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RISK FACTORS OF NON-AFFECTIVE PSYCHOSES

Metabolic Health Indicators and Physical Activity in Childhood and Adolescence

Elina Sormunen

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To my daughters, Seela and Saana

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ABSTRACT

Psychoses are often considered the most severe psychiatric conditions, characterized by an impaired sense of reality. Schizophrenia is the most common and severe form of non-affective psychoses. In addition to psychiatric symptoms, individuals with schizophrenia have higher rates of morbidity and mortality from somatic diseases compared to the general population. Abnormal glucose and lipid metabolism are commonly observed in first-episode schizophrenia patients, regardless of antipsychotic treatment. Schizophrenia is considered a developmental disorder with a typical onset in adolescence or early adulthood but also with delayed motor, neurological, and cognitive development in early childhood.

This study aimed to investigate whether physical activity, lipid or insulin levels, or being underweight or overweight during childhood and adolescence affects the risk of non-affective psychosis, particularly schizophrenia. The study population comprises a longitudinal epidemiological cohort study, the Cardiovascular Risk in Young Finns (YFS), begun in 1980 (N = 3596). Psychiatric diagnoses were collected from the Care Register for Health Care.

Lower physical activity in children and adolescents was an independent risk factor for later non-affective psychosis. In addition, being underweight at the age of 3 to 18 years increased the risk of non-affective psychosis. These results were even stronger for a subgroup of schizophrenia but did not relate significantly to the risk of affective disorders. No significant differences were observed in insulin or lipid levels in children and adolescents who later developed schizophrenia, any non-affective psychosis, or affective disorder, compared to the cohort control group. However, lower triglyceride levels in childhood/adolescence were associated with earlier onset of non-affective psychosis.

This study provides novel insights into the childhood and adolescent risk factors for non-affective psychosis, particularly those that can be modified. The results provide a rationale for including exercise and physical activity interventions as a part of psychosis prevention programs.

KEYWORDS: cohort study, schizophrenia, psychosis, risk factor, physical activity, underweight, lipid, insulin, metabolic

TURUN YLIOPISTO
Lääketieteellinen tiedekunta
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Psykiatria
ELINA SORMUNEN: Ei-affektiivisten psykoosien riskitekijät: Lapsuus- ja nuoruusiän metaboliset tekijät ja fyysinen aktiivisuus
Väitöskirja, 112 s.
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TIIVISTELMÄ

Psykooseja pidetään usein vakavimpina psykiatrisina sairauksina, joille on ominaista todellisuudentajun häiriintyminen. Skitsofrenia on yleisin ja vakavin ei-affektiivisen psykoosin muoto. Psykiatristen oireiden lisäksi somaattiset sairaudet ja niihin liittyvä kuolleisuus ovat skitsofreniaa sairastavilla yleisempiä kuin väestössä keskimäärin. Skitsofreniaa sairastavien sokeri- ja rasva-aineenvaihdunta on poikkeavaa jo ensimmäisen psykoosijakson aikana riippumatta antipsykoottisesta lääkityksestä. Skitsofreniaa pidetään kehityksellisenä häiriönä. Vaikka se alkaa tyypillisesti nuoruusiässä tai varhaisaikuisuudessa, siihen liittyy viivästynyt motorinen, neurologinen ja kognitiivinen kehitys jo varhaislapsuudessa.

Tutkimuksen tavoitteena oli selvittää, liittyvätkö lapsuus- ja nuoruusiän fyysinen aktiivisuus, rasva- tai insuliinitasot taikka ali- tai ylipainoisuus ei-affektiiviseen psykoosin, erityisesti skitsofrenian, riskiin. Tutkimusaineistona oli vuonna 1980 alkanut pitkittäinen epidemiologinen kohorttitutkimus Lasten Sepelvaltimotaudin Riskitekijät (N = 3596). Tutkittavien psykiatriset diagnoosit kerättiin valtakunnallisesta hoitoilmoitusjärjestelmästä.

Lasten ja nuorten matala fyysinen aktiivisuus oli itsenäinen riskitekijä myöhemmälle ei-affektiiviselle psykoosille. Lisäksi alipainoisuus 3–18 vuoden iässä lisäsi ei-affektiivisen psykoosin riskiä. Tulokset olivat vielä selkeämpiä skitsofrenian osalta, mutta eivät merkitsevästi liittyneet mielialahäiriöiden riskiin. Lasten ja nuorten insuliini- tai rasva-arvoissa ei havaittu tilastollisesti merkitseviä eroja, kun verrattiin myöhemmin skitsofreniaan, ei-affektiiviseen psykoosiin tai mielialahäiriöön sairastuvia kohortin kontrolliryhmään. Matala lapsuus/nuoruusiän triglyseriditaso kuitenkin liittyi aikaisempaan ei-affektiivisen psykoosin puhkeamiseen.

Tämä tutkimus tarjoaa uutta tietoa non-affektiivisen psykoosin lapsuus- ja nuoruusiän riskitekijöistä, etenkin sellaisista, joihin voidaan vaikuttaa. Lisäksi se antaa perusteen sisällyttää liikuntaa ja fyysistä aktiivisuutta edistäviä interventioita osaksi psykoosin ehkäisyohjelmia.

AVAINSANAT: kohorttitutkimus, skitsofrenia, psykoosi, riskitekijä, fyysinen aktiivisuus, alipainoisuus, rasva-aineenvaihdunta, insuliini, metabolinen

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Abbreviations

BDNF	Brain-derived neurotrophic factor
BMI	Body mass index
CNS	Central nervous system
CNV	Copy number variant
CRCH	The Care Register for Health Care
DSM	Diagnostic and statistical manual
GWAS	Genome-wide association studies
HDL	High-density lipoprotein
HPA	Hypothalamic-pituitary-adrenal
ICD	International classification of diseases, injuries and causes of death
IGF-1	Insulin-like growth factor 1
IL-6	Interleukin 6
LDL	Low-density lipoprotein
OGTT	Oral glucose tolerance test
OR	Odds ratio
PAI	Physical activity index
PET	Positron emission tomography
PsyMetRiC	Psychosis metabolic risk calculator
RR	Risk ratio
SNP	Single nucleotide polymorphisms
SPSS	Statistical package for the social sciences
SSRI	Selective serotonin reuptake inhibitors
TSPO	Translocator protein
VEGF	Vascular endothelial growth factor
WHO	World health organization

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Sormunen, E., Saarinen, M. M., Salokangas, R. K. R., Telama, R., Hutri-Kähönen, N., Tammelin, T., Viikari, J., Raitakari, O. T., Hietala, J. Effects of childhood and adolescence physical activity patterns on psychosis risk—A general population cohort study. *Npj Schizophrenia*, 2017; 3:5.

II Sormunen, E., Saarinen, M. M., Salokangas, R. K. R., Hutri-Kähönen, N., Viikari, J. S. A., Raitakari, O. T., Hietala, J. Body mass index trajectories in childhood and adolescence – Risk for non-affective psychosis. *Schizophrenia Research,*2019; 206(4): 313–317.

III Sormunen, E., Saarinen, M. M., Salokangas, R. K. R., Hutri-Kähönen, N., Viikari, J., Raitakari, O. T., Hietala, J. Metabolic trajectories in childhood and adolescence: Effects on risk for schizophrenia. *Schizophrenia,* 2022; 8(1):82.

1 Introduction

Patricia J. Ruocchio wrote in Schizophrenia Bulletin about her own experiences of living with schizophrenia: "*My greatest fear is this brain of mine, which torments me in times of psychosis, always threatens me, and seems to always be laughing at me, scorning my vulnerability. The worst thing imaginable is to be terrified of one's own mind, the very matter that controls all that we are and all that we do and feel.*" (Ruocchio, 1991).

Psychoses are often considered the most severe psychiatric conditions, characterized by an impaired sense of reality. Schizophrenia is the most severe of psychotic disorders, usually involving remarkable human suffering, as well as social and occupational decline. It is one of the leading causes of long-term disability worldwide (Mueser & Mcgurk, 2004) with a lifetime prevalence of 1% (Jablensky, 1997) and typical onset age in adolescence or young adulthood (DeLisi, 1992). The etiology of schizophrenia remains a challenge, and a curative treatment is unknown despite decades of intensive research and advances in treatment. The life expectancy of an individual with schizophrenia is about 15 years shorter than the general population (Plana-Ripoll et al., 2019), and the majority of it is explained by somatic diseases, especially cardiovascular diseases (Olfson et al., 2015).

Henry Maudsley wrote in 1879: "Diabetes is a disease which often shows itself in families in which insanity prevails" (1879). The diabetes-like glucose tolerance curves and abnormal insulin responses were linked to schizophrenia in the 20th century, decades before the advent of antipsychotic medication (Kohen, 2004). Multiple studies later showed changes in glucose and lipid metabolism in patients with their first psychotic episode of schizophrenia, irrespective of antipsychotic medication (Greenhalgh et al., 2017; Misiak et al., 2017; Pillinger, Beck, Gobjila, et al., 2017). These results suggest that schizophrenia is not just a brain disorder but one that also affects several other organ systems. However, the causality of the relationship is not clear, nor whether these changes appear before the onset of psychosis, in childhood or adolescence.

A growing amount of research supports the hypothesis that schizophrenia is a neurodevelopmental disorder with delayed motor, neurological, and cognitive development in early childhood (Insel, 2010). In fact, psychosis can be considered

as a late stage or a complication of the disease (Bleuler, 1950) that could possibly be prevented. Psychosis prevention programs have proven to be rather ineffective (Fusar-Poli et al., 2020), so it has been suggested that these programs should target the early risk factors of psychotic disorders rather than the symptoms.

This study aimed to find out whether physical activity, underweight or overweight, or insulin and lipid levels in childhood and adolescence affect the risk for non-affective psychosis and especially schizophrenia. An etiological understanding of the somatic aspects related to psychosis could lead us to major advancements in treatment and early prevention of psychosis.

2 Review of the Literature

2.1 Schizophrenia and other non-affective psychoses

Psychotic disorders are severe mental diseases characterized by episodes with an impaired sense of reality. Schizophrenia is the most severe of the psychotic disorders; besides psychotic episodes, it often involves social and functional decline and remarkable human suffering. The lifetime prevalence of schizophrenia, schizoaffective disorder, and schizophreniform disorder together is 1.26% in Finland (Perälä et al., 2007), and approximately 55–65,000 people in Finland suffer from schizophrenia (Schizophrenia (Current Care Guidelines), 2024). The burden of the disease of schizophrenia is remarkable, and due to increased incidence and prevalence driven by population growth and aging, it has been growing globally since 1990. Schizophrenia has been studied intensively for decades, but its etiology and treatment still remain a challenge. Despite the relatively effective impact of antipsychotic medication on the positive symptoms of psychosis, a curative treatment for schizophrenia is not known.

In the absence of specific biological markers, psychiatric diagnoses are based on a patient's clinical phenotypes and symptoms. Psychotic disorders can be divided into non-affective and affective psychoses (**Table 1).** Despite these classifications, clinical phenotypes and prognosis of psychosis, including schizophrenia, remain very heterogeneous. Increasing evidence also exists of genetic and neurobiological overlap between schizophrenia and bipolar disorder, suggesting a partly common etiology of these disorders (Clementz et al., 2016; Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013; Mortensen et al., 2010; Solmi et al., 2023). Therefore, psychosis is increasingly seen as a dimension rather than a category, and research concerning the etiology of psychosis is changing towards a wide-ranged methodology and outcomes beyond clinical diagnostic boundaries.

Table 1. A classification of psychotic disorders into non-affective and affective psychoses, with a brief description of disorders based on DSM-IV and a comparison to DSM-5.

Non-affective psychoses	**Description based on DSM-IV**	**Comparison to DSM-5**
Schizophrenia	A long-term and the most severe of psychotic disorders, characterized by positive symptoms (e.g., delusions, hallucinations), negative symptoms (e.g., emotional flattening), and cognitive impairments.	Differences described in detail in **Table 2**.
Schizophreniform disorder	Symptoms similar to schizophrenia, but their duration lasts from 1 to 6 months.	Same as in DSM-IV.
Schizoaffective disorder	Features both schizophrenia-like psychotic symptoms and severe mood symptoms.	Severe mood symptoms are present for the majority of the illness duration.
Delusional disorder	Characterized by persistent delusions without other symptoms typical of schizophrenia.	Hallucinations, if present, are not prominent and are related to the delusion theme
Brief psychotic disorder	A short psychotic episode lasting from at least one day to less than one month.	Same as in DSM-IV.
Psychosis not otherwise specified	Psychotic symptoms that don't meet the diagnostic criteria for any other specific psychotic disorder.	Removed in DSM-5, replaced with "Other Specified Psychotic Disorder" and "Unspecified Psychotic Disorder."
Affective psychoses		
Bipolar disorder with psychotic features	Bipolar disorder with psychotic symptoms, typically occurring during manic or major depressive episodes.	Same as in DSM-IV.
Major depressive disorder with psychotic features	A major depressive episode accompanied by psychotic symptoms in which depression is the dominant symptom.	Same as in DSM-IV.

2.1.1 Clinical characteristics of schizophrenia

The onset of the first psychotic episode of schizophrenia typically occurs in late adolescence or early adulthood (DeLisi, 1992). Psychotic episodes generally involve symptoms of hallucinations and delusions as well as disorganized speech and behavior (American Psychiatric Association, 2013; World Health Organization (WHO) 2019), referred to as positive symptoms. In addition to positive symptoms, patients with schizophrenia experience negative symptoms such as affective

flattening, which involves a marked reduction in emotional expression, and avolition, characterized by a lack of motivation to initiate and sustain even daily activities Negative symptoms also include social withdrawal, cognitive symptoms such as difficulties in memory, attention, and executive functioning, and affective symptoms such as depression, anxiety, and suicidal thoughts (van Os & Kapur, 2009). Somewhat surprisingly, patients with schizophrenia also have abnormalities in several other organ systems beyond the central nervous system (CNS), such as cardiometabolic and immune systems (Pillinger et al., 2019).

The first notable symptoms of schizophrenia appear years before the first psychotic episode, during, on average, a five-year-long period called the prodromal stage (Hafner et al., 2004), **Figure 1**. The first prodromal symptoms are typically non-specific, i.e., disturbed sleep or appetite, difficulties with concentration, nervousness, anxiety, or depression. Studies of clinically high-risk patients have also shown that cognitive deficit (Bora & Murray, 2014) and social cognition impairment (T. Y. Lee et al., 2015) are established before the first psychotic episode. On average, prodromal symptoms improve over time (Addington et al., 2015) and may not even lead to psychiatric treatment. In some cases, prodromal symptoms worsen over time, and approximately 25% of patients at clinical high risk for psychosis, (e.g., those with prodromal symptoms), develop psychosis within 3 years (Salazar de Pablo et al., 2021).

Research has increasingly supported the hypothesis of schizophrenia as a neurodevelopmental disorder, with deviant development starting already in early childhood (Insel, 2010). This hypothesis is supported by the finding that patients who later develop schizophrenia have subtle motor and cognitive deficits in childhood but not the marked developmental delays typically associated with autism or intellectual disabilities (McCutcheon et al., 2020). The idea of schizophrenia as a developmental concept is not new. Already Bleuler (1950) considered psychosis a late stage or a complication of the disease that could possibly be prevented.

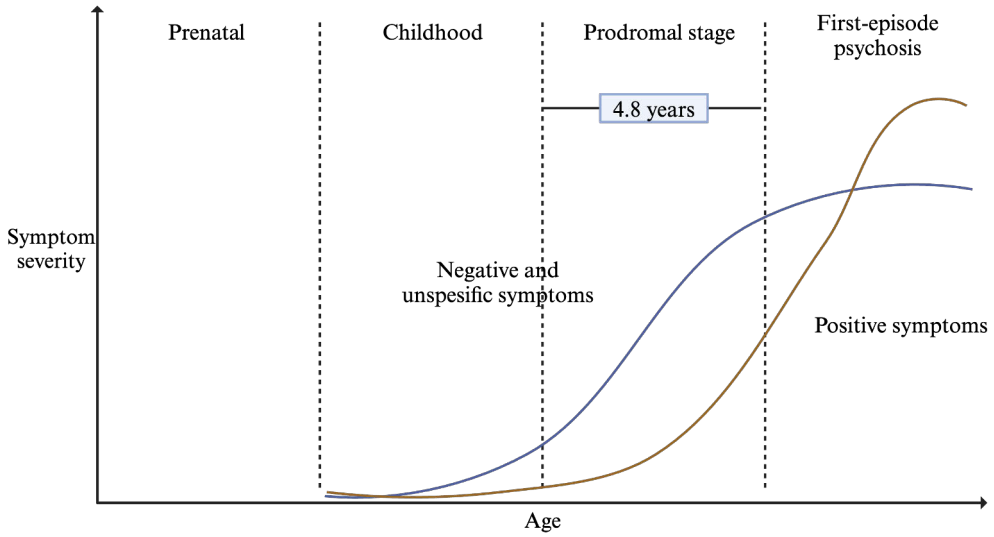


Figure 1. An illustration of the early stages and clinical course of schizophrenia. Subtle motor and cognitive deficits are common in children with later schizophrenia. Negative and unspecific symptoms, such as depressive symptoms, anxiety, disturbed sleep or appetite, and difficulties of concentration increase, along with functional impairment, during a prodromal stage in late adolescence or early adulthood. The first psychotic episode occurs when symptoms meet the threshold for a clinical diagnosis or psychosis. The first psychotic episode is also the most frequent phase for an individual to have contact with a psychiatric clinic and regularly leads to the initiation of psychiatric inpatient treatment. Modified from (Hafner et al., 2004; McCutcheon et al., 2020), created in BioRender. Sormunen, E. (2025).

2.1.2 Diagnosis of schizophrenia

The *International Classification of Diseases, Injuries and Causes of Death* (ICD) and *Diagnostic and statistical manual of mental disorders* (DSM) diagnostic manuals have been repeatedly revised in recent decades, and, by implication, the diagnostic criteria of schizophrenia have also changed. Despite an effort to identify specific biological markers associated with schizophrenia, the diagnosis is still based on characteristic symptoms, loss of function, and exclusion of some other disorders or conditions with similar manifestations.

The present thesis used these main diagnostic manuals: ICD-8 (WHO, 1967), ICD-9 (WHO, 1978), ICD-10 (WHO, 1992), and *Diagnostic and statistical manual of mental disorders, fourth edition* (DSM-IV) (American Psychiatric Association, 1994). The schizophrenia diagnosis was based mainly on the same symptoms, such as delusions, hallucinations, disorganized speech or behavior, and emotional blunting even in ICD-8 and ICD-9, as in the later, more advanced diagnostic manuals. The duration of the symptoms was not precisely defined in ICD-8 and ICD-9, although the duration had to be long-lasting, and the symptoms had to be severe.

ICD-9, ICD-10 and DSM-IV categorized the different subtypes of schizophrenia. DSM-5 (American Psychiatric Association, 2013) was published in 2013. Currently, the ICD-10 diagnostic classification system is in use in Finland, and ICD-11 (WHO, 2019) will be implemented next year, in 2026. **Table 2** presents the diagnostic criteria for schizophrenia in ICD-10, ICD-11, DSM-IV, and DSM-5. The main difference in schizophrenia diagnosis between earlier diagnostic manuals and ICD-11 and DSM-5 is that ICD-11 and DSM-5 eliminated the specific subtypes of schizophrenia. However, the changes in diagnostic criteria for schizophrenia had only a minimal effect on case identification, with concordance between DSM-IV and DSM-5 estimated at 98% (Tandon et al., 2013).

Table 2. Comparison of schizophrenia diagnostic criteria between ICD-10, ICD-11, DSM-IV, and DSM-5

	ICD-10	**ICD-11**	**DSM-IV**	**DSM-5**
DIAGNOSIS CODE	F20	6A20	295 (except 295.4 and 295.7)	295 (except 295.4 and 295.7)
DURATION OF THE SYMPTOMS	≥ 1 month	≥ 1 month	≥ 6 months of disturbance including ≥ 1 month of symptoms that meet criterion A	Same as in DSM-IV
CHARACTE-RISTIC SYMPTOMS	1) At least one of the following	At least two of the following and at least one must be a-d	A) At least two of the following	A) At least two of the following and at least one must be 1, 2 or 3
	a. Echoing/ insertion/ withdrawal/ broadcasting of thoughts	a. Persistent delusions	1. Delusions	1–4 same as in DSM-IV
	b. Delusional perceptions	b. Persistent hallucinations	2. Hallucinations	
	c. Hallucinatory voices	c. Disorganized thinking	3. Disorganized speech	
	d. Impossible delusions	d. Experiences of influence, passivity or control	4. Grossly disorganized or catatonic behavior	
	OR 2) At least two of the following	e. Negative symptoms (i.e. affective flattening, alogia or paucity of speech, avolition, asociality or anhedonia)	5. Negative symptoms (i.e., affective flattening, alogia, or avolition)	5. Negative symptoms (i.e., diminished emotional expression or avolition)

	ICD-10	ICD-11	DSM-IV	DSM-5
	e. Persistent hallucinations in any modality	f. Grossly disorganized behavior that impedes goal-directed activity	Note: Only one Criterion A symptom is required if delusions are bizarre or hallucinations consist of a voice keeping up a running commentary on the person's behavior or thoughts, or two or more voices conversing with each other	
	f. Incoherence or irrelevant speech	g. Psychomotor disturbances (i.e. catatonic restlessness or agitation, posturing, waxy flexibility, negativism, mutism or stupor)		
	g. Catatonic behavior		B) Significant and long-term disturbances in level of functioning	B) Same as in DSM-IV
	h. Negative symptoms		C) Continuous signs of the disturbance persist for at least 6 months, including criterion A symptoms for at least 1 month	C) Same as in DSM-IV
EXCLUSION CRITERIA	3) Schizoaffective or mood disorder	Schizotypal disorder, schizophrenic reaction or acute and transient psychotic disorder	D) Schizoaffective disorder and affective (depressive or bipolar) disorders with psychotic symptoms	D) Same as in DSM-IV
	4) Disorders caused by substance use or organic brain disease	Disorders caused by substance/medication use or another health condition	E) Substance use or other medical condition	E) Same as in DSM-IV

	ICD-10	ICD-11	DSM-IV	DSM-5
			F) If a patient has a history of autism spectrum or another pervasive develop-mental disorder, schizophrenia can be diagnosed if prominent delusions/hallucinations and other required symptoms or schizophrenia are present for at least 1 month	F) If a patient has a history of autism spectrum or communication disorder, schizophrenia can be diagnosed if prominent delusions/ hallucinations and other required symptoms or schizophrenia are present for at least 1 month
SPECIFIC TYPES OF SCHIZO-PHRENIA AND DIAGNOSIS CODES	F20.0 Paranoid schizophrenia	Specific types of schizophrenia omitted from ICD-11	295.1 Disorganized Type	Specific types of schizophrenia omitted from DSM-5
	F20.1 Hebephrenic schizophrenia		295.2 Catatonic Type	
	F20.2 Catatonic schizophrenia		295.3 Paranoid Type	
	F20.3 Undifferentiated schizophrenia		295.6 Residual Type	
	F20.4 Post-schizophrenic depression		295.9 Undifferentiated Type	
	F20.5 Residual schizophrenia			
	F20.6 Simple schizophrenia			
	F20.8 Other schizophrenia			
	F20.9 Schizophrenia, unspecified			

2.1.3 Treatment of schizophrenia

Several guidelines have been developed for the treatment of schizophrenia, e.g., Schizophrenia: The Current Care guidelines (Current Care Guidelines, 2024) in Finland as well as guidelines by the National Institute for Health and Care Excellence (National Institute for Health and Care Excellence (NICE), 2015), the American Psychiatric Association (American Psychiatric Association, 2020) and the World Health Organization (World Health Organization, 2016). All these guidelines suggest that the treatment of schizophrenia should include pharmacological treatment together with personalized psychosocial interventions, such as psychoeducation, cognitive-

behavioral therapy for psychosis, family interventions, and supported employment. The primary pharmacological treatment is antipsychotic medication, especially second-generation antipsychotics. Antipsychotic medication is relatively effective for treating positive psychotic symptoms, especially in first-episode psychosis, and preventing new psychotic episodes. However, the efficacy towards negative and cognitive symptoms of schizophrenia is poor (Leucht et al., 2013). Various side effects, including metabolic disturbances such as hyperlipidemia, hyperglycemia, and weight gain are common with second-generation antipsychotic medication (Leucht et al., 2013; Pillinger et al., 2020). Adverse side effects and the nature of schizophrenia often result in limited treatment adherence and interruptions in medication, which cause significant challenges of schizophrenia treatment and frequently lead to recurrent psychotic episodes (Acosta, 2012).

Current treatment guidelines for schizophrenia (Current Care Guidelines, 2024) recommend regular screening and monitoring of the physical health and cardiovascular risk factors of patients with schizophrenia due to metabolic disturbances, obesity, excess mortality and morbidity from cardiovascular diseases in patients with schizophrenia (Leucht et al., 2007; Olfson et al., 2015; Plana-Ripoll et al., 2019; Vancampfort et al., 2013). Nevertheless, the implementation of these health monitoring recommendations has been poor (Mackin et al., 2007).

2.1.4 Prognosis of schizophrenia and other non-affective psychoses

Schizophrenia is typically characterized by recurrent psychotic episodes and, in many cases, persistent or progressive functional impairment. However, the courses and outcomes of schizophrenia are very heterogenous, ranging from severe chronic state to full remission (Lang et al., 2013). According to a Danish study of 547 patients with any schizophrenia spectrum disorder, five years after the first psychosis episode, 18% had no psychotic or negative symptoms, lived independently, and were working or studying, whereas 13% were institutionalized either in supported housing or in a hospital (Bertelsen et al., 2009). Compared to other non-affective psychoses, a schizophrenia prognosis is even worse. Approximately as few as one in seven individuals with schizophrenia meet the remission criteria for both clinical and social functioning (Jääskeläinen et al., 2013). Despite intensive research efforts and advances in treatment, the proportion of recovered patients has not increased (Jääskeläinen et al., 2013). Some factors have been found to associate with a worse long-term functional outcome, such as the duration of untreated psychosis (Penttilä et al., 2014), premorbid functioning, severity of negative symptoms, and a genetic liability to schizophrenia (Peritogiannis et al., 2020), although the heterogeneity of the courses and outcomes of schizophrenia is still mainly unexplained.

2.1.5 Prevention of schizophrenia

Considering the often chronic and severe nature of schizophrenia (Jääskeläinen et al., 2013) and the limited response to treatment, research interest has shifted towards prevention and early intervention. Identifying individuals with a high risk for developing schizophrenia or psychosis, i.e., individuals at clinical high risk for psychosis (Yung et al., 2005), is the basis for secondary prevention and for the research into the prevention of schizophrenia. Approximately one-fourth of individuals with a clinical high risk for psychosis develop psychosis within three years (Salazar de Pablo et al., 2021), and the majority of those transitioning to psychosis are later diagnosed with schizophrenia spectrum disorder (Fusar-Poli et al., 2013).

2.1.5.1 Early interventions

Early interventions aim to prevent the onset of psychosis, improve overall functioning and quality of life, and to prevent and treat somatic and mental comorbidity in patients with high risk for schizophrenia. Early interventions generally comprise various psychosocial interventions or antipsychotic treatments. Intervening in the early stage of the illness is associated with better health and social outcomes, such as lower hospitalization risk, fewer bed days, lower positive and negative symptom severity, and better global functioning (Correll et al., 2018), as well as reduced costs of the health system (Tsiachristas et al., 2016). No intervention currently exists that could reliably prevent schizophrenia. Furthermore, no evidence has been found to favor any specific intervention over another to prevent psychosis or improve other outcomes (Fusar-Poli et al., 2020).

2.2 Etiological hypotheses of schizophrenia

The specific etiology of schizophrenia is widely studied but mainly remains unclear. Multiple genetic and environmental factors have been associated with the risk of schizophrenia, and the etiology is likely to be multifactorial.

2.2.1 Vulnerability-stress model

The etiology of schizophrenia is generally presented as a vulnerability-stress model, (Wahlberg et al., 1997; Zubin & Spring, 1977), **Figure 2**. The heritability of schizophrenia is likely due to both genes and environmental effects that genes moderate (van Os & Kapur, 2009). Genetic and early environmental factors together modulate neural development, leading to a vulnerable central nervous system, e.g., stress sensitivity, as well as subtle cognitive, motor and affective deviations. This vulnerable central nervous system is sensitive to the effects of environmental risk

factors such as psychosocial stress, traumatic experiences, or substance abuse. According to this model, schizophrenia develops in individuals with genetic and developmental vulnerabilities in interaction with environmental risk factors, e.g., stress, substance abuse or infections.

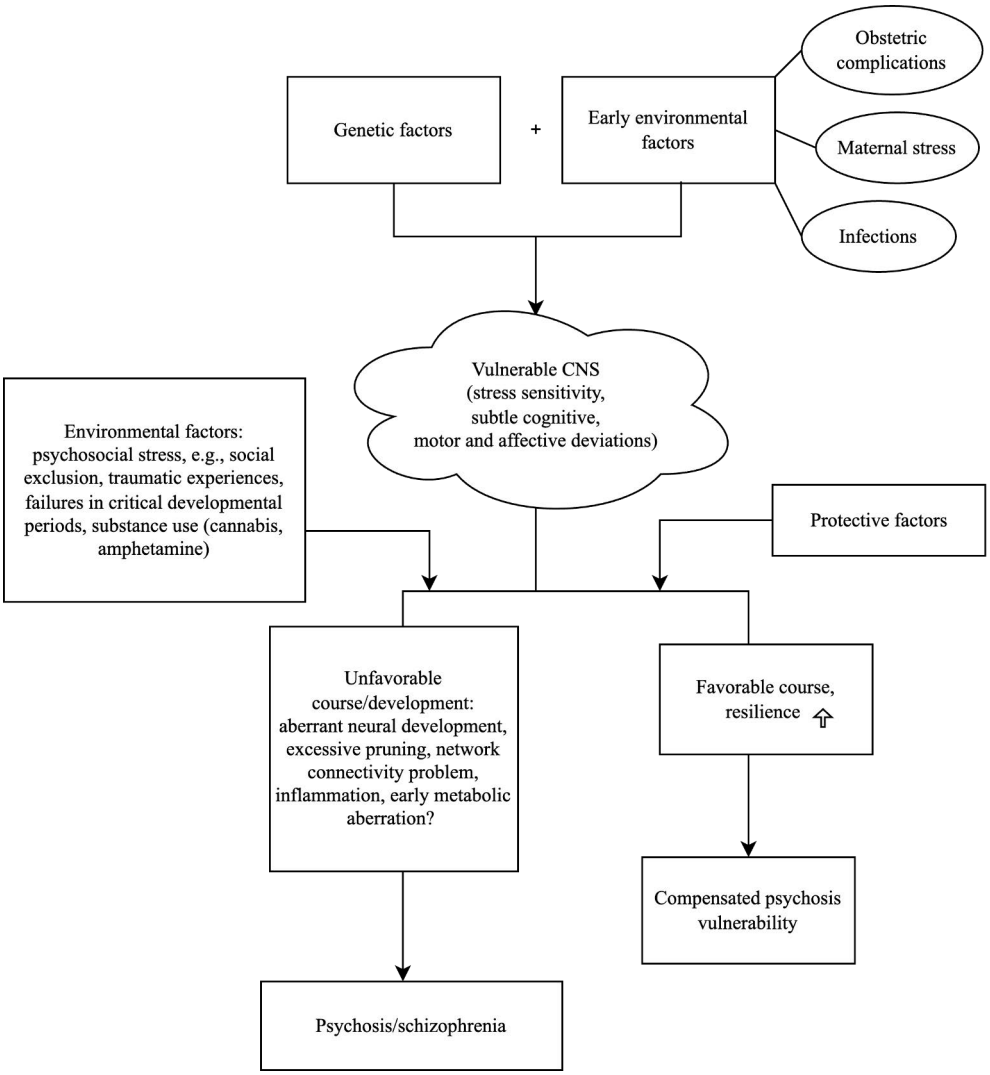


Figure 2. Factors influencing the risk of schizophrenia in the vulnerability-stress model, modified from (Hietala & Tuulio-Henriksson, 2021). Genetic and environmental risk factors lead to a vulnerable CNS. Furthermore, environmental factors and protective factors modulate the developmental course, leading to either the onset of psychosis or to compensated psychosis vulnerability. Most individuals with vulnerability to psychosis do not develop a psychotic disorder. However, due to common environmental risk factors and genetic liability, some individuals develop other psychiatric disorders, such as bipolar disorder or depression.

2.2.2 Neurodevelopmental model

The first psychotic schizophrenia episode typically occurs in early adulthood, although an increasing amount of evidence indicates that some problems are evident years earlier, even in childhood. Fish et al. found abnormal motor signs in infants, with a high risk for schizophrenia, as a predictor for schizophrenic development already in the 1950s (Fish, 1987). In 1990, Walker and Lewine studied home movies of children 8 years old and under and their healthy siblings who were later diagnosed with adult-onset schizophrenia. They showed that preschizophrenic children could be reliably identified from their healthy siblings, based on their behavior, less responsiveness, less eye contact, and poorer fine and gross motor coordination (Walker & Lewine, 1990). Several longitudinal cohort studies later showed, for instance, delayed developmental milestones in the first year of age (Sørensen et al., 2010) as well as early and persistent deficits in verbal reasoning, working memory, attention and processing speed (Reichenberg et al., 2010) in children who were diagnosed with schizophrenia as adults. These findings support the hypothesis of schizophrenia as a neurodevelopmental disorder (Murray & Lewis, 1987; Weinberger, 1987), with deviant neurological, cognitive, motor and somatic development starting years before the first psychotic episode (Insel, 2010), **Figure 1**.

2.3 Risk factors for non-affective psychoses

2.3.1 Genetic risk factors

The strongest known individual risk factor for schizophrenia is a familiar risk. The risk of psychosis in a child is increased 10 times when a parent has schizophrenia, compared to the risk in general (Mcglashan & Johannessen, 1996). The heritability of schizophrenia is estimated to be as much as 64–83% (T. D. Cannon et al., 1998; Lichtenstein et al., 2009; Sullivan et al., 2003). However, 85 % of patients with schizophrenia do not have a first degree relative diagnosed with schizophrenia (Mcglashan & Johannessen, 1996). A large, genome-wide association (GWAS) study with nearly 77,000 individuals with schizophrenia and over 243,000 controls recently reported common variant associations at 287 distinct genomic loci in patients with schizophrenia, especially in genes that are expressed in excitatory and inhibitory neurons of the central nervous system (Trubetskoy et al., 2022). However, these liability-associated single nucleotide polymorphisms (SNPs) do not have a practical relevance for an individual's risk for psychosis, because they are relatively common in the regular population and their effect on the risk of schizophrenia is very small (Trubetskoy et al., 2022). A higher risk of schizophrenia is associated with

some rare recurrent copy number variants (CNV), but the relevance for the general population risk is minor due to their rarity (Singh et al., 2022). It has been estimated that even the polygenic risk score that summarizes the cumulative effect of many genetic variations only explains 3.4% of susceptibility to schizophrenia (Agerbo et al., 2015). However, Genome-wide Association Studies (GWAS) studies have transformed our understanding about the genetic susceptibility of psychiatric disorders, because they highlight areas of biology as targets for further research aiming to understand the mechanism and pathophysiology of schizophrenia (Trubetskoy et al., 2022).

Interestingly, epidemiological and genetic studies have suggested that different mental disorders might have a partially common pathophysiological etiology. Schizophrenia is associated with not just schizophrenia in a relative but with a wide range of different mental disorders in first degree relative (Lichtenstein et al., 2009; Mortensen et al., 2010). This is supported by the finding that schizophrenia, bipolar disorder and major depression share a significant part of a common genetic susceptibility (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013).

2.3.2 Risk factors during pregnancy and birth

The developing brain is particularly vulnerable to neuroanatomical abnormalities due to unfavorable environmental influences during the prenatal period (Franke et al., 2020). Therefore, it seems plausible that many pre- and perinatal complications have been identified as a risk factor for schizophrenia, especially complications associated with fetal hypoxia or malnutrition (M. Cannon et al., 2002). There is strong evidence that obstetric complications, including preterm birth and preeclampsia, increase the risk for schizophrenia in the offspring (Dalman et al., 1999; Davies et al., 2020). Paternal age of 45 or more (Lehrer et al., 2016), maternal infections in gestation (Saatci et al., 2021), birth season from winter to spring, and maternal stress during pregnancy (Davies et al., 2020) are also associated with later development of psychosis. Both low birthweight (Abel et al., 2010; Sørensen et al., 2016; Wahlbeck et al., 2001) and short birth height (Gunnell et al., 2005; Wahlbeck et al., 2001), generally as an indication of suboptimal fetal growth or preterm birth, predict later schizophrenia. However, the effect of pre- and perinatal risk factors is found to be small separately, with the Odds ratios (ORs) of generally less than 2 (Davies et al., 2020).

2.3.3 Environmental risk factors

Childhood and adolescence, in addition to the fetal and the perinatal periods, have emerged as sensitive periods for many environmental risk factors to affect brain

development and, furthermore, to be vulnerable to the risk of schizophrenia. Central nervous system infections during childhood increase the risk of non-affective psychosis, including schizophrenia, as an adult (Khandaker et al., 2012; Rantakallio et al., 1997) and even cause long-term neurocognitive abnormalities, including lower full-scale IQ and psychological difficulties (Christie et al., 2011).

Many stressful life events, especially occurring during childhood, increase the risk for schizophrenia and other psychoses later in life (Cantor-Graae & Selten, 2005; Saarinen et al., 2023; Varese et al., 2012; Wicks et al., 2005). Adversity and trauma experiences, such as sexual, physical or emotional abuse, bullying and neglect, in childhood are well-studied risk factors for psychosis (Varese et al., 2012). Social adversity in childhood, including low socioeconomic status, has been shown to be associated with the higher risk of psychosis (Wicks et al., 2005), although this finding was not replicated in a recent Finnish cohort study (Saarinen et al., 2023). The effect of environmental factors is, at least in part, separate from genetic liability. A Swedish adoptive study showed increased risk for non-affective psychosis among adoptees living in a family of a single-parent household or with an unemployed parent (Wicks et al., 2010). Migration to another country or culture increases the risk for schizophrenia, especially for second-generation immigrants moving from developing countries to developed countries and migrants from areas where the majority of the population is black (Cantor-Graae & Selten, 2005). The mechanism underlying the increased risk of schizophrenia in immigrants is proposed to be a social defeat, hence migration often causes a chronic stressful experience of being an outsider (Selten et al., 2013). Social defeat, defined as the negative experience of being excluded from the majority group, might explain a part of other environmental risk factors for schizophrenia as well, for instance, childhood trauma or urban upbringing (Selten et al., 2013). In fact, living in the most urban environments is estimated to increase the risk of schizophrenia over 2.3 times higher compared to the most rural environments (Vassos et al., 2012). The relationship between stressful life-events and later psychosis might be dose-responsive or relate to long-term stress, because the risk for schizophrenia and other psychoses seems to increase with an increasing number of adverse social factors (Wicks et al., 2005) or associate especially with frequent stressful life-events (Saarinen et al., 2023).

Cannabis use, especially in adolescence, is well known to associate with an increased risk for psychosis (Moore et al., 2007), and the effect appears to be dose-responsive, i.e., people who use cannabis most frequently have a greater risk for psychotic disorders (Marconi et al., 2016).

2.3.4 Motor development and physical activity - effects on psychosis risk

As previously mentioned, the first signs of abnormal motor and neurological development in children who were later diagnosed with schizophrenia were found decades ago (Fish, 1987; Walker & Lewine, 1990). This phenomenon was later clarified by several cohort studies. Delay in early motor milestones, especially sitting, standing and walking unsupported (Filatova, 2017; Jones et al., 1994), deviance in motor coordination (Rosso et al., 2000; Schiffman et al., 2009) and motor functioning (Dickson et al., 2012) in childhood, are associated with later development of schizophrenia.

Three separate studies have shown that adolescents aged 15-17 years who later develop psychosis are physically less active compared to controls. Davidson et al. studied 16 to 17-year-old male adolescents who were later hospitalized for schizophrenia and found that future schizophrenia patients showed less interest in physical activity and had lower participation in physical activities compared to controls (Davidson et al., 1999). Koivukangas et al. studied adolescents aged 15 to 16 years in the Northern Finland Birth Cohort 1986. They found that adolescents who later developed psychosis were more likely to be physically inactive and had poorer cardiorespiratory fitness compared to controls (Koivukangas et al., 2010). Okkenhaug et al., in line with these findings, showed that adolescents who developed schizophrenia (n=15, mean age 16 years), were less physically active compared to adolescents who developed bipolar disorder and healthy controls (Okkenhaug et al., 2016). Individuals at high risk for psychosis also show low levels of physical activity (Carney et al., 2016; Lederman et al., 2017; Mittal et al., 2013; Provenzani et al., 2023).

2.3.5 Body mass index and the risk for psychosis

Suboptimal fetal growth is a risk factor for later schizophrenia, as previously mentioned (Abel et al., 2010; Gunnell et al., 2005; Sørensen et al., 2016; Wahlbeck et al., 2001). Large studies have showed that underweight in late adolescence or early adulthood (Gunnell et al., 2005; Sørensen et al., 2006; Weiser et al., 2004; Zammit et al., 2007), as well as short height in early adulthood (Gunnell et al., 2005), also predicts later schizophrenia. The number of subjects in many of these studies is impressive, but only one of those samples also includes women (Gunnell et al., 2005). Fewer studies have been conducted addressing the Body Mass Index (BMI) in childhood and adolescence in patients who later develop psychosis. Wahlbeck et al. have shown that patients who later developed psychosis were thinner than their peers at 7 to 15 years of age (Wahlbeck et al., 2001). Sørensen et al. similarly found that low BMI at the age of 7-13 years was associated with later schizophrenia

(Sørensen et al., 2016). However, divergent results have been shown. Jones et al. found no difference in weight or height of 7 to 11-year-old children with later development of schizophrenia and controls (Jones et al., 1994). Similarly, in the Northern Finland 1986 Birth Cohort, no significant difference was found in BMI or waist circumference of 15 to 16-year-old adolescents who later developed psychosis and controls (Koponen et al., 2008), though the follow-up was only four years. Perry et al. followed BMI from ages 1-24 years and found no association of five different BMI trajectories with later development of psychosis (Perry, Stochl, et al., 2021). Additionally, at least two large military cohort studies found no significant difference in BMI in males in early adulthood, between future schizophrenia patients and controls (Gunnell et al., 2003; Wyatt et al., 2003).

2.3.6 Metabolic aberrations and the risk for psychosis

Considering early disturbances in fetal growth and underweight in childhood and adolescence in patients with schizophrenia, as well as aberrant metabolic health indicators in first-episode psychosis patients, it has been hypothesized that changes in metabolic health might already be seen in childhood and adolescence. A few studies have tried to address this question, but the results have been inconsistent. Koponen et al. studied 15- to 16-year-old adolescents who later developed psychosis and found no significant difference in insulin resistance or lipid levels, compared to healthy controls (Koponen et al., 2008). The limitations of that study include a relatively small sample size of 21 patients with later psychosis, and the follow-up time was only to the participants' age of 20. Perry et al. recently studied 9- to 24-year-old participants and found that a persistently high insulin trajectory predicted a psychosis outcome at the age of 24 (Perry, Stochl, et al., 2021). Two additional studies have found changes in specific aspects of lipidome and proteomics in 11- or 12-year-old children who later developed psychosis (O'Gorman et al., 2017) or had psychotic experiences (Madrid-Gambin et al., 2019). One of these studies, O´Gorman et al., performed follow-up measurements when the participants were 18 years old and found no difference in lipids at that point, suggesting ongoing alterations in metabolic processes as the disease pathophysiology progresses further toward the onset of psychosis (O'Gorman et al., 2017).

It actually seems that glucose metabolism is also related to clinical outcomes, such as a transition to psychosis and poor level of functioning, in individuals with a clinical high risk of psychosis (Armio et al., 2024). In more detail, a recent study found that insulin levels and insulin resistance are increased in individuals with a clinical high risk of psychosis during a one-year follow-up, especially in those individuals who converted to psychosis (Armio et al., 2024).

2.3.7 Protective Factors and Resilience

One of the emerging areas of psychosis research is understanding why some individuals at very high risk for psychosis do not develop psychotic disorder, i.e., individuals with compensated psychosis vulnerability (**Figure 2**). One way to address protective factors for psychosis or schizophrenia is to identify individuals with compensated psychosis vulnerability and examine how they differ from those who develop psychosis (Keskinen et al., 2018). Better knowledge of protective factors is urgently needed to shift the focus from treatment to prevention of psychosis. However, the majority of the current evidence and literature covers the risk factors of psychosis rather than the protective factors (Oliver et al., 2020; Radua et al., 2018).

Adequate prenatal nutrition, including vitamins and other micronutrients, is essential for brain development (McGrath et al., 2011). Some prenatal nutritional factors, including vitamin D, iron, and folate substitution (McGrath et al., 2011), as well as choline supplementation (Freedman & Ross, 2015), have been suggested to lower the risk of schizophrenia. Although replication of these results and randomized controlled trials is first needed, vitamin D could potentially offer a cheap, safe, and relatively simple intervention for the primary prevention of schizophrenia. Breastfeeding also seems to have some protective effect against the risk of schizophrenia (Sørensen et al., 2005).

A positive family environment (González-Pinto et al., 2011) and the mother's better health and functioning, e.g., the mother's nondepressed mood during pregnancy and the mother's work outside the home or studies (Keskinen et al., 2018), were found to have a protective effect for individuals with a family history of psychosis. Adoptive cohort studies have also shown that adoptive parents with a clear communication style (Wahlberg et al., 1997) or overall healthy rearing patterns (Tienari et al., 2004) lower the risk of schizophrenia in an adoptee at high genetic risk for psychosis. Belonging to a Swedish-speaking minority with high socioeconomic status and social capital may protect against schizophrenia in Finland (Suvisaari et al., 2014).

Physical activity (Brokmeier et al., 2020; Crush et al., 2018; Tao et al., 2007) or having a sport hobby as a child (Keskinen et al., 2018) have been suggested as decreasing the risk of psychotic symptoms/disease. This is in line with studies suggesting physical inactivity as a risk factor for psychosis (Davidson et al., 1999; Koivukangas et al., 2010; Okkenhaug et al., 2016). A meta-analysis of five prospective studies showed that higher levels of physical activity were associated with a lower risk of later psychosis or schizophrenia (Brokmeier et al., 2020). However, only two of those studies included confounding factors, and when the analysis was limited to those two, the associations were no longer significant

(Brokmeier et al., 2020). One Mendelian randomization study found no evidence for physical activity as a protective factor for schizophrenia in adults (Sun et al., 2020).

A large Finnish cohort study also found that the BMI of 14-year-old individuals who did not develop psychosis later in life was more likely in the highest quartile when compared to their peers (Keskinen et al., 2018). They were also more likely born from a wanted pregnancy, less likely to have a grand multiparity in the family, and their performance at school was good, suggesting protective effects against psychosis (Keskinen et al., 2018). The role of physical activity and the metabolic profile in the pathogenesis of schizophrenia and a possible target for preventing schizophrenia will be discussed in detail later in this thesis.

Resilience refers to an individual's capacity or tendency, including personality traits, social skills and coping mechanisms, to foster a positive outcome when facing adverse circumstances (Marulanda & Addington, 2016). Individuals at high risk for psychosis have a lower resilience level. Furthermore, higher resilience in this group was associated with lower negative symptoms, depression and anxiety (Marulanda & Addington, 2016). It has been hypothesized that resilience may play a key role as a protective factor against psychosis among vulnerable people and that interventions aimed at increasing resilience, such as physical activity (Salmon, 2001), may help prevent psychosis.

2.4 Somatic comorbidity in non-affective psychoses – causes and consequences

2.4.1 Morbidity and mortality in somatic diseases in schizophrenia and other non-affective psychoses

Schizophrenia spectrum disorders are associated with a 10-to-20-year shorter life expectancy compared to the general population (Laursen, 2019; Plana-Ripoll et al., 2019). The mortality gap between patients with schizophrenia and the general population has been stable for decades in Finland, but deaths due to cardiovascular diseases and cancer have shown increasing trends, while suicide rates have declined (Tanskanen et al., 2018). A majority of the excess mortality of patients with schizophrenia is due, in fact, to natural causes (Plana-Ripoll et al., 2019), especially to cardiovascular diseases (Olfson et al., 2015). Besides increased mortality, morbidity from somatic diseases is also common in schizophrenia (Leucht et al., 2007). Medicated multi-episode patients with schizophrenia have an increased risk for abdominal obesity, hypertension, low high-density lipoprotein cholesterol, hypertriglyceridemia, and diabetes (Vancampfort et al., 2013). One-third of patients with schizophrenia fulfil the diagnostic criteria for metabolic syndrome (Vancampfort, Stubbs, et al., 2015). Interventions aimed at preventing, identifying,

and treating cardiovascular risk factors and somatic diseases in patients with schizophrenia are crucial and in need of special attention.

Metabolic aberrations and cardiovascular diseases are not specific to schizophrenia or non-affective psychosis but are associated with many other psychiatric disorders as well. In fact, depression is associated with cardiovascular disease morbidity and mortality (Rajan et al., 2020), and patients with depressive symptoms and metabolic dysregulation are at higher risk for type 2 diabetes (Schmitz et al., 2016). As another example, individuals with autism spectrum disorder are at greater risk of developing diabetes type 1 or 2, dyslipidemia, and heart disease (Dhanasekara et al., 2023).

2.4.2 Unhealthy lifestyle in patients with non-affective psychosis

Cardiovascular diseases and other somatic health problems in patients with schizophrenia are partly due to unhealthy lifestyles in this population (Correll et al., 2014). Compared to the general population, people with severe psychotic disorders have lower physical activity (Daumit et al., 2005) and an unhealthier diet (Roick et al., 2007), as well as a considerably increased risk of smoking, heavy alcohol use, and other substance use (Hartz et al., 2014). Physical inactivity is a risk factor for cardiovascular morbidity and mortality (I.-M. Lee & Skerrett, 2001), and the effect is actually comparable to cigarette smoking (P. Z. Pearce, 2008). Therefore, physical inactivity could even explain a part of excess morbidity and mortality in schizophrenia.

2.4.3 The effect of antipsychotic drugs

Antipsychotic medication, especially second-generation antipsychotics, has consistently been associated with adverse metabolic consequences (Pillinger et al., 2020) such as obesity (Correll et al., 2011), insulin resistance, hyperglycemia (Jin et al., 2004), hyperlipidemia (Meyer & Koro, 2004), and metabolic syndrome (De Hert et al., 2006). It seems that those antipsychotic drugs that are the most efficacious, such as olanzapine and clozapine, are associated with the greatest metabolic disturbance (Huhn et al., 2019; Pillinger et al., 2020).

2.4.4 Metabolic disturbances as an integral part of non-affective psychosis

The impact of antipsychotic medications and a sedentary lifestyle on the metabolic health of patients with schizophrenia is indisputable, but these factors alone do not account for the entire picture.

2.4.4.1 Historical perspective

The association between schizophrenia and diabetes has been documented in scientific reports since the early 20th century, decades before the advent of antipsychotic medication (Kohen, 2004). Although the sample sizes were very small and diagnostic reliability was not at the level of modern research, these early studies still provide valuable insights into the relationship between schizophrenia and diabetes, without the interference of antipsychotic treatment. Early studies found that patients with dementia praecox (a term formerly used for schizophrenia-like mental disorders) often had hyperglycemia, although similar relationships were reported in some other mental disorders as well (Kooy F. H., 1919; Raphael & Parsons, 1921). In addition, glucose tolerance curves of patients with dementia praecox were found to assemble diabetic characteristics (Lorenz, 1922). Insulin-induced coma therapy was used for psychotic symptoms during the 1940s and 1950s, before being largely replaced by antipsychotic medications in the 1950s. It was brutal and rather ineffective as a treatment, yet it led to the discovery of abnormal responses to insulin in patients with psychoses (Appel & Farr, 1929). These findings suggest that glucose dysregulation is also part of psychotic disorders themselves, not just a consequence of antipsychotic medication.

2.4.4.2 Metabolic disturbances in first episode psychosis

Several large meta-analyses have recently shown wide metabolic disturbances in antipsychotic-naïve first episode psychosis patients (**Figure 3**), supporting the idea of metabolic problems as a part of the illness itself. Patients with a first episode of non-affective psychosis (Greenhalgh et al., 2017) or more specifically schizophrenia (Pillinger, Beck, Gobjila, et al., 2017) have elevated fasting plasma glucose and insulin levels, elevated plasma glucose after an oral glucose tolerance test, and greater insulin resistance compared to healthy controls. In addition to aberrant glucose metabolism, patients with first-episode psychosis have lower levels of total and low-density lipoprotein (LDL) cholesterol and higher levels of triglycerides (Misiak et al., 2017; Pillinger, Beck, Stubbs, et al., 2017), as well as lower levels of high-density lipoprotein (HDL) cholesterol (Misiak et al., 2017; Perry et al., 2016), irrespective of antipsychotic medication. As a controversial finding compared to studies of chronic schizophrenia patients, a meta-analysis showed that BMI is actually lower in antipsychotic-naïve or minimally treated psychosis patients, compared to healthy controls, although their waist-to-hip ratio was elevated (Shah et al., 2019).

These findings reliably indicate that irrespective of antipsychotic medication, psychosis itself is involved with multiple systems in addition to the central nervous system, **Figure 3**. This leads us to think that schizophrenia might be a multisystem disorder despite the causality of the relationship being mainly unknown (Pillinger et al., 2019).

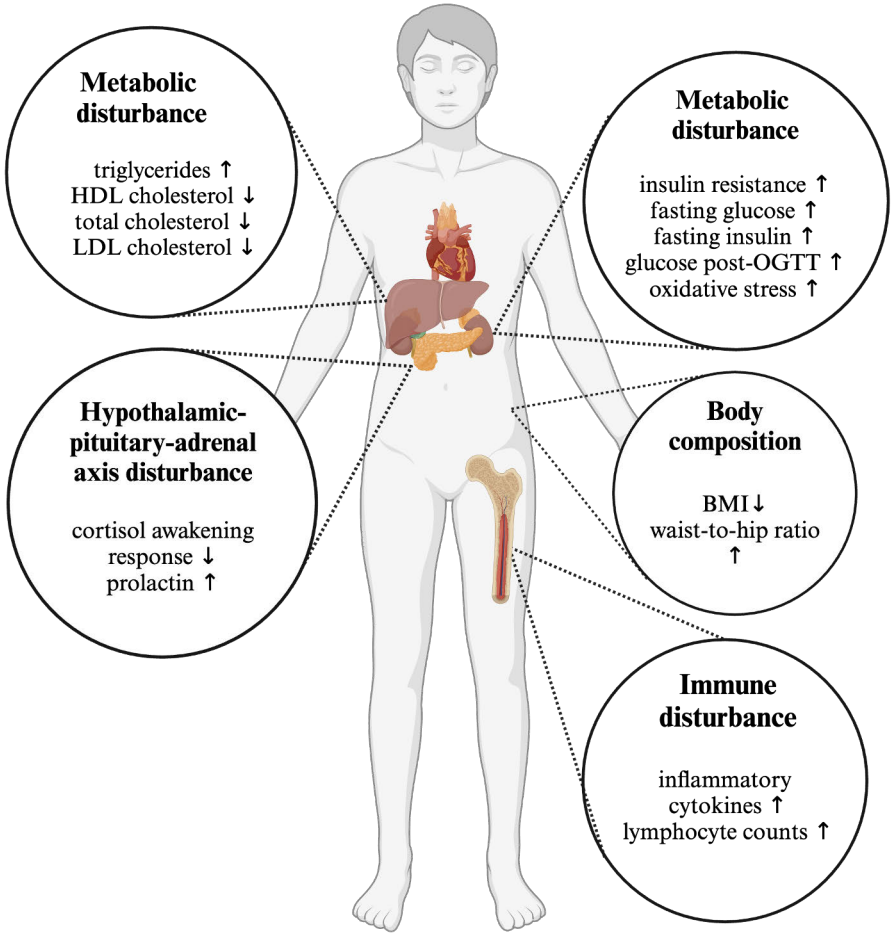


Figure 3 An illustration of non-CNS disturbances in first-episode psychosis. Modified from (Pillinger et al., 2019), created in BioRender. Sormunen, E. (2025).

2.4.5 Predicting the cardiovascular risk in patients with early psychosis

A psychosis metabolic risk calculator (PsyMetRiC) for metabolic risk assessment in young people with psychosis was recently conducted by Perry et al. (Perry et al., 2022) and validated in a Finnish sample (Keinänen et al., 2024). This risk calculator considers various cardiovascular risk factors, including BMI, high-density lipoprotein, and triglycerides concentrations, in patients with early psychosis. These studies showed that PsyMetRiC appears promising for future routine use and could help clinicians caring for young people with or at risk for psychosis to identify those with a higher cardiometabolic risk so that interventions can be directed effectively to reduce long-term morbidity and mortality to somatic diseases. If used routinely,

this could lead to a long-awaited achievement in reducing somatic morbidity and mortality in patients with schizophrenia.

2.4.6 Developmental aspects of glucose and lipid levels in children and adolescents

Horrobin et al. introduced "the membrane hypothesis of schizophrenia" in 1994, suggesting that schizophrenia involves abnormalities in the metabolism and structure of membrane phospholipids, not only in the brain but also in other tissues (Horrobin et al., 1994). Supporting that idea, cholesterol is essential for brain development and functional outcomes, especially as a fundamental constituent of myelination (Hussain et al., 2019). Puberty is a critical period of brain structure reorganization and a high-risk period for the development of mental health problems (Kretzer et al., 2024); thus, alterations of lipid and insulin metabolism during childhood and adolescence, especially during puberty, are an interesting field for research aiming to clarify the pathogenesis for psychosis and other mental disorders.

The metabolic profile, including insulin and lipid levels, changes naturally throughout childhood and adolescence, driven by growth, hormonal shifts, and puberty. It is well shown that insulin resistance increases significantly during puberty (Moran et al., 1999). As a result, more insulin is needed to help glucose enter the cells from blood serum. Insulin resistance eventually leads to higher levels of glucose in the blood, as well as overproducing the insulin in the pancreas as compensation. However, insulin resistance decreases nearly to prepubertal levels when puberty is completed (Moran et al., 1999).

Lipid levels change markedly during puberty. Total and LDL cholesterol levels generally decrease along with pubertal stage development and during the rapid growth phase. It is assumed that lipids are used for tissue development during these periods, leading to lower plasma concentrations. HDL cholesterol levels also seem to decrease, and triglyceride levels increase in males, while no such changes were observed in females (Eissa et al., 2016).

2.5 Exercise interventions in non-affective psychoses

Exercise is defined as "a subset of physical activity that is planned, structured, and repetitive and has as a final or an intermediate objective the improvement or maintenance of physical fitness" (Caspersen et al., 1985). A comprehensive amount of evidence supports the idea that "exercise is medicine" (P. Z. Pearce, 2008) in addition to the joy induced by physical activity, the improvement in fitness, and the social interaction often associated with exercise. It has preventative and therapeutic

effects on a wide range of chronic metabolic, cardiovascular, pulmonary, neurological, and psychiatric diseases, musculoskeletal disorders, and cancer (Pedersen & Saltin, 2015). Higher levels of physical activity are even associated with reduced risk of all-cause premature mortality. (Ekelund et al., 2019).

The effects of exercise in mental disorders have recently been a focus of interest in research, and multiple benefits of exercise on a wide range of mental disorders have been shown (Schuch & Vancampfort, 2021). It has even been suggested that exercise interventions should be included in the routine care of people with mental disorders (Schuch & Vancampfort, 2021).

2.5.1 Exercise interventions as a treatment of schizophrenia

Even though a major part of the literature focuses on exercise and depression, the results concerning schizophrenia are notable. Not so surprisingly, exercise interventions improve physical health, i.e., cardiorespiratory fitness, of people with schizophrenia (Vancampfort, Rosenbaum, et al., 2015). A meta-analysis by Vancampfort et al showed that lifestyle interventions, including physical activity, diet, and smoking cessation, are effective in reducing total cholesterol, LDL cholesterol, and triglycerides in patients with schizophrenia (Vancampfort et al., 2019), They also suggested, that exercise interventions, combined with individual lifestyle counseling, are the most effective strategies for weight reduction in patients with schizophrenia (Vancampfort et al., 2019). However, a large meta-analysis showed that the effect of individualized lifestyle interventions on weight reduction in people with serious mental illness was clinically insignificant, with a reduction in BMI by only approximately -0.63 kg/m2 compared to controls (Speyer et al., 2019). Furthermore, a Danish study compared an individual lifestyle coaching intervention with treatment as usual and found no significant effect on 10-year risk of cardiovascular disease, nor an increase in physical activity in patients with schizophrenia and abdominal obesity (Speyer et al., 2016). Recently, few studies on new GLP-1 receptor agonists have shown promising results in mitigating psychotropic drug-related weight gain (Menon et al., 2024). In addition to physical health benefits, meta-analyses have shown that regular moderate-to-vigorous exercise can reduce both the positive and negative symptoms of schizophrenia (Firth et al., 2015), as well as improve clinical symptoms, global functioning, depression, quality of life (Dauwan et al., 2016), and cognitive functioning (Firth et al., 2017) in patients with schizophrenia.

Several international and national guidelines for treating schizophrenia have proposed that physical activity and exercise should be integrated into the treatment plan. For example, the Current Care Guidelines for schizophrenia in Finland suggest that the exercise and physical activity habits of every patient with schizophrenia

should be established in the early phase of the disease, and their physical activity should be increased as a part of the treatment (Current Care Guidelines, 2024). In addition, the European Psychiatric Association's guidelines on the promotion of physical activity in people with mental illness suggest the use of aerobic exercise of moderate-vigorous intensity 2–3 times a week in order to improve outcomes in patients with schizophrenia spectrum disorders (Stubbs et al., 2018).

2.5.2 Effects of physical activity on brain morphology and function

Interestingly, physical activity has multiple and wide effects on the central nervous system. For example, it causes the release of neurotrophins, especially Brain-derived Neurotrophic Factor (BDNF), Insulin-like Growth Factor 1 (IGF-1), and Vascular endothelial growth factor (VEGF), that are associated with adult neurogenesis and attenuation of neuroinflammation, as well as modulation of cerebral blood flow, enhanced adult hippocampal neurogenesis, and structural reorganization (Augusto-Oliveira et al., 2023). Many of those systems have been found to relate to the pathogenesis of schizophrenia. The structural and functional abnormalities of the brain in patients with schizophrenia are well documented, including reduction of grey matter in the neocortex and limbic areas, larger lateral and third ventricles (Hulshoff Pol & Kahn, 2008; Shenton et al., 2001; Wright et al., 2000), as well as hippocampal volume reduction and abnormal functioning (Knight et al., 2022). Increase in cardiorespiratory fitness, potentially due to exercise (Abdullahi et al., 2024), has been shown to increase cerebral matter volume and decrease lateral and third ventricle volume in both patients with schizophrenia and healthy controls (Scheewe et al., 2013). In addition, regular physical exercise improves white matter integrity in both patients with schizophrenia and healthy controls, especially in those tracts involved in motor functioning (Svatkova et al., 2015).

It has been hypothesized that psychotic symptoms may be generated by hippocampal hyperactivity as a link to increased activity in regions involved in subcortical dopamine signaling (Lodge & Grace, 2011). Increased resting activity in the hippocampus, midbrain, and basal ganglia are already present in individuals at clinical high risk of psychosis, and a later reduction of the high-risk state is associated with a normalization of activity in the aforementioned regions (Allen et al., 2016). Aerobic exercise directly targets the hippocampus in healthy participants (Steventon et al., 2020), but a meta-analysis found no effect of exercise on total hippocampal volume in patients with schizophrenia (Firth et al., 2018). Due to the limited impact of aerobic exercise on hippocampal volume observed in studies, it has been suggested that exercise interventions should be initiated during childhood or adolescence, the developmental phases of the hippocampus, to potentially

influence vulnerability to schizophrenia (Knight et al., 2022). A recent clinical trial studied the effects of exercise intervention in individuals at clinical high risk for psychosis and found improvement in fitness and cognitive performance and reduced positive symptoms due to the exercise intervention (Damme et al., 2022). Furthermore, aerobic exercise was associated with increased hippocampal-occipital functional connectivity and stable hippocampal volumes, while individuals not participating in the exercise intervention showed decreased hippocampal volumes (Damme et al., 2022).

Physical activity modulates brain development across the lifespan (Stillman et al., 2020). The effects of exercise on cognition seem to be even more prominent in children and, somewhat surprisingly, elderly people (Stillman et al., 2020). A systematic review suggested that physical activity may modify white matter integrity and activation in regions related to cognitive processes in adolescents (Valkenborghs et al., 2019). Physical activity was also related to better white matter microstructure in 9 to 10-year-old children (Rodriguez-Ayllon et al., 2020). A recent study suggests that the white matter microstructure may mediate the association between exercise and cognition (Opel et al., 2019), but further studies are needed to address whether these structural and functional brain changes explain the reduced risk of psychiatric symptoms.

3 Aims

This study aimed to identify childhood and adolescent risk factors for non-affective psychosis that may contribute to its etiology and serve as potential targets for early intervention in psychosis prevention programs. We used the Cardiovascular Risk in Young Finns (YFS) cohort study and the Care Register for Health Care.

1. The aim of Study I was to find out whether the level of physical activity in children and adolescents affects the risk of non-affective psychosis or other psychiatric disorders.
2. The aim of Study II was to find out whether deviation from normal weight, i.e., underweight or overweight, affects the risk of non-affective psychosis and if so, whether the mechanism is specific to psychosis or is related to affective disorders as well.
3. The aim of Study III was to clarify the cardiovascular risk trajectory before the first episode of non-affective psychosis and to study whether insulin, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides differ in childhood and adolescence in patients with future non-affective psychosis compared to controls.

4 Materials and Methods

4.1 Study design

These studies were conducted following the ethical principles of the Declaration of Helsinki. All study protocols were approved by the Joint Ethical Committee of the University of Turku and the Turku University Central Hospital. Written informed consent was provided by all participants aged nine and above and by the participants' parents for younger children. The permissions for using register data and linking YFS data to diagnostic data were obtained from the respective organizations.

4.1.1 Subjects

4.1.1.1 The Cardiovascular Risk in Young Finns Study

"The Cardiovascular Risk in Young Finns" (YFS) is a population-based cohort study initiated in 1980 (Raitakari et al., 2008). Altogether 4,320 children and adolescents were randomly selected from the national register of five Finnish cities (Turku, Helsinki, Tampere, Oulu, and Kuopio) and their rural surroundings, **Figure 4**. At baseline, 3,596 (83% of those invited) children and adolescents from six different age groups (3, 6, 9, 12, 15, and 18) participated in the first cross-sectional survey. The participants were examined at 3-year intervals between 1980 and 1992.

Figure 4. An illustration of five cities of YFS study on a map of Finland.

4.1.2 Psychiatric outcome

Psychiatric diagnoses of all YFS participants were derived from the Care Register for Health Care (CRCH), formerly called the Finnish Hospital Discharge Register. This register contains data from all inpatient hospital discharges in Finland with linkable personal identification codes since 1969. Psychiatric diagnoses of the participants were obtained up to 2012 in Study I, 2014 in Study II, and 2018 in Study III (**Figure 5)** due to the availability of the register data in different phases of the thesis work. Hence, the number of subjects with psychiatric diagnoses has slightly increased. Some participants were diagnosed with psychiatric disorders or had their first hospital treatment after years 2012 or 2014 and therefore were not in the hospital discharge register before.

The diagnostic manuals and codes have changed in Finland during the YFS follow-up years. Therefore, the ICD-8, ICD-9, and ICD-10 codes were converted to the DSM-IV codes described in **Table 3.** We formed diagnostic groups of all non-affective psychoses (DSM-IV 295, 297, 298), a subgroup of only schizophrenia (DSM-IV 295), personality disorders (DSM-IV 301), affective disorders (mood and anxiety disorders, DSM-IV 296, 300, 311), substance related disorders (DSM-IV 291, 292, 303, 304, 305) and controls with no psychiatric diagnoses related to hospital care. Each participant was categorized into only one diagnostic group with diagnoses prioritized in the order of schizophrenia or other non-affective psychosis, personality disorders, affective disorders, substance related disorders and controls. **Figure 5** describes in detail the exclusion criteria and the number of subjects in the diagnostic groups among YFS participants in Studies I–III**.**

Table 3. The conversion of ICD codes to DSM-IV codes and formulation of diagnostic groups.

DIAGNOSIS		ICD-8 CODES	ICD-9 CODES	ICD-10 CODES	DSM-IV CODES
NON-AFFECTIVE PSYCHOSIS					
	Schizophrenia, schizophreniform disorder, schizoaffective disorder	295	295	F20 (except F20.4), F23.1, F23.2, F25	295
	Delusional disorder	297	297	F22, F23.3, F24	297
	Brief psychotic disorder NOS	298, 299	298	F23.0, F23.8, F23.9, F28, F29	298
PERSONALITY DISORDERS		301	301	F21, F34.0, F60, F61, F61.1, F62, F68.8, F69	301
AFFECTIVE DISORDERS		296, 300, 307,	296, 300	F20.4, F30–F34 (except F34.0), F38–42, F44–F45 (except F45.4), F48–F49, F68 (except F68.8), F93.1–F93.2	296, 300, 311
SUBSTANCE-RELATED DISORDERS		291 (except 291.0), 303, 304	291, 292, 303, 304, 305	F09–F19, F55	291, 292,303, 304, 305

We also explored in Study III whether childhood/adolescent insulin or lipid levels predict the onset of psychosis in this sample. Follow-up times (lag-time) were defined as the difference between the time of diagnosis and the last blood sample in the insulin or lipid trajectory (ages ranged from 9 to 18 years). The time of diagnosis was defined as the date of the first registered hospitalization entry with a psychosis diagnosis and was used as a proxy for psychosis onset. Prodromal periods could not be defined in this type of register study. All follow-up times are scaled in full years. Controls were censored at the last check of registry data in 2018.

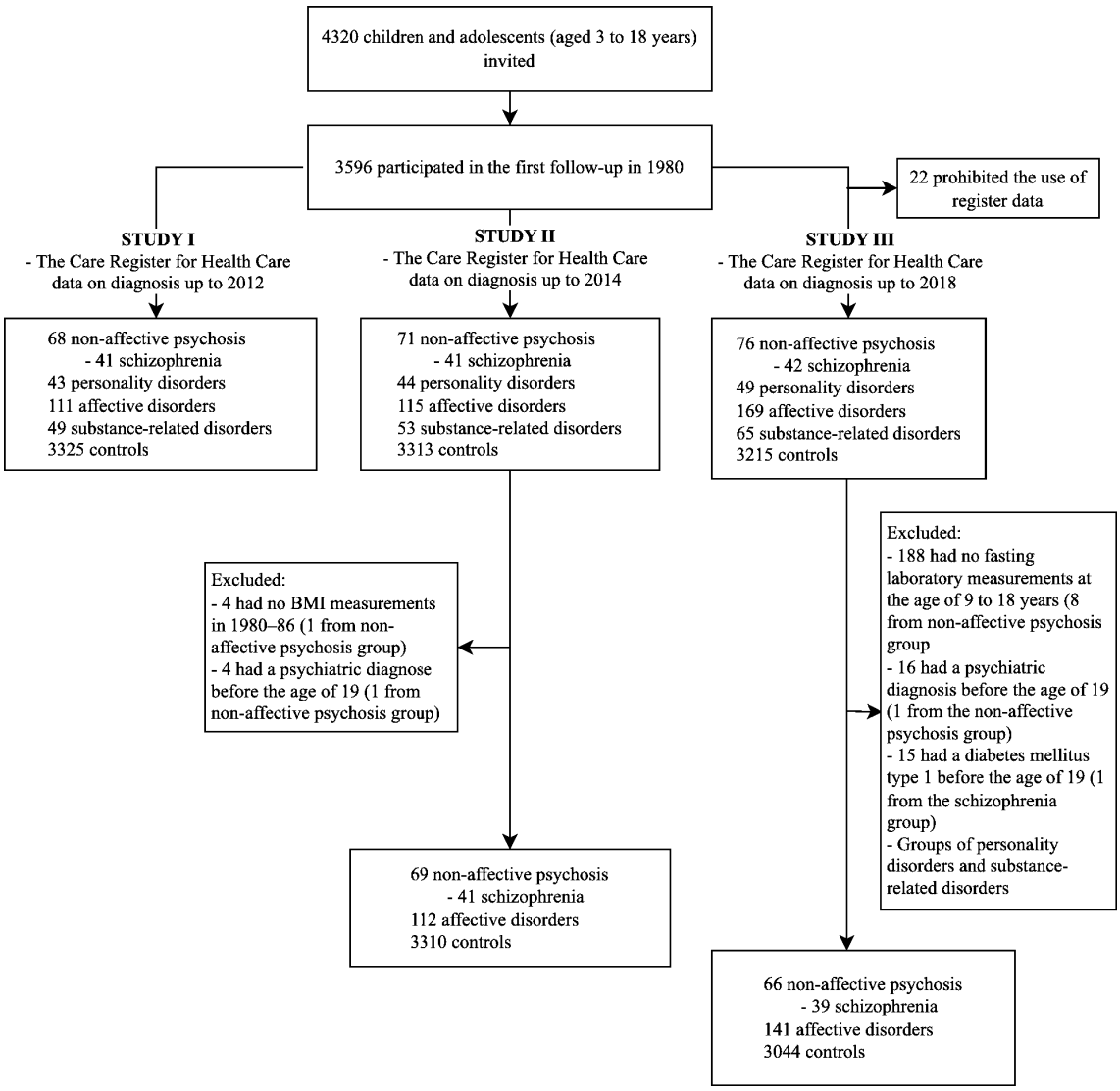


Figure 5. The diagnostic groups were formed based on hospital discharge register data up to the years 2012–2018 in Studies I–III. Describes exclusion criteria, and the final number of subjects in the diagnostic groups included in the analysis in Studies I–III.

4.1.3 Clinical characteristics

Follow-ups, including physical examinations and laboratory samples in this study, were performed in 1980, 1983, and 1986, up to the participants' age of 18 years, **Table 4**. The next full-scale follow-up in YFS was conducted in 2001 when all participants were over 18 years old and therefore were excluded from this study. Follow-up in the present study was possible for six years. Thus, none of the participants' data are

complete from ages 3 to 18, and for those who were already 18 years old in 1980, there cannot be data from more than one visit due to the study's design.

Table 4. Cohorts and design of the first three follow-up years (1980, 1983, and 1986) in Young Finns Study. The participants' fasting plasma insulin, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides levels, and height and weight were measured in all three study visits. Physical activity index (PAI) was assessed in 1980, 1983, and 1986, parental mental disorders in 1980 and 1983, and birthweight in 1983 and 1986 by a questionnaire. We included measurements of participants aged 9 to 18 years in Studies I and III, and 3 to 18 years in Study II. Measurements of 3- and 6-year-old children were excluded from analysis in Studies I and III due to a low number of fasting blood samples and unavailability of physical activity index of children under 9 years old. Table modified from Study III, supplementary table 1 (Sormunen et al., 2022).

STUDY DESIGN

YEAR	Number of participants	Age cohorts						Metabolic measurements	Assessed by a questionnaire
1980	3596	3	6	9	12	15	18	Height weight insulin total cholesterol LDL cholesterol HDL cholesterol triglycerides	PAI (from 9 years of age) Parental mental disorders
1983	2991		6	9	12	15	18	Height weight insulin total cholesterol LDL cholesterol HDL cholesterol triglycerides	PAI (from 9 years of age) Parental mental disorders Birthweight
1986	2799			9	12	15	18	Height weight insulin total cholesterol LDL cholesterol HDL cholesterol triglycerides	PAI (from 9 years of age) Birthweight

4.1.3.1 Physical activity

Physical activity was assessed with a self-report questionnaire (**Table 5**) during the study visits in 1980, 1983, and 1986 for participants aged 9, 12, 15, and 18 years old (**Table 4)**. The questions included the frequency and intensity of leisure-time physical activity, participation in sports club training and competitive sports events,

as well as common activity during leisure time. The answers to all questions, except the participation in competitive sports events, were coded from 1 to 3, with 1 representing inactivity or very low activity, 2 moderately intensive or frequent activity, and 3 vigorous or frequent activity. Answers to participation in competitive sports events were coded only to 1 representing no and 2 representing yes. The physical activity index PAI was calculated as a sum of the measurements in the five aforementioned questions, with the ratings ranging from 5 to 14. The physical activity index PAI has been validated in previous studies and found to correlate with the volume of movement assessed using accelerometers and pedometers (Mansikkaniemi et al., 2012), as well as physical fitness (Telama et al., 2005).

Table 5. The assessment of physical activity and creation of the physical activity index (PAI) in 1980 1989. Modified from Study I (Sormunen et al., 2017).

Question in the physical activity questionnaire	Code for PAI
How often do you engage in leisure-time physical activity at least half an hour per time?	
Not at all	1
Less than once a month	1
Once a month	1
2-3 times a month	1
Once a week	2
2-6 times a week	2
Every day	3
How much are you breath-taking and sweating when you engage in physical activity and sport?	
Not at all	1
Moderately	2
A lot	3
How many times a week do you usually engage in the training sessions of a sports club?	
Not at all	1
Occasionally	1
Less than once a month	1
Once a month or more	2
Once a week	2
Many hours and times a week	3
Do you participate in regional or sports clubs level competitions?	
No	1
Yes	2
What do you usually do in your leisure time?	
I am usually indoors and read or do something like that	1
I spend my time indoors and outdoors, outdoors I usually walk or spend time with my friends	2
I am usually outdoors and exercise a lot	3
PAI total, range	5–14

4.1.3.2 Body mass index and birthweight

The participants' height (m) and weight (kg) were measured, and their Body Mass Index (BMI) was calculated as kg/m2 in 1980, 1983, and 1986. BMI was further categorized as underweight, normal weight, and overweight by using Cole et al.'s classification for children and adolescents. This classification is based on pooled international data of 9,7876 males and 9,4851 females. Underweight in the present study represents adult BMI of ≤18.5 kg/m2 (Cole et al., 2007); normal weight represents adult of BMI >18.5 kg/m2 and <25 kg/m2; and overweight represents adult of BMI≥25 kg/m2 (Cole et al., 2000). BMI data were used from all available time points and analyzed longitudinally.

Birthweight was asked in a questionnaire for the participants' parents in 1983 and 1986 and dichotomized to low birthweight (<2500g) vs higher.

4.1.3.3 Metabolic health indicators

Venous blood samples were drawn after fasting overnight during the physical examinations at the study visits in 1980, 1983, and 1986. The adherence to fasting overnight was confirmed by questioning the participants or their parent; answers were coded yes vs. no. Serum total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, and insulin levels were determined from the blood sample.

4.1.3.4 Parental characteristics

The participants' parents' mental disorders or problems, diagnosed by a doctor, were asked about in a self-report questionnaire from the participants' mothers in 1980 and 1983. The parents' physical activity was also assessed by a questionnaire in 1986 and 1989. The parents' physical activity consisted of two questions, participation and frequency of leisure-time physical activity. The parent was asked if he or he engaged in regular physical activity (the answers were coded from 1 to 3, 1 = rarely or not at all, 2 = sometimes or with other hobbies, 3 = regularly). If a parent answered with option 3, the frequency of physical activity was also asked (answers were coded as follows, 1 = once a month or less, 2 = 2–3 times a month, 3 = once a week, 4 = 2–6 times a week, 5 = every day).

4.1.4 Statistical methods

We have no reason to assume any remarkable differences between the birth cohorts because the blood sample protocols, physical activity measurements, and physical examinations were similar in the years 1980–1986. Therefore, the follow-up series

from study visits in 1980, 1983, and 1986, including children and adolescents from six age points, were combined for the analyses.

All of the results are presented as risk ratios with 95% confidence intervals (RR [95% CI]) from univariate and multivariable modified Poisson regression models (Zou, 2004). The level of statistical significance was set to $p<0.05$. Generalized estimation equations were used to analyze repeated measures (Zou & Donner, 2013). The Bonferroni correction was used to control for type I error in multiple testing in Study II. Serum triglycerides and insulin levels were heavily skewed in Study III and were therefore log-transformed for the analyses; their data are given as geometric means. All multivariable models in all Studies I-III included sex, age, and mother's mental disorders as covariates. The multivariate analysis in Study I also included BMI in childhood and adolescence, birthweight, and non-preterm birth as covariates. Birthweight was categorized as low birthweight (≤2500 g) vs higher in Studies II and III. We added being underweight and the physical activity index to covariates in the multivariate analysis in Study III. The follow-up times (in full years, from the time of the last blood sample to diagnosis) were analyzed with univariate and multivariable Cox regression analyses in Study III using the same covariates as in the modified Poisson regression models above.

Statistical analyses were run using SAS® version 9.4 (SAS Institute, Cary, NC, USA) and IBM® SPSS® Statistics version 23 and 27 (IBM Corp., Armonk, NY, USA).

5 Results

Table 6 summarizes the main results of studies I-III, exploring the relationship between childhood and adolescent risk factors and the risk of schizophrenia or any non-affective psychosis.

Table 6. Summary of results in Studies I-III.

	Childhood and adolescent characteristics	Risk of schizophrenia*	Risk of any non-affective psychosis**
Physical activity (Study I) in 9–18 years of age	Lower physical activity index	↑	↑
	Lower common activity during leisure time	↑	↑
	Lower frequency of leisure-time physical activity	n.s.	n.s.
	Lower intensity of physical activity	↑	n.s.
	Lower frequency of participation in organized training	↑	n.s.
	Non-participation in sports competitions (no vs. yes)	↑↑↑	↑↑
BMI (Study II) in 3 to 18 years of age	Underweight vs. normal weight	↑↑	↑↑
	Overweight vs. normal weight	n.s.	n.s.
Lipid and insulin trajectories (Study III) in 9 to 18 years of age	Lower insulin	n.s.	n.s.
	Lower total cholesterol	n.s.	n.s.
	Lower LDL cholesterol	n.s.	n.s.
	Lower HDL cholesterol	n.s.	n.s.
	Lower triglycerides	n.s.	n.s.

↑ indicates positive correlation, ↑↑ RR (risk ratio) >2, ↑↑↑ and RR>4, n.s. = non-significant, * DSM-IV 295, **DSM-IV 295, 297 or 298

5.1 Study I: Physical inactivity in childhood and adolescence is a risk factor for non-affective psychosis and schizophrenia

Physical activity level was lower among 9 to 18-year-old children and adolescents who later developed non-affective psychosis, **Figure 6**. One-unit lower physical

activity index (PAI) was associated with a 26% higher risk of any non-affective psychosis (relative risk (RR) [95% CI] 1.26 [1.1, 1.5]; p = 0.005) and a 43% higher risk of schizophrenia (RR 1.43 [1.2, 1.7]; p < 0.001) later in life in multivariate analysis. Lower common activity during leisure time (RR 1.71 [1.2, 2.5]; p = 0.008) and non-participation in sports competition (RR 2.58 [1.3, 5.3]; p=0.009) increased the risk of non-affective psychosis when specific physical activity patterns were examined separately. The results were even stronger in the schizophrenia group. Lower common activity during leisure time (RR 1.76 [1.02, 3.0]; p=0.042), lower intensity of physical activity (RR 1.71 [1.1, 2.8]; p=0.030), and lower frequency of participation in organized training (RR 1.40 [1.1, 1.8]; p=0.005) increased the risk for schizophrenia. Non-participation in sports competitions was associated with a nearly 5-fold risk of later development of schizophrenia (RR 4.88 [1.4, 17.0]; p=0.013). PAI in childhood and adolescence did not relate to the risk of other mental disorders (p > 0.05 in all analyses). The physical activity of either parent was not associated with the risk of future psychosis or schizophrenia.

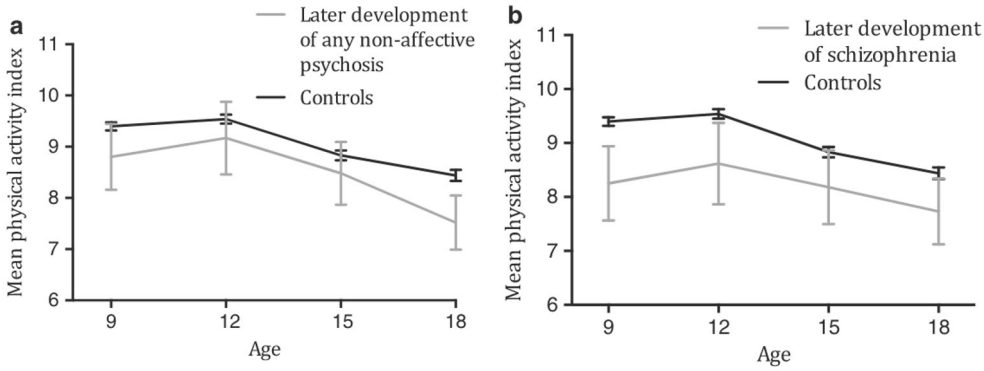


Figure 6. Mean (95% CI) physical activity index (range 5–14) in children and adolescents at age points of 9 to 18 years. Gray line = individuals who later developed any non-affective psychosis (a) schizophrenia (b) and black line = controls with no psychiatric diagnoses during the follow-up. Reprinted from (Sormunen et al., 2017).

5.2 Study II: Being underweight as a child or adolescent predicts later development of non-affective psychosis and schizophrenia

We found that being underweight in childhood or adolescence at ages 3 to 18 years independently predicted the later development of non-affective psychosis, increasing the risk of non-affective psychosis to two-fold (RR 2.3 [1.2, 4.4]; p=0.008) and the risk of schizophrenia nearly 2.5-fold (RR 2.4 [1.03, 5.8], p=0.041) in multivariate analysis. Being overweight in childhood or adolescence did not affect the risk of non-

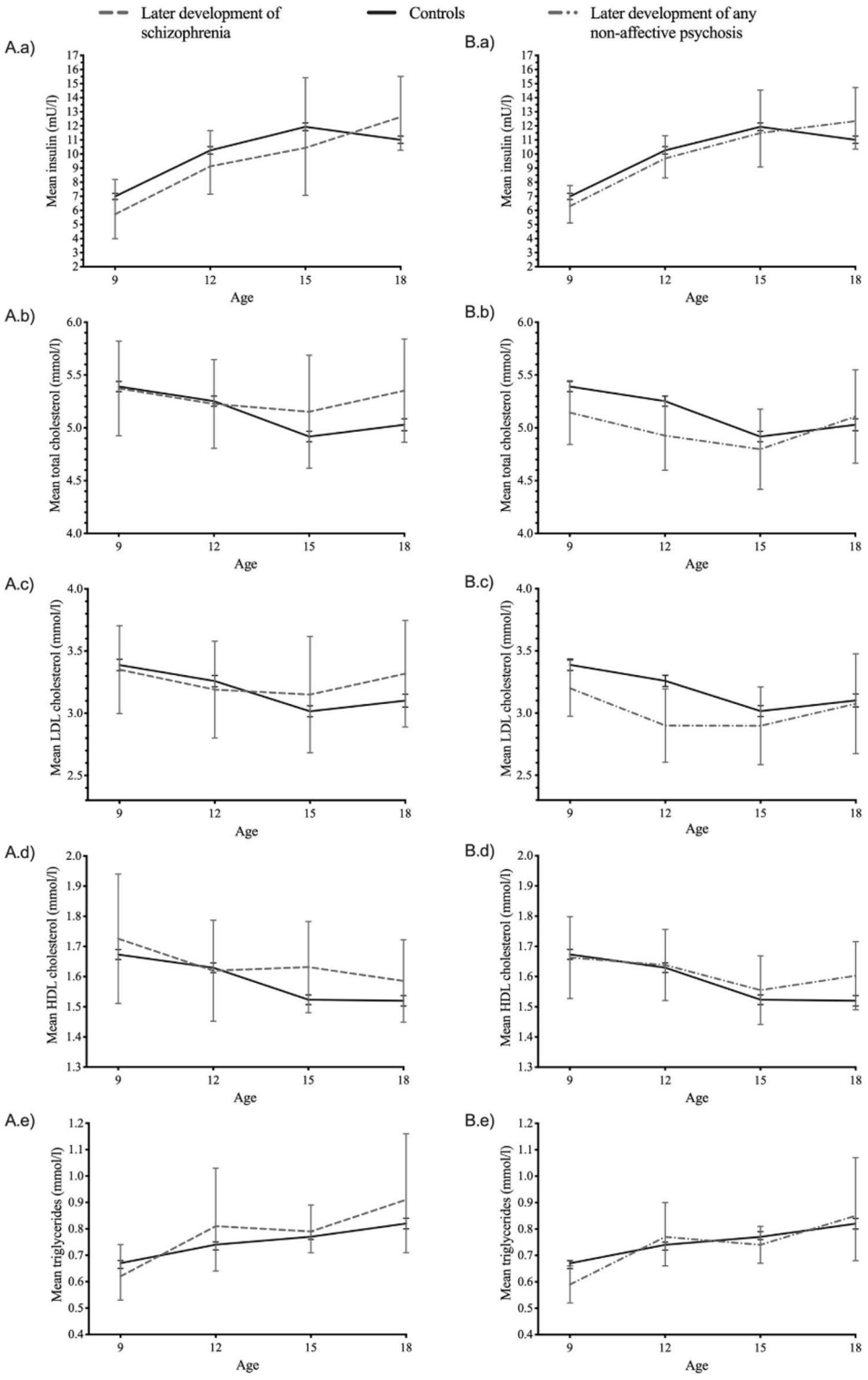
affective psychosis or schizophrenia. Additionally, being underweight or overweight in childhood or adolescence was not significantly associated with later affective disorder, personality disorder, or substance-related disorder ($p>0.05$ in all analyses). However, the results of the last two groups should be interpreted with caution due to the low number of participants at each follow-up time point and the limited number of repeated measurements of the same individual. Low birthweight (<2500 g) was also significantly associated with the risk of non-affective psychosis (RR 2.04 [1.2–3.6]) in univariate analysis, but the association did not remain statistically significant when adjusted for Body Mass Index (BMI) in childhood and adolescence. Low birthweight was not associated with later development of schizophrenia.

5.3 Study III: Metabolic trajectories in childhood and adolescence - effects on risk for schizophrenia

We found no statistically significant differences in this sample in fasting insulin or lipid levels between children and adolescents who later developed schizophrenia, any non-affective psychosis or affective disorder, and controls, **Figure 7**. Interestingly, LDL and total cholesterol seemed to be lower at the age points of 9 and 12 years in children who later developed non-affective psychosis. However, univariate analysis on the entire trajectory from 9 to 18 years of age did not quite reach statistical significance ($p = 0.054$ for LDL cholesterol, $p=0.124$ for total cholesterol). p-values were >0.1 in all analyses after adjusting for confounders in multivariate analysis. The results on total cholesterol, HDL cholesterol, triglycerides, and insulin did not indicate even a trend for association between these parameters and risk for any studied diagnosis.

We found in an additional analysis that a lower triglycerides level in childhood and adolescence predicted earlier psychosis onset, i.e., a shorter lag-time from the last blood sample in this study to diagnosis in the group of the later non-affective psychosis (hazard ratio [95% CI] 2.2 [1.01–5.1], $p = 0.047$)). Other lipid or insulin levels were not associated with the onset time of non-affective psychosis or schizophrenia.

Figure 7. ► Childhood and adolescence lipid and insulin levels in participants who later developed schizophrenia, any non-affective psychosis, and controls. Mean (95% CI) fasting plasma insulin*, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides* levels in children and adolescents (9–18 years of age) who later developed A schizophrenia (DSM-IV 295) or B any non-affective psychosis (DSM-IV 295, 297 and 298) and controls. Gray dashed line = individuals who later developed schizophrenia, gray dash-dotted line = individuals who later developed any non-affective psychosis and black solid line = controls with no psychiatric diagnoses during the follow-up 1980–2018. *geometric means. Reprinted from (Sormunen et al., 2022).


Later development of schizophrenia
Controls
Later development of any non-affective psychosis
A.a)
B.a)
Mean insulin (mU/l)
A.b)
B.b)
Mean total cholesterol (mmol/l)
A.c)
B.c)
Mean LDL cholesterol (mmol/l)
A.d)
B.d)
Mean HDL cholesterol (mmol/l)
A.e)
B.e)
Mean triglycerides (mmol/l)
Age

6 Discussion

6.1 Main findings

The unique setting of the Cardiovascular Risk in Young Finns (YFS) cohort enabled us to examine for the first time the longitudinal trajectories of physical activity and metabolic health indicators through childhood and adolescence, before and after puberty, and their effect on the risk of non-affective psychosis and schizophrenia. We found in Study I that physical inactivity in childhood and adolescence independently predicts the development of non-affective psychosis and schizophrenia. Furthermore, the less an individual engaged in physical activities, the greater the risk of later non-affective psychosis. As separate patterns of physical activity, a low level of common activity during leisure time and non-participation in sports competitions were risk factors for non-affective psychosis and schizophrenia, while a low intensity of leisure-time activity and a low frequency of participation in organized training were risk factors particularly for schizophrenia.

We showed in Study II that being underweight in childhood and adolescence independently increases the risk of schizophrenia and other non-affective psychoses over two-fold. Low physical activity and underweight in childhood and adolescence seemed to relate specifically to non-affective psychoses, because we found no association between these risk factors and the risk of other psychiatric disorders.

We found, somewhat surprisingly, no significant differences in insulin or lipid levels between children and adolescents who later developed schizophrenia, any non-affective psychosis or affective disorder, and controls. However, lower triglyceride levels during 9 to 18 years of age seemed to be associated with an earlier onset of psychosis.

6.2 Comparison to earlier studies

6.2.1 Study I

No previous studies have examined the association between physical activity in childhood and adolescence and the long-term risk of psychosis. However, three previous studies have shown physical inactivity in adolescents (aged 15 to 17 years)

who later developed psychosis or schizophrenia compared to controls (Davidson et al., 1999; Koivukangas, 2016; Okkenhaug et al., 2016). Our results in Study I are in line with these studies. The novel finding of Study I was that lower physical activity in future schizophrenia/non-affective psychosis patients is already evident in childhood and persists throughout puberty and adolescence. This is interesting, because puberty is one of the critical periods in the development of non-affective psychoses. The results remained unchanged when Body Mass Index (BMI) as a continuous variable or, in sensitivity analysis, BMI categorized to underweight or overweight, was added to multivariate analysis as a covariate. Neither the mother's mental disorders nor the parents' physical activity explained the results. This supports the idea that premorbid physical inactivity is an independent risk factor for non-affective psychosis, irrespective of BMI or genetic risk.

We know from earlier studies that children who later develop schizophrenia have poorer motor coordination (Rosso et al., 2000; Schiffman et al., 2009) and delayed motor development (Filatova, 2017; Jones et al., 1994) compared to their peers. Limited improvement in motor skills is one of the main reasons for non-participation in physical activities among children (Gould & Weiss, 1987). Therefore, it seems plausible that children and adolescents who later develop psychosis participate less in physical activities. Furthermore, poor performance in sports for these children is likely to affect their willingness to participate in competitive sports events. Non-participation in sports competitions was associated with a nearly 5-fold risk of schizophrenia in Study I. However, the causes of reduced physical activity in the premorbid phase of schizophrenia are multifactorial and not yet fully understood. They likely involve a complex combination of abnormal motor development, motivational and reward deficits, subtle affective problems, and difficulties in social interaction, all of which contribute to a diminished interest in physical activities, especially those that require social skills. Additionally, a low household income is associated with schizophrenia (Suokas et al., 2020), which likely affects the family's financial ability to support the child's participation in physical activities.

6.2.2 Study II

The Study II results support the previous studies that have reported the relationship between low BMI in childhood (Sørensen et al., 2016; Wahlbeck et al., 2001) or adolescence/early adulthood (Gunnell et al., 2005; Sørensen et al., 2006; Weiser et al., 2004; Zammit et al., 2007) and later development of schizophrenia or non-affective psychosis. As mentioned before in the chapter on risk factors, some contradictory results have also been published (Gunnell et al., 2003; Jones et al., 1994; Koponen et al., 2008; Perry, Stochl, et al., 2021; Wyatt et al., 2003). Many

earlier studies examining the effect of BMI on psychosis risk are military cohorts or otherwise include only men. The follow-up time for psychiatric outcomes in previous studies is also rather short. Our study adds the trajectory of BMI from the age of 3 to 18 in both boys and girls, and the follow-up for psychiatric diagnoses up to the participants' age of 37–52 years, compared to the previous studies.

Low birthweight is relatively well-studied risk factor for schizophrenia (Abel et al., 2010; Sørensen et al., 2016; Wahlbeck et al., 2001). However, in Study II, low birthweight (<2500 g) was not significantly associated with the risk of non-affective psychosis, when adjusted for Body Mass Index (BMI) in childhood and adolescence. Low birthweight is constantly shown to associate with low BMI in childhood (Chen et al., 2019) and therefore, adjusting for BMI may introduce an overadjustment bias. Overadjustment bias occurs when you control for variables that lie on the causal pathway between the exposure and the outcome.

A wide range of psychiatric disorders has a partly common pathophysiology based on studies examining, for instance, a common family history (Mortensen et al., 2010) and genetic susceptibility (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013) for psychiatric disorder, including schizophrenia. Low birthweight is also related to both schizophrenia (Abel et al., 2010; Sørensen et al., 2016; Wahlbeck et al., 2001) and depression (Gale & Martyn, 2004). Very few previous studies were found concerning underweight in childhood or adolescence and the risk of mental disorders other than psychosis. Being underweight in childhood or adolescence was not related to the risk of other mental disorders in our study but seemed to be specific to non-affective psychoses. Some studies suggest that being overweight in childhood or adolescence predicts later depression (Herva et al., 2006; Sanderson et al., 2011), at least in women (Anderson et al., 2007). However, being overweight did not predict any studied psychiatric disorder in our sample.

6.2.3 Study III

The results of Study III are in line with the earlier Finnish cohort study by Koponen et al. (Koponen et al., 2008). Koponen et al. found no significant differences in insulin resistance or lipid levels between 21 adolescents (aged 15 to 16 years) who later developed psychosis and the controls, although the follow-up time for psychiatric diagnoses was only with participants up to age 20. As a comparison, the number of children and adolescents with later psychosis in our study was 66, metabolic parameters were followed longitudinally with participants aged 9 to 18 years old, and the follow-up for psychiatric diagnoses were up to age 41 even for the youngest participants. In Study III, no significant association was found between lipid or insulin levels of children and adolescents and their future risk of non-

affective psychosis or schizophrenia. A recent study by Perry et al. reported persistently high fasting insulin levels in 9 to 24-year-old children and adolescents with a psychosis at-risk mental state, psychotic disorder, and negative symptoms, assessed by an interview at age 24 (Perry, Stochl, et al., 2021). However, the comparison is complex due to the differences in the study designs. For instance, Perry et al. used psychiatric outcomes assessed by a semi-structured, psychosis-like experiences interview, whereas our study used formal ICD diagnoses in psychiatry services. Additionally, by only following up with participants to age 24 means missing those patients with a later onset of psychosis. A subtype of psychosis with early aberrant insulin levels is certainly possible, although this was undetected with our study design.

A lower trend of total and LDL cholesterol in 9- and 12-year-old children who were later diagnosed with a non-affective psychosis in our study, even though not statistically significant, would be in line with the results of meta-analyses examining lipids in first-episode psychosis (Misiak et al., 2017; Pillinger, Beck, Stubbs, et al., 2017). Furthermore, in a more fine-grained analysis, Madrid-Gambin et al. reported altered lipidome and proteome at the age of 12 in children who report psychotic experiences at age 18 (Madrid-Gambin et al., 2019). Several lipids (lysophosphatidlycholines, phosphatidlycholines and sphingomyelin) are also shown to be elevated in 11-year-old children with a later psychosis but no longer at age 18 (O'Gorman et al., 2017). The difference in total- and LDL-cholesterol levels between the non-affective psychosis group and controls in our study were also more evident at the same age period but seemed to disappear by age 18. These results suggest ongoing alterations in the metabolic indicators and pathophysiological processes from prodrome to the onset of psychosis. Furthermore, there may be a critical developmental window in prepuberty/puberty relevant for later metabolic disturbances and possibly for a trajectory resulting in psychosis. In addition, only gross-level metabolic disturbances were captured in our study design, and thus, more fine-grained changes in lipid or glucose metabolism as a part of non-affective psychosis trajectory are possible (Madrid-Gambin et al., 2019; O'Gorman et al., 2017).

Additional analyses of lower triglycerides levels at 9 to 18 years of age predicted earlier onset of non-affective psychosis. These results must be cautiously interpreted because of the possible effect of a relatively large number of covariates fitted in the data on a relatively small number of participants in the psychosis group (Fusar-Poli et al., 2018). However, results are in concordance with a previous study suggesting that a dysregulated lipid metabolism predates the onset of psychosis and could, hypothetically, be used to predict which clinically high-risk individuals are most likely to develop psychosis (Dickens et al., 2021).

6.2.4 Summary of risk factors and protective factors of non-affective psychosis

The vulnerability to non-affective psychosis is determined by a combination of genetic and environmental risk factors, together with protective factors (Wahlberg et al., 1997; Zubin & Spring, 1977), **Figure 2**. The risk factors for schizophrenia are actively studied, although the pathophysiology is not clear. The protective factors for schizophrenia are also far less known. **Figure 8** summarizes our results with other risk factors and protective factors previously studied. Some of the risk and protective factors are impossible or hard to avoid, such as genetic risk or winter/spring birth, while others can be modified. Those risk factors and protective factors that can be modified provide interesting and much-needed targets for primary and secondary prevention of schizophrenia. For example, physical activity recommendations for children and adolescents might hypothetically, along with many other benefits, act as the primary prevention for psychosis, aiming to reduce the incidence of schizophrenia in the population. The secondary prevention for schizophrenia aims to reduce the progression of the disease and the onset of first-episode psychosis through early detection and interventions.

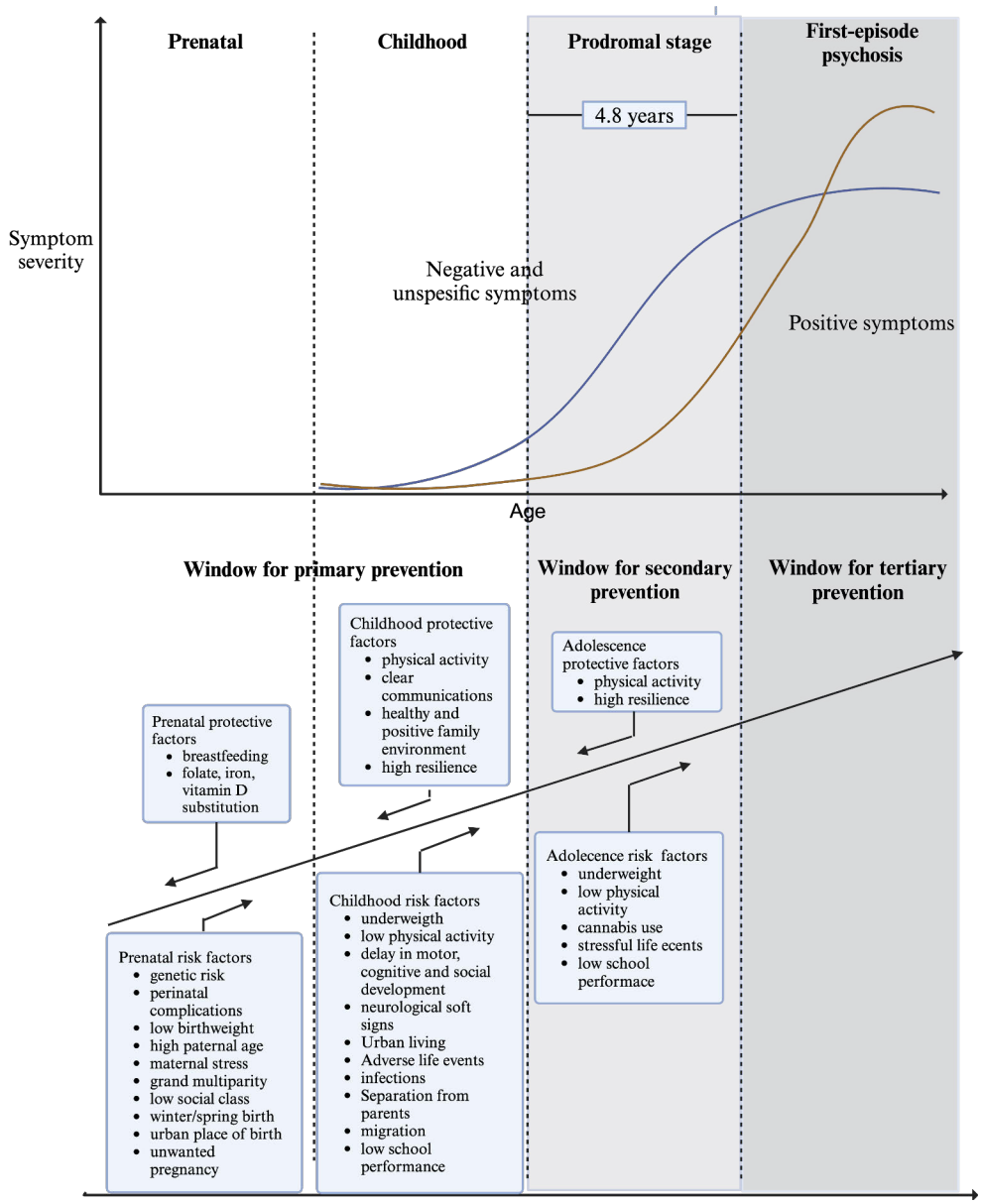


Figure 8. Summary of potential risk factors and protective factors in different phases of schizophrenia spectrum disorders. Modified from (Hafner et al., 2004; Keskinen, 2015; McCutcheon et al., 2020), created in BioRender. Sormunen, E. (2025).

6.3 Hypothesis of the relationship between metabolic dysregulation and psychosis risk

Our results together with earlier studies show that non-affective psychoses are related to multiple non-CNS abnormalities, such as deviation of BMI or physical inactivity in childhood and adolescence before the onset of psychosis or even prodromal symptoms. Previous studies have also shown disturbances in lipid and glucose metabolism in patients with schizophrenia, irrespective of antipsychotic medication and at least partly occurring before the first psychotic episode, although this was not evident in our study design in children and adolescents with later non-affective psychosis. However, the relationships' causality and mechanisms are still mainly unknown. Several hypotheses have been proposed, but none of them fully explain the pathophysiology of psychosis or the relationship between metabolic disturbances and psychosis development. It seems evident that the mechanisms are multifactorial.

6.3.1 Inflammation

Inflammation has been consistently shown to be associated with schizophrenia and cardiometabolic disorders and thus could explain the relationship between metabolic disturbances and psychosis. Meta-analyses have shown high levels of pro-inflammatory cytokines in patients with multi-episode schizophrenia (Müller et al., 2015) and also in medication-naïve patients with first-episode psychosis (Upthegrove et al., 2014). Inflammatory cytokines influence neurotransmitters like dopamine and glutamate (Müller et al., 2015), systems among the leading hypotheses of pathoetiology of schizophrenia (O. Howes et al., 2015). Positron emission tomography (PET) studies have shown lower availability of the translocator protein (TSPO) in patients with first-episode psychosis and schizophrenia compared to healthy controls (Plavén-Sigray et al., 2018), suggesting altered function or reduced density of immune and glial cells, and supporting the hypothesis that inflammation may have a role in the pathophysiology of psychosis.

Inflammation relates to insulin resistance, obesity, and diabetes (Dandona, 2004) as well as to overall cardiovascular risk (Danesh, 2000). Inflammation could even, hypothetically, explain the altered lipid metabolism, i.e., reduced total and LDL cholesterol in first-episode psychosis patients (Misiak et al., 2017; Pillinger, Beck, Stubbs, et al., 2017), via the mechanism called “lipid paradox” known from rheumatoid arthritis. The pro-inflammatory state in active, untreated rheumatoid arthritis, similar to first-episode psychosis patients, is associated with decreased total and LDL cholesterol levels (Myasoedova et al., 2010).

A Mendelian randomization study tried to clarify the causality of the relationships between inflammation, schizophrenia, and cardiovascular disorders,

including insulin resistance (Perry, Burgess, et al., 2021). They found a relationship of an inflammation-related insulin resistance phenotype with schizophrenia, suggesting that inflammation is, at least partly, the mechanism behind the comorbidity of schizophrenia and insulin resistance. They also found no evidence in support of cardiovascular disorders causing schizophrenia or vice versa.

An interesting link to Study 1 is that physical activity has an anti-inflammatory effect, and it even modulates neuroinflammation of the brain (Augusto-Oliveira et al., 2023). The anti-inflammatory effect is thought to partly explain why regular exercise reduces the risk of metabolic and cardiorespiratory diseases (Gleeson et al., 2011). A study with 25 patients with first-episode schizophrenia reported that the more a participant engaged in aerobic exercise sessions in a 6-month period, the more the pro-inflammatory interleukin 6 (IL-6) levels were reduced. Furthermore, decreases in IL-6 levels were related to decreases in depressive symptoms (Ventura et al., 2021). Among many other benefits, exercise may be a promising intervention to reduce brain inflammation in patients with schizophrenia.

6.3.2 Common risk factors

One explanation for the comorbidity of schizophrenia and metabolic alterations is an effect of a common risk factor that results in separate developments of psychosis and non-CNS dysfunction. Some studies have suggested a shared genetic background of schizophrenia and cardiovascular risk factors (Hackinger et al., 2018; Maj et al., 2020). However, a recent meta-analysis did not support this hypothesis, because they found no association between familiar liability to psychosis and altered fasting parameters of glucose homeostasis in unaffected first-degree relatives of schizophrenia patients (Misiak et al., 2020). Our findings, along with the consistently observed metabolic dysregulation in neuroleptic-naive patients experiencing their first episode of non-affective psychosis, indicate that changes in glucose tolerance and lipid metabolism likely begin around the time of the first episode.

Many prenatal and perinatal risk factors also increase the risk of both CNS and non-CNS disorders and could contribute to the development of both schizophrenia and metabolic disorders. For example, low birthweight and preterm birth are risk factors for both schizophrenia (Abel et al., 2010; Dalman et al., 1999; Davies et al., 2020; Sørensen et al., 2016; Wahlbeck et al., 2001) and type 2 diabetes (Kajantie et al., 2010).

6.3.2.1 Insulin-like growth factor 1

Low levels of Insulin-like growth factor 1 (IGF-1) may represent a possible unifying factor that could contribute to the risk of schizophrenia, underweight during

childhood and adolescence, and metabolic dysregulation. IGF-1 is a hormone mainly produced in the liver in response to stimulation by growth hormone. It is essential for tissue growth and development, especially in childhood and adolescence, but it continues to have anabolic effects later in life (Aleman & Torres-Alemán, 2009). IGF-1 modulates the brain development, maturation, and cellular plasticity (Dyer et al., 2016) in the CNS as well as cognitive functioning (Aleman & Torres-Alemán, 2009).

Low levels of IGF-1 are found to be associated with low birthweight (Ong et al., 2000), low BMI, and short stature in childhood (Juul et al., 1994), the risk factors that are also associated with the risk of schizophrenia (Abel et al., 2010; Wahlbeck et al., 2001; Zammit et al., 2007). IGF-1 also modulates glucose and lipid metabolism and is even proposed as a key hormone in the pathophysiology of metabolic syndrome (Aguirre et al., 2016).

The "IGF-1 deficiency hypothesis" of schizophrenia pathogenesis suggests that low levels of IGF-1 may increase susceptibility to schizophrenia (Gunnell & Holly, 2004). A recent meta-analysis showed that schizophrenia patients with antipsychotic treatment seemed to have lower IGF-levels compared to healthy controls. However, no significant difference was found between antipsychotic naïve patients with schizophrenia compared to controls in the same meta-analysis (Pejcic et al., 2023), although additional studies are needed to confirm these results and to learn if IGF-1 could play a role in the pathophysiology of psychosis. If so, it could be, again, one mechanism behind the benefits of physical activity on reducing the risk of schizophrenia. IGF-1 levels increase by exercise, resulting in cognitive functioning improvements such as better attention, learning, and memory (Augusto-Oliveira et al., 2023).

6.3.3 Stress

Psychosis is, without a doubt, a shattering and stressful event in an individual's life. In fact, elevated stress levels are linked to the development of psychosis, even in individuals at risk for psychosis and in the prodromal phase, resulting in hypothalamic-pituitary-adrenal (HPA) axis activation and increased cortisol levels (Holtzman et al., 2013). Excess cortisol is associated with hyperinsulinemia, hyperglycemia, insulin resistance, dyslipidemia, and overall cardiovascular risk (Whitworth et al., 2005). Therefore, psychosis may contribute to metabolic alterations through hypercortisolemia. Our findings in Study III together with the consistently observed metabolic dysregulation in patients with first-episode psychosis suggest that the onset of changes in glucose and lipid metabolism occur around the first episode and therefore are in line with this hypothesis. However, the relationship is likely more complicated, because stress may also be partly causing

the development of psychosis (O. D. Howes & Murray, 2014). Again, aerobic exercise has benefits targeting psychosis risk and metabolic dysregulation in many ways, because it improves resilience to stress (Salmon, 2001), a mechanism that could partly explain the preventive effect of exercise towards psychiatric and cardiovascular disorders.

6.4 Exercise interventions

6.4.1 Exercise in the prevention of psychosis

Advances in the prevention of psychosis are much needed in clinical practice. It has been suggested that early interventions should be largely targeted to the key neurobiological processes or risk factors associated with the development of psychosis, rather than symptoms of psychosis (Fusar-Poli et al., 2020). Many of the risk factors identified so far are difficult or even impossible to modify through early clinical interventions. Some of those can be affected by political decisions aiming for the better mental health of the population generally and, therefore, also the primary prevention of schizophrenia. However, the evidence is largely lacking on the potential effectiveness of those actions in the prevention of psychosis.

The benefits of exercise have been indisputably demonstrated for both healthy individuals and patients with schizophrenia, although there is limited knowledge about the potential of exercise interventions to prevent psychosis. A recent clinical trial studied the effects of an exercise intervention of a high-intensity interval exercise protocol twice a week over three months for individuals at clinical high risk for psychosis. They found improvement in fitness and cognitive performance as well as reduced positive symptoms due to the exercise intervention compared to the individuals on the waitlist (Damme et al., 2022). Furthermore, aerobic exercise was associated with increased hippocampal-occipital functional connectivity and stable hippocampal volumes, while individuals not participating in the exercise intervention showed decreased hippocampal volumes (Damme et al., 2022). A preclinical study on schizophrenia model mice also showed that low-intensity exercise training during adolescence prevented abnormal behaviors and improved neurodevelopmental abnormalities, such as increased dopamine turnover (Koizumi et al., 2021). The results, although not directly applicable to humans, suggest that exercise could indeed have a preventive effect against schizophrenia.

6.4.1.1 Timing of the early intervention – windows for opportunity

Brain development in humans is not a linear but rather a stagewise phenomenon. Rapid phases of brain development occur after infancy during the years 2–4, 6–8,

10–12, and 14–16. (Epstein, 2001). Brain development is largely modified by the environment's stimulation, but the effect of a stimulus is not equally effective in every development phase. Some evidence shows that educational interventions lead to much better cognitive results if timed to the earlier rapid brain growth period (Campbell & Ramey, 1995). A critical period of brain development was first described in the 1960s by Wiesel and Hubel, who found that visual deprivation during a certain time window, a critical period, led to an alteration in visual cortex networks (Wiesel & Hubel, 1963). Afterward, a critical period has been found, for an example, for synaptic plasticity or even some higher cognitive functions and behaviors (Hensch, 2004). In addition to critical periods, brain development includes sensitive periods, defined as the time window(s) during which the effect of experience on brain development is unusually profound and can strongly modulate the neural circuits (Ismail et al., 2017). Neural circuits have a high potential during a sensitive period to change based on stimulus, but this capacity decreases after the period. For instance, the effects of exercise on cognition are found to be most prominent in children and elderly people (Stillman et al., 2020). These findings about sensitive and critical periods of brain development suggest that the right timing of interventions might be crucially important.

6.4.2 Exercise interventions and other mental disorders

6.4.2.1 Exercise interventions as a treatment for depression and anxiety disorders

Physical activity as a treatment of depression is relatively well-studied, and the results have been impressive. A recent large meta-analysis by Noetel et al. showed that the effect sizes of exercise as a treatment of major depressive disorder is comparable with cognitive behavioral therapy, although the confidence in the evidence for exercise is less strong (Noetel et al., 2024). They also suggest that some forms of exercise, for instance, walking or jogging, yoga, and strength training even have a stronger effect on depression than selective serotonin reuptake inhibitors (SSRIs), the most common antidepressants. Additionally, physical activity seems to increase the SSRIs' effect when used as an adjuvant treatment (Noetel et al., 2024). However, another meta-analysis by Krogh et al found no antidepressant effects of exercise in patients with major depression after excluding trials that appeared to have a high risk of bias (Krogh et al., 2017). Physical activity has also been proposed as an additional treatment option for anxiety disorder (Kandola et al., 2018). The effects of exercise on depression are unlikely to be explained by a single mechanism. Instead, they may result from a combination of factors, including social interaction, mindfulness or experiential acceptance, increased self-efficacy, immersion in green

spaces, neurobiological mechanisms, and acute positive effects (Noetel et al., 2024). The same likely applies to other mental disorders as well.

6.4.2.2 Exercise interventions in the prevention of depression and anxiety disorders

The results of the effect of physical activity on depression risk are more congruent, when compared to the results of physical activity and the risk of psychosis. Meta-analyses have shown that higher physical activity reduces the risk not only of later depression for people of all ages (Schuch et al., 2018) but also of anxiety symptoms and disorders (McDowell et al., 2019; Schuch et al., 2019). Two Mendelian randomization studies have supported the hypothesis that physical activity has a causal protective effect against depression (Choi et al., 2019, 2020) and could offset the risk of depression even in people at higher genetic risk (Choi et al., 2020). A recent meta-analysis confirmed the finding by showing an inverse dose-response relationship between physical activity and the risk of depression; even physical activity levels below the public health recommendations decrease the risk of depression (M. Pearce et al., 2022). The mental health benefits of physical activity in adolescents and young adults appear to extend even to reductions in psychiatric hospitalizations (Fahim et al., 2024). The World Health Organization's (WHO) latest guidelines reported that psychiatric symptoms, especially depression and anxiety, are included among the conditions that can be prevented by physical activity in childhood and adolescence (Bull et al., 2020).

6.4.2.3 Exercise as primary prevention of mental disorders?

Regular exercise has wide and irrefutable benefits for the health and well-being of an individual without a doubt. It has also been suggested that the mental health burden could be reduced by increasing the level of physical activity in populations (Schuch & Vancampfort, 2021). In fact, the WHO recommends physical activity for everybody, for all ages and regardless of disabilities and chronic conditions (Bull et al., 2020). The importance of physical activity, especially for children and adolescents, has been recognized in Finland, and the concern about extended and excessive sedentary activity of many children and adolescents has risen. According to the recommendation of the Ministry of Education and Culture along with the UKK Institute, all children and adolescents aged 7 to 17 years should be physically active for at least 60 minutes a day, in a versatile, brisk, and strenuous manner (Working group for the recommendation on physical activity for children and adolescents, 2021). In 2022, only one in three children and adolescents aged 7 to 15 in Finland met these recommendations, showing a decline compared to 2018. (Kokko et al.,

2023). The proportion decreases with age, and girls engage in physical activity less than boys in all age groups (Kokko et al., 2023). Therefore, much work remains to be done to address the population's mental health crisis through physical activity.

6.5 Strengths and limitations

Strengths

The data in these studies are based on a randomly selected population cohort, the Cardiovascular Risk in Young Finns (YFS), with a longitudinal and observational study design. The follow-ups with clinical examinations, laboratory samples, and comprehensive questionnaires were made every third year from early childhood to young adulthood (at ages 3, 6, 9, 12, 15, and 18 years). This allowed us to study several risk factors longitudinally, years before evidence of any psychotic disorder and years before and after puberty. The number of participants lost to follow-up in YFS has been exceptionally low. For example, in the last follow-up used in our studies in 1986, 2,737 subjects (77%) were still actively participating.

Psychiatric diagnoses were obtained from the Care Register for Health Care (CRCH), one of the oldest individual-level hospital discharge registers in the world, covering all public and private hospitals in the whole country (Sund, 2012). The diagnostic validity of schizophrenia (Pihlajamaa et al., 2008) and non-affective psychosis (Holm et al., 2024) in CRCH has been found to be good, especially when excluding diagnoses made for children under 7 years old, dementia diagnosis and preliminary diagnoses during psychiatric hospitalization that were not confirmed by discharge diagnosis (Holm et al., 2024). The follow-up for psychiatric diagnoses in Studies I-III was up to the participants' ages of 35–50 in Study I and even up to the ages of 41–55 in Study III, broadly covering the regular age periods of the onset of psychosis. It is also likely that some patients in the group of other non-affective psychosis actually have schizophrenia.

The large amount of data in YFS allowed us to include several potential covariates in the analyses. As the purpose of this thesis was to study the risk factors before the illness, we excluded the participants who had a psychiatric diagnosis in CRCH before the age of 19 to prevent their possible effect on the analysis. In Study III, we also excluded participants diagnosed with diabetes before the age of 19.

Limitations

A full-scale follow-up of one participant was possible for only 6 years because of the study design. Therefore, none of that subject's data covers all follow-up points from 9 to 18 years of age in Studies I and III and from 3 to 18 years in Study II,

which limits detailed analyses of the individual's physical activity, BMI, or metabolic trajectories throughout the study period. However, the number of participants is relatively high at each time point, and we have no reason to assume significant differences between the age cohorts.

Despite the diagnostic validity of schizophrenia-spectrum disorders in the hospital discharge register being found to be good (Pihlajamaa et al., 2008), the reliability of other diagnoses is less studied (Sund, 2012). Only diagnoses related to hospital treatment were used. Most individuals with psychosis require hospital care at some point and are therefore included in this work. However, it is clear that patients who need hospital treatment in the diagnostic groups other than psychosis represent more severe forms of these disorders. Furthermore, we were unable to exclude the participants with a psychiatric diagnosis given only in outpatient clinics before the age of 19, which is a limitation mostly in other diagnostic groups than psychosis. The number of participants in our studies who will develop non-affective psychosis, and especially schizophrenia, is relatively low. Our triglycerides finding in Study III should especially be interpreted with caution, because it may be affected by the relatively large number of covariates fitted in the data on a relatively small number of participants in the psychosis group (n=66). The number of participants with relevant data available in the groups of personality disorders and substance-related disorders in each age point is also low; therefore, those groups were excluded from the analysis in Study III. However, the longitudinal design from early childhood and low drop-out percentage still makes this sample valuable.

The physical activity of 9 to 18-year-old children and adolescents was assessed using a self-report questionnaire given alongside the clinical examination. Self-report questionnaires, especially when assessed retrospectively, may be limited by their lack of validity and reliability (Shephard, 2003). However, the physical activity questionnaire was validated in previous studies with independent populations. These studies show significant positive correlations between the physical activity questionnaire or relevant components of the Physical Activity Index (PAI) (i.e., intensity or frequency) and the volume of movement assessed with accelerometers and the number of steps measured with pedometers (Mansikkaniemi et al., 2012), and physical fitness measured by the bicycle ergometer test (Telama et al., 2005).

As in any cohort study, due to a study design and the number of subjects with non-affective psychosis, it was not possible to examine all known risk factors for non-affective psychosis or include all potential covariates in the analysis. For example, we were unable to include the stage of puberty in the analysis due to the low number of participants with later non-affective psychosis in each pubertal stage. Therefore, it is possible that the results may be explained by a factor we are unaware of.

7 Conclusions

7.1 Main conclusions

- A low level of physical activity in childhood and adolescence is an independent risk factor for later development of non-affective psychosis and especially for schizophrenia. Physical activity level does not seem to relate to the risk of other psychiatric disorders. The results provide a rationale for further studies addressing the effects of exercise interventions in the prevention of psychosis.
- Being underweight in childhood and adolescence is an independent risk factor for later non-affective psychosis but not for affective disorders. Being overweight in childhood and adolescence does not affect the risk of non-affective psychosis or affective disorders.
- Cholesterol, triglycerides, and insulin levels do not differ in group level of children and adolescents with later development of schizophrenia, any non-affective psychosis, or affective disorder compared to healthy controls. These results have relevance not only for the etiologic research of psychoses but also for the risk of later metabolic problems in this patient group.
- Lower triglyceride levels in childhood and adolescence may be associated with psychosis onset.
- The results support the hypothesis that non-affective psychoses are not only brain disorders but also systemic disorders.

7.2 Clinical and future implications

- It is well documented that schizophrenia is associated with low physical activity and underweight in childhood and adolescence, as well as with metabolic dysfunction around the onset of psychosis. Further studies are

essential to understand the causal and pathophysiological mechanisms of these relationships and to achieve advances in the treatment and prevention of psychosis and its somatic comorbidities.

- It is reasonable to assume that the level of physical activity also contributes to the development of psychosis, even though low physical activity may partly be a consequence of abnormal motor development and social withdrawal of children and adolescents with future schizophrenia. Regardless of the causes of lower physical activity levels in the premorbid phases of non-affective psychoses, our results in Study I provide a putative rationale for including exercise in early intervention programs for psychosis. Implementing exercise during the early stages of illness also seems to offer an optimal timeframe not only to delay or prevent the onset of psychosis but also to provide young people with a self-management strategy for improving their psychological well-being, increasing cognitive functioning, and protecting their physical health (Firth et al., 2020). Exercise interventions in childhood and adolescence may also reduce the risk of cardiovascular morbidity and mortality in patients who develop schizophrenia. However, further studies are crucially needed to assess the precise role and possibilities of early exercise and physical activity intervention as a part of psychosis prevention.
- Further studies are needed to gather information about specific types of exercise, as well as the frequency and intensity of exercise that have the greatest effect on psychosis risk, in order to provide clinicians with the most optimal and cost-effective methods for increasing physical activity in individuals with clinical high risk for psychosis.
- Exercising has very few if any relevant side effects. However, implementing exercise interventions in individuals at clinical high risk for psychosis may be a challenge, because they tend to perceive even more barriers to engaging in physical activity, compared to healthy controls (Newberry et al., 2018). Therefore, actions aiming to increase motivation, such as using motivational interviews, providing supervised exercise opportunities, or offering obtainable goals or fitness trackers, need to be carefully considered when implementing physical activity in psychosis prevention programs.
- An intriguing hypothesis is that physical activity could be used as the primary prevention of psychosis and other mental disorders in the population. The evidence of the potential effectiveness of physical activity of children and adolescents at the population level in reducing psychosis incidence is missing and in need of further research. However, wide

benefits of physical activity to individuals' physical and mental health support policy actions and health recommendations aiming to increase the level of physical activity of all children and adolescents.

- One hypothesis that requires testing is whether metabolic assessments – including lipid and glucose levels, Body Mass Index (BMI), and physical activity during childhood and adolescence – can predict future cardiovascular risk in patients with schizophrenia.
- Our finding in Study III of lower triglycerides levels in 9 to 18-year-old children predicting shorter time to onset of psychosis is interesting but should be replicated in further studies. However, we hypothesize that patients with late-onset psychosis may have fewer metabolic alterations in childhood and adolescence or early metabolic abnormalities may relate to a specific type of non-affective psychosis with a relatively early onset of the first psychotic episode.
- Previous studies suggest that changes in lipid levels may occur around the onset of psychosis. Further studies are needed to discover if changes in metabolic profile could be used to identify those individuals with a high clinical risk for psychosis who will develop the disease. That said, further studies are needed on the more fine-grained lipid changes with possible etiological and clinical significance.

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