolic syndrome in one year follow-up.

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1. Introduction

Metabolic syndrome is associated with a four times higher risk of developing diabetes (Hanley et al., 2005) and a three times higher risk of dying from coronary heart disease (Lakka et al., 2002). Between 25% (Spain) (Bobes et al., 2007) and 41% (US) (McEvoy et al., 2005) of patients with schizophrenia have metabolic syndrome. This is a much higher prevalence than in comparable general populations (McEvoy et al., 2005). The higher prevalence of metabolic syndrome in patients with schizophrenia may be explained by medication-related, disease-related, and lifestyle-related factors. Second generation antipsychotic drugs cause, to a varying extent, dyslipidemia, weight gain, and diabetes (American Diabetes Association et al., 2004). A high prevalence of diabetes was found in drug naive schizophrenic patients (Spelman et al., 2007) and in parents of patients with psychotic diseases (Fernandez-Egea et al., 2008). These findings suggest a link between schizophrenia and diabetes. Similar to the general population, lifestyle factors

such as smoking, unhealthy food intake, and little physical exercise contribute to the development of cardiovascular and metabolic diseases in patients with schizophrenia (Zhu et al., 2004). But an unfavorable lifestyle is more prevalent in this patient group than in the general population (Poirier et al., 2002; Peet, 2004; Brown et al., 1999; McCreadie, 2003). Reasons for this include negative and cognitive symptoms, prescribing of drugs with sedative effects, sedentary lifestyle, and insufficient (self-)care. Recently, several prospective studies investigated changes in cardiovascular risk factors in patients with schizophrenia (Meyer et al., 2008; Saddichha et al., 2008; Graham et al., 2008; L'italien et al., 2007; De Hert et al., 2008; Srisurapanont et al., 2007). Most of the studies focused on first episode patients (Saddichha et al., 2008; Graham et al., 2008; De Hert et al., 2008) and showed that patients with low metabolic risk at baseline had increased metabolic risk after starting with antipsychotic drug treatment.

So far, three follow-up studies were conducted in chronic populations (Meyer et al., 2008; L'italien et al., 2007; Srisurapanont et al., 2007). Two of the three studies investigated the differences in the prevalence of metabolic syndrome due to antipsychotic drug prescribed. A randomized double-blind trial investigated the

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metabolic side-effects of five different antipsychotic drugs (ziprasidone, quetiapine, perphenazine, olanzapine and risperidone) (Meyer et al., 2008). After three months the prevalence of metabolic syndrome had increased in the group of patients treated with olanzapine (+9.1%) and had decreased in the group of patients treated with ziprasidone (−7.8%) compared to baseline (Meyer et al., 2008). A post hoc analysis of data from an extension phase of a clinical trial found significant differences in the yearly incidence of metabolic syndrome between olanzapine (27%) and aripiprazole (16%) (L'italien et al., 2007). Both studies excluded patients receiving clozapine even though around one third of chronic schizophrenic patients receives clozapine; clozapine is known for its elevated risk of causing metabolic syndrome (Lamberti et al., 2006). One small-sized study ($n = 35$) followed chronic schizophrenic patients over one year in a naturalistic setting and found an incidence of metabolic syndrome of 20% (Srisurapanont et al., 2007). However, this study, as the study conducted by L'italien et al. (2007), excluded patients with metabolic syndrome at baseline and did not follow them further, because the authors assumed that the reversal of metabolic syndrome occurred very rarely. In contrast to the studies described above, we followed the natural course of metabolic and cardiovascular risk in a non-preselected cohort of chronic psychotic patients in routine practice. We aimed to determine the incidence of metabolic syndrome and its reversal and to find variables to describe the development and reversal of metabolic syndrome in one-year follow-up.

2. Material and methods

This study was a non-controlled cohort study. It was carried out in the department of psychotic disorders of a mental health care centre in the Netherlands covering about 175,000 inhabitants. Between January 2003 and April 2006 patients were included if they had a psychotic disorder, received two complete assessments in a

one-year follow-up, and gave their informed consent. As part of a disease management program, patients received yearly assessments of their somatic and psychiatric health. Trained nurses conducted the assessments using a standardized patient interview including questions about medication and psychiatric symptoms, the measurement of laboratory values, and a short physical examination. The physical examination included the manual measurement of the blood pressure using a sphygmomanometer and a stethoscope. Interventions for patients with elevated cardiovascular risk were consultation by a dietician, exercise programs, referral to a general practitioner for further medical treatment, and/or changes in antipsychotic treatment, such as starting treatment with aripiprazole (Schorr et al., 2008).

Metabolic syndrome was defined by fulfilling three or more of the five criteria defined by ATP III/NCEP (Grundy et al., 2004). The five criteria are hypertriglyceridemia (≥ 1.7 mmol/l), low HDL cholesterol level (female ≤ 1.3 mmol/l, male ≤ 1.0 mmol/l), elevated blood pressure ($\geq 130/85$ mmHg), abdominal obesity (waist circumference: female > 88 cm, male > 102 cm) and hyperglycemia (fasting glucose ≥ 6.1 mmol/l). When a fasting assessment was not available hyperglycemia was defined by HbA1c $> 6.2\%$ instead of glucose, and a hypertriglyceridemia by triglycerides > 2.2 mmol/l. For family history of cardiovascular or metabolic diseases, patients were asked for occurrence of diabetes, hypertension, hypercholesterolemia and/or cardiovascular diseases in first line family members, defined as parents, brothers and sisters. To describe symptom severity an average value of positive symptoms, negative symptoms, depressive symptoms, and cognitive dysfunction rated as absent (1), moderate (2), and severe (3) was calculated. For antipsychotic drugs chlorpromazine equivalents were calculated as described by others. (Woods, 2003; Atkins et al., 1997; Taylor and Paton, 2005) Receiving cardiovascular/antidiabetic drug treatment was defined as receiving lipid-lowering drugs, antihypertensive drugs, and/or antidiabetic medication. Changes in

Table 1
Patient characteristics at first assessment.

Patient characteristics	Total population ($n = 260$)	Patients without metabolic syndrome ($n = 168$)	Patients with metabolic syndrome ($n = 92$)	p-Value
Male	62% ($n = 162$)	61% ($n = 102$)	65% ($n = 60$)	$p = 0.474^a$
Female	38% ($n = 98$)	39% ($n = 66$)	35% ($n = 32$)	
Average age in years (SD)	38 (11.9)	37 (11.9)	39 (11.7)	$p = 0.160^b$
Family history of cardiovascular disease	16% ($n = 42$)	12% ($n = 20$)	24% ($n = 22$)	$p = 0.012^a$
Smoking	63% ($n = 140$)	50% ($n = 84$)	61% ($n = 56$)	$p = 0.093^a$
Schizophrenia	64% ($n = 166$)	60% ($n = 100$)	72% ($n = 66$)	$p = 0.077$
Schizoaffective disorder	18% ($n = 47$)	18% ($n = 30$)	18% ($n = 17$)	
Other psychotic disorder	16% ($n = 41$)	20% ($n = 33$)	9% ($n = 8$)	
Other psychiatric disorder	2% ($n = 6$)	3% ($n = 5$)	1% ($n = 1$)	
Median duration of disease in years (IQR ^c)	9 (4–16) missing: $n = 25$	8 (4–15) missing: $n = 19$	10 (6–17) missing: $n = 6$	$p = 0.072^b$
Clozapine	23% ($n = 59$)	17% ($n = 28$)	34% ($n = 31$)	$p = 0.000^a$
Olanzapine	23% ($n = 59$)	29% ($n = 49$)	11% ($n = 10$)	
Risperidone (depot and oral)	18% ($n = 46$)	19% ($n = 32$)	15% ($n = 14$)	
Other monotherapy	14% ($n = 37$)	13% ($n = 21$)	17% ($n = 16$)	
Combination of antipsychotic drugs	13% ($n = 33$)	10% ($n = 16$)	18% ($n = 17$)	
No antipsychotic drug	10% ($n = 26$)	13% ($n = 22$)	4% ($n = 4$)	
Median chlorpromazine equivalent (IQR ^c)	3 (1–5) missing: $n = 22$	2 (1–4) missing: $n = 13$	4 (2–7) missing: $n = 9$	$p = 0.000^b$
Antihypertensive drugs	10% ($n = 25$)	6% ($n = 8$)	18% ($n = 17$)	$p = 0.000^a$
Antidiabetic drugs	3% ($n = 8$)	2% ($n = 4$)	4% ($n = 4$)	$p = 0.380^a$
Lipid-lowering drugs	5% ($n = 13$)	4% ($n = 6$)	8% ($n = 7$)	$p = 0.153^a$
Antidepressants	37% ($n = 96$)	38% ($n = 63$)	36% ($n = 33$)	$p = 0.794^a$
Antimuscarinic drugs	6% ($n = 16$)	7% ($n = 11$)	5% ($n = 5$)	$p = 0.721^a$
Mood stabilizing drugs	15% ($n = 38$)	14% ($n = 24$)	15% ($n = 14$)	$p = 0.839^a$
Antiepileptic drugs	3% ($n = 7$)	3% ($n = 5$)	2% ($n = 2$)	$p = 0.702^a$
Hypnotics and anxiolytics	34% ($n = 87$)	32% ($n = 54$)	36% ($n = 33$)	$p = 0.543^a$

^a χ^2 -Square test was performed to test for differences between patients with metabolic syndrome and without metabolic syndrome at first assessment.

^b Mann–Whitney test was performed to test for differences between patients with metabolic syndrome and without metabolic syndrome at first assessment.

^c IQR: Interquartile range.

antipsychotic drug therapy were defined as starting treatment with aripiprazole and/or stopping with clozapine or olanzapine between the two assessments. Favorable lifestyle was defined as taking part in a dietary or exercise program and/or reporting regularly exercise and/or not smoking at second assessment.

Patient characteristics were calculated for the total patient group and for patients with and without metabolic syndrome at first assessment. Mann–Whitney and χ -square test were performed to analyze if the characteristics at first assessment differed between patients with and without metabolic syndrome. Prevalence of metabolic syndrome was calculated by dividing the number of patients with metabolic syndrome by the number of all patients. Incidence was calculated by dividing the number of new cases by patients at risk i.e. all patients who did not have metabolic syndrome at first assessment. New cases were considered to be patients who did not have metabolic syndrome at first but did at second assessment. Reversal was calculated by dividing the number of reversed cases by the number of patients who had metabolic syndrome at first assessment. Reversed cases were patients who had metabolic syndrome at first but not at second assessment.

We compared patients who developed metabolic syndrome within one year with patients who did not develop metabolic syndrome. Furthermore, we compared patients who reversed the metabolic syndrome with patients who did not reverse the metabolic syndrome. Finally, we compared the criteria for metabolic syndrome (as continuous variables) between the first and second

assessment of the different subgroups using signed rank test. We performed a χ -square test to investigate if antipsychotic drug therapy differed between subgroups and a Mann–Whitney test to investigate if the duration of disease, the symptom severity, and chlorpromazine equivalents differed between subgroups. We conducted two logistic regressions: the first to describe which patients developed metabolic syndrome; the second to describe which patients reversed the metabolic syndrome within one year. Variables included in the models were sex, age, duration of disease, smoking, family history of cardiovascular or metabolic disease, receiving cardiovascular/antidiabetic drug treatment, having changes in antipsychotic drug therapy, and fulfilling the individual criteria for metabolic syndrome at first assessment.

3. Results

Complete data of two assessments were available for 260 patients. This was 37% of all patients treated in the study centre ($n = 709$) during inclusion period. Most patients were excluded due to missing data or missing follow-up ($n = 349$) and not because they refused to participate ($n = 100$). Of included patients, average time difference between the two assessments was 12.7 (SD = 3.1) months. Sixty-two percent ($n = 162$) of the included patients were male and 38% ($n = 98$) female. (Table 1) Patients were on average 38 (SD = 11.9) years old. At first assessment, patients with metabolic syndrome differed from patients without metabolic syndrome for diagnosis, antipsychotic drugs prescribed, chlorpromazine

Table 2
Patient characteristics in the different subgroups.

Patient characteristics	Assessment	Patients with metabolic syndrome at second, not at first assessment ($n = 21$)	Patients without metabolic syndrome at both assessments ($n = 147$)	Patients with metabolic syndrome at first, not at second assessment ($n = 30$)	Patients with metabolic syndrome at both assessments ($n = 62$)
Male		67% ($n = 14$)	60% ($n = 88$)	63% ($n = 19$)	66% ($n = 41$)
Female		33% ($n = 7$)	40% ($n = 59$)	37% ($n = 11$)	34% ($n = 21$)
Average age in years (SD)		40 (10.4)	37 (12.1)	37 (12.7)	40 (11.2)
Median duration of disease in years (IQR ^a)		11 (3–19) missing: $n = 3$	8 (4–15) missing: $n = 16$	9 (3–14) missing: $n = 4$	12 (6–23) missing: $n = 2$
Median psychotic symptoms (IQR ^a)	1st	1.4 (1.3–1.8)	1.5 (1.3–1.8)	1.8 (1.5–2.0)	1.5 (1.4–2.0)
	2nd	1.5 (1.3–2.0) missing: $n = 1$	1.5 (1.3–1.8) missing: $n = 10$	1.5 (1.3–1.8) missing: $n = 3$	1.8 (1.3–2.0) missing: $n = 1$
Antipsychotic drugs					
Clozapine	1st	14% ($n = 3$)	17% ($n = 25$)	33% ($n = 10$)	34% ($n = 21$)
	2nd	19% ($n = 4$)	16% ($n = 24$)	27% ($n = 8$)	31% ($n = 19$)
Olanzapine	1st	38% ($n = 8$)	28% ($n = 41$)	7% ($n = 2$)	13% ($n = 8$)
	2nd	24% ($n = 5$)	25% ($n = 37$)	7% ($n = 2$)	11% ($n = 7$)
Risperidone (depot and oral)	1st	14% ($n = 3$)	20% ($n = 29$)	13% ($n = 4$)	16% ($n = 10$)
	2nd	19% ($n = 4$)	19% ($n = 28$)	17% ($n = 5$)	16% ($n = 10$)
Aripiprazole	1st	5% ($n = 1$)	4% ($n = 6$)	7% ($n = 2$)	2% ($n = 1$)
	2nd	10% ($n = 2$)	7% ($n = 11$)	3% ($n = 1$)	8% ($n = 5$)
Other monotherapy	1st	10% ($n = 2$)	8% ($n = 12$)	20% ($n = 6$)	11% ($n = 7$)
	2nd	10% ($n = 2$)	8% ($n = 12$)	17% ($n = 5$)	13% ($n = 8$)
Combination of antipsychotic drugs	1st	10% ($n = 2$)	10% ($n = 14$)	10% ($n = 3$)	17% ($n = 5$)
	2nd	5% ($n = 1$)	9% ($n = 13$)	23% ($n = 14$)	18% ($n = 11$)
No antipsychotic drug	1st	10% ($n = 2$)	14% ($n = 20$)	10% ($n = 3$)	2% ($n = 1$)
	2nd	14% ($n = 3$)	15% ($n = 22$)	13% ($n = 4$)	3% ($n = 2$)
Median chlorpromazine equivalent (IQR ^a)	1st	2 (1–3)	2 (1–4)	3 (2–7)	4 (2–8)
	2nd	2 (1–5) missing: $n = 2$	2 (1–4) missing: $n = 17$	3 (1–6) missing: $n = 3$	4 (2–8) missing: $n = 7$
Family history of cardiovascular or metabolic disease		24% ($n = 5$)	10% ($n = 15$)	27% ($n = 8$)	23% ($n = 14$)
Smoking		76% ($n = 16$)	46% ($n = 68$)	60% ($n = 18$)	61% ($n = 38$)
Receiving cardiovascular/antidiabetic drug treatment		24% ($n = 5$)	9% ($n = 13$)	27% ($n = 8$)	29% ($n = 18$)
Changes in antipsychotic drug therapy		10% ($n = 2$)	10% ($n = 14$)	13% ($n = 4$)	13% ($n = 8$)
Favorable lifestyle		67% ($n = 14$)	69% ($n = 101$)	80% ($n = 24$)	63% ($n = 39$)

^a IQR: Interquartile range.

equivalents, antihypertensive drugs prescribed, and family history of cardiovascular and metabolic diseases. Ninety-two (35%) patients at first assessment and 83 (32%) patients at second assessment had metabolic syndrome. Fifty-seven percent ($n = 147$) of all patients did not have and 24% ($n = 62$) had metabolic syndrome at both assessments. Eight percent ($n = 21$) of all patients developed and 12% ($n = 30$) reversed the metabolic syndrome. This was an incidence of 13% (21/168) for development of metabolic syndrome and 33% (30/92) for reversal of metabolic syndrome within one year.

The patients who developed metabolic syndrome within 1 year were on average 40 (SD = 10.4) years old and 67% of them were male. (Table 2) At second assessment, these patients had significantly greater waist circumference (male patients), and lower HDL cholesterol values when compared to the first assessment. However, also patients who did not fulfill the criteria for metabolic syndrome at both assessments had a significantly greater waist circumference and a significantly lower HDL cholesterol value at second assessment than at first assessment. (Table 3) Antipsychotic drug therapy did not differ between the two groups, neither at first assessment (0.971, $df = 6$) nor at second assessment ($p = 0.996$, $df = 6$). Median duration of disease was higher in patients who developed metabolic syndrome (11 years) compared to patients who did not develop metabolic syndrome (8 years), but this difference was not statistically significant ($p = 0.401$). In the logistic model (Table 4), the variables smoking, having a family history of cardiovascular diseases, and suffering from the disease longer than 6 years were associated with a higher risk of developing metabolic syndrome within one year. Patients who fulfilled the criteria for abdominal obesity, triglycerides, and HDL cholesterol at first assessment also had a higher risk of developing metabolic syn-

drome. The model indicated no difference in risk between older and younger patients and male and female patients.

The patients who reversed the metabolic syndrome within one year were on average 37 (SD = 12.7) years old, 63% of this group was male (Table 2). Eighty percent ($n = 24$) of these patients had a favorable lifestyle and two of these patients stopped smoking between assessments. Eight (27%) patients received cardiovascular/antidiabetic drug treatment (antihypertensive drugs: 10% ($n = 3$); lipid-lowering drugs: 20% ($n = 6$); antidiabetic drugs: 3% ($n = 1$)); All three patients receiving antihypertensive drug treatment reached normal values for blood pressure, four patients on lipid-lowering drugs still had HDL cholesterol and/or triglyceride values outside the normal range and the one patient on antidiabetic medication still had elevated blood glucose values. Thirteen percent of the patients had changes in their antipsychotic drug therapy. Two patients (7%) stopped taking clozapine or olanzapine and two patients (7%) started aripiprazole between the two assessments additionally to their clozapine treatment. Patients who at the second assessment indicated a reversal of the metabolic syndrome had at the first assessment significantly lower blood pressure and triglyceride values. (Table 3) Median duration of disease was lower in patients who reversed metabolic syndrome (9 years) compared to patients who did not (12 years), but this difference was not statistically significant ($p = 0.074$). At first assessment psychiatric symptoms were slightly more severe in patients who reversed metabolic syndrome than in those who did not ($p = 0.993$). At second assessment patients who reversed metabolic syndrome had less severe symptoms than those who did not ($p = 0.108$), but both differences were not significant. Antipsychotic drug therapy did not differ between patients with metabolic syndrome at both

Table 3
Criteria for metabolic syndrome at first and second assessment.

	Patients with metabolic syndrome at second, not at first assessment ($n = 21$)			Patients without metabolic syndrome at both assessments ($n = 147$)			Patients with metabolic syndrome at first, not at second assessment ($n = 30$)			Patients with metabolic syndrome at both assessments ($n = 62$)		
	1st assessment	2nd assessment	p-Value	1st assessment	2nd assessment	p-Value	1st assessment	2nd assessment	p-Value	1st assessment	2nd assessment	p-Value
Median waist circumference in cm (range):												
Female (>88 cm ^a)	104 (102–106)	104 (102–112)	1.000	90 (81–98)	93 (81–103)	0.031	101 (89–136)	101 (73–140)	0.344	133 (90–136)	114 (93–156)	1.000
Male (>102 cm ^a)	101 (97–106)	105 (103–109)	0.022	91 (84–97)	93 (86–99)	0.005	103 (80–119)	99 (90–115)	0.238	113 (92–138)	118 (92–137)	0.256
Median systolic blood pressure in mmHg (range), (≥ 130 mmHg ^a)	120 (120–130)	130 (120–136)	0.454	120 (110–130)	120 (110–130)	1.000	130 (115–150)	120 (90–145)	0.002	130 (100–180)	130 (90–180)	0.253
Median diastolic blood pressure in mmHg (range), (≥ 85 mmHg ^a)	80 (75–88)	80 (75–90)	1.000	80 (70–80)	80 (70–80)	0.198	80 (60–95)	75 (50–90)	0.001	85 (60–110)	85 (50–110)	0.358
Median triglycerides in mmol/l (range), (≥ 1.7 mmol/l ^a)	1.7 (1.0–2.0)	1.9 (1.2–2.3)	0.064	1.2 (0.9–1.5)	1.2 (0.8–1.6)	0.931	2.1 (0.8–9.7)	1.6 (0.9–3.6)	0.001	2.1 (1.0–15.1)	2.3 (0.8–10.6)	0.245
Median HDL cholesterol in mmol/l (range):												
Female (≤ 1.3 mmol/l ^a)	1.3 (1.1–1.7)	1.2 (1.0–1.2)	0.031	1.7 (1.4–1.9)	1.6 (1.3–1.9)	0.004	1.2 (0.6–1.5)	1.3 (0.8–2.3)	0.004	1.1 (0.7–1.6)	1.1 (0.6–1.7)	0.791
Male (≤ 1.0 mmol/l ^a)	1.2 (1.1–1.4)	1.0 (0.9–1.2)	0.000	1.3 (1.1–1.6)	1.3 (1.1–1.4)	0.001	1.0 (0.6–1.3)	0.9 (0.7–1.3)	1.000	1.0 (0.4–2.1)	0.9 (0.3–3.1)	0.012
Median fasting glucose in mmol/l (range), (≥ 6.1 mmol/l ^a)	5.1 (4.6–5.3) missing: $n = 12$	5.0 (4.7–5.3) missing: $n = 12$	1.000	4.8 (4.6–5.3) missing: $n = 90$	5.0 (4.7–5.3) missing: $n = 90$	0.784	5.3 (4.5–11.3) missing: $n = 15$	5.3 (4.3–10.4) missing: $n = 15$	1.000	5.6 (4.6–13.8) missing: $n = 5$	5.9 (4.8–11.4) missing: $n = 5$	0.405
Median HbA1c in % (range), ($\geq 6.2\%$)	5.5 (5.3–5.8)	5.5 (5.2–5.6)	0.146	5.3 (5.1–5.6) missing: $n = 5$	5.3 (5.1–5.5) missing: $n = 5$	0.320	5.5 (5.0–7.7)	5.4 (4.9–7.1)	0.003	5.7 (4.9–13.3)	5.7 (4.7–16.0)	0.061

^a Cut-off levels of the metabolic syndrome.

Table 4

Logistic regressions to describe incident cases (Nagelkerk R Square: 0.554) and reversed cases of the metabolic syndrome (Nagelkerk R Square: 0.226).

	Incidence of the metabolic syndrome			Reversal of the metabolic syndrome		
	Odds Ratio	95% CI	p-Value	Odds Ratio	95% CI	p-Value
Sex (male)	1.5	0.2–10.0	0.704	0.8	0.2–2.6	0.712
Age (≥ 40 years)	0.3	0.0–1.6	0.137	1.3	0.4–4.4	0.667
Duration of disease (>6 years)	7.8	1.1–54.4	0.038	1.3	0.4–4.5	0.724
Family history	10.4	1.4–77.6	0.022	1.0	0.3–3.5	0.995
Smoking	18.8	2.9–120.9	0.002	0.7	0.3–2.1	0.574
Receiving cardiovascular/antidiabetic drug treatment	3.0	0.4–25.8	0.314	0.6	0.2–2.3	0.479
Changes in antipsychotic drug therapy	1.4	0.2–13.3	0.974	2.3	0.5–10.2	0.290
Waist circumference ^a	33.8	4.6–250.0	0.001	0.1	0.0–0.5	0.004
Blood pressure ^a	1.1	0.2–5.3	0.941	1.6	0.3–7.8	0.573
Triglycerides ^a	42.6	5.5–330.4	0.000	0.4	0.1–1.6	0.188
HDL cholesterol ^a	16.3	1.9–139.7	0.011	0.8	0.2–3.4	0.785
Fasting glucose/HbA1c ^a	0.0	–	0.999	0.6	0.1–2.3	0.410

^a Criterion for metabolic syndrome fulfilled.

assessments and reversed cases, neither at first ($p = 0.204$, $df = 6$) nor at second assessment ($p = 0.592$, $df = 6$). Chlorpromazine equivalents were higher in patients with metabolic syndrome at both assessments, however this difference was not significant (1st assessment: $p = 0.343$, 2nd assessment: $p = 0.235$). In the logistic model, patients who fulfilled the waist circumference criterion at first assessment had a significantly lower chance of reversing metabolic syndrome within one year. (Table 4) All other included variables did not differ significantly between patients who reversed the metabolic syndrome and those who did not.

4. Discussion

In our study, between 31% and 35% of the patients had metabolic syndrome. This was higher than in studies conducted in patients with schizophrenia in other European countries (De Hert et al., 2006; Bobes et al., 2007) but lower than in the United States (McEvoy et al., 2005). This prevalence of metabolic syndrome is much higher than the prevalence in the general population in the Netherlands ranging from 5% for females younger than 40 years (Bos et al., 2007) to 26% for male with an average age of 60 years (Dekker et al., 2005; Balkau et al., 2002).

Surprisingly, a substantial number of patients developed or reversed the metabolic syndrome over the course of one year. We found a yearly incidence of 13%. This was lower than published incidence rates in a randomized controlled trial (16%, 27%) (L'italien et al., 2007) and in a naturalistic study (20%) (Srisurapanont et al., 2007). Duration of disease longer than 6 years, a family history of cardiovascular and metabolic disease, and smoking were associated with a higher risk of developing metabolic syndrome. Also patients with abdominal obesity and dyslipidemia had an elevated risk of developing metabolic syndrome. The values of these criteria deteriorated significantly in patients who developed metabolic syndrome in the course of a year. However, patients who did not have metabolic syndrome at both assessments and those who had metabolic syndrome at both assessments also showed deterioration. This might imply that all patients worsen gradually, and some of them did not yet reach the cut-off values for the criteria of the metabolic syndrome. These findings are consistent with other prospective studies, where patients showed significant deterioration of several factors, especially abdominal obesity and dyslipidemia (Meyer et al., 2008; Saddichha et al., 2008; Graham et al., 2008).

In our population, there was also a group of patients who reversed the metabolic syndrome and who improved on most of the criteria for metabolic syndrome. These patients differed at first assessment only slightly from the patients who did not reverse the metabolic syndrome. Patients with abdominal obesity had a signif-

icantly lower chance of reversing the metabolic syndrome. Other variables such as for example duration of disease were not significantly associated with a lower chance of reversing the metabolic syndrome. Also none of the interventions (receiving cardiovascular/antidiabetic drug treatment, changes in antipsychotic drug therapy) significantly altered the chance of developing or reversing the metabolic syndrome. Less than one third ($n = 8$) of the patients in this group received cardiovascular/antidiabetic medication and treatment was only partially successful. One explanation for this may be that treatment was often started between the two assessments and therefore patients might not have fully benefited from it by second assessment. Additionally, we did not record compliance with drug therapy.

Interestingly, a longer duration of disease increased the risk of developing metabolic syndrome, but the duration of disease did not alter the risk of reversing the metabolic syndrome. Studies conducted in first-episode patients suggested that the early treatment window is the most dynamic one (Saddichha et al., 2008). Our findings indicate that the risk of developing metabolic syndrome is even higher at a later stage of the disease.

At first assessment, antipsychotic drug therapy differed significantly between patients with and without metabolic syndrome. Patients with metabolic syndrome received more often clozapine or a combination of antipsychotic drugs than patients without metabolic syndrome. Significantly higher dosages of antipsychotic drugs (chlorpromazine equivalents) were prescribed to patients with metabolic syndrome at first assessment compared to those without. However, there were no significant differences in antipsychotic drug therapy between the analyzed subgroups: antipsychotic drug therapy did not differ between incident cases and patients who did not develop metabolic syndrome. There was also no difference in antipsychotic drug therapy between patients who reversed metabolic syndrome and those who had metabolic syndrome at both assessments.

This study was limited by several factors. First, the cohort of patients was followed only for one year. A long-term follow-up is necessary in order to analyze the course of the metabolic syndrome especially for those patients who reversed metabolic syndrome. Second, this study has been conducted in routine practice. Variables not taken into account in the analysis might have influenced our results. For example we did not measure compliance with drug therapy and symptom severity was measured based on a simple scoring system. Third, due to missing data many patients were excluded. However, the prevalence of metabolic syndrome was similar to a cross-sectional analyses of 433 patients conducted in this population (32%) (Schorr et al., 2009). This would suggest that our findings could be representative for a larger group of patients.

In conclusion, our study shows that in routine practice the natural course of metabolic syndrome in patients with psychotic disorders is dynamic. In one year follow-up a considerable number of patients developed metabolic syndrome. Abdominal obesity and dyslipidemia played an important role as early marker for the metabolic syndrome. Furthermore a longer duration of disease was associated with the development of metabolic syndrome. But, also, a large number of patients reversed their metabolic syndrome. The chance of reversing metabolic syndrome was much smaller if patients were overweight. Other variables such as receiving cardiovascular/antidiabetic drug treatment or duration of disease did not alter the risk of reversing the metabolic syndrome. Further long-term studies are needed to follow the clinical course of patients who reversed metabolic syndrome.

Contributors

All authors were involved in the design of the study. C.J. Slooff initiated the study and organized the data collection. S.G. Schorr undertook the statistical analysis and wrote the first draft of the manuscript. R. Bruggeman, K. Taxis and C.J. Slooff supervised the analyses and supported the writing of the manuscript. All authors contributed to and have approved the final manuscript.

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Conflict of interest

S.G. Schorr, C.J. Slooff and K. Taxis declare that they have no conflicts of interest. R. Bruggeman reports having received speaking fees from Astra Zeneca, Eli Lilly and Janssen Cilag.

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