Metabolic risk in people with psychotic disorders
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Psychotic disorders

Psychotic disorders affect people in multiple ways and patients often have to cope with a wide range of symptoms.\(^1\) Commonly experienced positive symptoms are hallucinations, defined as sensory perceptions in the absence of an external stimulus (i.e. hearing voices), and delusions, which are false or erroneous beliefs that usually involve a misinterpretation of perceptions or experiences. Some patients also exhibit conceptual disorganisation: they have problems in forming coherent thoughts accompanied by incoherent speech that is often difficult to understand. They may have to cope with other impairments in cognitive functioning as well, such as impaired memory and executive functioning, attention deficits, decreased processing speed and impairments in social and visual learning and in social cognition.\(^2,3\) Symptoms can also be affect-related: patients with manic symptoms can exhibit agitated behaviour, distractibility and racing thoughts. Patients can experience depressive symptoms as well.\(^4\) More than half of the people with psychotic disorders suffer from so-called negative symptoms of psychosis, such as apathetic social withdrawal, blunted affect, anhedonia and avolition.\(^4,5\) Blunted affect is the reduced intensity of emotional expression, anhedonia is the inability to experience pleasure during normally pleasant activities and avolition is a general lack of motivation to pursue meaningful goals. These negative symptoms can have a great impact on patients’ quality of life. Apathy can make it very difficult for patients to maintain a job or to function in an educative setting.\(^6\) Also, negative symptoms may limit a patient’s ability to give a desired response to social cues from friends and family members, putting pressure on their interpersonal relationships. The lack or loss of social contacts can cause great suffering and can lead to loneliness and social isolation.\(^6\)

Besides the symptoms of the mental illness, people with psychotic disorders also experience more physical health problems than the general population.\(^7,8\) More specifically, they have an increased risk of developing obesity and metabolic risk factors, such as hypertension, dyslipidaemia and diabetes mellitus type 2 at an early age. The metabolic syndrome, a constellation of these interrelated risk factors, puts patients at risk

**Box 1: The metabolic syndrome**

The metabolic syndrome is defined by the National Cholesterol Education Program - Adult Treatment Panel III (NCEP-ATP-III) as the presence of three out of five of the following risk factors:

1. Waist circumference \(\geq 88 / 102 \text{ cm} \quad (f/m)\)
2. Blood pressure \(\geq 130/85 \text{ mmHg}\)
3. HDL cholesterol \(<1.3 / 1.3 \text{ mmol/l} \quad (f/m)\)
4. Triglycerides \(\geq 1.7 \text{ mmol/l}\)
5. Fasting glucose \(\geq 6.1 \text{ mmol/l}\)

The criterion for a risk factor is also fulfilled when medication for said risk factor is prescribed.
for cardiovascular diseases (BOX 1). The increased metabolic risk can reduce their life expectancy with thirteen to thirty years. People with psychotic disorders have a two- to threefold risk of dying from cardiovascular diseases, with cardiovascular mortality rates ranging between 40-50%.

The Lalonde Model
Traditionally, health care and medicine were considered the source of all health improvements, where the level of health equalled the quality of medical care. However, in 1981 Marc Lalonde, the Canadian minister of National Health and Welfare of that time, proposed a health field concept in which he suggested that health and well-being were dependent on determinants outside of the health care systems as well. Specifically, Lalonde identified four broad factors that determine health: human biology, environment, lifestyle and health care organisation (BOX 2). This report inspired several changes in policy and contributed to overall health improvements in the population, such as a drop in smoking rates, healthier diets and increasing levels of physical activity.

Human biology
The human biology factor is a combination of the organic make-up of an individual and the basic general biology of the human species. Among others, it includes a persons’ genetic inheritance and the process of maturation and aging. With regard to genetic inheritance, 108 different loci, specific positions of DNA sequences on chromosomes, have been implicated in schizophrenia. Most of these were protein-coding genes. Interestingly, the Neuregulin 1 (NRG1) gene can make people more susceptible for psychosis, but can also increase the risk of developing diabetes mellitus type 2. Several gene pathways associated with psychotic disorders were also associated with diabetes mellitus type 2, such as calcium, g-secretase mediated ErbB4, adipocytokine, insulin and AKT1 signalling. People with certain variations of the AKT1 gene have an increased risk of developing a psychotic disorder when they are using cannabis. At the same time, variations of the AKT1 gene have been also associated with an increased Body Mass Index (BMI, kg/m²), increased insulin resistance and fasting glucose concentrations, and a higher risk of developing the metabolic syndrome. Moreover, increased C-Reactive Protein levels (CRP) were associated with both psychosis and metabolic risk factors in people with psychotic disorders. In addition, a family history of non-affective psychosis has been associated with a family history of diabetes as well.

* The NCEP-ATP-III has updated the metabolic syndrome criteria in 2005, changing fasting glucose to ≥ 5.6 mmol/l. However, the motives and justification of lowering this threshold were questioned by the European Diabetes Epidemiology Group (EDEG). The EDEG and the World Health Organisation (WHO) therefore recommend to continue using fasting glucose to ≥ 6.1 mmol/l.
With regard to the process of maturation and aging, the vascular system of people with psychotic disorders appears to age more rapidly compared to the general population. In a study that compared obese people with a psychotic disorder to matched obese controls without mental illness, the patients’ vascular age was on average 14.1 years higher compared to their actual age, whereas the vascular age of obese controls was 6.7 years higher. The same study showed that the patients’ general estimated cardiovascular risk was 23% higher compared to their matched controls. Furthermore, metabolic risk factors appear to develop ten to fifteen years earlier in people with psychotic disorders compared to the general healthy population.

Environment
The environmental factor includes both the physical and social environment. These are the health-related issues that are external to the human body, over which the individual can exert little to no control. An important aspect of the environmental factor is the fact that people with psychotic disorders often have a low socioeconomic status, which has been associated with high unemployment rates and financial difficulties, less physical activity and unhealthy eating behaviour. Most of the long-term and residential care facilities can be characterised as ‘obesogenic’, due to abundant provision of unhealthy food products and
a lack of daily activities, in which it can be difficult to make healthy choices.\textsuperscript{25} In recent years, nurses increasingly recognise these health risks and try to stimulate healthy lifestyle behaviour in patients.\textsuperscript{26} Impeding access to the market and cheaper supermarkets however, sometimes limits patients’ abilities to opt for healthy alternatives. Some psychiatric institutions have gyms and offer psychomotor therapy, but other institutions have little or no adequate exercise facilities. Inpatients may not always be able or allowed to visit external sporting facilities.

For patients who live independently or in protected housing, going to a sporting facility may not be an option either, because many patients cannot afford an expensive gym membership.\textsuperscript{24} Travel distance to external facilities may be a threshold for participating in physical activity as well, especially when patients’ personal means of transportation are limited.\textsuperscript{27-29} Also, living in a city can limit patients’ physical activity, because they have easy access to any daily service they may need, whereas patients living in rural areas may have to walk or bike much further to get their basic needs.\textsuperscript{30} Many patients are unemployed and have a lack of occupation during the day.\textsuperscript{31,32} Sometimes daytime activities are offered, but again, not all patients can afford the financial contributions for these activities that are often required. This lack of daily occupation not only limits physical activity opportunities, but also contributes to high prevalence of substance use among people with psychotic disorders in comparison to the general population.\textsuperscript{33,34}

Season and location of birth is an environmental factor that overlaps with human biology, as people born in the winter or spring, at a greater distance from the equator, are more likely to develop a psychotic disorder.\textsuperscript{35,36} Likely vitamin D levels play an important role, because these are highly dependent on sun exposure and the zenith angle of the sun, which is lowest during the winter and spring, especially in countries far north of the equator.\textsuperscript{37} Therefore, prenatal and neonatal vitamin D levels would be lowest during these seasons and affect the developing foetal brain the most.\textsuperscript{38} Moreover, in adult people with psychotic disorders vitamin D insufficiency is a common finding.\textsuperscript{39,40} It was found to be associated with more severe psychotic symptoms, negative symptoms in particular.\textsuperscript{41} Studies in the general population have also suggested an association between vitamin D deficiency and increased metabolic risk, although the direction of this association remains unclear.\textsuperscript{42-47}

Another environmental factor over which patients have little control but with high impact are the stigmatising attitudes within the patient’s environment. People with psychotic disorders are considered by some to be aggressive, dangerous and unreliable, a stereotype that is further boosted by the over-simplified manner in which they are often portrayed in the media.\textsuperscript{48,49} Consequently, they have difficulties in finding and keeping a job, finding a place
to live and staying in contact with friends and family, which altogether leads to social isolation. This in turn could lead to self-stigma, where patients internalise these negative beliefs and attitudes and eventually expect to be rejected and devaluated by others, because they suffer from a psychotic disorder. Feeling stigmatised, vulnerable and isolated with a low self-esteem may be additional thresholds for patients to join a gym or to attend sporting events, because they wish to avoid social situations. When they do engage in these social situations, patients often misinterpret social interactions and lack social support, which leads to demoralisation and further decreases their internal motivation to participate in physical activity.

**Lifestyle**

The lifestyle factor concerns the decisions and behaviours of individuals that affect their health. Compared to the general population, people with psychotic disorders are more likely to have diets that are high in saturated fat, high in calories and sugar and low in fibres, and are less likely to eat 400 grams of fruit and vegetables on a daily basis, as recommended by the World Health Organisation (WHO). Patients also have a high intake of fast food and instant meals, often add salt to their food and have a low intake of fish. Overall, these unhealthy dietary habits can cause weight gain, aggravate metabolic risk factors, such as hypertension, dyslipidaemia and diabetes mellitus type 2, and increase patients’ overall metabolic risk. Certain nutritional habits such as not eating enough fatty fish and fortified products, for instance margarine and milk, also obstruct the production of vitamin D in the body. Lack of knowledge with regard to food content contributes to unhealthy decision making.

Physical activity rates are generally lower in people with psychotic disorders compared to the general population as well. Physical inactivity has been associated with a higher prevalence of the metabolic syndrome, thus contributing to the increased metabolic risk in people with psychotic disorders.

There is also a much higher prevalence of smoking, alcohol consumption and illicit drug use in people with psychotic disorders compared to the general population. Smoking is known to lead to increased blood pressure and increased blood pressure variability, as well as an increased risk of developing diabetes mellitus type 2. Heavy use of alcohol is associated with a greater risk of obesity, a higher BMI, a greater waist circumference and increased hypertension. Consequently, the high prevalence of smoking and alcohol

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† Saturated fats are mostly found in birds and land animals, whereas unsaturated fats, or polyunsaturated fats, are most commonly found in vegetables, fish and seafood. Diets high in polyunsaturated fats are considered healthier than diets high in saturated fats.
use further increases metabolic risk in people with psychotic disorders. There is also a high prevalence of cannabis use, the most commonly used illicit drug among people with psychotic disorders. The effects of cannabis use on psychotic symptoms have been well studied. Several studies have shown that cannabis use can increase the severity of psychotic symptoms, but can also trigger a psychosis and lead to a persistence of the symptoms. However, very little is known about the effects of cannabis use on metabolic risk factors.

All of these unhealthy behaviours individually contribute to an increased metabolic risk in people with psychotic disorders, but they are also highly interrelated. For example, smoking is associated with unhealthy eating habits, unhealthy eating is associated with increased substance use, and smoking, substance use and eating unhealthy food often coincide with low physical activity.

Personal decisions are an important factor in the realisation of lifestyle behaviours, but unhealthy habits are not always entirely self-imposed. The four factors described by Lalonde are not isolated determinants, but also influence each other. Symptoms of an illness and environmental factors can influence unhealthy behaviour, making these habits not necessarily a voluntary lifestyle choice. Cognitive impairments and negative symptoms, for example, make self-management of a healthy lifestyle very difficult for people with psychotic disorders. Smoking is considered a lifestyle choice, but is highly influenced by personal environment and socioeconomic status. It is also difficult to make a healthy lifestyle choice with regard to physical activity, when possibilities to exercise are limited or lacking completely.

Health care organisation

The health care organisation factor refers to the people and resources involved in the provision of health care. Among others, it includes medical practice, hospitals, medical drugs, nursing and health care services. Similar to patients’ home environment, stigma is also present in the health care setting. Somatic and mental health care workers have stigmatising attitudes towards people with psychotic disorders, which can interfere with the quality of care that patients receive.

During short-term admissions of people with psychotic disorders, health care providers often have little attention for exercise and healthy nutrition. Although psychiatrists seem to be aware of the patients’ increased metabolic risk, there often appear to be difficulties in communication between mental health care workers and primary care physicians with regard to who is responsible for monitoring and treating metabolic disorders in these patients. Psychiatrists may not consider this type of treatment a part of their job and may
feel that primary care physicians are better equipped to treat metabolic disorders. On the other hand, primary care physicians may feel reluctant to prescribe medication to a patient who is already receiving different types of medication in the care of another health care professional. Patients may also not be referred to a primary care physician for their metabolic disorders, or not follow-up on a referral. About forty years ago in the Netherlands, psychiatric care was deinstitutionalised on a large scale and gradually moved from being hospital-based to a more ambulant care setting, which led to a clear distinction between somatic care and mental health care. Consequently, the physical health of people with a severe mental illness has been ignored for years and the main focus of mental health treatment has been management of psychotic symptoms, either by Cognitive Behavioural Therapy or antipsychotic medication. This is especially unfortunate because of the side effects of antipsychotic medication. The first generation antipsychotics were mostly known for their extrapyramidal side effects, but important and common side effects of the recent generation antipsychotics are weight gain and an increase in metabolic risk factors.

The severity of the metabolic side effects of antipsychotics varies per drug type. Olanzapine and clozapine present the greatest risk of clinically significant weight gain, increased levels of low-density lipoprotein (LDL) cholesterol and triglycerides, decreased high-density lipoprotein (HDL) cholesterol and developing diabetes mellitus type 2. Risperidone and quetiapine are also associated with moderate weight gain and intermediate elevations of cholesterol and glucose concentrations, whereas aripiprazole and ziprasidone have little to no metabolic side effects.

Several underlying mechanisms have been suggested to explain antipsychotic induced weight gain. It appears that a number of the serotonin-dopamine antagonists alter appetite sensations. The satiating efficiency of food is less strong in people prescribed with these antipsychotics compared to healthy controls of similar age and physical activity levels, and patients are twice as susceptible to feelings of hunger. The 5-hydroxytryptamine receptors (5-HT) are known for their importance in signalling satiety and 5-HT2C antagonists have been shown to increase food intake. Especially olanzapine and clozapine were found to have high affinities for the 5-HT2C receptor. Antipsychotic drugs also affect hypothalamic regions in the brain that are involved in controlling food intake. Working as a dopamine-D2 antagonism, antipsychotics influence feeding behaviour by blocking the hypothalamic D2 receptors, which leads to increased food intake. With regard to the development of diabetes, olanzapine and clozapine work as strong antagonists on the muscarinic M3 recep-

‡ Extrapyramidal side effects include but are not limited to dystonia (repetitive movements or abnormal posture due to sustained muscle contractions), tardive dyskinesia (involuntary and repetitive movements of the body), akathisia (feelings of inner restlessness) and parkinsonism (rigidity, tremor and bradykinesia).
They can cause insulin dysregulation by inhibiting the cholinergic stimulation of insulin production and secretion.\textsuperscript{103,106}

Apart from the direct metabolic side effects, antipsychotic drugs indirectly influence metabolic risk as well through their sedative effects.\textsuperscript{103} Indeed, they are even prescribed to promote sleep in people with sleeping disorders in several countries, including the Netherlands.\textsuperscript{28,55,99,107,108} The sedative effects of antipsychotic medication, combined with an obeseogenic environment and common negative symptoms such as apathy and loss of initiative, render it difficult for patients to engage in physical activities. Therefore, their activities tend to be more often of a sedentary\textsuperscript{\S} than a strenuous nature.\textsuperscript{29,62}

In spite of the serious impact of negative symptoms, positive symptoms are often the primary focus of treatment in psychotic disorders. Cognitive Behavioural Therapy (CBT) is effective in reducing positive symptoms and preventing relapse, but has little effect on the negative symptoms of psychosis.\textsuperscript{109-112} Similarly, most antipsychotics effectively treat the positive symptoms, but many have no or limited effects on the negative symptoms. Some antipsychotics, such as clozapine, olanzapine and amisulpride do sometimes slightly improve negative symptoms.\textsuperscript{96} However, they often coincide with more metabolic dysregulation. The extrapyramidal side effects are generally found in antipsychotics with strong D2 antagonistic effects.\textsuperscript{96} The strong D2 antagonism may also lead to flattening of affect, anhedonia and loss of initiative, a process referred to as secondary negative symptoms. Interestingly, repetitive transcranial magnetic stimulation (rTMS) was found moderately effective in alleviating negative symptoms.\textsuperscript{113}

When metabolic disorders emerge, the first step guidelines recommend is to switch to antipsychotic medication that is associated with less metabolic dysregulation.\textsuperscript{114} The second step is that patients receive an intervention aimed at adopting a healthier lifestyle. Lifestyle interventions can lead to an immediate loss of body weight as well as prevent patients from gaining weight.\textsuperscript{115,116} If changing the prescribed antipsychotic medication and stimulating participation in a lifestyle intervention are not effective, or when the metabolic disorders are too severe, treatment with antihypertensive, lipid-lowering and antihyperglycemic drugs is recommended.\textsuperscript{117}

The increased metabolic risk in people with psychotic disorders has been ignored for a long time. During the last ten years, two large studies investigated treatment rates for metabolic

\textsuperscript{\S} Sedentary activities require low physical intensity, such as office work, driving, watching TV, eating, reading, cooking, going for a walk, shopping and tidying up. Strenuous activities require moderate to rigorous physical intensity, such as jogging, renovating, cleaning, biking, carrying loads, competitive sport and ball games.\textsuperscript{62}
disorders in US patients with psychotic disorders. Alarming reports from these studies showed that only 38-54% of the patients with hypertension, 11-41% of the patients with dyslipidaemia and 55-60% of the patients with diabetes mellitus received treatment for these metabolic disorders.\textsuperscript{118,119} Since then, the increased metabolic risk of people with psychotic disorders has received growing international attention and there is an overall agreement that these risk factors need to be monitored.\textsuperscript{91,120} Routine Outcome Monitoring (ROM; BOX 3) has been implemented from 2003 onwards in several mental health institutions in the northern Netherlands.\textsuperscript{8,121-126} After more than ten years of somatic screening, it might be expected that patients are more frequently treated for their metabolic disorders and that overall metabolic risk will have decreased, but no longitudinal studies to date have confirmed this so far.

Lalonde convincingly showed that health is not solely the product of medical care, but that human biology, environment, lifestyle and the way we organise our health care system influence health at least as much. The increased metabolic risk in people with psychotic disorders has received ample attention in the past two to three decades, ranging from epidemiological reports on shortened life expectancy to genetic and molecular studies into pathways and polymorphisms explaining this increased metabolic risk.\textsuperscript{127,128} Many issues however are still unresolved and although this thesis by no means can complete the puzzle, it aims to try and fill in some missing pieces of our current knowledge regarding metabolic risk factors in people with psychotic disorders. Data from the Pharmacotherapy Monitoring and Outcome Survey (PHAMOUS) allows for the possibility of investigating several of these issues. PHAMOUS is an ongoing Dutch cohort study that started in 2006 in four mental health institutions in the northern Netherlands. Patients with severe mental illness using antipsychotic medication are invited to participate in annual ROM screenings as part of regular clinical practice. Data are used for health evaluation purposes and ROM procedures are fully explained to participants, after which they are free to opt-out for the use of their anonymised data in the research database. Using these data we aim to find out if treatment rates for metabolic risk factors in people with psychotic disorders have increased, now that ROM has been implemented as part of regular clinical practice for several years. As discussed in this introduction, there are many known factors in Lalonde’s health field concept that contribute to the increased metabolic risk.

\textbf{Box 3: Routine Outcome Monitoring}

Patients participate in annual assessments by a trained nurse practitioner to determine their physical and mental health status. Mental health measurements include depression, the severity of psychotic disorders, social functioning and quality of life. Physical health measurements include waist circumference, body weight, blood pressure and a fasting blood sample to determine concentrations of cholesterol, glucose, \textit{HbA}\textsubscript{1c} and vitamin D among others.
lic risk of people with psychotic disorders, but there are still factors of which the effect on patients’ metabolic risk remain unclear or completely unknown. By investigating vitamin D, cannabis use and the mediating role of AKT1 as potentially contributing factors, this thesis attempts to fill in some missing pieces of the complicated puzzle that is the metabolic risk of people with psychotic disorders. Furthermore, several reviews have demonstrated that lifestyle interventions are able to reduce patients’ body weight. This thesis aims to find out if lifestyle interventions are also able to improve patients’ metabolic risk factors, and if the effects on body weight are only immediate or long term as well.

Outline of thesis

In chapter 2 the current treatment rates and course of metabolic disorders over time is investigated in a large cohort of people with psychotic disorders, using yearly ROM assessments. The prevalence, incidence and remission rates of the metabolic syndrome is assessed over the course of three assessments. Furthermore, the rates of treatment recommendation with antihypertensive, lipid-lowering and antihyperglycemic drugs and rates of patients receiving the recommended treatment according to guidelines is investigated. Predictors for receiving treatment (e.g. age, illness duration, substance use) and the course of metabolic risk factors with and without the recommended treatment are explored.

Chapter 3 discusses the associations between vitamin D, negative symptom severity and metabolic risk, using a continuous Z-score of the metabolic syndrome and its individual components. The associations are examined within the four different seasons and separately for patients with and without vitamin D supplementation.

In Chapter 4 it is examined whether cannabis use is associated with metabolic disorders. In addition, changes in metabolic disorders from the first to second assessment are investigated for patients who have continued, discontinued, started or never used cannabis.

Chapter 5 discusses a possible genetic explanation for the association between cannabis use and metabolic disorders in people with psychosis. It is examined if certain variations of the AKT1 gene, which was found to be associated with the metabolic syndrome, schizophrenia and the use of cannabis in previous studies, is a mediating factor in the association between cannabis use and BMI and glycated haemoglobin (HbA$_{1c}$), a measure of average blood glucose levels over an extended period of time.

Chapter 6 is a meta-analysis that investigates the immediate and long-term effectiveness of lifestyle interventions on body weight in people with psychotic disorders. It evaluates both the effects on weight loss and the prevention of weight gain. Furthermore, the effects of
lifestyle interventions on metabolic risk factors and depressive symptoms are investigated.

**Chapter 7** is a summary of the findings followed by a general discussion and future perspectives.
PART I: SEVERITY OF METABOLIC RISK