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## Metabolic risk in people with psychotic disorders

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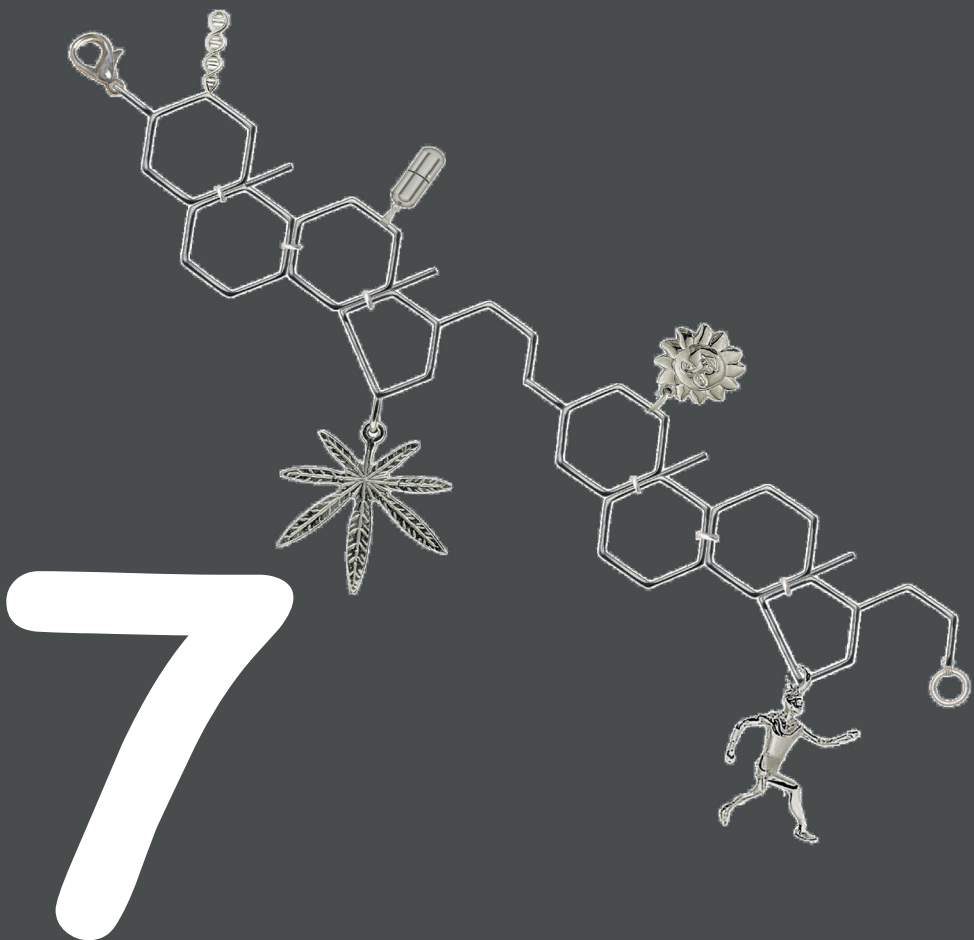
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# Chapter 7

## Summary and General Discussion



Increased metabolic risk is a serious and common problem in people with psychotic disorders. Patients are susceptible to cardiovascular diseases and have a reduced mean lifespan with 13-30 years. The attention for metabolic risk in people with psychotic disorders has finally been increasing during the last decade, after it has been neglected for a long time. An important development is the implementation of Routine Outcome Monitoring (ROM) in many mental health institutions over the last years. PHAMOUS is a comprehensive ROM program in the northern Netherlands for people with a psychotic disorder that started in 2006. It is used to assess patients' mental and physical health and social conditions, and is designed for the use of data in scientific research. The somatic screening in PHAMOUS includes a physical examination of height, weight, waist circumference and blood pressure and the collection of a blood sample to examine metabolic risk factors. The main aim of this thesis was to investigate the severity of metabolic risk and treatment rates for metabolic risk factors in patients of the PHAMOUS cohort. Secondly, this thesis aimed to study the associations of patients' metabolic risk with vitamin D insufficiency and cannabis use and investigate the effects of lifestyle interventions on body weight and metabolic risk factors in a meta-analysis. First, the findings of this thesis will be briefly summarised. Next, it will be discussed how these findings have increased our knowledge about metabolic risk in people with psychotic disorders. Finally, methodological considerations of this thesis and implications for the clinical practice will be discussed.

## MAIN FINDINGS

This thesis emphasises the severity of metabolic risk in people with psychotic disorders. It has demonstrated that more than 50% of the patients was suffering from the metabolic syndrome in three consecutive PHAMOUS assessments (**chapter 2**). In comparison, the prevalence of metabolic syndrome in the general Dutch population of the same age is approximately 22%. According to international treatment guidelines, treatment with antihypertensive, lipid-lowering and/or antihyperglycemic drugs was recommended for more than half of the patients in the PHAMOUS cohort (**chapter 2**). Of the patients with dyslipidaemia, 56% received the recommended treatment with lipid-lowering drugs and 74% of the patients with diabetes mellitus received the recommended antihyperglycemic drug treatment. Treatment rates with antihypertensive drugs for patients with hypertension significantly increased from 31% to 38% in the timespan of three PHAMOUS assessments, each approximately one year apart. Important to note is that up to one third of the patients who did not receive the recommended pharmacotherapy had severe metabolic risk factors, with a systolic blood pressure  $\geq 155$  mmHg, LDL-cholesterol  $\geq 4.0$  mmol/l and/or fasting glucose  $\geq 8.5$  mmol/l. It demonstrates that there was a clear indication for pharmacotherapy.

This thesis also discussed several factors associated with the increased metabolic risk of people with psychotic disorders (**chapters 3, 4 and 5**). There is a high prevalence of vitamin D insufficiency (serum 25(OH)D < 50 nmol/l) in people with psychotic disorders: approximately 63%, as opposed to 40% in the general Dutch adult population (**chapter 3**). Low serum 25(OH)D levels predicted increased metabolic risk, and negative symptom severity mediated this relation. However, negative symptoms were no longer identified as mediator after correction for antipsychotic drugs and season of assessment. Serum 25(OH)D levels were highest in summer and lowest in winter, but negative symptom severity and metabolic risk did not follow the seasonal fluctuation of serum 25(OH)D. Patients using supplementation had serum 25(OH)D levels above the insufficiency cut-off in all seasons, but their metabolic risk and negative symptom severity were not significantly different from patients without supplementation. Moreover, serum 25(OH)D levels were not associated with metabolic risk and negative symptom severity in patients using supplementation. These findings implicate that the relation between vitamin D insufficiency, metabolic risk and negative symptom severity asks for a more complex model invoking the role of antipsychotics, clinical features such as apathy, and a poor lifestyle in general with a lack of outdoor activities and exercise.

Another factor studied in this thesis was cannabis. Patients using cannabis had a lower BMI (**chapter 4**), smaller waist circumference and lower diastolic blood pressure than non-users, but also more severe psychotic symptoms (**chapter 4**). Patients who discontinued their cannabis use had a greater increase in BMI, waist circumference, diastolic blood pressure and triglyceride concentrations than other patients, and a greater decrease in psychotic symptom severity.

The inverse association between cannabis and BMI was replicated in the GROUP-cohort (**chapter 5**). Here, in an attempt to explain the association between cannabis use and metabolic risk factors, it was demonstrated that the Single Nucleotide Polymorphism (SNP) rs2494732 of the AKT1 gene on chromosome 14 was associated with cannabis use, but that AKT1 did not mediate the association between cannabis use and BMI.

A systematic review and meta-analysis demonstrated that interventions aimed at improving lifestyle could be effective treatments of metabolic risk. These interventions were shown to prevent weight gain and reduce body weight, waist circumference, triglycerides and fasting glucose concentrations (**chapter 6**). However, lifestyle interventions did not significantly improve blood pressure and cholesterol levels, which suggests that lifestyle interventions alone are not enough to decrease these risk factors.

## PIECES OF THE PUZZLE

This thesis contributes to current knowledge about metabolic risk in people with psychotic disorders in all aspects of the Lalonde model, a health field concept suggesting that health and well-being are dependent on human biology, environment, lifestyle and health care organisation. The current treatment of and treatment guidelines for metabolic risk factors in people with psychotic disorders, vitamin D levels, negative symptoms, cannabis use, genetic predisposition and lifestyle interventions are factors associated with the severity of patients' metabolic risk. Important to note is that most of these factors are covered by multiple rather than one of determinants of the Lalonde model, which is further elaborated on below.

### Human Biology

The role of human biology in health behaviours may be underestimated at times. Lifestyle behaviours can be influenced by an underlying genetic predisposition. An example of such behaviours demonstrated in this thesis is the use of cannabis (**chapter 5**). Although considered a lifestyle choice, the use of cannabis is also codetermined by patients' make-up of the AKT1 gene, the rs2494732 genotype being associated with a greater risk of using cannabis. A genetic predisposition may not necessarily make patients more likely to initiate cannabis use,<sup>316</sup> but it increases the risk of repeated use and cannabis dependency, possibly by moderating the dopamine response system.<sup>317</sup> A gene-environment correlation has also been suggested, where the risk of cannabis use in people with a specific genetic predisposition is enhanced by environmental factors.<sup>318</sup>

The consequences of antipsychotic medication on metabolic risk are covered by both the human biology determinant and health care organisation. Several mechanisms have been proposed to explain the metabolic side effects of antipsychotics. Most postulate that antipsychotics affect receptors that increase patients' appetite, such as the 5-hydroxytryptamine (5-HT),  $\alpha$ 2-adrenergic and hypothalamic D2 receptors, which causes patients to eat more and subsequently leads to weight gain.<sup>103,319</sup> Furthermore, antagonistic effects of antipsychotics on muscarinic M3 receptors have been suggested to lead to diabetes by causing insulin dysregulation.<sup>103,105,106,319</sup> In a recent study, antipsychotic drugs were found to activate SMAD3, a protein involved in insulin promotion, through a transforming growth factor beta (TGF $\beta$ ) signalling pathway.<sup>320</sup> Increased serum TGF $\beta$  levels and SMAD3 in particular, are associated with obesity, diabetes and insulin resistance.<sup>321-323</sup> Thus metabolic side effects of antipsychotics may be caused by various biological processes and not just by increased food intake. Interestingly, neurotransmitter receptor targets of antipsychotics that are relevant for the treatment of psychotic symptoms are unrelated to the TGF $\beta$  and SMAD3 receptor targets.<sup>320</sup> This suggests the possibility of designing an antipsychotic drug that affects thera-

apeutically relevant neurotransmitter receptors, but not the TGF $\beta$  pathway, thereby possibly reducing the metabolic side effects of antipsychotics.<sup>320</sup>

Age is a biological factor that affects treatment for metabolic risk factors. Metabolic risk increases with age and this thesis demonstrated that older patients were more likely to receive treatment for their metabolic risk factors than younger patients (**chapter 2**). However, metabolic risk factors develop at a younger age in people with psychotic disorders: severity of patients' metabolic risk at age 40 was found comparable to that of adults in the general population who were approximately ten to fifteen years older.<sup>23</sup> Several studies have shown an already increased metabolic risk in first-episode, drug-naïve people with a psychotic disorder, prior to the accumulating effects of unhealthy lifestyle behaviour and treatment with antipsychotic drugs.<sup>324-327</sup> Monitoring and treating metabolic risk factors is therefore of great importance in this high risk patient group and are needed from a younger age than in the general population, preferably from the moment patients enter psychiatric care.

### Environment

People with psychotic disorders appear to be about 1.5 times more likely to suffer from vitamin D insufficiency compared to the general population. The risk of vitamin D insufficiency is highly influenced by seasons throughout the year,<sup>37,186</sup> but seasonality does not appear to affect metabolic risk or negative symptom severity (**chapter 3**). Supplementation can effectively treat vitamin D insufficiency, as patients using supplementation were shown to have serum 25(OH)D to levels above the insufficiency cut-off even during the winter (**chapter 3**). This thesis supports a model where low vitamin D predicts increased metabolic risk and that this association is mediated by negative symptom severity. However, that the effects of antipsychotic medication and lifestyle may overlap with the effects of negative symptoms on this relation. It is more likely that the relation between vitamin D insufficiency, metabolic risk and negative symptoms is more complex, and is heavily influenced by the side effects of antipsychotic medication, clinical features and a poor lifestyle in general with a lack of outdoor activities.<sup>69,70</sup> Prospective studies are needed to confirm and further validate this theory.

An environmental factor with high impact is the stigma surrounding psychotic disorders, which can lead to self-stigma. Obesity adds to this stigma with its own negative stereotypes of overweight patients being lazy, unmotivated, incompetent and lacking willpower and control.<sup>328,329</sup> Experiencing stigma is a negative emotional stressor that elevates the secretion of cortisol, which is a mediator for hypertension and cardiovascular diseases. It also drives comfort-seeking eating behaviour by sensitizing the food reward system, thus creating a vicious circle.<sup>330-332</sup> Experiencing stigma can be demoralising and lead to self-stigma,

defeatisms and avoidance behaviour. When patients feel incapable of doing something or assume they will fail, avoiding to try it at all is a form of self-protection against inevitable pain and disappointment.<sup>333,334</sup> This can be a barrier for trying to adopt a healthier lifestyle and lose weight. It can also impair patients' ability to regulate and control their own actions. Lowered self-control affects and complicates many behaviours such as getting out of bed in the morning, drinking in moderation, going outside and exercise and many other aspects of daily living.<sup>335</sup> Breaking this cycle by reducing stigma and aiding patients in managing their body weight and reducing metabolic risk factors will arguably contribute to their physical health as well as their emotional well-being.

### Lifestyle

Lifestyle behaviour affects metabolic risk factors in people with psychotic disorders, but it is also associated with the severity of psychotic symptoms and the general course and outcome of psychotic disorders. A high intake of saturated fat and refined sugar was found to be associated with a poor long-term outcome of psychotic disorders and depression.<sup>336-338</sup> Diets rich in unsaturated fatty acids on the other hand, are associated with less severe psychotic symptoms, positive symptoms in particular,<sup>339</sup> and a more favourable course and outcome of psychotic disorders.<sup>337,338</sup> Physical activity has the ability to relieve and improve the management of psychotic symptoms.<sup>30,55,340</sup> It can also lead to a more structured sleeping routine<sup>341</sup> and better functional outcome in people with psychotic disorders.<sup>342</sup> Dietary intake and physical activity levels affect the metabolic risk of people with psychotic disorders and offering lifestyle interventions has been shown to reduce metabolic risk (**chapter 6**). However, this thesis has demonstrated that unhealthy lifestyle behaviour does not fully explain patients' increased metabolic risk. Lifestyle interventions had positive effects, but they did not improve all metabolic risk factors.

The complicated consequences of cannabis use are important lifestyle issues. Although cannabis is widely accepted in Dutch society, the use of cannabis can be seen as unhealthy behaviour. Discontinuing cannabis use is therefore considered an improvement of lifestyle. Cannabis use is associated with more severe psychotic symptoms, discontinuing cannabis use coincides with a decrease in psychotic symptom severity (**chapter 4**) and continued substance use contributes to premature disengagement of treatment.<sup>343</sup> Discontinuing cannabis use is therefore an important treatment goal in mental health care. However, this particular lifestyle improvement does not reduce, but actually increases metabolic risk factors of people with psychotic disorders as demonstrated in **chapter 4**. These findings were recently confirmed in another study that found people with psychotic disorders using cannabis were less likely to have the metabolic syndrome and diabetes, and had lower BMI than non-users.<sup>344</sup> The effects of using versus discontinuing cannabis with regard to metabolic

risk and psychotic symptoms create a conflict of what is in patients' best interest. One can argue that priority should be given to improving mental health in this situation. As a result, measures to counteract the increase in metabolic risk caused by discontinuing cannabis use are highly recommended.

Lifestyle is a complex concept. What are healthy and effective lifestyle behaviours is not always as straightforward as often thought. In the cannabis example, an 'unhealthy lifestyle behaviour' is actually associated with some beneficial effects on metabolic health, whereas lifestyle interventions were not shown to improve all metabolic risk factors (**chapter 6**).<sup>345</sup> However, changing and improving lifestyle is a difficult process. If patients do not adhere to all aspects of lifestyle interventions or if only small lifestyle changes are made while leaving other unhealthy behaviours intact, it may be difficult to show effects on all metabolic risk factors. In general, following food pyramid guidelines (de schijf van vijf), limiting snacking behaviour and exercising on a daily basis is likely to improve overall health and reduce metabolic risk. Moreover, specifically improving blood pressure and cholesterol levels through lifestyle modifications could still be achieved with targeted dietary interventions that focus on the consumption of nuts, soy protein, plant sterols, and viscous fiber.<sup>345,346</sup>

Although the importance of a healthy lifestyle and offering lifestyle interventions are often recognised, there are several factors complicating the implementation of lifestyle interventions.<sup>184</sup> It usually takes a long time before interventions that have shown to be effective are included in standard treatment guidelines and become part of regular health care. A qualitative review found that mental health care workers are more comfortable and feel more secure about focusing on the patients' mental health problems rather than discussing their lifestyle behaviour.<sup>347</sup> Mental health care workers have pointed to the organisation of mental health care, their heavy workloads and a lack of time, empowerment, training and skills as barriers for offering lifestyle interventions.<sup>348,349</sup> Some mental health care workers may also feel uncomfortable to ask patients to change unhealthy lifestyle habits that they have themselves. On a patient-level negative symptoms, cognitive impairments, the side effects of antipsychotic medication, absence of support, financial limitations and stigma were reported as factors interfering with lifestyle interventions.<sup>184,347</sup>

### **Health care organisation**

This thesis addresses several issues that might be improved in the current health care organisation. Mental health care workers need to be aware of the increase in metabolic risk when cannabis use is discontinued. When encouraging patients to discontinue cannabis use, appropriate measures need to be taken to prevent an increase in metabolic risk, such as informing patients of this risk, monitoring metabolic risk factors and offering lifestyle in-



terventions and pharmacologic treatment when necessary. Also important is the awareness of patients' low vitamin D status, especially during the winter. Prescribing vitamin D supplementation can increase vitamin D to a more optimal level.

Age serves as a predictor in most models commonly used for determining cardiovascular risk, such as the Cox Framingham and the SCORE model.<sup>142,350</sup> These models are developed for the general population, but are also used for people with psychotic disorders without taking the increased metabolic risk of these patients at younger age into account. The Dutch College of General Practitioners (NHG) guidelines estimate cardiovascular risk based on the SCORE risk model, in which people below the age of 40-45 years are not considered to be at heightened cardiovascular risk regardless of the severity of their blood pressure or cholesterol.<sup>142</sup> This affects the identification of metabolic risk factors and subsequently whether or not patients receive treatment. In particular treatment recommendations for lipid-lowering drugs, as these are based on the SCORE risk score. The Dutch multidisciplinary guidelines for schizophrenia currently advise to add fifteen years to patients' actual age when establishing metabolic risk.<sup>351</sup> In **chapter 2** of this thesis it was reported that of the 20-32% of the patients with dyslipidaemia, approximately half received the recommended pharmacotherapy. In a posthoc analysis, fifteen years were added to the patients' actual age and the SCORE model risk score was recalculated to get a better estimate of patients' risk. With the age adjustment, treatment with lipid-lowering drugs was now recommended for 36.6%, 43.3% and 47.5% of the patients at the three PHAMOUS assessments respectively. Moreover, only 32.1%, 35.0% and 37.0% received the recommended treatment during the three assessments respectively. Guidelines for cardiovascular diseases in the UK already acknowledge that standard risk scores do underestimate metabolic risk in people with mental health issues and in people using antipsychotic medication.<sup>352</sup> Although adding fifteen years to patients' actual age to account for this underestimation of risk is a pragmatic solution, updating guidelines with risk models specifically designed for this high risk patient group may give a better and more reliable estimation of their metabolic risk. Good examples are the two recently developed PRIMROSE models, one based on BMI and one based on lipids.<sup>157</sup> They include psychiatric diagnosis and the use of antidepressant and antipsychotic medication as additional predictors on top of the standard risk factors used in most other prediction models, such as age, gender, systolic blood pressure, cholesterol and smoking. In comparison with the Cox Framingham model, both PRIMROSE models are able to predict the cardiovascular risk of people with psychotic disorders more accurately.<sup>157</sup>

### **Routine Outcome Monitoring**

Routine Outcome Monitoring (ROM) has been implemented in psychiatric institutions in the northern Netherlands for several years and has become mandated by health insurance

companies in the meantime. The Dutch Health Inspection has also created guidelines for somatic screening in people with psychotic disorders.<sup>353</sup> However, the agreement between health insurance companies and mental health institutions mandates that overall functioning, symptom severity and quality of life are monitored by ROM, but not metabolic risk factors.

In PHAMOUS, the ROM assessments do include a somatic screening, which has structurally provided mental health care workers with information on patients' metabolic risk factors. Although PHAMOUS identified increased metabolic risk in a large number of patients at each assessment, treatment rates for metabolic risk factors remained low (**chapter 2**). Measuring metabolic risk factors does not equal treatment of these risk factors. In fact, there are multiple steps needed before a somatic screening of patients leads to the treatment of metabolic risk factors, a process that is complicated by confusion and misconceptions about who is responsible for monitoring and treating metabolic risk factors in people with psychotic disorders.<sup>91-94,158,354</sup> It is important to define who is responsible for each step in the treatment process, in order to provide patients with adequate treatment.

Over the last 30 to 40 years, it has been suggested several times that mental health care workers should take the primary responsibility for the overall health of their patients.<sup>354-358</sup> ROM is already implemented as a part of regular patient care in psychiatry. Including a standard somatic screening would be a logical next step, since screening is mandatory for those patients who use antipsychotics. Many psychiatrist still consider the treatment of metabolic risk factors the sole responsibility of primary care physicians. Therefore, it is important to acknowledge that a somatic screening is not a goal in itself, but a first step in the process of treating metabolic risk factors. A somatic screening is a tool that helps physicians to monitor and identify metabolic risk in patients.<sup>120</sup> Active referral to primary care physicians is a separate step, that follows after the initial identification of risk based on ROM results. Ideally, primary care physicians, mental health care workers and patients acknowledge the increased risk and set up an adequate treatment plan together based on the results of monitoring.<sup>93,120,160</sup>

An agreement between health care organisations and health insurance companies to make somatic screenings a standard part of ROM would be highly recommended. Furthermore, it would be helpful if this agreement provides full reimbursement of the process of monitoring and treating metabolic risk factors. Reserving time in job specifications to carry out the follow-up actions needed after ROM could reduce the problem of heavy workloads, whether the follow-up actions are performed by nurse practitioners, primary practice-based mental health care workers or primary care physicians working in mental health institutions.<sup>359</sup>

Although many individual institutions may already have adopted an effective approach, it would be advisable to formalise the responsibility for each step in the process of monitoring and treating metabolic risk factors. Then the risk of confusion, misconceptions and miscommunication between mental health care workers and primary care physicians will be minimised. This approach will likely improve the treatment of metabolic risk factors in people with psychotic disorders and ultimately lead to healthier patients.

Health care organisation is constantly changing and evolving and mental health care is no exception. In the Netherlands a distinction is made between basic mental health care, with complaint-oriented and usually brief treatments for people with mild to moderate mental health problems, and specialised psychiatric care, for people with more severe, complex and recurring mental health problems. The current Dutch mental health care organisation is reducing specialised psychiatric care and moving towards a system of more basic mental health care and care from primary care physicians with the support of practice-based mental health care workers. The aim is to reduce the number of patients currently receiving specialised residential patient care with one third, as well as reducing the number of patients receiving specialised outpatient treatment such as Flexible Assertive Community Treatment (FACT).<sup>360,361</sup> Among other things, this means that more people with psychotic disorders will receive care from primary care physicians.<sup>360</sup> Primary care physicians and mental health care workers supporting the general practice can take an integrated approach in treating psychiatric symptoms and metabolic risk factors of people with psychotic disorders. Previous studies have shown that when physical health care is offered at the same location as mental health care, patients have better access to care in general and their overall physical health improves.<sup>159,362</sup> Also, in an integrated care system patients are more likely to receive education about nutrition, exercise and smoking compared to patients in regular care.<sup>159</sup> One study showed that people with mental health problems were more likely to succeed in achieving goals for reducing BMI, blood pressure, LDL-C and triglycerides in an integrated setting.\* However, it also means a changing environment for part of the current residential patients who will henceforth receive ambulatory care. Residential patients may be offered help to transition from specialised into ambulatory care. The main focus is often on continuity of care and treatment adherence in order to prevent readmissions, while there is little attention for lifestyle.<sup>363</sup> For patients with insufficient knowledge on healthy living, it may be very difficult to make healthy lifestyle choices when they transition to a less intensive level of health care, which affects their metabolic risk.<sup>67</sup> Supporting patients during this transition by providing information and teaching them skills to help make healthier choices may therefore prevent a deterioration of physical health. Such a project currently under development in the

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\* Set goals were reaching BMI <30, blood pressure <140/90 mmHg or <130/80 mmHg (for patients with diabetes), LDL-C <3.36 mmol/l or <2.59 mmol/l (for patients with diabetes) and triglycerides <1.69 mmol/l.

northern Netherlands is the 'living school' (woonschool). This is a dynamic, module-based project that helps patients transition to ambulatory care. It focuses on skill-development and teaching patients how to use resources to create a successful and satisfactory autonomous living situation. Including a module on awareness of lifestyle behaviour could help patients obtain the knowledge to make healthier choices. People with psychotic disorders treated outside of specialised psychiatric care still have an increased metabolic risk and therefore still need monitoring. This emphasises the importance of an agreement where the responsibility for each step of the monitoring and treatment of metabolic risk factors is formalised, while taking the different health care settings into account.

## **METHODOLOGICAL CONSIDERATIONS**

Most studies in this thesis have been conducted with ROM data from the PHAMOUS cohort. Using data from large clinical cohorts for research purposes has several benefits. These data hold an incredible amount of valuable information from a large number of patients. PHAMOUS allows for the examination of many variables that influences the lives, health and well-being of patients with sufficient statistical power. In many cases, patients have had one or more follow-up assessments, which allows for longitudinal analyses. And a great benefit is that findings from ROM research can be more easily generalised than randomised controlled trials (RCTs), because it provides real world data from patients. Results from RCTs are more difficult to generalise, because inclusion criteria and patients' readiness to participate cause a selection bias.

Although it serves as a great data source, using PHAMOUS data for research purposes also has several limitations. PHAMOUS assessments are extensive, it takes a long time to assess and then record all information. There is a substantial amount of missing data and the reason for missing is often lacking. Patients may have refused to provide certain information, assessors could have overlooked items, been unable to obtain the information or made registration mistakes. There are also patients in care who do not participate in PHAMOUS at all. Furthermore, even research with ROM data can have a selection bias, because patients are usually in- or excluded from analyses based on information that is either present or missing. This makes the generalisation of findings more complicated. Only patients with sufficient information on multiple assessments were included in **chapter 2** and **chapter 4**. Part of the excluded patients had severe symptoms and were unable to complete assessments, some were patients who were in psychiatric care for too short a duration to participate in enough screenings and others had missing information for unknown reasons. However, despite the missing data, more than 1000 patients were included in all studies conducted with

PHAMOUS in this thesis. Selection bias of patients in a less severe stage of illness may have led to an underestimation of the reported findings.

The PHAMOUS test battery is subjected to yearly updates and changes. Variables measured in one year may not be measured in consecutive years or vice versa. Blood samples were processed in multiple laboratories that used different methods. Although the Roche and LC-MS method used to measure serum 25(OH)D have a high inter-rater agreement ( $\kappa=0.93$ ),<sup>364</sup> the Roche method tends to identify slightly lower serum 25(OH)D levels than the LC-MS method.<sup>364,365</sup> Had all patients been measured using the Roche method, we would have likely found a higher prevalence of vitamin D insufficiency than reported in **chapter 3**.

In the PHAMOUS assessments used in this thesis, physical activity was documented as number of hours per week on a scale of one to hundred, without specifying the definition of physical activity. In a recent update, a dichotomous item was added where patients are asked whether or not they spend at least 30 minutes per day on physical activity. Even when physical activity is clearly defined, one or two questions can arguably not capture the complex construct of physical activity, given that even extensive physical activity questionnaires have problems with reliability and validity.<sup>366</sup>

Self-report could have led to socially desirable answers, especially with regard to unhealthy lifestyle behaviours such as cannabis use. However, in chapter 5 current cannabis use was measured with both self-report and a urine sample. Considering that only 7% of the self-reported non-users had a positive urine screening for cannabis, it is unlikely this would have biased our results.

There is a limit to research opportunities with PHAMOUS data, since only basic information is provided on many variables. Information on physical activity, diet, sun exposure and the type, size and compound of the cannabis that patients used was of great importance with regard to this thesis. However, these items were either not assessed in detail or not assessed at all. Information on the amount of sun exposure would likely explain more of the variation in serum 25(OH)D than the general categorisation of seasons (**chapter 3**). Also, without being able to correct for physical activity and food intake, our findings on the association between cannabis with metabolic risk factors may have been overestimated (**chapter 4**). With PHAMOUS data we were able to investigate associations but not study treatment effects, because patients were not randomly assigned to treatment conditions. The effects of pharmacotherapy on metabolic risk factors could not be measured, because patients were not randomised into receiving the recommended treatment or not (**chapter 2**). Similarly, we could not study the effects of cannabis use, or more specifically discontinuing

cannabis, on metabolic risk factors (**chapter 4**). Important to note is that information on when patients started or discontinued cannabis use in between the two assessments was not provided in PHAMOUS. The changes in metabolic risk factors found in **chapter 4** would likely be smaller in patients who discontinued the use of cannabis only one month before the second assessment than in patients who discontinued their cannabis use shortly after the first assessment. Changes in metabolic risk factors and psychotic symptom severity after discontinuation of cannabis use for a year may therefore be stronger than demonstrated in this study.

## **PATIENT AUTONOMY AND RESPONSIBILITY**

Providing information about and discussing treatment options with patients is important in mental health care settings. Explaining the pros and cons of each option makes the information more clear and it clarifies that patients have a right to choose.<sup>367</sup> For example, psychiatrists can inform patients about the effectiveness of an antipsychotic drug, but also need to explain its metabolic side effects and offer alternatives that may have less severe side effects. It encourages patients to define their own treatment preferences and helps patients and mental health care workers to reach decisions based on mutual understanding.<sup>367</sup> Participation in health decision-making is not only a basic right, but will help patients to form realistic expectations of treatment, improve adherence and increase patient satisfaction.<sup>368</sup>

However, shared decision-making does not occur as often as patients desire.<sup>369</sup> A physician's lack of time and a patient's impaired cognitive functioning, lack of illness insight, reduced decisional capacity and negative psychotic symptoms are factors interfering with shared decision making in mental health care.<sup>369-371</sup> More importantly, negative symptoms such as apathy, avolition and amotivation can make it difficult for patients to care for themselves and thus interfere with patients' health.<sup>372,373</sup>

With regard to metabolic risk, this means that they may not be able to independently improve lifestyle or seek medical aid from a primary care physician. When the conscious decision-making process is being overshadowed by the impact of patients' illness symptoms, active encouragement of mental health care workers may be necessary. Urging and facilitating visits to a primary care physician, stimulating and educating healthy lifestyle, and actively offering treatment for metabolic risk should therefore not be viewed as power asymmetry, but more as a way to counteract illness symptoms that are interfering with patients' recovery.<sup>369,373</sup>

Autonomy also means that patients can make decisions that may not be in their best interest. Mental health care workers need to assess in such situations whether to attempt and persuade patients to opt for healthier choices using motivational interviewing or to accept patients' autonomous decisions.<sup>373</sup> It is a dynamic equilibrium where mental health care workers can inform patients about the consequences of their choices and let them consider these consequences, while the patient can still make the final decision. By monitoring patients' health, providing information, actively offering treatment and enhancing patients' motivation, mental health care workers can help patients reach health decisions and to accept and participate in treatment.<sup>373</sup> Listening, getting to know the patient and reinforcing self-care capacity can optimise patients' participation in treatment.<sup>374</sup> Checking with patients if the discussed information is clear and writing down the agreed upon concrete actions, may also help patients to follow-up on the treatment plan.<sup>375</sup> Respecting patients and seeing them as individuals regardless of symptom severity, is essential in such situations. Patients feel more respected and taken seriously when asked and encouraged to participate in designing a treatment plan and when their decision-making is not overruled.

## IMPLICATIONS

### Clinical implications

The results of this thesis have several implications for our current health care organisation, that could contribute to better care and reduce the metabolic risk of people with psychotic disorders. It is important to consider biological factors such as the young age at which patients are faced with an increased metabolic risk. Implementing cardiovascular risk models specifically designed for this high risk patient group in (inter)national guidelines will allow health care providers to make a better and more reliable estimate of patients' metabolic risk. It would be helpful to change the obesogenic environment of people with psychotic disorders in residential facilities and provide opportunities for them to make healthier choices. Monitoring metabolic risk factors is not enough. Lifestyle interventions are already recommended by multidisciplinary guidelines for people with psychosis and should be offered from the moment patients enter care. Furthermore, using motivational interviewing to help patients discontinuing cannabis use will likely prevent worsening of or even reduce psychotic symptoms. Patients need to be made aware of the increased metabolic risk their illness and its treatment impose, such as the metabolic side effects of antipsychotic drugs. Using techniques such as motivational interviewing and offering lifestyle interventions could help patients in preventing the increase of metabolic risk and maintaining their physical health.

### Future research

Severe negative symptoms can interfere with healthy lifestyle behaviour, thus increasing metabolic risk. Therefore, creating psychosocial and pharmacologic interventions that effectively decrease negative symptom severity is a priority in psychiatric research. It is important that pharmacological research considers the metabolic side effects in the development of new effective antipsychotic drugs. It could be examined if avoiding to target the TGF $\beta$  pathway could reduce the metabolic side effects of antipsychotics. Causality of the relations of vitamin D with metabolic risk and negative symptoms is still unclear and should be further examined. Using repeated measures within patients throughout the year may provide more insight in the effects of seasonality and sun exposure on these relations. Discontinuing cannabis is important to improve patients' mental health. Future studies should focus on identifying reasons for cannabis use and their underlying biological mechanisms in people with psychotic disorders, in order to develop customised interventions that can help patients discontinue their cannabis use. Previous studies found that physical activity can decrease cannabis use in the general population<sup>376,377</sup> and it should be investigated if combining cannabis discontinuation interventions with lifestyle interventions will nullify the negative impact of discontinuing cannabis use on patients' metabolic risk. It would be helpful if studies examining lifestyle interventions would include metabolic risk factors as well as BMI or body weight.

One thing this thesis has demonstrated is that ROM provides invaluable insight into the lives and health of patients. Continuing to use ROM data for research purposes is therefore highly recommended. To this end the PHAMOUS cohort reveals that several elements of the assessments could be improved. Although PHAMOUS assessments inquire about patients' physical activity, eating behaviour and sun exposure, the current items proved unsuitable for research purposes. These factors are essential in understanding metabolic risk and should be a more elaborate part of the PHAMOUS assessment. Properly evaluating these behaviours in a single assessment may not be feasible, but it should be investigated if experience sampling methods can be used as an additional source of information in PHAMOUS. Because PHAMOUS is an ongoing project and has no expiration date at this point, proper funding could allow for the development of new assessment tools and be used to expand and improve current PHAMOUS measures. With the use of modern technology, such as a smartphone app, information on health behaviour, mood, daily activities, psychotic symptoms and social conditions could be collected continuously instead of once during a yearly assessment. This will likely yield information that is suited for research purposes and can provide valuable insight into factors affecting patients' mental and physical health. Furthermore, researchers need to take responsibility in monitoring the quality of ROM assessments. They should provide ROM assessors with feedback on how the data is properly collected and registered, and



how it is eventually used in research. It is important to share the results of ROM research with the assessors to emphasise the importance of their work. Concrete examples of how ROM research has contributed to health care and improved patients' lives will hopefully enthuse ROM assessors and convince them of the importance of the data they collect. This would greatly benefit the quality and reliability of research conducted with ROM data and it will ensure that we can continue to unravel more pieces of the complicated puzzle that is the health of people with psychotic disorders.

Having said all this, it is now time to end the traditional separation of mental health and physical health and take a more holistic approach, because there is no mental health without physical health.





**References**

**List of abbreviations**

**Nederlandse samenvatting**

**Dankwoord**

**List of RGOc dissertations**

**List of SHARE dissertations**

