ADIPOSE TISSUE DYSREGULATION AND SOCIAL DETERMINANTS OF HEALTH AT THE ORIGIN OF A METABOLIC DIATHESIS IN PSYCHOTIC DISORDERS

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ABSTRACT

Introduction

Cardiovascular disease (CVD) is the main contributor to the excessive and premature mortality observed in psychosis spectrum disorders (PSD). This phenomenon has been hypothesized to stem from noxious lifestyle factors, and from the side effects of antipsychotic medications which contribute to the development of metabolic disorders such as diabetes mellitus, and in turn to CVD. However, high rates of diabetes in schizophrenia had already been documented long before the introduction of the first antipsychotics. Furthermore, recent studies have documented clinical anomalies of metabolism already at the first episode of psychosis. At this stage, exposure to antipsychotics is minimal, and unhealthy lifestyles have not lasted enough to result in metabolic dysregulation. Thus, other factors acting early in life might be fostering these metabolic disturbances. The search for genetic polymorphisms explaining this association has not been fruitful. In contrast, social determinants of health (i.e., childhood trauma, ethnic minority background, migrant status, social and material deprivation), which are highly prevalent in PSD, and promote metabolic disease, CVD, and PSD, have not been examined as potential etiological factors. The goal of this project is to determine the presence of metabolic disturbances in first-episode psychosis (FEP), and examine the role of social determinants of health in this association. It is hypothesized that social determinants of health would promote metabolic anomalies in FEP. Furthermore, given the central role of the adipose organ in the pathophysiology of metabolic disorders and CVD, it is hypothesized that adipose tissue dysregulation would be already present in FEP.

Methods

Three different studies were conducted to examine the presence of metabolic alterations in FEP: glycemic control (Glycated hemoglobin), lipid levels (Total cholesterol, LDL, HDL, triglycerides), and adipose tissue dysregulation (Adipokines: leptin, adiponectin, resistin, chemerin). Data was analyzed with linear regression models controlling for covariates.

Results

Glycated hemoglobin was increased in FEP patients with a minority background and a history of childhood physical abuse. Total cholesterol and HDL were reduced in FEP patients with affective psychosis who live in environments with high levels of social deprivation. All tested adipokines had significantly different levels in FEP patients when compared to controls. Childhood physical abuse was associated with increased resistin, and belonging to a visible minority group with reduced chemerin. Ancillary analyses indicated a paradoxical effect of tobacco smoking on leptin in FEP patients.

Conclusions

The findings demonstrate that metabolic dysregulation is already present during the first episode of psychosis, suggesting that changes related to such dysregulation originate during development. This implies that patients with a PSD have an innate susceptibility for the development of metabolic disease, a diathesis. The findings of this project suggest that insulin resistance, anomalous cholesterol clearance, adipose tissue dysregulation, and potentially adipose-derived inflammation, are aspects of such metabolic dysregulation. Patients who experienced some adverse social factors had worse metabolic profiles, suggesting a higher cardiometabolic risk in this subgroup. As such, metabolic disease in PSD has multiple origins. The present findings can help identify molecular pathways of energy metabolism affected by social factors, and have implications for the identification of FEP patients at a higher risk of cardiometabolic disease.

RÉSUMÉ

Introduction

Les maladies cardiovasculaires ou accidents cardiocérébraux (AVC) sont la cause principale des taux de mortalité excessifs et permanents qu'on observe dans les troubles du spectre de la psychose (TSP). L'hypothèse soutenue est que ce phénomène découle d'une part des facteurs nuisibles liés au mode de vie et d'autre part des effets secondaires provoqués par les antipsychotiques. Cela favorise la formation de troubles métaboliques (comme le diabète sucré) qui, à leur tour, déclenchent des AVC. Or, le taux élevé de diabète chez les cas de schizophrénie a été documenté bien avant l'introduction des premiers antipsychotiques. De plus, des études récentes ont démontré la présence d'anomalies du métabolisme lors d'un premier épisode de psychose (PEP). À ce stade de la psychose, il y a une faible exposition aux antipsychotiques et les modes de vie malsains n'ont pas duré suffisamment longtemps pour engendre des dérèglements métaboliques. Par conséquent, d'autres facteurs agissant plus tôt au cours de la vie pourraient être liés au développement de ces troubles métaboliques. Les recherches tentant de démontrer un lien avec les polymorphismes génétiques sont peu fructueuses. En revanche, bien qu'ils soient répandus dans les TSP et favorables au développement de maladies métaboliques, d'AVC et de TSP, les déterminants sociaux de la santé (traumatismes de l'enfance, appartenance à un groupe ethnique minoritaire, statut de migrant, défavorisation matérielle et sociale) ne sont pas considérés comme des facteurs étiologiques potentiels. Ce projet vise à déterminer la présence de troubles métaboliques lors d'un PEP et à analyser l'implication des déterminants sociaux de la santé dans cette corrélation. On soutient l'hypothèse selon laquelle les déterminants sociaux de la santé favoriseraient le développement d'anomalies métaboliques lors d'un PEP. En outre, étant donné le rôle central des organes adipeux dans la pathophysiologie des troubles métaboliques et des AVC, l'on croit que la dysfonction des tissus adipeux serait déjà présente lors d'un PEP.

Méthodes

Trois études différentes ont été menées afin d'examiner la présence de modifications métaboliques lors d'un PEP : contrôle glycémique (hémoglobine glyquée), taux de lipides

(cholestérol total, LDL, HDL, taux de triglycerides) et dysfonction des tissus adipeux (Adipokines: leptine, adiponectine, résistine, chémérine). Les données ont été étudiées par des modèles de régression linéaire multiple.

Résultats

L'hémoglobine glyquée a augmenté chez les patients PEP issus de groupes ethniques minoritaires et ayant subi des abus durant l'enfance. Le cholestérol total et le HDL ont diminué pour les patients PEP ayant une psychose affective et vivant dans des environnements où le niveau de défavorisation sociale est élevé. Par rapport aux contrôles, toutes les adipokines des patients PEP ont eu des niveaux très différents. Les violences corporelles subies durant l'enfance ont été associées à une augmentation de la résistine, tandis que l'appartenance à un groupe ethnique minoritaire a été reliée à une diminution de la chémérine. De plus, des recherches connexes ont démontré un effet paradoxal du tabagisme sur la leptine.

Conclusion

Les résultats démontrent que des dérèglements métaboliques sont déjà présents lors d'un PEP, ce qui laisse entendre que ces changements se sont formés durant le développement. Cela signifie que les patients du TSP ont une grande susceptibilité naturelle à contracter des maladies métaboliques, une diathèse. Ces changements révèlent la présence d'une insulinorésistance, une élimination anormale du cholestérol, une dysfonction des tissus adipeux et une inflammation pouvant dériver d'une adipose. Les patients ayant vécu des facteurs sociaux défavorables ont un profil métabolique moins favorable, et ils présentent donc un risque cardiométabolique plus élevé. Ainsi, les maladies métaboliques du TSP ont plusieurs origines. Les résultats de cette présente étude peuvent permettre d'une part de repérer les voies moléculaires du métabolisme énergétique qui sont sensibles aux facteurs sociaux, et d'autre part d'identifier les patients PEP qui présentent un risque de maladie cardiométabolique plus élevé.

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STATEMENT OF ORIGINALITY

The first original contribution of the present study is the proposal, examination, and testing of the influence of social factors on metabolic function and health in the context of psychosis. While there is a rich literature looking at these relationships in a binary way, the simultaneous exploration of the three elements (psychosis, social adversity and metabolism) is almost absent. This has only been explored by one other study in the case of childhood trauma, and it was only published in the previous year. To the best of my knowledge, no other study has examined social and material deprivation, migrant background, or minority status as determinants of metabolic health in psychosis. More importantly, no other study has proposed that the high rates of comorbidity (in this particular case metabolic comorbidity, and potentially explaining cardiovascular comorbidity) in psychotic disorders might stem in part from the exposure to adverse social conditions. All three components of my doctoral project tested the effects of social determinants of health on metabolic homeostasis.

The second original contribution is the identification of the role of the adipose tissue as an important locus of metabolic changes in psychosis. Some studies had looked at leptin and adiponectin in psychosis, mostly embedded within a battery of other clinical tests with the anticipation of ascribing these molecules as biological markers of psychosis. The present project took a different view, proposing for the first time that metabolic regulation, depending on adipose biology, is innately altered in psychosis. Only one other study had looked at resistin in psychotic disorders. Again, none of these studies considered the effects of social factors on adipokine secretion. As such, this is the first study in psychosis to study chemerin, a molecule

whose importance in the biology and the prediction of metabolic and cardiovascular disease is increasingly being recognized.

Other original aspects of my project were the articulation of geographical measures of social and material deprivation with health outcomes in the context of psychosis, the illustration of the use of glycated hemoglobin for research purposes, and the exploration of how the type of diagnosis might affect physical health outcomes in psychosis.

Finally, my project showed that the adoption of contemporary theories on the etiopathogenesis of disease can provide a wider angle from complex disorders such as psychosis would be better understood, and can shift the current paradigm by bringing more attention to the intersection between the social and biological layers of disease.

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INTRODUCTION

As it often happens in medicine, and particularly in psychiatry, some things need to be rediscovered. Just two years before the discovery of insulin, when schizophrenia was still known as Bleuler's dementia praecox, a manuscript entitled "Hyperglycemia in mental disorders" was published in the journal Brain [1]. This and other papers over the following years demonstrated higher rates of diabetes in dementia praecox, concluding that "mental disorders carry metabolic changes more often that what would be led to believe by casual observation" [2]. It is bewildering to see how this remarkable discovery was forgotten by time, and that a wealth of knowledge from different disciplines was needed to bring it back to light. Indeed, meta-analytical evidence from studies in first-episode psychosis has suggested that metabolic disease is closely associated with psychotic disorders, to a greater extent than what would be expected solely from the side effects of antipsychotic medications. However, little is known about the origins of this association, and probable etiological factors have seldom been tested.

The doctoral project embodied in this monograph aimed to delve into this phenomenon in order to identify some of the etiological factors and underlying physiological processes that give rise to the metabolic anomalies observed at the onset of psychosis. The principles that guided this doctoral journey included three important theories: that most disorders have a developmental origin, that environmental factors interact with the individual's vulnerabilities (inherited or acquired), and that some complex conditions have common etiological roots. This endeavor covered epidemiological, physiologic and molecular aspects of metabolic and psychotic disorders, which led to the identification of adipose dysregulation as one of the pathophysiological substrates of metabolic disease in psychosis, and the documentation of the role of social determinants of health in this phenomenon.

CHAPTER I

BACKGROUND AND COMPREHENSIVE LITERATURE REVIEW

I.A Brief overview of psychosis: Psychosis-Spectrum Disorders (PSD)

The term "psychosis" applies to a group of disorders characterized by a mixture of symptoms that more or less cluster together and are thought to make part of a syndrome for which none of its potential causes has been identified with certainty.

The most salient group of symptoms stem from abnormal sensory experiences such as hallucinations and delusions. Hallucinations are complex perceptual experiences that can arise from any sensory system. Auditory hallucinations are the most common, and often take the form of voices. Delusions indicate the presence of strongly held beliefs that contradict those of the reference group, regardless of their plausibility. Conviction is often unwavering despite patent impossibility or tangent evidence against the belief, which leads to maladaptive social interactions.

The second group of symptoms involve the loss of inherent behavioural capacities. Emotional responsiveness, social interactions, language, and motivation are frequently impaired and can significantly disrupt daily functioning. The behavioural impairments resulting from these deficits often limit the capacity of the individual to lead a normal life. This creates significant difficulties in social, occupational, and other aspects of functioning, which are unfortunately more common than rare. Impairments in social function and motivation are important mediators of disability in psychotic disorders [3].

The third group of symptoms also imply functional impairment, but in this case in the cognitive sphere. Cognitive disruption is found in areas such as memory, attention, executive capacity and processing speed [4]. Such deficits can restrict the ability of the individual to perform everyday tasks adding to the limitations caused by behavioural impairments.

Finally, other symptom domains that are usually ascribed to major mental health disorders, such as mood (mania and depression) and anxiety (including obsessions), often accompany the psychotic syndrome. The most prominent association of psychosis is with affective symptoms, and the extent of the presence of these symptoms has profound implications on diagnosis, prognosis, therapeutic approach, and long-term function [5].

The permutations caused by the presence and absence of the aforementioned groups of symptoms roughly cluster into defined disorders, but there is extensive overlap. This phenomenon is reflected in the need for the use of the term "spectrum" to describe psychotic disorders, which underscores that no clinical picture is the same, and reflects that these entities are closely related. Moreover, a substantial proportion of these clinical presentations do not fit into the defined psychotic disorders and end up being classified as "psychoses not otherwise specified". As mentioned, mood symptoms have a weighty influence on the diagnostic classification; psychoses are compartmentalized as non-affective or affective depending on the overall dominance of psychotic or mood symptoms.

The quintessential example of a psychosis-spectrum disorder (PSD) is schizophrenia. Schizophrenia is a non-affective disorder, characterized by the presence of behavioral and cognitive symptoms which are often severe enough to disrupt the individual's life. While there is a wide heterogeneity in the natural history of schizophrenia, the most common course is chronic and intermittent, and the limited social and occupational stability associated with the disease can contribute to a progressive deterioration in all spheres of life. On the other hand, entities as different as a delusional disorder –in which the only manifestation is the presence of a very defined false belief without behavioral and cognitive deficits–, or a depressive disorder with psychotic features –where psychotic symptoms are only a secondary manifestation– are considered part of the spectrum. Given

that schizophrenia is the most common PSD [6], with a prevalence estimated between 1.4 to 4.6 per 1000 [7], and because it exacts a heavy toll on the individual's quality of life, this is the most studied psychotic disorder; thus most of the research on this syndrome is based on it (and will be often found to exemplify PSD in this monograph).

The multitude of clinical presentations embodied in the psychosis spectrum, and the fact that it represents a syndrome (a condition that can be originated through multiple different etiologies) reveals the difficulties in determining its causes. Few things are certain regarding the etiology of PSD. Heredity plays an important role, as illustrated by the concordance between monozygotic twins in schizophrenia, which is estimated to be around 40-50% [8]. However, despite this fact, the identification of candidate genes has proven to be extremely difficult. While some genes have been identified in specific populations, no gene has proven to increase risk by itself. This also indicates that the environment plays a fundamental role in the emergence of PSD. Indeed, epidemiological evidence indicates that predictable risk associations come from maternal infection or famine, caesarean section, upbringing in an urban or socioeconomically deprived environment, discrimination, having a migrant background, and cannabis use among others [9]. The combination of these facts with some neurophysiological hints has led to hypothesize that PSD are developmental in nature, and follow a stress-diathesis etiological model [10].

Early intervention services for psychosis have a fundamental role in PSD, as providing care at early stages using this model has been demonstrated to have a greater impact in the amelioration of clinical and functional aspects of psychosis compared to regular care [11]. This stems from a personalized and intensive follow-up, which allows close monitoring of all aspects of health, including physical parameters [12]. Furthermore, the early intervention field has often promoted a close association between academic and research programs, which can help accelerate the adoption of evidence-based knowledge.

I.B Mortality in PSD: the burden of cardiovascular disease (CVD)

I.B.1 Epidemiology of CVD in PSD

One of the main characteristics of PSD is their disproportionate rates of morbidity and mortality in comparison to population norms. It has been estimated that having a diagnosis of schizophrenia reduces life expectancy by up to 20 years [13] and almost triples the odds of all-cause mortality[14]. Moreover, there is a lack of improvement in mortality rates that has not paralleled population trends, creating a widening gap in longevity [15]. While the main cause of mortality in the first years after diagnosis in PSD is suicide [16], natural causes are still dismally higher in psychosis than in the general population. The main causes of global mortality such as cardiovascular disease [17], cancer [18], and even infectious diseases [19]are overrepresented in this population.

Cardiovascular disease is the leading cause of natural death in psychosis, and all major causes of cardiovascular mortality are increased in psychosis. Having a diagnosis of schizophrenia confers higher odds for coronary heart disease [20], cerebrovascular disease[20], and peripheral vascular disease [21]. However, cardiovascular disease is the result of a series of pathophysiological events that affect the individual for long periods of time. Thus, it is not surprising that conditions underlying the pathophysiology, and preceding the development of cardiovascular disease, have also an increased prevalence in PSD. For instance, in schizophrenia, hypertension [21], dyslipidemia [22], hemostatic dysfunction [23] and metabolic disease (which will be further explored in detail) [24] are commonly found comorbid phenomena.

I.B.2 Theories on the origin of the high prevalence of CVD mortality in PSD

The notion that the rates of cardiovascular and metabolic disorders in psychotic disorders are exceptionally high vis-à-vis the general population is relatively recent, and the present study focuses on the factors underlying these associations. Nonetheless, various observations provided clues on this issue for more than a century [2]. For instance, methods such as insulin-induced coma were mainstream treatments before the advent of antipsychotics [25].

The main current hypotheses posited to explain the strong association between CVD and PSD primarily depend on external factors to which the individual is exposed. Indeed, there is a substantial body of evidence documenting the high prevalence of certain cardiovascular risk factors in individuals suffering from PSD. One of the most notorious is tobacco smoking, which is globally one of the most impactful risk factors associated with CVD. Its relevance is reflected in the weight that smoking has in the Framingham-derived risk algorithms, being a dominant driver of risk scores especially at younger ages [26]. Tobacco smoking promotes cardiovascular disease through multiple mechanisms such as oxidative stress, endothelial damage, and dyslipidemia among others [27]. When compared to the general population, patients with schizophrenia are almost six times more likely to smoke tobacco, and the prevalence of smoking in these patients has been estimated to be between 70-80% [28]. Furthermore, approximately half of the population with schizophrenia is classified as heavy smokers [28]. It is worth noting that the prevalence of tobacco smoking is already high at the debut of psychosis when compared with non-psychotic controls, and that on average, patients start smoking 5.3 years before the onset of psychosis[29]. These alarmingly high rates have been proposed to depend on the effects that nicotine has

on multiple neurotransmitter pathways [30,31], hypothesizing that patients use nicotine to self-medicate. Such psychosis-specific effects would add to nicotine's highly addictive potential, complicating the already difficult process of smoking cessation. Preventing or discontinuing tobacco smoking is particularly important as it is perhaps the most important malleable risk factor for CVD (as well as for a multitude of other disorders) [32].

A growing body of evidence indicates that physical inactivity has a substantial (and often overlooked) role in the promotion of cardiovascular disease. The motivational impairment observed in PSD contributes to the development of sedentary lifestyles [33]. When compared to non-psychotic controls, patients with PSD spend almost three hours more per day being sedentary [34]. Nutritional habits have an important role in the development of metabolic disorders and CVD, and achieving a healthy diet is one of the core preventive and therapeutic goals when approaching cardiovascular health [35]. While quantifying and determining what a good diet should be is challenging, various studies have shown that patients with schizophrenia often have poor nutritional habits. Diets high in saturated fats and sugars, fewer portions of vegetables and fruits, and less total dietary fiber, antioxidants and vitamins are commonly seen in schizophrenia [36]. Thus, the combination of a sedentary lifestyle with poor nutritional habits adds another element to the cardiovascular risk profile in PSD.

In addition to this cluster of noxious lifestyle factors, patients with PSD inevitably face a specific and prominent contributor to cardiovascular risk: antipsychotic medications. Second generation antipsychotics (SGA) are the current backbone of therapy in PSD. The widespread use of these molecules is a result of their relative lack of neurological side effects (e.g., extrapyramidal symptoms or tardive dyskinesia), which are the main limitation of the previous generation of antipsychotics [37]. However, the downside of these newer pharmacological options is their metabolic side effect profile, a feature considerably less relevant with older antipsychotics. SGAs promote weight gain, dyslipidemia,

insulin resistance, and oxidative stress [38]. These pathophysiological changes, coupled with the above-mentioned lifestyle risk factors, favour the development of metabolic comorbidity such as diabetes mellitus type 2 (DM2) [39], a leading cause of vascular damage in big and small arterial systems, and hence a promoter of coronary and cerebrovascular disease [40].

Finally, some studies have tried to find common genetic variants that could potentially explain cardiovascular and metabolic comorbidity, but results have been scanty. In one study, an allele of lipoprotein lipase –an enzyme responsible for hydrolyzing triglycerides– was associated with schizophrenia [41]. However, the association was only found in males, and has yet to be replicated in other populations. A different study applied Mendelian randomization to meta-analytical data to explore the association of schizophrenia with metabolic cardiovascular and traits [42]. While the authors suggest the presence of "tentative" polygenic associations, they conclude that this association might be due to shared genetic liability or environmental risk factors. A different study also implementing Mendelian randomization of GWAS meta-analytical data neither found a causal relationship between schizophrenia and T2DM or impaired glucose homeostasis, nor genetic overlap between these traits [43]. The fact that no single gene has been consistently associated with schizophrenia across different populations suggests a low probability of finding a shared genetic variant with metabolic disorders or CVD.

In sum, to date, the high cardiovascular morbidity and mortality observed in schizophrenia is assumed to essentially depend on lifestyle risk factors such as tobacco smoking, physical inactivity and unhealthy diets, and on the metabolic dysregulation caused by the use of antipsychotic medications. Studies looking for genetic associations have been mostly unsuccessful, and other alternative theories have not been explored.

I.B.3 Discrepancies in the theories explaining metabolic disease and CVD with PSD

While the cardiovascular risk factors illustrated above are almost ubiquitously present in PSD, and are sufficient enough to promote CVD, their presence cannot explain some phenomena. First, historical records have documented the association between schizophrenia and DMt2 for more than 100 years, with the first records preceding the introduction of antipsychotics for at least five decades [2]. Second, studies with siblings of patients with schizophrenia suggest that metabolic and vascular dysfunction in schizophrenia have either a hereditary, or a shared environmental origin. In one study, non-affected siblings of patients with schizophrenia had impaired glucose tolerance (2-hour glucose test) [44,45]. A second study with drug-naïve or unmedicated patients with schizophrenia and their siblings demonstrated that both had higher systolic and diastolic blood pressure levels when compared to controls. The same study showed also lower HDL in patients and siblings, but the difference was not statistically significant in post-hoc analyses for siblings versus controls [46]. Finally, and perhaps more importantly, studies focusing on the first episode of psychosis stage, when most patients are young and unexposed to antipsychotics have documented the presence of established metabolic dysregulation. One meta-analysis revealed that patients with first-episode psychosis (FEP) had higher levels of insulin, insulin resistance and impaired glucose tolerance [47]. In two different meta-analyses (which included almost the same studies), it was shown that having FEP was associated with higher levels of triglycerides, but lower levels of total and LDL cholesterol [48,49]. Higher insulin levels and resistance, impaired glucose tolerance, and hypertriglyceridemia are all markers of a pre-diabetic state. While lower levels of cholesterol would imply lower cardiovascular risk (which as mentioned is not the case), such changes indicate a profound alteration of the mechanisms responsible for the physiologic

regulation of lipids. Thus, it is clear that substantial changes at the metabolic level are present at the onset of psychosis.

The significance of these discrepancies cannot be overlooked. Having metabolic alterations at the onset of psychosis is of central importance since most patients at this stage are young (mean age 23 years), which implies that they have not yet been exposed to the above-mentioned lifestyle risk factors and antipsychotic medications. The changes leading to metabolic disease and CVD typically evolve over decades before the appearance of the first symptoms unless a rare Mendelian disorder causing a premature onset is present [50]. Thus, finding pathophysiological changes as serious as insulin resistance at the onset of psychosis implies that the factors promoting these changes would have been acting for a long period of time. Since antipsychotic medication has not been considerably implemented at this stage (and patients with PSD do not invariably develop metabolic disease), and exposure to the described lifestyle factors has not lasted enough to lead to metabolic disease, other processes must be fostering these changes. Such determinants would be either shared genetic variants, or environmental factors acting throughout development. Given that current efforts geared towards finding genetic associations between PSD and metabolic disease or CVD have been largely unsuccessful, alternative hypotheses are needed. Such determinants then must have an environmental origin, act throughout development, and more importantly, be able to increase the risk for PSD, metabolic disease, and CVD.

I.B.4 The evolving landscape of CVD risk prediction

The Framingham Heart study (FHS) was the first project to provide conclusive evidence of the noxious effects of tobacco smoking, obesity, and hypercholesterolemia (among many others) as promoters of CVD [51]. These outstanding contributions also facilitated the identification of the metabolic syndrome (explained later), and through its algorithms, it provided the first method to

quantify and predict cardiovascular risk. This allowed the establishment of tailored treatments aimed to prevent CVD. However, this seminal study is not without limitations. For example, given that age and sex are key factors with a high weight in the scores, the algorithms fail to identify some patients at risk, particularly women and younger individuals [52]. More important perhaps is the fact that the algorithms were developed in a predominantly middle-class Caucasian population, and thus their performance in other ethnic groups or in disadvantaged populations is reduced.

Ethnicity is deeply ingrained in the factors associated with the development of disease, and CVD is not an exception. This becomes evident by understanding how risk is calculated. Not all cardiovascular risk can be explained by the risk factors identified by the FHS. Total risk is the sum of the proportion attributable to the risk factors used by the FHS algorithms (i.e., "attributable risk") plus the proportion that is not explained by these factors (i.e., "baseline risk"). Baseline risk depends on factors rooted in ethnicity such as the genetic makeup of the population, environmental aspects (e.g., dietary practices), and prevailing behaviours (e.g., social support). Thus, since baseline risk varies across populations, places, ethnicities and ages, the performance of the FHS algorithms would depend on how much the studied population resembles the participants from the Framingham cohort. This was indeed demonstrated by a study comparing the FHS with six other studies of cardiovascular morbidity and mortality conducted in cohorts with different ethnic, age group, and socioeconomic compositions[53]. For example, the FHS algorithms overestimated cardiovascular risk in an African-American population but underestimated it in the Asian-American cohort.

Longitudinal studies with populations that differ from the FHS cohort and originating in other countries are still limited. Nevertheless, there are important efforts to examine risk factors worldwide. The INTERHEART study is a collaborative study across 52 countries, and its objectives are to gauge the magnitude of the association between various risk factors and myocardial infarction, and to

determine how these associations are modified by geography, ethnicity, sex, and age [54]. The INTERHEART study has provided important insights into the differential impact that conditions such as DM2, dyslipidemia, abdominal obesity and hypertension have across diverse populations [55,56]. In addition, it has provided important evidence for the role of other non-traditional factors such as psychological stress, depression, socioeconomic deprivation, alcohol use, and number of dietary vegetable/fruit portions. Indeed, multiple lines of evidence have emerged in recent years documenting the role of social determinants of health as important predictors of CVD.

I.C Metabolic Dysregulation as a main contributor of CVD

As mentioned earlier, metabolic dysregulation is a common denominator in the cardiovascular risk factors traditionally examined in PSD. This is not a coincidence, and in fact the emergence of different pathophysiological mechanisms of energy metabolism is central for the manifestation of cardiovascular disease. As a side note, the term "metabolism" encompasses all the biochemical processes that allow the cell to live. While the use of this term to denote only a portion of these processes is restrictive (i.e., only to imply a part of energy metabolism), it will be used for the purpose of simplicity, which coincides with its utilization in the medical literature.

I.C.1 The concept of metabolic syndrome

The metabolic processes most commonly associated with CVD encompass deviations of the mechanisms geared to maintain a continuous supply of energy to the brain in the form of glucose, and to provide lipids for energy and structural purposes. From the clinical perspective, alterations that result in excessive storage and circulation of glucose (i.e., DM2) and lipids (i.e., dyslipidemia and obesity)

are core elements associated with increased risk of CVD. These changes do not appear to be isolated, as they frequently coexist and stem from common etiopathological processes. This concomitance has led to ascribe these alterations as integrated parts of a larger phenomenon, the metabolic syndrome.

The metabolic syndrome can be defined as a combination of interrelated physiological anomalies that often coexist and are associated with an increased risk for the development of CVD as well as DM2. Since its first recognition (initially as the "X Syndrome") [57], the core elements that define the metabolic syndrome have essentially remained the same except for obesity. Currently, these elements include dyslipidemia, hyperglycemia, hypertension, and abdominal obesity. However, the presence of a multitude of institutions dedicated to the study of CVD has led to the formulation of numerous definitions, each subject to the particular principles and objectives of its proponents. Thus, some definitions have different cut-off points for some criteria or give special emphasis to certain elements. This abundance of characterizations has hampered the establishment of a consensus. Despite this issue, new epidemiological data is constantly refining these criteria, and new efforts are being put in place to arrive at an evidence-based consensus. Recently, five different groups (American Heart Association, International Atherosclerosis Society, International Diabetes Federation, National Heart, Lung, and Blood Institute and World Heart Federation) have published a joint consensus statement [58]. The consensus criteria from this joint statement are: 1) a population and country-specific threshold for waist circumference definition which replaces the concept of BMI, and underscores the notion of central obesity as a better indicator of risk, 2) elevated triglycerides (≥ 150mg/dl / ≥1.7mmol/L) or pharmacological treatment (e.g. fibrates), and low HDL cholesterol (<50 mg/dl for women / <1.3mmol/L, <40mg/dl / <1.0mmol/L for men) or lipid-lowering pharmacotherapy (e.g. statins), 3) elevated fasting glucose (≥100mg/dl / ≥5.6mmol/L) or pharmacological treatment (e.g. insulin), and 4) high blood pressure: Systolic ≥130 and/or diastolic ≥85 mm Hg or pharmacological treatment (i.e. antihypertensive).

As mentioned before, ethnicity is an important determinant of cardiovascular risk. Thus, the inclusion of ethnic-specific cut-offs for abdominal obesity in these guidelines is noteworthy, as it pinpoints one of the elements where ethnicity is most consequential, and indicates a change of direction towards acknowledging the importance of this factor. Given that the development of metabolic syndrome importantly depends on environmental factors (e.g., nutrition), and marks the presence of and increased risk for the development of CVD, it is not surprising that the prevalence of the metabolic syndrome is also modified by ethnicity and geographical location. Indeed, some of the most recent estimates indicate notorious differences in its prevalence across the globe, varying from 14% in Japan to 41% in India [59,60]. In Canada, the crude overall prevalence has been estimated to average around 16%, with a marked difference depending on sex, with a prevalence of 18.5% for men compared to 13.5% for women[61]. The different prevalence estimates around the world can be attributed in part to the use of different criteria and regional-ethnic variation, but the burden is still alarmingly high. Indeed, there is a global tendency towards an increase in its prevalence [60].

I.C.2 Etiopathogenesis of cardiovascular disease

Despite recent advances at the epidemiological and clinical levels, the origin and pathogenesis of the metabolic syndrome has not been completely elucidated. As it is the case for other complex pathological phenomena, the origin of the metabolic syndrome likely resides in the interaction between environmental and genetic factors. The observation that the risk for the manifestation of the metabolic syndrome varies depending on ethnicity and clusters in families, has led to active research into its potential genetic components. This task has been complicated by its syndromic nature, which implies that diverse factors or combinations of factors could be responsible for its appearance. Nevertheless, some relevant gene variant associations have been found for genes coding for adipokines (e.g. RSTN),

lipoproteins (e.g. APOC3), inflammatory cytokines (e.g. IL6) and thermogenic proteins (e.g. UCP2) among others [62]. These studies however await confirmation. In addition, the contribution of genetic factors in explaining the variance of the metabolic syndrome phenotype has only been estimated to be around 10% [63]. Thus, environmental factors may play a more significant role in the origin of this syndrome. The most well-characterized environmental factors associated with the metabolic syndrome are an energy-saturated diet and a sedentary lifestyle. Dietary factors include the degree of metabolic availability of carbohydrates (measured by glycemic index) but not their amount [64], the amount of trans-fats, branched-chain amino acids, ethanol and fructose [65]. In parallel, sedentary behaviors (e.g. lack of physical exercise, watching TV.) increase the risk for the development of the metabolic syndrome (odds ratio 1.73), independent of sex or its conceptual definition [66].

The pathophysiology of the metabolic syndrome can be regarded as a chain of events in which subsequent phenomena are functionally linked, and in some cases, are mutually enhancing (reviewed in detail by [67]). The process leading to the development of the metabolic syndrome and subsequently to CVD is promoted in part by exposure to the above-mentioned environmental factors (i.e. unhealthy diet and sedentary lifestyle). The increased energy input from food sources, coupled with the decreased output of energy from reduced activity, results in a positive balance of energy. This leads to the accumulation of excessive amounts of energy in the form of fatty acids in the adipose tissue, resulting in the expansion of fat depots[65]. There are two main adipose tissue compartments: subcutaneous and visceral. Increased accumulation of fat, particularly in the latter, is associated with pathological phenomena such as dyslipidemia and insulin resistance[68]. The expansion of the visceral adipose depot drives it to release excessive amounts of free fatty acids into the bloodstream, which are subsequently assimilated by the liver via portal circulation. The resulting hepatic imbalance of lipids stimulates the production of triglycerides, which in turn increases LDL and reduces HDL cholesterol [69]. The augmented supply of free fatty acids also induces insulin resistance in the liver and other tissues,

triggering glucose dysregulation. Furthermore, the macrophages in the visceral adipose tissue start secreting pro-inflammatory cytokines (e.g. TNF-α and IL-6), creating a chronic inflammatory milieu, a phenomenon known to favour insulin resistance[70]. Finally, excessive adiposity will result in the reduction of adiponectin [71], a hormone with regulatory activity on glucose (increase of glucose uptake, decrease of gluconeogenesis) and lipid (oxidation, triglyceride clearance) metabolism. Chronic inflammation and insulin resistance amalgamate to induce progressive Beta-cell failure, resulting in the clinical expression of glucose intolerance first, and the subsequent progression to DM2[72]. The inflammatory milieu and the rising levels of glucose also promote endothelial dysfunction, which contributes to the appearance of hypertension. High blood pressure levels further damage the endothelium, which after being lost leaves deeper arterial layers susceptible to chemically react with lipoproteins. Lipoprotein oxidation and accumulation in the arterial wall attracts macrophages, creating local inflammation and accumulation of cells, lipids, and matrix proteins (e.g., collagen), a process known as atherosclerosis. Atherosclerotic plaques grow and obstruct the arterial lumen, but also favour intravascular thrombosis, and can rupture creating emboli. Atherosclerotic build-up is particularly active in the coronary arteries, leading to the disruption of blood supply to the myocardium, causing ischemia or infarction [67]. In sum, it is clear that the pathophysiology of metabolic disease is a fundamental component of that of CVD.

I.C.3 The adipose tissue as an endocrine organ

As illustrated in the previous section, the metabolic syndrome is one of the leading precursors of CVD. When tracing back the origins of the metabolic syndrome, all its elements seem to emerge from dysfunctional processes in the adipose tissue. Thus, metabolic disease, as embodied by the clinical construct of metabolic syndrome, is a consequence and a manifestation of adipose tissue dysregulation [73]. The notion that the adipose organ is merely a chemical energy warehouse otherwise inert is now

obsolete. The functions performed by the adipose tissue are consistent with those of an endocrine organ with an active engagement in immune signaling.

Adipocytes are the constitutional cellular elements of the adipose organ, and the functional and morphological characteristics of the adipose tissue are essentially defined by those of adipocytes. Adipocytes derive from non-hematopoietic mesenchymal stem cells that have the potential to also develop into myocytes, osteoblasts and chondrocytes [74]. These mesenchymal progenitors give rise to the different pools of adipose tissue in the body, and further develop into committed lineage-specific preadipocyte precursors. As committed cells, preadipocytes can only give rise to unique types of mature adipocytes. Adipose depots are composed of mature adipocytes, but a reservoir of preadipocytes that differentiate into mature cells in response to specific stimuli is always present [75].

There are two main types of adipocytes: white and brown. Each gives rise to a different type of adipose tissue, which are respectively named after these cells. White adipocytes are large cells that enclose an individual droplet of lipid that occupies most of the cytoplasm. White adipocytes control this lipid depot depending on the balance of energy, storing it as triacylglycerols or releasing it in form of triglycerides and fatty acids. White adipocytes also secrete adipokines, which are hormones with metabolic and immune functions, acting at the auto, para, and endocrine levels. In contrast, brown adipocytes are cells with a more typical cytoplasm in which lipids are stored in smaller droplets, and contain increased numbers of mitochondria. While brown adipocytes can also store energy and release adipokines, their main function is thermogenesis via lipid oxidation [74]. An intermediate phenotype, beige adipocytes has been recently documented. These cells coexist with white adipocytes, stem from these, and their differentiation seems to be inducible by cold exposure [75].

Adipose tissue appears in the second trimester of gestation, and an important buildup of brown adipose tissue (BAT) occurs before birth [76]. This expansion is necessary to prepare the neonate to sustain the hypothermic stress taking place at birth when the stable conditions provided by the uterine milieu are replaced by the uneven extra-uterine environment. The relay in thermal regulation from the mother to the newborn seems to be the most important function of the BAT. Shortly after birth, brown adipose tissue is rapidly replaced by white adipose tissue (WAT), which is the predominant form in children and adults, although some depots of BAT remain throughout life.

Adipocytes make only half of the total cells in the adipose tissue, the remainder being composed of preadipocytes, immune cells, fibroblasts, vascular endothelial cells, and nerves. The most notable immune cells in this tissue are macrophages, which can be resident or recruited cells, but T lymphocytes, B lymphocytes, neutrophils, eosinophils and mast cells are also found. Macrophages can comprise up to 10% of total cells, and in non-pathological states, they are responsible for "healthy inflammation", which allows clearing apoptotic debris and remodeling the extracellular matrix during adipose tissue expansion, both central processes required for normal adipogenesis [74]. In the non-pathological state, adipose immune cells exhibit an "anti-inflammatory" state, e.g., macrophages have an M2 phenotype, and T lymphocytes are shifted towards Th2 (T-helper type2) and T-reg (regulatory) phenotypes[77]. The cytokine milieu reflects this state, with a predominance of IL-10, IL-4, and IL-13 [78]. Macrophages are also involved in the maintenance of insulin sensitivity via the peroxisome proliferator-activated receptor gamma pathway (PPAR-γ), an important nuclear receptor at the center of glucose metabolism and lipid storage[79].

I.C.4 Adipokines: Molecular Mediators of Adipose Endocrine and Autocrine Function

The endocrine character of the adipose tissue resides in the capacity of white adipose cells to secrete adipokines. The capability of the adipose tissue to interact with multiple organs indicates that this tissue is actively involved in homeostasis at a systemic level, intervening in processes such as energy expenditure, satiety, and pancreatic function among others [80]. The first indication of the endocrine nature of the adipose tissue came with the discovery of leptin two decades ago [81]. Since then, more than six-hundred adipocyte mediators have been identified or proposed [80].

Leptin, which derives from the Greek word *leptos*, which means slender, is a peptide hormone primarily produced by white adipose cells. Leptin targets hypothalamic nuclei, stimulating the ventromedial nucleus ("satiety center") and inhibiting the lateral nucleus ("hunger center") [82]. Leptin levels correlate with the amount of adipose tissue. As such, leptin acts as a negative feedback control mechanism reducing appetite when adipose mass increases. Leptin also has other important actions, particularly boosting energy consumption via sympathetic stimulation, and acting as a pro-inflammatory cytokine among other properties [83].

Discovered one year after leptin, *adiponectin* is another primary adipokine that sparked active research on the endocrine functions of the adipose tissue [84]. Adiponectin is also primarily produced by adipose cells, and its secretion is inversely correlated with body mass, although it is not completely understood if its downregulation in obesity is causal or consequential [85]. Adiponectin bolsters energy intake and reduces its expenditure through a varied repertoire of actions. Adiponectin has prominent roles in the regulation of energy homeostasis, increasing insulin sensitivity, enhancing oxidative metabolism in (skeletal) muscle, suppressing gluconeogenesis in liver and muscle, and curtailing lipolysis in adipocytes. Overall, adiponectin actions promote energy storage and thus, it has been proposed to act as a "starvation hormone". As such, it can be said that –at least at the metabolic level– leptin and adiponectin have antagonistic effects, suggesting that these are among the main mediators of

the regulatory effects of adipose tissue on systemic energy balance. The immunological properties of adiponectin are more complex than initially thought. These have mostly been identified as anti-inflammatory, but in some cases, adiponectin has been associated with inflammatory conditions such as rheumatoid arthritis [86]. This implies that context is particularly relevant for adiponectin function (and perhaps for adipokines in general). One of the most relevant immunological actions of adiponectin is exerted on macrophages, where it suppresses differentiation of the M1 inflammatory phenotype but promotes proliferation of the M2 anti-inflammatory phenotype [87]. This is of central importance, as this favours adequate adipose function.

Resistin is another peptide hormone produced by adipose cells. Resistin was discovered in 2001 and was shown to increase insulin resistance when injected to mice, hence its name [88]. This role has been put into question in recent years, particularly in humans, although it is clear that this mediator has such potential under specific circumstances [89]. Perhaps more prominent are resistin's ability to restrict adipocyte differentiation acting as a feedback regulator, and its pro-inflammatory and pro-atherogenic properties. Leptin, adiponectin and resistin have been called "true adipokines" since they are mostly produced by adipocytes.

Chemerin is an additional adipokine with important endocrine capacity and diverse actions across different systems [90]. Chemerin is actively produced in the adipose tissue, as well as in the liver, lung and skin. At the metabolic level, chemerin is associated with increased insulin resistance in muscular tissue, but active research is going on to pinpoint the mechanisms responsible for this effect in other tissues [91]. Chemerin is also associated with increased body mass, and similarly to adiponectin, it has still not been completely elucidated if obesity is the result or the source of this association. Chemerin and its receptors are present in the brain, including the hypothalamus, but it is still not clear which processes are targeted by this molecule. Perhaps more importantly, chemerin activation is central for

the proliferation and differentiation of preadipocytes, and the regulation of the expression of multiple genes associated with metabolism, including leptin and adiponectin. Finally, chemerin is also considered as a cytokine, acting as an important chemoattractant for dendritic cells, as well as having pro and anti-inflammatory actions [92].

Given their importance in the regulation of metabolic function, and their known associations with CVD, the previous four adipokines were selected as the main focus for the last part of this project. However, a myriad of other mediators are associated with the physiology and pathophysiology of the endocrine and immune systems. Molecules such as omentin, apelin, visfatin, and vaspin are found in the adipose tissue and influence insulin signaling, but at the same time have important roles in cell differentiation, particularly of immune cells [93]. By the same token, cytokines (the main molecular mediators of immune action) such as TNF-α, IL-6, IL-10, and MCP-1 (Macrophage-monocyte chemoattractant protein) are actively produced in the adipose tissue [94]. Such diversity of mediators and their functions is also a reminder of the complexity of metabolic control, and the challenges to understand and find effective therapies to curtail metabolic disorders such as obesity, dyslipidemia, and DM2, and by extension to prevent CVD.

The presence of this important repertoire of messenger molecules in the adipose tissue exemplifies the active communication that exists between this tissue and other organs. Furthermore, there is an important outflow of sympathetic innervation targeted at the adipose tissue, and adrenergic-dependent lipid mobilization as well as WAT "browning" (a phenotypic change in white adipose cells equipping them with the molecular tools to produce heat) have been amply documented [95]. In addition, there is an important expression of glucocorticoid and mineralocorticoid receptors in the adipose tissue, and it has been hypothesized that products from glucocorticoid-dependent lipolysis (such as free fatty acids) could exert a negative feedback inhibition on the HPA axis. In sum, there is no shortage of mediators in

the adipose tissue conferring it with its status as an endocrine organ. Moreover, such profuse biochemistry and physiology would qualify it as an immuno-endocrine or even neuro-endocrine organ. The central role that the adipose tissue plays in health and disease is thus predictable.

I.C.5 Adipose Tissue Dysregulation at the Origin of Metabolic Disease

Up to this point, it has been illustrated that the pathophysiology of CVD widely relies on metabolic phenomena such as insulin resistance, and that the adipose tissue is an important element in the normal physiology of metabolism. Hence, understanding the processes leading to adipose tissue dysregulation is fundamental to understand the origins of cardiovascular disease. Before going further, it is important to indicate that not all adipose depots are made equal. Different WAT depots are metabolically distinct, a phenomenon that originates in important differences in developmental gene expression, and particularities in the molecular profiles in mature adipocytes [96]. As previously mentioned, visceral WAT in particular (i.e., the adipose tissue depot in the abdominal cavity) has been distinctively associated with increased insulin resistance and cardiovascular risk [70].

The main intrinsic factors associated with adipose tissue dysregulation are age, sex (mediated by sex hormones), genes, ethnicity, growth hormone levels, and HPA sensitivity to different stimuli such as psychosocial stress or cold exposure [97]. These elements clearly overlap with those identified as those associated with baseline cardiovascular risk, which was anticipated given the important pathophysiological links among these phenomena. Similarly, environmental factors play important roles in triggering adipose tissue dysfunction.

The first of these elements is diet, in which two important circumstances: excessive loads of energy and an anomalous composition of obesogenic nutrients, synergize to induce metabolic imbalance. Among the latter, fructose and saturated fats are notable examples as these nutrients are metabolized through alternative molecular pathways leading to an abnormal accumulation of triglycerides and promoting the expansion of visceral fat. Unfortunately, these nutrients are commonly and abundantly found in "Western diets" [98]. The second element is the presence of a sedentary lifestyle. Regarding adipose tissue accumulation, the amount of physical activity is associated with visceral adipose mass, and instituting a regular routine of physical activity is associated with a reduction in visceral adipose depot size [70].

The accumulation of visceral adipose tissue caused by the positive balance of energy resulting from over nutrition leads to the saturation of the capacity of the tissue to accumulate fat, and other tissues start to assimilate this excess. However, the observation that some individuals have the capacity to accumulate significantly higher amounts of adipose mass before developing the pathophysiological anomalies associated with metabolic and cardiovascular disease, has led to the hypothesis that there is a "target" level of adipose tissue, i.e., an individually determined level of body fat [99]. This level would depend on the great adaptability of the regulatory mechanisms described above, and would explain why pharmaceuticals targeted at the modulation of such processes (e.g., appetite-lowering drugs) generally fail. This has not been completely elucidated, but this concept is at the core of the main theories explaining adipose tissue capacity and weight control.

It has been proposed that one of the most important mechanisms sparking adipose tissue dysregulation is hypoxia [100]. Since the white adipocyte accumulates lipids in a single goblet, cellular size largely depends on the amount of stored lipid. At some point, adipocyte hypertrophy would surpass the vascular capacity of the tissue, i.e., the size of the hypertrophic cell would become larger

than the distance at which oxygen can diffuse. The abnormally hypertrophic tissue would become hypoxic resulting in the generation of reactive oxygen species and triggering apoptosis. It is plausible that such changes are responsible for the abnormal activation of resident macrophages, which would undergo a phenotypic change from their normal M2 anti-inflammatory to a M1 pro-inflammatory state. The change in the inflammatory milieu would trigger a cascade of events that impairs normal adipose tissue function. Indeed, a study comparing subjects with a nascent metabolic syndrome (at least three criteria but without diabetes, severe dyslipidemia, symptomatic atherosclerosis or alcohol abuse) and healthy controls measured levels of different markers at the tissue level (via adipose tissue biopsy) [101]. Individuals identified as having a nascent metabolic syndrome had significantly higher levels of inflammatory markers such as IL-1β, IL-6, MCP-1, as well as leptin [102,103]. Apart from hypoxia, other factors such as the accumulation of organic pollutants (e.g., pesticides, flame retardants, PVC) in the adipose tissue have been proposed to contribute to adipose functional impairment [104]. However, the role of social factors closely associated with the development of metabolic and cardiovascular health has seldom been addressed. In summary, adipose tissue dysregulation is one of the foundations on which metabolic disorders –and subsequently cardiovascular risk– stand on.

I.D Social Determinants of Health

The previous sections were dedicated to document how the etiopathogenesis of CVD is rooted in metabolic dysfunction, and how this is in turn considerably dependent on adipose tissue dysregulation. In addition, it was illustrated how the burden of CVD cannot be fully attributed to traditional risk factors, and that risk determinants inherent to the individual's environment are increasingly being studied to fill this theoretical gap. This is particularly relevant in the context of psychosis, where the abnormally high prevalence of CVD is a critical problem. Among those environmental factors, social

determinants of health are of prime importance in this context since these are significantly associated with an increased prevalence of CVD, metabolic disorders and PSD.

I.D.1 Overview

Although the importance of the environment for health was recognized in ancient Greece, and some of these ideas –such as aqueducts and sewage– were implemented on a large scale by the Romans, it was the advent of the industrial revolution that brought with it the first modern ideas of public health, prevention of disease, and the notion that social conditions are associated with health [105]. The expanding need for a labour force in the first part of the 19th century resulted in a rapid influx of population into England's cities. For instance, London's population rose from 958,000 in 1801 to 1,948,000 in 1831. Unfortunately, mortality rates soared as well, almost doubling in some places (e.g., Bristol: 14.6 per 1000 in 1831, 27.2 per 1000 in 1844). Soon it became evident that the lack of available housing resulted in overcrowded neighborhoods. As such, it was common to see large families living in one room, and for hundreds of persons to share one outdoor toilet. Regrettably, the impact of social conditions on health only became evident to the authorities after a series of typhoid outbreaks pummeled these factory-working communities (which jeopardized economic expansion). While this resulted in the creation of commissions to understand this problem, tangible sanitary measures took at least four decades to start being implemented [105]. Another century was needed to arrive at the recognition of the pervasive impacts of social conditions on health. This breakthrough came also from England with the demonstration that socioeconomic gradients are inversely associated with mortality rates [106]. Since then, research on the social factors that determine health has grown exponentially [107], and this issue is currently being pondered by multiple stakeholders. Although still primarily based on the socioeconomic dimension, a report produced by the World Health Organization in 2008 stated that: "together, the structural determinants and conditions of daily life constitute the

social determinants of health and are responsible for a major part of health inequities between and within countries" [108]. Besides, many other aspects of the social environment beyond socioeconomic deprivation have profound impacts on the individual's health. As such, the definition used in the present study is inclusive, and encompasses all the factors from the social environment that have been proven to exert an influence on the individual's health.

Given that PSD are developmental in nature, the relevance of a social determinant of health in the context of psychosis –and the comorbidities commonly associated with it– would depend on its presence and preponderance during developmental periods (e.g., childhood). In addition, such determinants should also be affiliated with the risk for such comorbidity. This is central when looking at the onset of psychosis, since the unfolding of comorbid conditions –metabolic in this case– is a long process that takes decades [109]. Among the social determinants of health that correspond to these criteria, four factors are supported by substantial volumes of evidence: childhood trauma [110], social and material deprivation [111], immigrant background [112], and minority status [113]. The latter three have common origins in inequity and discrimination, although there is adequate evidence documenting independent effects on health for each of these factors. Moreover, their effects are not only associated with disparities in healthcare or living in deprived areas, but also with chronic psychological stress, particularly during development [114]. More specifically, lifetime discrimination (e.g., inequitable access to housing or healthcare) has been associated with heightened cortisol responses [115]. The four phenomena described above are thus the focus of the study of the social dimension in the present project.

I.D.2 Social Determinants of Health and Psychosis-Spectrum Disorders

One of the most compelling indications of the role of the environment on psychosis is its recurrent association with urbanicity [116]. Indubitably, the urban environment is a proxy for the presence of a multitude of factors such as air pollution, overcrowding (increasing the risk of communicable disease), and cannabis use among many others [117]. However, independent and important associations between PSD risk and social phenomena have also been documented, including social deprivation, social cohesion, social fragmentation, and even voting turnout [118]. These factors are representative of social capital, and are indicators of the social conditions in which the individual is reared. In addition, social adversity is not an isolated phenomenon, and there is important evidence indicating that different forms of adversity have a cumulative effect on the risk for PSD.

The association between PSD and childhood trauma is robust, and has been thoroughly studied. A recent meta-analysis scrutinized a 30-year span of research on this field, gathering 26 studies with a total number of 79,397 participants [119]. The risk for developing a PSD was increased almost three-fold (OR= 2.78) in individuals with a history of childhood trauma, irrespective of its type. When looking separately at different types of trauma, the odds for the development of a PSD were significantly increased in those individuals who were victims of sexual abuse, physical abuse, emotional abuse, neglect or bullying. Among other adverse or traumatic experiences, death of a parent did not reach statistical significance.

The relationship between socioeconomic deprivation and PSD has been observed for decades[120]. Two opposing theories were initially formulated: the "social drift theory", which stated that suffering from a PSD will cause economic hardship and economic loss, and the "breeder" hypothesis which primarily pointed towards environmental risk factors as the origin of psychosis [121]. After decades of research, it has become evident that both are true [122,123], although the debate between the proponents of these hypotheses seems to continue [124,125]. As mentioned before, socioeconomic deprivation,

particularly when growing up in a deprived neighborhood, is a risk factor for PSD. This finding has been reported in multiple cohorts across different countries [126,127]. Of particular relevance for the present study is the documentation of this phenomenon at the Prevention and Early Intervention Program for Psychosis in Montreal, Canada (PEPP-Montreal), where the project described in the present monograph is based. In the epidemiological catchment area served by PEPP-Montreal, living in neighborhoods with worse indices of social and material deprivation significantly increased the risk for having a PSD diagnosis (RR-social= 1.84; RR-material= 1.75) [128].

Migration has been one of the most conspicuous factors associated with a higher risk for PSD, but as in the case of socioeconomic deprivation, this observation has not been without controversy. The notion that migration is associated with PSD was initially documented in 1932 based on a review of a series of cases of Norwegian migrants to the United States of America [129]. It was proposed that since these migrants had a history of poor social adaptation in their home country, migrants have a hereditary predisposition to schizophrenia. This theory came to be known as the "selection hypothesis". In addition, the methodological challenges stemming from the fact that migration is intimately associated with ethnicity further blurred the picture. In recent years, the risk conferred by being a migrant, independent from the individual's ethnic background, has been widely documented and accepted, while at the same time, the selection hypothesis has been disproven [130,131]. A compelling example comes from a study conducted in Sweden with Finnish immigrants, two populations with shared genetic [132], ethnic and cultural roots. Using national hospital discharge records (a total of 2.2 million), cases with a diagnosis of any PSD or schizophrenia were identified. The authors found that when compared to the majority population (Swedes), first-generation immigrants of Finnish origin had a significantly higher risk of being hospitalized for any PSD (HR women =2.25, HR men =2.75) or schizophrenia (HR women =2.33, HR men =2.10). Moreover, the risk was still found to be significant for second-

generation immigrants for both diagnostic entities: any PSD (HR women =2.20, HR men =2.44); and schizophrenia (HR women =2.20, HR men =2.43) [133].

Belonging to an ethnic minority group is associated with an increased risk for PSD. In a meta-analysis of studies conducted in the United Kingdom from 1950 to 2009, it was ascertained that, when compared to the baseline incidence for the majority population (white British), some ethnic minorities had significantly higher incidences of PSD. For example, having an African ancestry, regardless of immediate origin (e.g., Caribbean, African), is associated with a four-fold increase in the prevalence of schizophrenia. Furthermore, differences are also seen between specific immediate ethnic origins within African ancestry, where the prevalence of schizophrenia was even higher in groups such as Caribbean (RR=5.6) or black African (RR=4.7). Moreover, while the highest rates of schizophrenia were found in the population with African ancestry, other ethnicities were affected as well. For instance, having South Asian ancestry also carried significantly higher risk increase (RR=2.4) when compared to the baseline population (White British) [134]. While minorities often face multiple social adversities, being a victim of ethnic discrimination has been associated with psychotic symptoms. In two community-derived, non-clinical populations, experiencing frequent ethnic discrimination at moderate or high levels was associated with higher odds for having psychotic experiences such as hallucinations and delusions even after controlling for demographic characteristics [135,136].

While the present study focuses on the factors mentioned above, in recent years, other social phenomena have been gaining recognition as unquestionable determinants of health. Among these, peer victimization is worth mentioning given its pervasiveness and the growing recognition of its role. While not as thoroughly studied as other forms of childhood adversity, evidence of the sequelae of peer victimization has been mounting in the last decade. A recent review and meta-analysis explored this issue, focusing on psychotic-like experiences in non-clinical populations, and in cohorts of patients

with psychotic disorders [137]. In non-clinical samples, a history of peer victimization in childhood increased the risk of psychotic-like experiences more than two-fold (OR= 2.3). In clinical populations, patients with psychosis were four times more likely to report a history of peer victimization, and in one surveyed study, bullying was predictive of antipsychotic use. However, the modest number of studies hindered the formulation of definitive conclusions. Nevertheless, further studies with longitudinal designs have confirmed the noxious impact of bullying on the risk for the development of psychotic symptoms [138-140]. This is also supported by the higher frequency of reports of peer victimization in childhood among FEP patients when compared to controls [141].

Finally, it is important to mention that childhood adversity in general, and trauma in particular, seem to have a cumulative (i.e., dose-response) effect. The presence of childhood adversity was retrospectively assessed in a sample of outpatients (recruited from specialized mental health services) with diagnoses of schizophrenia, other PSDs, and bipolar or unipolar depressive disorders. The authors employed a questionnaire appraising seven different types of childhood adversity, which were aggregated to construct a composite measure. A dose-effect relationship was documented between the number of childhood adversity events and the presence of hallucinations or delusions [142]. In an epidemiological study analyzing two large-scale nationally representative surveys (from the U.K. and the U.S.), the cumulative effect of childhood adversity was estimated [143]. In both samples, the magnitude of the odds ratios increased proportionally to the number of traumatic events.

In summary, there is ample evidence documenting the negative effects of different aspects of the social environment on mental health as reflected in the increased rates of PSD in populations exposed to noxious psychosocial phenomena. Moreover, it has also become clear that such exposures have a cumulative effect.

I.D.3 Social Determinants of Health and Metabolic Disease

While it would seem easier to acknowledge that there is an important link between the social environment and mental health, this might seem less obvious to assume when it comes to physical health. Nevertheless, as illustrated at the beginning of this chapter, the association between social factors and physical health is clear and robust, and its relevance has been increasingly being recognized in the study of the etiopathogenesis of disease and in epidemiological models of disease. As it was the case for PSD, a brief overview of the social determinants of health that are the focus of this project will be examined in the context of cardiometabolic disease.

The consequences of childhood trauma on metabolic health have been amply studied. A recent meta-analysis estimating the effects of maltreatment during childhood on body weight from 41 different studies found that victims of childhood abuse had an increased likelihood to be obese (OR= 1.36 CI= 1.26–1.47) [144]. Moreover, most types of trauma examined by these studies, except emotional neglect, carried a significant increase in the odds for obesity, with sexual abuse having the strongest effect (OR=1.43; CI=1.27–1.62). A different meta-analysis exploring the influence of childhood trauma on the prevalence of DM2 found a significantly increased risk in those individuals exposed to adversity (OR=1.32; CI=1.16–1.51) [145]. Regarding specific forms of trauma, it was found that the impact of sexual abuse on the prevalence of DM2 was similar to that of obesity (OR=1.39; CI=1.28–1.52), although in this case, neglect was demonstrated to have an even stronger weight (OR=1.92; CI=1.43–2.57). Furthermore, a separate study found that a history of childhood abuse of moderate to severe magnitude predicted the number of criteria that individuals met for metabolic syndrome [146]. When examining different types of trauma, a sexual dimorphism was observed: sexual and physical abuse were significant predictors for women, while physical and emotional abuse were for men. Likewise, peer victimization in childhood has also been linked with obesity. Data from the 1958 British birth

cohort (n= 7102) provided evidence that obese women were more likely to report being victims of peer victimization during childhood [147].

Several studies in different parts of the world have found an association between the presence of metabolic anomalies and having grown up in a deprived environment. In Canada, a population-based study conducted in Ontario determined that a childhood history of socioeconomic deprivation, as determined by growing up in a household that received social assistance, significantly predicted a higher BMI in early adulthood [148]. A different study, using the income-to-needs ratio metric to estimate income trajectories in childhood (birth to age 15), illustrated that growing up in a family with a stable low income or an unstable low income predicted higher measures of BMI and waist circumference, compared to being raised in a family with an unstable or stable adequate income [149]. In a more comprehensive fashion, a systematic review of childhood socioeconomic status (SES) included 30 different studies and concluded that there was an inverse relationship between family SES in childhood and obesity in adulthood, with a stronger association among women [150].

Given the important influence of genetics, nutrition, and geography on the incidence of any medical condition, it is not surprising that the role of ethnicity on metabolic disease has been thoroughly studied. A meta-regression analysis based on studies produced by four large nation-wide epidemiological surveys in the U.S. documented that having an ethnic minority background predicted a higher prevalence of obesity when compared to the majority white (non-Hispanic) ethnic group [151]. African-Americans (non-Hispanic) had the largest difference (10 percentage points) with the difference being worse for women (20 percentage points). The only ethnicity with a lower prevalence than the national average was the Asian-American group. The authors had hypothesized that these differences mainly stem from the fact that minorities are more likely to live in socially disadvantaged environments. However, in an ancillary analysis including only those studies that had controlled for

SES, the individual effect of ethnicity was still evident, and the authors concluded that: "ethnic/racial differences in BMI are not fully explained by individual SES". In a longitudinal study that examined health factors in a cohort of African-American women, participants were asked to answer questionnaires on perceived racism and provide information on their place of residence to match the data with neighborhood ethnic composition [152]. Perceived racism was significantly associated with a higher incidence of obesity (IRR=1.31; CI=1.20–1.43). This relationship was particularly evident when clustering scores of perceived racism by quartiles, where it was shown that as perceived racism increased, the incidence of obesity rose in parallel. The relationship between perceived discrimination and body mass composition (BMI and waist circumference) was assessed in a different study [153]. Contradicting the main assumptions of the study, perceived discrimination was not associated with either anthropometric measure in African-Americans or Hispanic-Americans. However, the association was significant in white participants with an Irish, Italian, Jewish, or Polish ancestry. These seemingly paradoxical findings prompted the authors to postulate that minorities with an African or Hispanic ancestry could have developed mechanisms to cope with discrimination given their recurrent experiences of discrimination.

The observation that the duration of U.S. residency for Hispanic minorities shows a positive correlation with obesity rates has been dubbed the "unhealthy assimilation model". This has been demonstrated by looking at the prevalence of obesity across multiple generations of Hispanic immigrants, where it has been observed that second- and third-generation immigrants have significantly higher odds of being obese (OR= 1.49 and 1.35 respectively) than first-generation immigrants [154]. This remained true after taking into account other environmental variables. It was concomitantly revealed that living in a disadvantaged neighborhood conferred additional risk (OR=1.32). On the other hand, if the person's neighborhood was composed of more foreign-born residents (i.e., ethnically diverse), a protective effect was observed (OR=0.87).

Perhaps more critical is the documentation of such effects already during childhood. In a large representative sample also from the U.S., the prevalence of overweight and obese children aged 10 to 17 was determined in different immigrant groups (N = 46,707) [155]. After controlling for socioeconomic and behavioural factors, which accounted for a significant proportion of the variance, second- and third-generation immigrant children had increased rates of obesity and overweight. More importantly, the protective effect seen in first-generation immigrants (e.g., Asian ancestry) was lost by the third generation. This phenomenon is not exclusive to the U.S. In Canada, a study conducted in Montreal with immigrant youth documented that the rate of BMI increase in first-generation children was significantly lower when compared to their second- generation and non-immigrant peers [156].

In the Netherlands, migrant groups from Suriname, Morocco and Turkey –with the exception of Turkish women and Moroccan men– were shown to have a higher prevalence of overweight individuals (i.e., BMI≥25 kg/m2) [157]. The illustration of the loss of the protective effect associated with being a first-generation migrant across countries and in migrants from different backgrounds is a testament to the pervasiveness and the magnitude of the burden that migration exerts on metabolic and physical health.

In summary, resembling what happens in the case of PSD, different forms of adversity act as determinants of metabolic health, and the influence of such social phenomena seem to be more calamitous during childhood. While adverse social factors often coalesce and have an additive effect, the current level of evidence allows the unambiguously assertion that each of the illustrated social determinants of health has an independent effect on the risk for metabolic disease.

I.D.4 Social Determinants of Health and Cardiovascular Disease

As illustrated earlier, cardiovascular disease is the result of the confluence of multiple chronic pathophysiologic phenomena resulting in arterial damage, which in turn leads to ischemia and tissue necrosis, having devastating or fatal consequences in organs such as the heart, brain and kidney. Since these phenomena are chronic, their onset is typically observed after the fifth decade of life. As such, the study of social determinants of health, particularly when exposure occurs during childhood, becomes methodologically challenging. In addition, disadvantaged social conditions would also lead to different types of noxious behaviors and exposures such as tobacco smoking [158] or unhealthy diets, which would also mediate the effects of social deprivation. Nevertheless, considerable evidence linking social determinants of health and CVD is available.

Two different meta-analyses have confirmed the noxious effects of childhood trauma on cardiovascular health in adulthood. The first one included a total of 123, 663 participants and found that a history of adverse experiences in childhood carried a two-fold increase in the risk for CVD (OR=2.07; CI=1.66–2.59) [159]. The second found a significant relationship between childhood abuse and cardiovascular outcomes (i.e., myocardial infarction and cerebrovascular disease), with an effect size higher than the average for other medical conditions [160]. This phenomenon has gained important notoriety, and indeed the American Heart Association has recently produced a statement underscoring the strength of the evidence, pinpointing the challenges of tackling this problem at the public health level, and providing recommendations for research and detection in the clinical setting [161].

The differences in rates of CVD by ethnicity have been widely reported, and multiple theories have been formulated to explain this phenomenon, including differences in exposure to risk factors [162], pathophysiological vulnerability [162], disparities in healthcare access [163], and gene polymorphisms [164]. Thus, dissecting the different factors associated with ethnicity is a difficult task. However, lifetime

racial discrimination has been associated with increased blood pressure, and this effect was found to be significant in older persons, even after controlling for different covariates such as BMI, education, social deprivation, personality and life stress [165]. Moreover, everyday racial discrimination predicts higher nocturnal resting blood pressure in normotensive subjects [166]. However, another study failed to determine an effect of discrimination on CVD risk, although it was conducted in a population of African-Americans with higher socioeconomic and educational backgrounds, which are not representative of the reality of the majority of this (and many other) ethnic groups in the U.S. [163].

The study of the effect of migration on the long-term and intergenerational incidence of CVD presents its own complexities and challenges, often requiring the utilization of systematic national records to determine such associations. In a study employing nationwide population registries from the Netherlands, a total of 944,280 individuals from a minority background (making 12.5% of the surveyed population) were included [167]. This study documented that the incidence of CVD events varied widely depending on ethnic background, but incidence in second-generation migrants tended to resemble that of the host population. In a different study using the Swedish national register, the incidence of myocardial infarction was found to be higher in migrants after controlling for age and calendar registry year (men RR=1.17; CI 1.13-1.21; women RR=1.15; CI 1.09-1.21) [168].

It has already been laid out how socioeconomic deprivation was the first social determinant associated with health and disease. Importantly, the recognition of the effects of a deprived environment, particularly on cardiovascular health, has now been documented in different parts of the world. In one of the most recent examples, a study from the Asia-Pacific region included a total of 24 cohorts which amounted to more than two million persons [169]. Despite important regional discrepancies, it was documented that after taking into account conventional risk factors and alcohol

use, low SES was associated with a significant increase in cardiovascular mortality (HR=1.78; 95%CI 1.42 -2.23).

In conclusion, despite important methodological challenges, and a multitude of moderating factors, social determinants of health have been documented as predictors of cardiovascular morbidity and mortality, which is congruent with the effects that social conditions exert on its leading causes such as metabolic disease.

CHAPTER II

HYPOTHESES

II.A Historical, Philosophical and Theoretical Foundations of the Research Hypothesis

Schizophrenia has not only been the most representative of psychotic disorders but perhaps the most recognized mental health condition. Much of what psychiatry is has been shaped by the study of schizophrenia as a disorder, and the history of psychiatry is considerably contingent on the history of schizophrenia. The revolutions in medical thinking that occurred in the 19th century such as the cellular theory (Schwann 1838), associated with advances in techniques such as microscopy, fostered the identification of the biological substrates of disease[170]. The demonstration of neuronal injury in relation with some sensorimotor conditions galvanized the cellular explanation of neurological disease and brought about an explosion of neuropathological correlations for syndromes such as multiple sclerosis, tabes dorsalis, and Brown-Sequard's paralysis, to name a few. Such a way of thinking permeated the study of behavioral disorders, and indeed in the 19th century, some authors were already proposing the localization of 'madness' in the brain (Brigham 1844). However, the lack of observable cellular changes in these conditions, which did not parallel what was happening in neurology, resulted in the gradual relinquishment of the hunt for a neuropathological substrate of mental disorders. The resulting theoretical shift towards doctrines proposing purely functional explanations for the origins of psychiatric disorders, such as psychoanalysis, dominated psychiatric thinking for almost a century. After the mid-20th century, the growing understanding of genetics, and the discovery of antipsychotics reignited the interest in the search for the biological foundations of schizophrenia, but even two decades after the latter, progress was minimal, which resulted in declarations such as the discouraging "Schizophrenia is the graveyard of neuropathologists" [171]. However, neuropathology and other fields like radiology were just awaiting the advent of new technologies to acquire the capability for documenting such biological substrates. Nowadays, there is a plethora of brain changes demonstrated in schizophrenia such as hemispheric asymmetry, reduced neuronal sizes, quantitative and qualitative alterations in the synaptic-dendritic architecture, and neuroinflammation to name a few [172].

While today it would be easy to dismiss outdated psychiatric doctrines that have come and gone throughout history, these theories have contributed enormously to understanding the multiple aspects that influence psychiatric disorders. A unifying theory of mental health (and the mind) cannot be attained without taking into account the knowledge gathered along the course of this history. In other words, any purely reductionist doctrine, whether molecular, physiologic, social, or anthropological, is fated to fail.

The previous chapter was dedicated to the factors associated with the onset and development of psychotic, metabolic and cardiovascular disease. The objective of this chapter is to provide an overview of the major theoretical frameworks explaining the emergence of pathological processes, with a focus on those relevant to the present study. The inclusion of these is necessary to articulate the concepts illustrated in the previous chapter, and to apprehend the objectives of the project embodied in this monograph.

II.A.1 Developmental Origins of Health and Disease

Despite the important volume of evidence documenting the presence of biological changes in schizophrenia, two paramount ideas that stemmed from the purely functional doctrines of psychiatry are central to understand the origins of PSD: important etiological elements are laid down during the development of the individual, and the psychosocial environment is an important contributor to such determinants [173].

The articulation of clinical observations, epidemiological data, neuroscience, and social theory has made it possible to postulate that schizophrenia is a neurodevelopmental disorder [174]. Some

observations have been decisive to arrive at this conclusion. The first one is the presence of a premorbid state, in which behavioral and cognitive impairments largely predate the manifestation of patent symptoms of psychosis. That this premorbid state often overlaps with childhood and adolescence, periods during which the brain is still developing and being "fine-tuned" [175], strongly suggests a progressive deviation from normal brain function in schizophrenia [174]. The second is the robust association between perinatal insults and the incidence of schizophrenia [9], and the recognition of specific windows of vulnerability temporally related to such injuries [176]. The final observation pertains to the diathesis-stress model, the notion that psychotic disorders arise if an individual with an increased susceptibility is exposed to stress [177]. This concept will be further explored.

On the other hand, while metabolic and CVD disease are not commonly considered to be developmental disorders, the notion that health and disease have developmental origins was greatly supported by epidemiological observations regarding these conditions. A key piece of evidence leading to this hypothesis was the observation that low weight at birth predicts the appearance of insulin resistance, obesity, dyslipidemia, and hypertension (i.e., metabolic syndrome), and a consequential increase for the risk of CVD [178]. This hypothesis was further supported by the revelation that individuals born to mothers who were pregnant during the 1944-45 Dutch famine (caused by the German blockade of basic supplies) were likelier to become obese and develop coronary heart disease [179].

That physiologic function can be altered by the environment to result in health or disease implies the presence of the flow of information between the environment and the organism [180]. First, the organism needs to have the capacity to respond to information from the environment, at least to a certain degree. This "plasticity" allows the implementation of changes that will alter the trajectory of development guided by the environment. Second, the information from the environment should be

capable of being recognized and acted upon by the organism, in other words, environmental information "programs" the organism's physiology. The objective of this phenomenon is to provide adaptive advantages for the organism to thrive under the prevailing ecological conditions. Under normal circumstances, this would confer an evolutionary advantage as the organism would have better odds of surviving these changes. However, if there is a mismatch between the adaptive results of programming and the actual conditions, the organism will be "maladapted" to its environment. This is patently exemplified in the Dutch famine study, where individuals were programmed for scarcity, but were maladapted to live with abundant sources of energy [181].

Until recently, the genome was regarded as a monolithic collection of instructions with the sole purpose of building up molecules, whose structure determined the fate of physiological function. The paradigm shift brought by epigenetics, i.e., the recognition of the plasticity of gene expression, and the capacity of the environment to modulate it, has allowed for a deeper insight into the factors that determine the onset of disease. It has also provided the biological foundations for the developmental origins of health and disease and has validated the role of environmental determinants in the etiology of disease. It is important to indicate that epigenetic changes have been documented across different systems and organs of the body [182], which is also relevant for the theoretical propositions of the present monograph.

II.A.2 The "Common Soil" Hypothesis

One of the messages that hopefully have been conveyed by the previous chapter of this monograph is that metabolic disease is an important component of the pathophysiology of CVD, and that this implies the sharing of common origins. The wealth of evidence available today in this regard makes this obvious, but this idea is relatively new, and was initially formulated two decades ago based on a

series of clinical and epidemiological clues [183]. First, a collection of different observations had been pointing out some inconsistent etiopathological relationships, and some established ideas were put into question. One of the first publications in this regard explored the paradoxical effect of vascular size in the association between atherosclerosis and DM2 [184]. While it was clear that microvascular disease manifestly depended on DM2, macrovascular disease did not. It was also pointed out that there were no differences in the prevalence of CVD when comparing newly-diagnosed versus chronic DM2 patients. In parallel, the increasing understanding on the association between insulin resistance and the degree of glucose intolerance; the accumulation of evidence on the pathophysiological roles that insulin resistance plays in DM2, hypertension and dyslipidemia; and the observation that these conditions frequently overlap prompted the formulation of the concept of metabolic syndrome [57]. Finally, the first epidemiological associations between childhood mortality and adult chronic disease, metabolic disease and CVD in particular were illustrated [178]. These three examples led to the proposal of the "common soil hypothesis", the notion that "cardiovascular disease and diabetes share common genetic and environmental antecedents, i.e., that they spring from a "common soil." [183].

In psychiatry, the proposal of an etiological overlapping among disorders has been guided by clinical observations and largely attributed to genetic factors. A well-characterized example in the context of PSD is the implication of various loci in the susceptibility for both schizophrenia and bipolar disorder, which is greater than that of the latter with major depression [185]. However, environmental determinants seem to have not been considered as potential risk factors shared across different mental health disorders. As an example, perinatal complications have been among the hallmark risk factors associated with schizophrenia [9]. However, while this phenomenon has been documented to also increase risk for other mental health disorders such as obsessive-compulsive disorder [186], attention deficit hyperactivity disorder [187], depression [188], and autism-spectrum disorders [189], the recognition of the potential of this phenomenon as a common determinant of mental health has not been proposed.

As previously mentioned, most of the research on the phenomenon of the excessive comorbidity in psychotic disorders has focused on the noxious effects of tobacco smoking [190] and sedentary behaviors [191], and on the side-effects of antipsychotics [22]. Some authors have made important inroads in the determination of the aspects associated with this phenomenon. Studies taking place during the first-episode of psychosis are particularly relevant, as participants have not, or have just recently been treated with antipsychotics, and have shorter exposure to the effects of tobacco smoking. Recently, a meta-review provided a picture of the landscape of comorbidity in FEP [48]. Significant associations were found between FEP and immune, cardiometabolic, hypothalamic-pituitary-adrenal and neural (neuroanatomical, neurophysiological, and neurochemical) manifestations. It was concluded that: "Although the evidence presented indicates that these alterations are present in early psychosis, this does not indicate whether these abnormalities are linked to the clinical expression of the disorder". Such conclusion is congruent with the objective of the authors, which was to demonstrate that psychosis is a "multisystem disorder". This objective contradicts that of the present monograph, but the unquestionable value of such a body of evidence exceptionally supports one of the main theoretical components of the hypothesis of the present project: that comorbidity in PSD is explained by the presence of common risk factors, in particular, social determinants of health. In other words, this project hypothesizes that a multitude of disorders across different systems are promoted by the same environmental risk factors i.e., that PSD and metabolic disease (and by extension CVD) "spring from a common soil".

II.A.3 The Stress-Diathesis Model

In medicine, the term "diathesis" has traditionally been employed in hematology to describe the tendency of some individuals to bleed excessively. The presence of an inherent predisposition for the

abnormal hemorrhagic phenomena that runs in some families has been known for centuries. For instance, in writings from the Talmud dating around the 2nd century, circumcision in boys whose brothers had died from bleeding after this procedure, was proscribed [192]. In the 19th century, the term "bleeding diathesis" was utilized to describe this phenomenon [193], although it took more than a century of discoveries to unravel the complex biochemistry of blood coagulation factors, and by extension, understand the myriad of possible etiological sources for this syndrome.

The word "diathesis" is not restricted to hematology though. The Greek word *diathithenai*, which literally translates to "to arrange", and indicates disposition or state is the source of this expression. Thus, in a generic sense, a diathesis connotes the presence of an increased susceptibility for the development of a particular condition. Perhaps the most definite summary of what a diathesis is was formulated at the end of the 19th century by Hutchinson –a surgeon with a deep interest in the origins of disease– in his book The pedigree of disease (1885): "If there be distinct proclivity, we must then use a stronger term, and speak of diathesis; and I would define a diathesis to be any bodily condition, however induced, in virtue of which the individual is, through a long period, or usually through the whole life, prone to suffer from some peculiar type of disease. Some diatheses are inherited, others are acquired. Of some, the effects are permanent or constant; of others, they are transitory, or recurrent after intervals of health" [194]. Despite the period from which these observations come from, this insightful definition applies to this day.

In psychiatry, the term "diathesis" has been used in the context of schizophrenia for more than four decades [177]. Its utilization stemmed in part from the growing recognition of the role of genetics in schizophrenia (and was further endorsed by the observations on heritability), but also because of its limitations [195]. At this point, the difference in the concordance rates between monozygotic and dizygotic twins had been recently acknowledged [196], but an explanation was still needed to understand

this discrepancy. On the other hand, the role of stress in the development of disease had been recognized since the mid-20th century [197]. This was actively studied in schizophrenia (Rosenthal 1970), leading to the recognition of its associations with it, particularly as a trigger of psychosis [198]. Further research has demonstrated that stress is a key mediator of the effects that social determinants of health have on the development and appearance of various medical conditions, including PSD, metabolic disease, and CVD [199-201].

II.B Hypotheses: Rationale, Formulation, and Objectives

To sum things up, it has been indicated that psychotic disorders are marked by excessive rates of comorbid conditions, with CVD having the most detrimental impact on mortality. The magnitude of this phenomenon seemingly surpasses what would be expected to arise from traditional risk factors, suggesting the involvement of other determinants, although this has not been explored yet. In order to delve into the origins of this conundrum, it was first pointed out that metabolic dysregulation is one of the pillars of the pathophysiology of CVD, and as such, any inquiry should start there. Indeed, there is a strong association between PSD and metabolic disease, but more importantly, the presence of clinically relevant metabolic changes already at the debut of psychotic symptoms is well-supported by current evidence. The importance of the latter fact cannot be underscored enough given that at that point exposure to antipsychotics is minimal. Thus, the effects of traditional risk factors such as tobacco smoking and physical inactivity have been only present for a short period of time in relation to the natural history of metabolic disease. This is a compelling argument pointing to the existence of other etiological elements promoting risk early in life. Next, it has been indicated how the landscape of risk factors has been expanded, and that there is unmistakable evidence supporting the role of various social factors as pivotal determinants of health. Of particular importance is the fact that some of these social determinants of health are risk factors shared by CVD, metabolic disease and PSD, and that their effect

sizes are substantial. In parallel, it was reviewed how a wealth of evidence indicates that the adipose organ is the cradle of metabolic disease, and by extension of CVD, at least at the pathophysiological level.

Since it was argued that comorbidity might be better explained by environmental rather than genetic influences, it was necessary to look for factors that have a ubiquitous presence, and are pervasive enough to increase the odds for the appearance of all these conditions. Four social determinants of health fit these criteria, and as such they make part of the "common soil" (among many other influences) from where PSD, metabolic disease, and CVD spring. These are: childhood trauma, belonging to an ethnic minority, having a migrant background, and socioeconomic deprivation (the latter three associated with discrimination). This notion is reinforced by the influential role that these social determinants of health have during childhood and adolescence, where they are increasingly being recognized as prominent elements in the developmental origins of all three pathological conditions. Finally, it is important to bear in mind that the influence of genetic variants and early-life environmental factors (e.g., prenatal stress or maternal undernutrition) is definite for the genesis of specific disease vulnerabilities, i.e., diatheses. On the other hand, the above-mentioned social determinants of health have one thing in common: stress. As stressors, depending on their timing in the life of the individual (early childhood versus adulthood), these social determinants of health could either "program" disease promoting a diathesis, or interact with a diathesis, to trigger disease. This is the classical diathesis-stress model previously postulated for PSD. As mentioned, these effects depend on when in the life of the individual these insults occur, blurring the line where diathesis ends, and stressor begins. This can be recognized in models of PSD postulating the interaction between the environment and the individual's constitution, often referred as "two-hit" or "three-hit" hypotheses [202,203]. Despite the recognition of these processes, comorbidity in PSD has not been examined through the lens of the above-mentioned models of disease theories.

As such, adhering to the philosophy, and following the lessons from these models of disease led to the formulation of first main hypothesis of this project:

Patients with PSD bear a metabolic diathesis, i.e., an increased vulnerability for the development of metabolic disease. This metabolic diathesis is mostly acquired (as opposed to being inherited), and is importantly determined by social factors.

When also taking into account the pathophysiology of CVD, it was also possible to postulate that:

Given that metabolic disease is rooted in adipose tissue dysfunction, drug-naive patients going through a first episode of psychosis will already demonstrate unmistakable signs of adipose tissue dysregulation.

Therefore, the main objective of the present study was to examine the influence that social determinants of health have on the clinical and physiologic parameters of metabolic function in patients undergoing a psychosis for the first time. To fulfill this objective, this project was conducted in three phases, each one materialized in a manuscript. The first phase explored the effects of social determinants of health on the physiological regulation of glucose as indicated by levels of glycated hemoglobin. The next step was to investigate this relationship in lipid regulation manifested by clinical parameters of lipid metabolism: total cholesterol, high-density lipoprotein, low-density lipoprotein, and triglycerides. Finally, the last stage was to probe the presence of adipose tissue dysregulation as indicated by levels of adipokines: leptin, adiponectin, resistin, and chemerin, and to determine if these are influenced by the aforementioned social determinants of health.

The findings of my project were expected to help clarifying the origins of the differences in metabolic physiology associated with PSD. This could deepen the understanding of the factors promoting physical comorbidity in this population. This also contributes to build the base on which preventive and therapeutic measures addressing metabolic disease in PSD could be supported. The practical implementation of this knowledge could ultimately result in the improvement of the quality of life of these patients, as well as in a reduction in their excessive rates of mortality.

CHAPTER III

SOCIAL DETERMINANTS OF HEALTH AND PRECLINICAL GLYCEMIC CONTROL IN NEWLY DIAGNOSED FIRST-EPISODE PSYCHOSIS PATIENTS

III.A Preface

After the development of the main hypotheses of this project, the next step was to put them to test. Since Diabetes mellitus type 2 is the archetypical metabolic disorder, the examination of the hypotheses of this project started by appraising glycemic homeostasis. Previous studies in first-episode psychosis had been limited to comparisons of cases and controls, and had approached this issue mostly through the measurement of fasting plasma glucose levels [204-206]. The results were mixed, but it seemed that most studies indicated the absence of significant differences. Since glucose levels have a greater day-to-day variation, and are more easily affected by psychological stress (common at the onset of psychosis) and the length of fasting, this might have hampered the documentation of such anomalies. Indeed, those studies that had included more sensitive measures such as the HOMA-IR (Homeostatic Model Assessment for Insulin Resistance) were more likely to point to the presence of glucose dysregulation. This was further confirmed by a meta-analysis, which corroborated the presence of differences in glucose tolerance and HOMA-IR, but not in fasting plasma glucose [207]. As such, testing fasting plasma glucose levels was discarded in favour of other measures. The selected tool was glycated hemoglobin, an ingenious method to appraise the global state of glycemic control. Since the average lifespan of erythrocytes is three months, the proportion of glycated (an irreversible, non-enzymatic chemical reaction) hemoglobin reflects an average of glycemic control in the previous 8-12 weeks. This property of glycated hemoglobin was particularly advantageous for the present study because it provided a window into the past, which enormously aided in validating the notion that metabolic dysregulation in psychosis precedes antipsychotic utilization (although it will be further worsened by antipsychotic utilization). In addition, the wealth of supporting knowledge on social determinants of health allowed selecting the most relevant factors associated with psychotic and metabolic disorders, which were tested throughout the entire project.

III.B Manuscript Information

Title
Social Determinants of Health and Preclinical Glycemic Control in Newly Diagnosed First-Episode Psychosis Patients

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III.C MANUSCRIPT

ABSTRACT

Background: The abnormally high incidence of disorders of glucose metabolism (DGM) in psychotic-spectrum disorders (PSD) has often been attributed to the side effects of antipsychotics and poor life style. The influence of social determinants of health has been largely ignored, despite ample evidence linking social adversity with both PSD and DGM. The aim of this study is to examine the influence of well-established social determinants of health on preclinical levels of glycated hemoglobin (HbA1c) in a sample of first-episode psychosis (FEP) patients.

Methods: In a sample of newly admitted FEP patients, univariate analyses were used to select the main predictors of HbA1c levels from the following social determinants of health: childhood trauma, immigrant background, visible minority status, and indices of social and material deprivation. The predictors identified in the univariate analyses were tested in multivariate linear regression models including age, sex, BMI, depression, and physical anergia (proxy of sedentary behavior) as covariates.

Results: Univariate analyses identified visible minority status and childhood physical abuse as predictors of HbA1c. After controlling for covariates, minority status significantly predicted higher levels of glycated hemoglobin (β=0.23; p=0.01), and physical abuse had a marginally significant effect (β=0.23; p=0.06). Other predictors were not significantly associated.

Conclusion: FEP patients from a visible minority or who were victims of childhood physical abuse have higher levels of HbA1c at admission when compared with other patients. This might suggest an increase in risk for the development of future DGM. If confirmed, preventive strategies could be tailored for these groups.

Keywords: First episode psychosis; Social determinants; Biopsychosocial; Child maltreatment; Race; Immigrant mental health; Income inequality.

INTRODUCTION

Patients with psychosis-spectrum disorders (PSD) have twice the risk of developing diabetes mellitus compared to the general population[208]. This is a concerning public health problem directly implicated in the increased cardiovascular morbi-mortality and reduced life expectancy observed in PSD [14,209]. The epidemiological association between PSD and disorders of glucose metabolism (DGM) – such as diabetes mellitus– has been attributed to the secondary effects of second-generation antipsychotics[210], and lifestyle changes associated with the negative symptoms of psychosis[211]. However, it has been known for more than a century (already in the pre-neuroleptic era) that schizophrenia and diabetes mellitus often co-occur[2,212]. More recently, meta-analytical evidence has documented the presence of different pre-diabetic metabolic anomalies in first-episode psychosis (FEP) patients[207]. Thus, some patients with PSD might bear an increased vulnerability for the development of DGM –independent of, but aggravated by– the secondary effects of antipsychotic medications and sedentary behaviors. The origin of such shared vulnerability is unknown, but an exploration of potential etiological factors implicated in both syndromes might provide some answers.

Environmental factors known to increase the risk for both syndromes might (partially) account for this relationship. Notably, social determinants of health occurring during childhood and adolescence have been documented to increase the risk for the emergence of both syndromes, providing a conceptual framework to explain this association. Specifically, the most studied social risk factors common to PSD and DGM (examined in each population independently) are: socioeconomic deprivation[126-128,150], first and second-generation migration background[133,154], ethnic minority status[134,151,213], and childhood trauma[119,144,145]. The level of evidence linking each of these factors with either PSD or DGM comes from meta-analytic studies (e.g. childhood sexual abuse victim: OR=2.38 for psychosis, Varese et.al. 2012; OR=1.43 for obesity, Huang et.al. 2015); national cohort studies (e.g.

2nd-generation migrants: HR=2.25 for psychosis, Leao et.al. 2006; OR=1.49 for obesity, Ishizawa et al. 2015); and has been replicated in different countries (e.g. material deprivation and psychosis: RR=1.75 in Montreal, Canada, Anderson et al.2012; IRR=3.79 in London, U.K, Boydell et al. 2004; IRR=3.4 in Dublin, Ireland, O'Donoghue et al.2016).

Thus, since social adversity has been demonstrated to be associated with an increased risk in both PSD and DGM, it is plausible that social factors might (partially) explain their frequent coexistence. The objective of the present study is to determine the extent to which social adversity is associated with the physiological control of glucose levels in FEP patients at entry to treatment. We hypothesize that, in FEP patients with little or no previous exposure to antipsychotic medication, greater degrees of childhood trauma, higher levels of socioeconomic deprivation, being part of a visible minority, and being an immigrant (first or second-generation) will impair preclinical glucose regulation as indicated by higher levels of glycated hemoglobin (HbA1c). The FEP context is ideal to test this hypothesis given the limited prior exposure to antipsychotic medication or to longstanding sedentary lifestyles.

METHODS

Participants and Setting

The Prevention and Early Intervention Program for Psychosis (PEPP-Montréal) provides specialized care for all potential cases of FEP in an urban catchment area of just over 300,000 inhabitants in Montreal, Canada[12]. Services comprise assertive case-management, psychological and psychosocial interventions, and low-dose antipsychotic medication for a period of two years[12]. Inclusion criteria for follow-up at PEPP are: age 14 to 35 years old; DSM-IV diagnosis of non-affective or affective psychotic disorder. Exclusion criteria are: organic causes (e.g. epilepsy), IQ of less than 70, and previous exposure to antipsychotic medication of greater than one-month duration. The Research

Ethics Board of the Douglas Mental Health University Institute approved this study; all included participants granted written informed consent.

A research team conducts regular structured assessment of symptoms (Scale for the Assessment of Positive Symptoms –SAPS[214]; Scale for the Assessment of Negative Symptoms –SANS[215]), social and vocational function (Social and Occupational Functioning Assessment Scale –SOFAS[216]), duration of untreated psychosis/illness[217], medication adherence, and side effects. Inter-rater reliability coefficients for symptoms range between 0.60 and 0.84.

Outcome Variable: Glycated Hemoglobin

Since FEP patients are young, the presence of a fully developed DGM is not expected. Instead, we rely on detecting variability in HbA1c levels as an indication of the state of glycemic control[218]. The percentage of HbA1C is a function of the amount of plasma glucose available to chemically react (spontaneously) with the circulating hemoglobin molecule during the previous 8-12 weeks[219], acting as an indirect marker of insulin resistance. Clinically, HbA1C levels reflect the average state of glycemic regulation, hence its use for treatment monitoring in diabetes. Thus, measuring HbA1c at admission reflects the state of glycemic control over the previous three months (i.e., before entry), while marginally overlapping with previous medication exposure. This minimizes the potential influence of prior medication exposure. HbA1C levels were obtained from standardized clinical laboratory tests.

Predictor Variables: Social Determinants of Health

A brief description of the social adversity variables most consistently associated with both PSD and DGM follows.

The *Childhood Trauma Questionnaire* (CTQ)[220] was used to assess the degree of exposure to five different types of childhood trauma: physical abuse or neglect, emotional abuse or neglect, and sexual

abuse. This questionnaire consists of 25 items pertaining to trauma exposure during childhood (5 questions per type of trauma). Individual type and composite scores, and critical exposure thresholds were computed following the authors' guidelines.

Social and material deprivation indices were obtained from the "*Institut National de Santé Publique*" (INSPQ) in Quebec, Canada[221]. These indices are developed from the Canadian census data using six socioeconomic indicators that strongly predict health outcomes: the proportions of the population aged 15 years or more with secondary education or equivalent, employment, living alone, and without a stable relationship (separated, divorced or widowed); the average income of the population aged 15 years or more; and the proportion of single-parent families. These neighborhood-level indicators of socioeconomic disadvantage are obtained by matching the participants' postal codes with the INSPQ database.

Visible ethnic minority status was ascribed as being part of a visible minority (dichotomized yes/no) following the Statistics Canada definition: "persons, other than Aboriginal peoples, who are non-Caucasian in race or non-white in colour"[222]. Participants were considered as belonging to a visible minority if they were of non-European ancestry.

Finally, *immigrant background* refers to a familial history of recent immigration to Canada, either as a first-generation (migrating to Canada after being born elsewhere) or second-generation immigrant (being born in Canada and having at least one parent who was born elsewhere).

Potential Confounders

Levels of inactivity (depicting sedentary lifestyle), and depression scores were selected as potential clinical confounders. Scores at entry of physical anergia from the SANS scale[215] were used as a proxy of sedentary lifestyle, and those from the Calgary Depression Scale for Schizophrenia[223] as a measure of depressive symptoms. Three biological covariates are included in the analyses: age, sex, and body mass index (BMI). BMI was calculated upon entry into the service by treating clinicians, and aims to control for differences in body composition[224]. Although patients need to have less than 30 days of pharmacological treatment to be admitted to the program, we assessed the influence of previous pharmacological exposure given the metabolic side effects of antipsychotics and antidepressants. Thus, an index of previous medication exposure was calculated by multiplying the number of days of pharmacological treatment (from date of first treatment to date of HbA1c analysis) by a medication adherence coefficient for the first month of treatment. Medication adherence was rated in percentages (0%, 25%, 50%, 75% or 100%) by trained research staff[225].

Statistical Analyses

Univariate analyses were conducted first to determine whether each of the social determinants of health and the medication exposure index had a potential influence on the levels of HbA1c. Univariate analyses consisted either of Pearson product-moment correlations between HbA1c and continuous predictors (childhood trauma categories, deprivation indices, medication exposure), or t-tests for nominal variables (ethnic minority status, immigrant background). Continuous variables with skewed distributions were treated with logarithmic transformations. The different categories of childhood abuse (physical neglect, physical abuse, emotional neglect, emotional abuse, and sexual abuse) were studied separately as evidence shows that specific types of abuse differentially influence distinct physical and behavioral outcomes[226,227]. Results from univariate analyses were used to select the main predictors in the multivariate analyses. A p-value <0.1 was set as the threshold for inclusion. The multivariate

hierarchical models follow a theoretical path in which, apart from the relevant social determinants of health, biological, environmental and psychosis-associated factors are included by blocks, controlling for potential confounding effects. Thus, the first block includes biological confounders, i.e., age, sex and BMI. The second block includes the indices of material and social deprivation as standalone environmental predictors given their strong association with other examined social determinants of health[228]. The third block includes the main predictors, i.e., the social determinants of health identified in the univariate analyses. The final block includes depression and anergia scores, representing psychosis-associated factors metabolic confounders. Finally, descriptive analyses of each subsample assess their representativeness vis-a-vis the main sample. Data were analyzed using IBM SPSS Statistics 22 (2013, IBM Corp).

RESULTS

Univariate effects of the predictors of HbA1c are shown in tables 2a/2b. Childhood physical abuse had a marginally significant positive correlation with HbA1C (r= 0.17; n= 100; *p*= 0.08). Visible minority status significantly predicted higher levels of HbA1C (*t*= 1.63; n=219; *p*=0.05). Other social determinants of health did not predict levels of HbA1C. The average number of days of pharmacological treatment prior to the HbA1c testing was 22.8 days (95% C.I. 16.9-28.7, N=179), the mean medication adherence coefficient was 0.81 (SD: ±0.36), and the average medication exposure coefficient was 18.6 (95% C.I. 14.2-23.0 N=171). The medication exposure index was not significantly correlated with HbA1c (r= –0.14; n= 130; *p*= 0.12). No significant difference was found in the levels of childhood physical abuse between Visible minority and White participants (*t*=0.94; df=201; *p*=0.17). None of the participants had abnormal levels of hemoglobin (Supplementary table 1). A diagnosis of substance abuse at admission did not significantly predict levels of HbA1c (Supplementary table 2).

Based on the results of the univariate analyses, two main multivariate models were analyzed: one testing visible minority status, and another testing physical abuse as main predictors. With all other variables controlled for, participants from visible minorities had significantly higher levels of HbA1c (Table 3). Given the reduced number of participants who had answered the CTQ, the neighborhood indices of deprivation (second block) were dropped in the physical abuse model. The relationship between childhood physical abuse and HbA1c was significant when age, sex, BMI, were accounted for in the model, and became marginally significant when adding depression and physical anergia scores (Table 4).

Not all participants had information on the entire set of variables. Hence, multivariate models have different number of participants. Demographic comparisons of the subsamples employed in both models versus the main sample were conducted to assess their representativeness (Table 1). In the visible minority model subsample, a significantly lower proportion of participants with a migrant background was found, and a mean age difference of 11 months was marginally significant (included participants were older). There was a non-significant trend towards a lower proportion of participants from visible minorities. In the physical abuse model subsample the average ages varied similarly, but the difference was not statistically significant. No significant differences were found in this subsample.

DISCUSSION

We examined the effect of five different social determinants of health on the physiological control of glucose in patients newly diagnosed with a psychotic disorder. Based on our hypothesis, and given the demographic characteristics of our sample, we sought to document preclinical variability rather than conducting diagnostic screening. We tested how childhood trauma subtypes, social and material deprivation, immigrant background, and visible minority status influenced HbA1c levels at admission.

The initial univariate analyses demonstrated that visible minority status and childhood physical abuse were the only factors significantly associated with levels of HbA1c at admission. After controlling for sex, age, BMI, indices of social and material deprivation, and depression and physical anergia scores, the effects of visible minority status remained significant, and in fact became more robust. A similar trend was observed for the effect of childhood physical abuse on HbA1c levels, although without controlling for socioeconomic deprivation. After controlling for depression and anergia, a slight decrease in significance was observed, putting it just over the 0.05 cut-off.

Controlling for sex differences was fundamental given the important variability observed in body composition[229] (e.g. percent body fat) and glucose levels between females and males[230], and their differential susceptibility to different forms of childhood trauma[146,226,227]. The purpose of adding BMI to the models was to control for differences in body composition. This was particularly important in the visible minority model, due to the association that ethnicity has with both body composition [231], and HbA1c[232]. Indeed, BMI was significant in the visible minority model but not in the physical abuse one. Thus, adjusting for BMI was a way to control for biological –and thus genetic– variability. This suggests that part of the observed effect of ethnic minority status might originate from other non-biological, ethnicity-associated circumstances (i.e., social factors). Including the deprivation indices in the multivariate model (despite not being significant in univariate analyses) provided a way to control for the influence of neighborhood-level socioeconomic factors linked with metabolic disease. It has been documented that this association can be mediated by food quality[233], food availability[234], and neighborhood resources for physical activity[235]. Moreover, some evidence indicates that the relationship between deprivation and obesity is not significantly influenced by gender or ethnicity[236]. Again, this was of particular importance for the minority status model, as some studies indicate that the excessive metabolic disease observed in minority groups is largely attributable to their higher rates of

deprivation[237]. Finally, although most of our population fell into the young adult age range category (with similar distributions of BMI), both models controlled for age, increasing their accuracy[152].

Since not all patients might have been tested for HbA1c within a short period of time after the introduction of pharmacological treatment (given the 23-day average of previous exposure), we also assessed if previous exposure to medication could have influenced the levels of HbA1c. The index combining number of days in pharmacological treatment with reported rates of adherence was not significantly correlated with the levels of HbA1c. While there was a significantly lower number of participants with a migrant background in the subsample from the visible minority model, this variable did not have an effect on HbA1c, thus it is unlikely that this factor had affected the results. The trend showing a lower proportion of participants from visible minorities in this subsample should have acted against –rather than for– the documented results. By the same token, the age difference of this subsample was 11 months, which is not epidemiologically relevant for HbA1c.

Despite that the overall effects appear small, finding a significant change in the variability of HbA1c needs to be interpreted in the context of two observations. First, HbA1c has a numerically narrow range (4.2-6.2% in this sample), and clinical laboratories report only one decimal figure, making differences difficult to detect. Second, and more importantly, given the young age of FEP patients, a full-blown DGM was not expected; a clinical condition such as diabetes mellitus has been estimated to take around 15 years or more to develop[109]. While our finding cannot be automatically translated as an increase in the risk for the development of metabolic disease in the future (and thus it should be interpreted with caution), the observed increase in the level of HbA1c reflects a palpable preclinical alteration in glucose homeostasis, offering an opportunity for the prospect of early preventive interventions.

Strengths of the present study include the systematic and detailed phenotyping conducted at PEPP by a well-trained, experienced research team. An example of such phenotyping is the CTQ, a widely used validated instrument for the assessment of childhood trauma. Our phenotyping also allowed us to control for levels of depression and physical anergia as possible confounders. The neighborhood-level social and material deprivation indices are methodologically robust (derived from census data), and supported by extensive research linking neighborhood characteristics with health outcomes[238]. In addition, participants' mean levels and 95% confidence intervals of red blood cells and hemoglobin measures reflected those of the international norms, validating the levels of HbA1c. Finally, our sample was representative of a FEP population.

Limitations of this study include the assessment of social factors associated with an increased risk for psychosis in a sample of patients with psychosis, which implies a selection bias; i.e., individuals with psychosis are more likely to come from socially burdened environments. This phenomenon has been demonstrated across multiple settings, including our catchment area[128]. Indeed, in our sample, the proportions of participants belonging to the worst quintiles of social and material deprivation were 50% and 34%, respectively, which contrasts with the corresponding proportions for the catchment area (2006 census) estimated to be 24% and 22% respectively[239]. Such proportions of deprivation in the sample reduced variability, which might have made the detection of these effects more difficult given the sample size. We also tested if individual levels of socioeconomic deprivation had a significant influence on the levels of HbA1c using the Hollingshead's index of social position[240]. As it was the case for the social and material deprivation indices, this indicator was also not predictive of HbA1c (Supplementary table 3). The number of participants with overlapping data on HbA1c, childhood abuse and minority status did not allow for the analysis of both main adversity predictors in the same regression model due to the number of covariates. However, there were no significant differences in the degree of experienced physical abuse between migrants and non-migrants, and thus both variables

seemed to be independent. Controlling for differences in body composition with BMI has some limitations. Other measures more directly associated with visceral abdominal fat such as the waist-to-hip ratio would have provided a more accurate way to control for variability in percent body fat, which in turn is associated with insulin resistance[229]. However, when comparing differences across ethnicities in young adults, the differences in percent body fat between Blacks, Hispanics and Whites at the same BMI levels ranged only between 2% and 6%[241] suggesting an acceptable accuracy. In addition, at the same BMI values, the risk for diabetes varies across ethnicities[242,243]. Nevertheless, contrary to what happens with waist circumference, there is no consensus regarding BMI cut-off values by ethnicity, and experts advise caution[244]. Moreover, these cut-offs are calculated after controlling for age, sex and socioeconomic status, which were already included in the multivariate equations. Controlling for these cut-offs would have duplicated their effects, distorting their true influence.

The number of participants was a limitation, which forced the dichotomization of the visible minority variable. This hindered the analysis of specific ethnic differences beyond body mass composition. We did not have information on the diets of the participants, due to the potential differences in nutritional composition –particularly of energy-rich foods– found by ethnicity. Nevertheless, these differences are highly dependent on the rate of acculturation, where higher levels of acculturation have been associated with lower fruit and vegetable consumption[245]. The same study found this outcome to also be predicted by food insecurity, which might have been partially controlled for by the indices of social and material deprivation in the multivariate model. In addition, since we only had access to participants' current postal codes, the influence of social mobility could not be accounted for. Information on neighborhood environment in childhood might have provided a cleaner picture of the developmental influence of deprivation. This would have been particularly meaningful in the case of first-generation immigrants. Information on previous smoking status was not available. Smoking has been correlated with HbA1c, although smokers have multiple associated unhealthy risk

factors[246]. On the other hand, our ancillary analysis on the influence of diagnosis of abuse at admission showed that the latter did not significantly influence levels of HbA1c. It is expected that a greater number of participants might had produced more robust results.

While our results do not allow us to pinpoint the exact origin of our findings, we can hypothesize that after controlling for age, sex, and BMI, the effect of visible minority status might have depended on non-biological factors associated with this variable. Moreover, since we also controlled for the indices of social and material deprivation, the association between social disadvantage and ethnic minorities was also adjusted for in the analysis. Thus, other social determinants of health might have been driving the effect of visible minority. Two important societal factors associated with ethnicity are known to significantly predict differences in health outcomes. First, ethnic minorities often encounter barriers that affect their access to health services[247]. Second, racial victimization has been linked to increased visceral fat[248], and a higher incidence of obesity[152]. In the case of childhood physical abuse, the connection with chronic stress becomes more discernible, although in both cases, this might be one of the common underlying mechanisms. Chronic stress has been linked with the development of metabolic alterations which might be mediated through different pathophysiological pathways such as changes in oxidative stress, increased inflammation, and circadian disruption[200]. The above-mentioned root factors were not measured in this sample, and thus these arguments remain hypothetical.

In conclusion, at the same age, sex, socioeconomic conditions, and BMI levels, patients with a diagnosis of FEP who belong to a minority, or who were victims of childhood physical abuse, already present with comparatively increased levels of glycated hemoglobin at admission, which might indicate an increase in risk for the development of future disorders of glucose metabolism such as diabetes mellitus. These effects were present after: 1) minimizing biological differences in body composition (sex, age, BMI), which are in turn dependent on physiological and genetic factors, and linked to

ethnicity, and 2) reducing the potential influence of some neighborhood-linked environmental factors such as diet quality, food insecurity, and available resources for physical activity (indices of social and material deprivation). Thus, in the case of minority status, it is plausible to hypothesize that factors other than genetic differences or low income were driving this relationship. One of the possible candidates is racial victimization, which has already been documented outside of the context of psychosis. If true, patients with a diagnosis of psychosis who belong to a minority group, or who have been victims of physical abuse, have an additional burden on their physiological control of glucose (on top of medication side effects and sedentary behaviors), explaining their increased risk for developing DGM. Such burden would be environmental in origin, and developmental in nature, indicating that it acts through gene-by-environment mechanisms such as epigenetic changes. While the physiological and clinical significance of the present findings remains to be determined, further studies should therefore test epigenetic differences in genes responsible for metabolic control in FEP populations, while clinical research should examine the behavior of glucose regulation after two or five years of treatment, and explore its interaction with social determinants of health.

Table 1: Demographic comparisons between the model subsamples and the main sample

	Visible minority model N=144				Physical abuse model N=69			
Chi-square tests	**Excl**	**Incl**	x^2	***p***	**Excl**	**Incl**	x^2	***P***
Gender Male N (%)	269 (69.2%)	101 (74.3%)	1.37	0.24	327 (70.5%)	49 (71.0%)	0.01	0.93
High school Yes N (%)	231 (64.0%)	94 (68.6%)	0.95	0.33	276 (64.0%)	49 (73.1%)	2.19	0.14
Diagnosis Non-affective N (%)	264 (70.6%)	96 (67.1%)	0.84	0.66	314 (70.0%)	46 (66.7%)	1.94	0.38
Substance diagnosis Yes N (%)	178 (56.2%)	87 (63.5%)	2.15	0.14	223 (57.5%)	42 (62.6%)	0.89	0.35
In relationship Yes N (%)	37 (9.6%)	16 (11.1%)	0.28	0.60	47 (10.2%)	6 (8.7%)	0.16	0.68
Visible minority Yes N (%)	139 (38.1%)	43 (29.9%)	3.09	0.08	159 (36.0%)	23 (34.3%)	0.07	0.79
Migrant background Yes N (%)	105 (28.2%)	26 (18.6%)	5.14	0.02	116 (26.0%)	15 (22.4%)	0.41	0.52
Student's t tests	**Excl**	**Incl**	***t***	***p***	**Excl**	**Incl**	***t***	***p***
Age - Mean (SD)	23.4 (±4.6)	24.3 (±4.3)	1.89	0.06	23.5 (±4.6)	24.3 (±4.4)	1.33	0.18
Log-DUP Mean (SD)	2.9 (±1.6)	2.6 (±1.8)	-1.48	0.14	2.84 (±1.7)	2.69 (±1.7)	-0.67	0.51

Excl: Participants excluded from the model; Incl: Participants included in the model; Diagnosis: Non-affective psychosis vs. Affective psychosis; High school: Completed high school vs. not completed; SD: Standard deviation. *t*: t-test value Significance **:$p<0.01$; *:$p<0.05$; †:$p<0.10$

Table 2a Univariate analyses: Correlations for continuous variables

		HbA1c	Phys. Negl.	Phys. Abuse	Emot. Negl.	Emot. Abuse	Sexual Abuse	Mat. Deprv.	Soc. Deprv	Med Expo
HbA1c	*r*	1.00	0.01	0.17	0.10	-0.08	-0.10	0.03	-0.02	-0.14
	p		0.91	0.08†	0.35	0.44	0.34	0.67	0.82	0.12
	N	231	100	100	100	100	100	213	213	130
Phys. Negl.	*r*		1.00	0.29**	0.60**	0.44**	0.31**	0.09	0.10	0.09
	p			0.00	0.00	0.00	0.00	0.22	0.15	0.30
	N		210	210	210	210	210	199	199	147
Phys. Abuse	*r*			1.00	0.33**	0.50**	0.36**	-0.13	0.07	-0.08
	p				0.00	0.00	0.00	0.07	0.33	0.33
	N			210	210	210	210	199	199	147
Emot. Negl.	*r*				1.00	0.60**	0.29**	0.06	0.09	0.05
	p					0.00	0.00	0.44	0.18	0.52
	N				210	210	210	199	199	147
Emot. Abuse	*r*					1.00	0.48**	0.04	0.07	0.04
	p						0.00	0.54	0.32	0.59
	N					210	210	199	199	147
Sexual Abuse	*r*						1.00	-0.02	0.05	0.10
	p							0.76	0.50	0.22
	N						210	199	199	147
Mat. Deprv.	*r*							1.00	0.19**	0.01
	p								0.00	0.86
	N							489	489	291
Soc. Deprv	*r*								1.00	0.02
	p									0.73
	N								489	291
Med Expo	*r*									1.00
	p									
	N									307

Emot. Abuse: Emotional abuse, Emot. Neglect: Emotional neglect, HbA1c: Glycated hemoglobin, Mat. Deprv: Material deprivation, Phys. Abuse: Physical abuse, Phys. Neglect: Physical neglect, Sex. Abuse: Sexual abuse, Soc. Deprv: Social deprivation. Med Expo: Medication exposure index, *r*: Pearson's r, *p*: correlation significance, *N*: number in correlation. Significance **:$p<0.01$; *:$p<0.05$; †:$p<0.10$

Table 2b Univariate analyses: t-tests for HbA1c by nominal variables

Categorical Variable	t	DF	*p* (1-side)
Immigrant background	1.34	217	0.39
Visible minority status	1.57	219	0.05

t: t-test value DF: Degrees of freedom. *p*: t-test significance. Significance **:$p<0.01$; *:$p<0.05$; †:$p<0.10$

Table 3: Baseline HbA1c by visible minority controlling for associated factors

	Step 1		**Step 2**		**Step 3**		**Step 4**	
N=144	Biological		Psychosocial		Minority		Clinical	
Coefficient Statistics	**β**	***p***	**β**	***p***	**β**	***p***	**β**	***p***
Age	0.09	0.29	0.09	0.29	0.14	0.11	0.16	0.07†
Sex	-0.09	0.30	-0.09	0.31	-0.11	0.18	-0.13	0.13
BMI	-0.16	0.06†	-0.16	0.06†	-0.16	0.07†	-0.19	0.03*
Material deprivation			-0.01	0.89	0.00	0.97	-0.01	0.91
Social deprivation			-0.03	0.72	-0.02	0.84	-0.01	0.88
Visible minority					0.21	0.02*	0.23	0.01**
Depression							0.13	0.13
Physical anergia							-0.08	0.32
Step Statistics	**ΔR^2**	**Δp**	**ΔR^2**	**Δp**	**ΔR^2**	**Δp**	**ΔR^2**	**Δp**
	0.04	0.17	0.00	0.92	0.04	0.02	0.02	0.25
Model Statistics	**R^2**	***p***	**R^2**	***p***	**R^2**	***p***	**R^2**	***p***
	0.04	0.17	0.04	0.39	0.08	0.09	0.10	0.09

β: Standardized beta regression coefficient; ΔR^2: R-square change; Δp: step significance *p*: regression/step significance; N: sample size; R^2: R-square; BMI: Body mass index; CTQ: Childhood trauma questionnaire; Significance **:$p<0.01$; *:$p<0.05$; †:$p<0.10$

Table 4: Baseline HbA1c by (log) Physical Abuse in Childhood controlling for associated factors

	Step 1		**Step 2**		**Step 3**	
N=69	Biological		Physical Abuse		Clinical	
Coefficient Statistics	**β**	***p***	**β**	***p***	**β**	***p***
Age	0.16	0.18	0.15	0.23	0.16	0.19
Sex	-0.11	0.38	-0.11	0.37	-0.13	0.30
BMI	-0.09	0.46	-0.11	0.37	-0.12	0.36
CTQ Physical Abuse			0.24	0.05*	0.23	0.06†
Depression					-0.03	0.83
Physical anergia					0.13	0.30
Step Statistics	**ΔR^2**	**Δ*p***	**ΔR^2**	**Δ*p***	**ΔR^2**	**Δ*p***
	0.04	0.41	0.10	0.15	0.12	0.25
Model Statistics	**R^2**	***p***	**R^2**	***p***	**R^2**	***p***
	0.04	0.41	0.06	0.05	0.02	0.58

β: Standardized beta regression coefficient; ΔR^2: R-square change; Δp: step significance *p*: regression/step significance; N: sample size; R^2: R-square; BMI: Body mass index; CTQ: Childhood trauma questionnaire; Significance **:$p<0.01$; *:$p<0.05$; †:$p<0.10$

Note: Given the number of participants, the number of covariates had to be reduced to seven. The deprivation indices were dropped from the model

CHAPTER IV

SOCIOECONOMIC DEPRIVATION AND BLOOD LIPIDS IN FIRST-EPISODE PSYCHOSIS PATIENTS: IMPLICATIONS FOR CARDIOVASCULAR RISK

IV.A Preface

The preceding component of the project identified that glycemic control was altered in first-episode psychosis, and documented significant associations with visible minority status, and a history of childhood physical victimization. The next logical step was to test the presence of other metabolic anomalies in this population. Along with glycemic control, lipid homeostasis is one of the major constituents of the biochemistry and physiology of energy metabolism, as well as an essential element in the prediction of cardiovascular disease. However, a previous case-control study with the same cohort had found no differences in blood lipid levels. While the source of the data is the same, the objectives of the present study are different, aiming to examine blood lipid levels in the context of the social factors that determine health. Nevertheless, the availability of average values and confidence intervals of blood lipid levels from the Canadian population (Statistics Canada) for a similar age range allowed a comparison of the study sample with population-level estimates. This provided additional evidence supporting the presence of metabolic anomalies at the onset of psychosis. In addition, the following study included a novel angle, testing how the type of diagnosis altered the influence of the social environment on physical health in psychosis. The results of this study seemed contradictory at first, but after an updated review of the literature it was found to be congruent in the light of some the latest advances in the understanding of lipid biology.

IV.B Manuscript Information

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Socioeconomic Deprivation and Blood Lipids in First-Episode Psychosis Patients: Implications for Cardiovascular Risk

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ABSTRACT

Background: The influence of socioeconomic deprivation on the cardiovascular health of patients with psychosis-spectrum disorders (PSD) has not been investigated despite the growing recognition of social factors as determinants of health, and the disproportionate rates of cardiovascular mortality observed in PSD. Discordant results have been documented when studying dyslipidemia –a core cardiovascular risk factor-– in first-episode psychosis (FEP), before chronic exposure to antipsychotic medications. The objective of the present study is to determine the extent to which socioeconomic deprivation affects blood lipids in patients with FEP, and examine its implications for cardiovascular risk in PSD.

Methods: Linear regression models, controlling for age, sex, exposure to pharmacotherapy, and physical anergia, were used to test the association between area-based measures of material and social deprivation and blood lipid levels in a sample of FEP patients (n=208).

Results: Social, but not material deprivation, was associated with lower levels of total and HDL cholesterol. This effect was statistically significant in patients with affective psychoses, but not in schizophrenia-spectrum disorders.

Conclusions: Social deprivation plays a role in the dysregulation of lipid homeostasis in FEP. Interestingly, animal models of social isolation have documented a similar pattern of lipid changes (low HDL with low total cholesterol). Contrary to expectations, the effect was only seen in affective psychosis patients. Since cholesterol-lowering therapies seem less effective in PSD, an integral approach to physical health that considers type of diagnosis and psychosocial factors is required. Further research on lipid physiology in PSD is necessary.

INTRODUCTION

Patients with schizophrenia have an average 15.4 years reduction in their life expectancy [209], and three-fold higher rates of all-cause mortality than the general population [14]. Increased mortality rate ratios are seen in schizophrenia, schizoaffective, and bipolar disorder [13]. Unsurprisingly, cardiovascular disease is among the most important contributors to natural causes of death in schizophrenia. Being diagnosed with schizophrenia doubles the risk of dying from cardiovascular disease (RR=2.2 $p<0.01$), particularly in middle-aged men (45-64 years: RR=4.0 $p<0.01$) [249]. Moreover, recent advances in pharmacotherapy, other treatment modalities, and prevention strategies have not reduced cardiovascular mortality in psychosis-spectrum disorders (PSD) as they have in the general population. Instead, evidence suggests that the health gap has kept growing [250]. Multiple hypotheses have been put forward to explain these phenomena such as, antipsychotic side effects, sedentary lifestyles, and tobacco smoking. Indeed, second-generation antipsychotics –the mainstream therapeutic choice in PSD– often induce metabolic changes such as weight gain and dyslipidemia [38]; sedentary behaviors, which are commonly observed in patients with psychosis [34], increase the risk for cardio-metabolic disease [33]; and the prevalence of tobacco smoking –a major cardiovascular risk factor– is almost twice as high in schizophrenia compared to the general population [251].

While the aforementioned factors are established predictors of cardiovascular risk, they cannot fully account for three important facts. First, historical records preceding the introduction of antipsychotics for more than five decades had already identified cardiovascular disease as an important cause of mortality [252], as well as an increased incidence of metabolic disorders in patients with schizophrenia [2]. Second, a family history of diabetes increases the odds for a family history of schizophrenia [253]. Finally, recent evidence challenges the conventional understanding of the link between blood lipid levels and cardiovascular risk. Two recent meta-analyses –albeit including almost the same studies– agreed that patients with a first episode of psychosis (FEP) already show changes in

blood lipid levels, namely higher levels of triglycerides, but lower levels of total and LDL cholesterol, when compared to controls [48,254]. HDL levels were found either lowered or unchanged. Since LDL is the pivotal therapeutic target for curbing cardiovascular risk, the lower levels observed in FEP would imply an advantageous cardiovascular risk profile, which as mentioned above, is not the case. Thus, an explanation is needed for this apparent discrepancy.

In recent years, research in cardiovascular prevention has begun to explore non-biological risk factors such as psychosocial stress, and social adversity. Socioeconomic deprivation has been shown to be a robust predictor of cardiometabolic health [255] and dyslipidemia [256]. Similarly, socioeconomic disadvantage has an intricate relationship with PSD: while socioeconomic adversity increases the risk for PSD [120], having a diagnosis of a PSD is associated with increasing social hardship in the long term (social drift theory) [257]. Thus, part of the unexplained risk leading to the high incidence of CVD observed in PSD, despite a favourable lipid profile at the onset of the illness, might be explained by the pervasive influence of socioeconomic deprivation on both conditions.

Compared to individual measures of socioeconomic deprivation, area-based approaches have the advantage of providing an ecological scope. Area-based measures are associated with health-related aspects such as quality and availability of healthy food [258], access to leisure areas [259], social cohesion, and access to health care [260]. Indeed, area-based indices of socioeconomic disadvantage have been significantly associated with an increased risk for PSD [122], and with cardiovascular mortality [261].

The first episode of psychosis allows for a better appraisal of the effects of material and social deprivation on blood lipid levels since the exposure to antipsychotic medication and the impact of sedentary behaviours are still limited. Moreover, material and social deprivation might have a larger

impact during development which would be more discernible at the FEP stage rather than during chronic phases.

The objective of the present study is to examine the influence of socioeconomic deprivation determined with an area-based, ecological approach on the lipid profile (a cornerstone predictor of cardiovascular risk) of a sample of FEP patients upon entry to treatment. In addition, given that patients with affective psychoses (AP) have higher educational and socioeconomic levels when compared to those with schizophrenia-spectrum disorders (SSD) [6], and cardiovascular mortality is lower in bipolar disorder when compared to schizophrenia (albeit higher than the general population) [13], we examined if the effects of deprivation on blood lipid levels could be influenced by the primary diagnosis of SSD vs. AP.

METHODS

Participants and Setting

The present study was conducted in the Prevention and Early Intervention Program for Psychosis in Montreal, Canada (PEPP-Montréal), a specialized service for patients with a FEP. PEPP-Montréal accepts patients from an urban catchment area of roughly 300,000 inhabitants Patients are accepted for treatment and follow-up if they fulfill the following criteria: a first episode of non-affective or affective psychosis (DSM-IV-TR criteria), not secondary to an organic brain disorder (e.g. epilepsy); age 14 to 35 years old; a minimum IQ of 70; and less than one month of antipsychotic pharmacotherapy. Treatment is based on comprehensive case-management, psychosocial interventions, and low-dose antipsychotic medication during a two-year intensive follow-up period. A comprehensive medical

assessment is conducted upon entry, which includes a routine laboratory assessment of blood lipid levels. Following admission to the program, patients are requested to participate in the PEPP research protocol, which includes periodic symptom and psychosocial evaluations by a trained research team. The present study is part of a longitudinal research protocol that examines the outcomes of patients treated in the PEPP program and has been approved by the Ethics Research Board of the Douglas Mental Health University Institute. All participants provided written informed consent, which included the authorization to access relevant data from clinical files for research purposes.

Variables

To assess socioeconomic disadvantage, we relied on data produced by the "*Institut National de Santé Publique du Québec*" (INSPQ), the public health reference institution for the province of Quebec, Canada. The INSPQ calculates neighborhood-level indices of both social and material deprivation based on data from the quinquennial Canadian census [262]. The proportion of the population aged 15 years or more with secondary education or equivalent, the proportion of the population aged 15 years or more that is employed, and the average income of the population aged 15 years or more are used to estimate the material deprivation index. Likewise, the proportion of the population aged 15 years or more living alone, the proportion of the population aged 15 years or more without a stable relationship (separated, divorced or widowed), and the proportion of single-parent families, provide the information to determine the social deprivation index. The INSPQ grants public access to these indices, which are assigned to almost every postal code in the province. Participants' postal codes were thus matched with the deprivation indices from the INSPQ database. Values of both deprivation variables range from 0 to 100, with higher numbers indicating higher levels of deprivation. Both indices represent the main predictor variables.

Based on their potential confounding influence, other variables included were: participants' age, their level of physical activity, and the duration of previous use (if applicable) of antipsychotic medications. To appraise the degree of sedentary lifestyle of the participants, we relied on the levels of physical anergia, which were rated as part of the avolition-apathy domain of the Scale for the Assessment of Negative Symptoms (SANS). The SANS, a widely-used instrument with good reliability and was administered by trained research symptom evaluators upon entry to the program. The level of physical anergia was coded from 0 to 5 according to the proportion of time that the patients spend being idle, or in passive activities such as watching television. Despite focusing on a FEP sample, we acknowledge that patients might have been medicated at their referral institutions. Therefore, we calculated their previous exposure by counting the number of days from the initiation of first treatment, to the date on which the laboratory analyses were performed, and multiplied this number by the rate of medication adherence reported by the patients during their baseline symptom evaluation (0%, 25%, 50%, 75%, or 100%) [263].

As indicators of cardiovascular risk, blood lipid levels represented the outcome variables. These included high density (HDL), low-density (LDL) and total cholesterol, (TC) and triglycerides. Laboratory analyses followed standard clinical protocol (i.e., eight-hour minimum fasting time); this information was also obtained from clinical records.

Statistical Analyses

The demographic characteristics of the participants were compared with those of patients who were not included. Non-participants were patients who consented to the research protocol but had one or more of the analyzed variables missing (e.g., no postal code). Continuous variables were analyzed with t-tests; and proportions with chi-square tests. Bivariate correlational analyses were conducted between

the predictors and covariates (indices of deprivation, age at entry, levels of physical anergia, and the medication exposure index) to explore associations among predictors. The main analyses consisted of multiple linear regression models in which the effects of material and social deprivation were tested while controlling for demographic characteristics (i.e., age and sex), exposure to medication, and physical anergia. All statistical analyses were conducted using the SPSS statistical software version 22.

RESULTS

The proportions of sex distribution, persons with completed high school or with a partner, and the means of age at admission, age of onset of psychosis, deprivation indices, duration of untreated psychosis or illness, medication exposure index, or scores of physical anergia did not differ between participants and non-participants (Table 1). When compared to the Canadian population [264] within a similar age range (20-39 years Canadian population, 16-35 years PEPP patients), participants included in the study had significantly lower levels (i.e., non-overlapping C.I.) of total and HDL cholesterol, overall and when grouped by gender.. A trend towards lower levels of LDL and triglycerides was also observed (Supplementary table 1). Bivariate correlations among predictors are shown in table 2. Both indices of deprivation were significantly and positively correlated, and while material deprivation had a significant correlation with the scores of physical anergia, social deprivation did marginally with age at entry. Age at entry was positively correlated with medication exposure.

Multiple regression analyses conducted to test the effects of social and material deprivation on the lipid levels of first–episode psychosis patients are presented in Table 3. The total cholesterol model significantly explained 11% of the variance (R^2=0.11, F[6,201]=4.09 p<0.01). Total cholesterol significantly increased with age (β=0.26, p<0.01), and decreased with social deprivation (β= –0.15, p= 0.03). For LDL cholesterol, the model significantly explained 7% of the variance (R^2= 0.07, F[6,198]=

2.56 p= –0.02). Only age significantly increased this blood lipid (β= 0.23, p<0.01). A 12% of the variance of HDL levels was significantly explained by the model (R^2= 0.12, F(6,201)= 4.69 p<0.01), with females having higher levels (β= 0.23, p<0.01); higher social deprivation predicting lower HDL levels (β= –0.18, p= 0.01); and medication exposure significantly increasing them (β= 0.17, p= 0.02). For triglyceride levels, the model explained 8% of variance (R^2= 0.08, F[6,202]= 2.75 p= 0.01), and was only significantly explained by increasing age (β= 0.23, p<0.01), and male sex (β= –0.14, p= 0.04).

As mentioned above, since the general and cardiovascular mortality rates are higher in schizophrenia when compared to bipolar disorder, we tested if social deprivation could have a differential effect on blood lipids depending on the main diagnostic categories. This analysis was conducted by splitting the sample between the two main diagnostic categories: SSD and AP. No significant differences were found in the indices of material (t= –1.51, df= 200, p= 0.13), and social deprivation (t= –0.05, df= 200, p= 0.96) between patients with a SSD and those with AP (Supplementary table 2). Lipid levels were not significantly different between SSD and AP patients. However, SSD patients had significantly higher levels of physical anergia (t= –3.34, df= 200, p<0.01), and lower indices of medication exposure (t=2.33, df= 200, p= 0.02). Multiple regression analyses revealed that neither material, nor social deprivation predicted blood lipid levels in patients with a diagnosis of a SSD (N=147) (Table 4). Since there were fewer (N=55) participants in AP group, the multiple regression analyses needed to be conducted with a maximum of five predictors. As such, the levels of physical anergia were dropped given their lack of association in the model using data on all participants (table 5). In contrast to what was observed with SSD patients, lipid levels were notably associated with social deprivation in AP patients. In this subgroup, 28% of the variance of the levels of total cholesterol was significantly predicted by the model. Total cholesterol levels increased with age and decreased with increasing social deprivation. A similar picture emerged for HDL, where 20% of the variance was explained by the model, and social deprivation again significantly predicted lower

levels. While the triglyceride model significantly explained 30% of the variance, the effect of social deprivation had a borderline significance. The levels of LDL were only predicted by increasing age, but the model was not statistically significant. Collinearity statistics are illustrated in supplementary table 3. Variance inflation factors and respective tolerance indices remained within acceptable levels for all variables in all three regression models.

Given these results, we sought to determine if our findings could be explained by a decline in socioeconomic position (from parental to personal), which is often observed in association with psychotic disorders [257]. Socioeconomic position change was calculated using the Hollingshead two-factor indices of social position; patient SES was subtracted from parental SES (mother or father). We hypothesized that AP patients would have experienced a greater change in socioeconomic position compared to their SSD pairs. Mean change from mother SES was –0.67 (SD±1.55) for patients with SSD, and –0.68 (SD±1.49) for patients with AP. Change from father SES was –0.97 (SD±1.60) for patients with SSD, and –1.09 (SD±1.35) for patients with AP. No significant differences between SSD and AP patients were found for change from mother SES (t= –0.02, df= 91, one sided p= 0.49), or change from father SES (t= –0.32, df= 86, one sided p= 0.38).

DISCUSSION

In the present study our objective was to determine if socioeconomic deprivation affects blood lipid levels in patients with a first episode of psychosis and document the character of such changes. Social deprivation, determined by area-based measures, significantly predicted lower levels of total and HDL cholesterol. In contrast, material deprivation had no influence on any of the measured lipids. Given differences in risk of cardiovascular and metabolic disease between patients with schizophrenia and

bipolar disorder, we tested the effects of deprivation according to main diagnostic categories. This analysis revealed that social deprivation only altered lipids in patients with AP, and not in those with SSD. Furthermore, we tested if such findings could be explained by a decline in socioeconomic position. Change from parental to personal SES was not associated with changes in blood lipid levels. The findings documented by the present study do not concur with what it is found in the general population. As such, these differences need to be analyzed in light of the characteristics of our sample, particularly the psychosocial aspects associated with psychotic disorders, and the early phase of the disorder.

First, since low socioeconomic conditions are associated with a higher risk of metabolic and cardiovascular disorders, we expected deprivation to be significantly associated with lipid dysregulation. Indeed, our finding showing lower levels of total and HDL cholesterol might indicate an early deviation of some of the mechanisms involved in lipid homeostasis. One candidate is the dysregulation of reverse cholesterol transport, the process by which HDL reduces excess cholesterol from the body, and explains HDL's independent protective association with cardiovascular risk (i.e., unrelated to the amount of total cholesterol) [265]. A comprehensive study with mice showed that stress reduced both total and HDL cholesterol without altering triglyceride levels, a pattern congruent with our results [266]. More importantly, these changes were associated with an increase in reverse cholesterol transport. These effects were mimicked by corticosterone and shown to be mediated by the repressive effects of this hormone on the expression of molecular mediators of cholesterol homeostasis. Such findings reflect subacute rather than chronic lipid dysregulation.

Second, since dyslipidemia is more prevalent in low-income households [267], we expected to see an effect from both the material, and the social components of deprivation. Moreover, multiple lines of evidence strongly support the association between social adversity and lipid dysregulation. Animal

models provide compelling evidence for the relationship between psychosocial stress and lipid metabolism. In mouse models of dyslipidemia (Apo-E gene knockout), stress protocols that emulate psychosocial stress (e.g. social isolation) induce dyslipidemia [268]. In contrast, more typical protocols (e.g. physical stressors) fail to generate such changes [269]. In humans, lipid imbalances have been documented in multiple contexts, including army veterans with post-traumatic stress disorder [270]. Perhaps more relevant is the fact that the INSPQ's social deprivation index is a composite score of the number of people living alone, without a stable relationship, and in single-parent households. As such, it appraises the objective degree of social isolation. The effects of social isolation on neuroendocrine responses provide a pathophysiological link between the psychosocial environment and physical health. Indeed, social isolation has been associated with dyslipidemia [271] and increased cardiovascular mortality [272]. It is still possible though, that factors linked to the social deprivation index at the ecological level (e.g., food quality), could mediate the effects on blood lipid levels.

Finally, –as indicated above– few studies have compared cardiovascular mortality in schizophrenia and bipolar disorder, finding higher rates in the former. Thus, we expected to see a greater degree of lipid dysregulation in patients with SSD when compared to patients with AP. Therefore, it was unexpected to find the effect of social deprivation being exclusive to AP patients. Additional testing indicated that there were no significant differences between SSD and AP patients in terms of area-based levels of social or material deprivation, the degree of change from parental socioeconomic position, or in the proportion of male vs female patients. These ancillary findings minimize the probability of a sampling bias. Thus, taking into account that the main driver of our findings is a measure of social isolation, that the objective degree of exposure to social isolation is similar between diagnostic groups, and the fact that SSD patients have higher degrees of negative symptoms and cognitive impairment [273], we hypothesize that differences in the appraisal of social isolation could explain why social deprivation had a more pronounced effect on AP patients. Research in the cognitive

aspects of perceived social isolation (i.e., loneliness) in schizophrenia is still scarce. However, support for our conjecture comes from a recent report indicating that the perception of social isolation in patients with schizophrenia is not related with social cognition, and the authors propose that its processing would be done through different psychological mechanisms [274]. As such, differences in social cognition might mediate the differential effects that social isolation has on blood lipids (and perhaps other health outcomes) between SSD and AP patients. Two competing explanation are possible. First, cardiovascular risk factors other than blood lipids (e.g., tobacco smoking) might have a higher attributable risk for cardiovascular disease in SSD patients. Second, differences in antipsychotic prescription (i.e., through side effects) might have caused such changes. In the present sample, a higher proportion of AP patients had a prescription of olanzapine at admission than SSD patients (57% vs. 41%; x^2=3.76, p=0.052). However, lipid changes after olanzapine initiation require several weeks [275], and the difference in time of exposure in our sample was only 7 days (9 versus 16 days). Moreover, medication exposure was not statistically associated with social deprivation (R=0.02, F=0.08, p=0.77).

Strengths of the present study include sampling from an epidemiological catchment area which assures a representative cohort of FEP patients; the use of a standardized clinical laboratory for the analysis of the samples; and the collection of clinical information by a well-trained research team. The demographic trends observed in our findings, i.e., increasing levels of LDL and triglycerides with age, and higher levels of LDL and HDL in males, are congruent with what is observed in the general population, and attest to the quality and representativeness of our data. Moreover, our patients had significantly lower total and HDL cholesterol levels when compared to the Canadian population, which are similar to results from meta-analytical studies. The main limitation of our study is the lack of information on smoking. Tobacco smoking causes HDL dysfunction (e.g. impaired HDL-mediated liver cholesterol clearance, hampered cholesterol efflux activity), overall impairing its anti-atherogenic properties [276]. Besides, FEP patients have higher odds of smoking when compared to healthy controls,

and start smoking on average 5.3 years before their first episode [29]. Since there is an inverse dose-response relationship between cigarette smoking and HDL levels [277], and proven associations among different aspects of material deprivation (low socioeconomic status, unemployment, and education level) and tobacco use [158], it can be postulated that the reduction in HDL levels might have been partially mediated by smoking. Nevertheless, the relationship between smoking and social isolation is surprisingly equivocal, and this association is considered to have a small effect size [278]. Another potential limitation is the "ecological fallacy" inherent to the indices of social and material deprivation [279], i.e. living in a deprived area does not necessarily indicate being deprived at an individual level. However, area-level deprivation indices have proven to be valuable predictors of cardiovascular [255], and mental health [122]. Moreover, it has been documented that in patients with schizophrenia, individual and area-based measures of deprivation have independent effects on mortality, and both interact in individuals with lower individual SES who live in low-SES neighborhoods [280]. In addition, we did not have information on dietary composition and eating behaviours. Low-income households, particularly in the case of single-parent families, have a limited capacity to obtain foods with quality nutrients such as vegetables and fruits [281]. Low-priced foods have a high proportion of refined carbohydrates, fats and sodium, providing consumers with an inexpensive source of energy-rich nourishment [282]. This information could have perhaps clarified the lack of association between material deprivation and blood lipid levels.

The results of the present study agree with the current sociobiological literature and highlight some important concerns. Post-Framingham studies such as the INTERHEART project [54] have already identified the importance of including psychosocial risk factors and studying their differential impact on the risk of cardiovascular events across countries and ethnicities. Some groups, such as patients with a PSD, often face social disadvantage [257] and this might be one of the reasons why the rates of comorbidity are higher in these populations. Hence, it becomes important to clarify how much of the

association between PSD and cardiovascular disease depends on social disadvantage. Furthermore, management of cardiovascular risk is chiefly based on lowering LDL cholesterol through the use of statins. However, this approach has failed to have an impact on cardiovascular risk reduction in populations whose predominant abnormality is low HDL, such as patients with genetic disorders of HDL metabolism [283]. If the excessive cardiovascular risk observed in patients with PSD stems at last partially from disproportionate levels of social disadvantage, and is determined by HDL dysfunction, this could explain why current pharmacological approaches have had a poor impact in patients with psychotic and bipolar disorders [284]. This would add to the already lower rates of access to follow-up and treatment of dyslipidemia experienced by chronic PSD patients when compared to the general population. Taking into account that exercise is one of the few effective measures to increase HDL, and that negative symptoms –especially the motivational loss and inactivity dimension– have a chronic and generally unremitting course due to poor response to antipsychotics or other treatments, a picture of the enormous challenge facing cardiovascular risk prevention in PSD emerges. A longitudinal follow-up of PSD patients is needed to ascertain the aforementioned hypotheses. Altogether, our findings may have implications for clinical practice, research, and if confirmed in future studies, health policy strategies. Clinicians treating FEP patients should not acquiesce to exclusively approaching dyslipidemia through the prescription of statins, but vigorously promote the implementation of nutritional and lifestyle changes. Research should continue examining the role of emerging indicators of cardiovascular risk, which would become essential for the formulation of preventive strategies, particularly in populations with different risk profiles such as PSD patients. Indeed, the use of demographic indicators to identify those individuals bearing a higher risk for any disease is incredibly cost-effective, as it has no additional cost associated with it, thus allowing for a better channeling of resources. Such knowledge would allow policy-makers to recognize the social dimension of PSD patients in order to delineate preventive strategies and health initiatives that reach the community level, i.e., recognizing and tackling poverty and social isolation as important determinants of health.

In conclusion, the present study demonstrates that social deprivation predicts lower total and HDL cholesterol levels in FEP patients with an affective psychotic disorder. Based on recent advances in the understanding of the pathophysiology of blood lipids, psychosocial stress might induce functional changes in HDL physiology, such as the dysregulation of the reverse transport of cholesterol rather than bulk imbalances of lipid fractions. The early appearance of this alteration implies long-term exposure to a pro-atherogenic factor, which would converge with other mechanisms to increase the risk for the development of cardiovascular disease. This would also explain why current therapies do not have a significant impact on the reduction of cardiovascular risk in patients with PSD. Regardless of the mediating mechanism, a change in the approach and management of cardiovascular risk in populations with high levels of social disadvantage, such as patients with PSD, is needed. Our evidence suggests that the promotion of healthy lifestyles would be more effective than cholesterol-reducing pharmacological therapies alone, an enormous challenge in the context of PSD.

Table 1 Demographic Comparisons Between Participants and Non-Participants

Variable	Participants		Non-participants		Stat	Sig
Nominal Variables	**N**	**%Yes**	**N**	**%Yes**	x^2	***p***
Sex (male)	207	70.1	327	70.0	<0.01	0.99
High School completed	201	65.4	295	64.7	0.03	0.86
Has a partner	207	9.1	319	11.6	0.86	0.35
Continuous Variables	**N**	**Mean(SD)**	**N**	**Mean(SD)**	***t***	***p***
Age at entry	207	23.5 (4.3)	325	23.7 (4.8)	-0.65	0.51
Age at onset	193	22.2 (4.1)	296	22.8 (4.8)	-1.31	0.19
Material Deprivation	207	61.4 (30.7)	280	62.1 (29.4)	-0.22	0.82
Social Deprivation	207	75.4 (19.3)	280	74.4 (21.3)	0.52	0.60
Log-DUP	181	2.8 (1.7)	270	2.8 (1.7)	-0.34	0.73
DUI	188	290.2 (280.4)	266	311.7 (294.6)	-0.78	0.43
Medication Exposure	207	11.4 (20.5)	97	15.8 (29.4)	-1.52	0.13
Physical Anergia Score	207	2.3 (1.6)	320	2.1 (1.5)	1.11	0.27

DUI: Duration of Untreated Illness; Log-DUP: natural logarithmic transformation of Duration of Untreated Psychosis; Stat: test statistic; Sig: Significance value; SD: Standard deviation; *t*: t-test value; x^2: Chi-square statistic; *p*: test statistic significance, values: **:p<0.01; *:p<0.05; †:p<0.10

Table 2 Univariate Analyses: Correlations for Continuous Variables

		Material Deprivation	Social Deprivation	Age at Entry	Medication Exposure	Physical Anergia
Material Deprivation	*r*	1	0.19	0.03	0.01	0.11
	p		<0.01	0.55	0.86	0.01
	N	489	489	485	291	480
Social Deprivation	*r*		1	0.09	0.02	0.03
	p			0.06	0.73	0.53
	N		489	485	291	480
Age at Entry	*r*			1	0.16	-0.08
	p				0.01	0.06
	N			534	299	528
Medication Exposure Index	*r*				1	-0.03
	p					0.62
	N				306	299
Physical Anergia	*r*					1
	p					
	N					529

r: Pearson's r, *p*: correlation significance, *N*: number in correlation

Table 3. Multiple Linear Regression: All Patients

All patients	**Total Cholesterol**		**LDL**		**HDL**		**Triglycerides**	
N	208		205		208		209	
Model	**R^2**	***p***	**R^2**	***p***	**R^2**	***p***	**R^2**	***p***
	0.11	<0.01	0.07	0.02	0.12	<0.01	0.08	0.01
Predictors	**β**	***p***	**β**	***p***	**β**	***p***	**β**	***p***
Sex	-0.01	0.86	-0.04	0.53	0.23	<0.01	-0.14	0.04
Age	0.26	<0.01	0.23	<0.01	-0.02	0.77	0.23	<0.01
Material Deprivation	0.01	0.85	-0.02	0.83	0.06	0.37	-0.03	0.66
Social Deprivation	-0.15	0.03	-0.11	0.12	-0.18	0.01	0.01	0.93
Physical anergia	0.01	0.91	0.05	0.50	-0.06	0.41	0.01	0.88
Medication Exposure	0.12	0.08	0.07	0.34	0.17	0.02	0.02	0.76

β: Standardized beta regression coefficient; HDL: High-density Lipoprotein; LDL: Low-density Lipoprotein; N: regression sample size; ; *p*: regression model or predictor significance; R^2: R-square

Table 4. Multiple Linear Regression: Patients with a SSD diagnosis

SSD	Total Cholesterol		LDL		HDL		Triglycerides	
N	147		144		147		148	
Model	R^2	*p*	R^2	*p*	R^2	*p*	R^2	*p*
	0.09	0.03	0.07	0.12	0.12	0.01	0.04	0.38
Predictors	β	*p*	β	*p*	β	*p*	B	*p*
Sex	-0.02	0.79	-0.08	0.35	0.24	<0.01	-0.09	0.28
Age	0.20	0.01	0.19	0.03	-0.03	0.68	0.16	0.06
Material Deprivation	0.00	0.97	-0.02	0.84	0.04	0.59	-0.07	0.43
Social Deprivation	-0.11	0.20	-0.10	0.22	-0.12	0.16	0.05	0.52
Physical anergia	-0.08	0.33	-0.04	0.65	-0.14	0.07	0.05	0.51
Medication Exposure	0.16	0.06	0.12	0.14	0.16	0.05	0.00	0.96

β: Standardized beta regression coefficient; HDL: High-density Lipoprotein; LDL: Low-density Lipoprotein; N: regression sample size; ; *p*: regression model or predictor significance; R^2: R-square

Table 5. Multiple Linear Regression: Patients with an AP Diagnosis (5 predictors, anergia not included)

Affective Psychosis	**Total Cholesterol**		**LDL**		**HDL**		**Triglycerides**	
N	55		55		55		55	
Model	**R^2**	***p***	**R^2**	***p***	**R^2**	***p***	**R^2**	***p***
	0.28	<0.01	0.16	0.12	0.20	0.04	0.30	<0.01
Predictors	**β**	***p***	**β**	***p***	**β**	***p***	**β**	***p***
Sex	0.03	0.83	0.03	0.84	0.23	0.08	-0.21	0.09
Age	0.56	<0.01	0.44	<0.01	0.16	0.25	0.50	<0.01
Social Deprivation	-0.36	0.01	-0.20	0.16	-0.40	0.01	-0.25	0.06
Material Deprivation	0.07	0.59	0.02	0.89	0.18	0.16	-0.01	0.97
Medication Exposure	-0.11	0.41	-0.11	0.45	-0.06	0.65	-0.01	0.95

β: Standardized beta regression coefficient; HDL: High-density Lipoprotein; LDL: Low-density Lipoprotein; N: regression sample size; ; *p*: regression model or predictor significance; R^2: R-square

CHAPTER V

ADIPOKINES IN FIRST-EPISODE PSYCHOSIS: EVIDENCE FOR A METABOLIC DIATHESIS IN PSYCHOTIC DISORDERS, ROLE OF PSYCHOSOCIAL FACTORS, AND LINKS WITH INFLAMMATION

V.A Preface

The previous projects demonstrated the presence of clinical anomalies in glucose and lipid homeostasis at the onset of psychosis. Bearing in mind the natural history of diabetes, the onset of clinical disturbances such as hyperglycemia has been estimated to take at least two decades. Thus, finding such alterations at the beginning of adulthood indicates that their precursory pathophysiological processes started early in life. Thus, the next step was to identify these underlying changes. Such pathophysiological factors should be active at the beginning of the cascade of mechanisms leading to cardiovascular disease, and have a global influence. Adipose tissue dysregulation is recognized as one of such precursory changes, and has extensive repercussions in endocrine and immune physiology. For instance, altered adipose physiology is involved in the promotion of other pathophysiological anomalies leading to cardiovascular disease such as insulin resistance, dyslipidemia, inflammation, hypercoagulability, and endothelial dysfunction. These arguments provided a strong rationale for the selection of the adipose tissue as the focus for the next step of the project. Adipokines, as the hormonal mediators of adipose tissue function and dysfunction, were thus selected as the outcomes to measure.

This project was conducted with data from the Signature biobank. Signature recruits participants from the emergency department of an institution exclusively dedicated to provide mental healthcare, and records biological and psychosocial markers. This allowed measuring adipokines in patients with negligible exposure to antipsychotics and antidepressants, comparing their levels with controls from the same community, and testing the effects of social determinants of health.

V.B Manuscript Information

Title
Adipokines in first-episode psychosis: Evidence for a metabolic diathesis in psychotic disorders, role of psychosocial factors, and links with inflammation.

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Abbreviations: CCHS: Canadian Community Health Survey; CVD: Cardio-Vascular Disease; DSM: Diagnostic and Statistical Manual of Mental Disorders; FEP: First-Episode Psychosis; IL-6: Interleukin 6; NF-κB: Nuclear Factor kappa-B; PHQ-9: Patient Health Questionnaire; PSD: Psychosis Spectrum Disorders; TNFα: Tumor Necrosis Factor-alpha; WHeR: Weight-to-Height Ratio; WHODAS: World Health Organization Disability Assessment Schedule (Version 2.0).

V.C MANUSCRIPT

ABSTRACT

Introduction: Psychosis-spectrum disorders (PSD) are characterized by high rates of metabolic comorbidity such as diabetes mellitus and dyslipidemia. While the etiology and pathophysiology of these phenomena are unknown, metabolic anomalies have been documented as early as the first-episode of psychosis (FEP), suggesting the influence of early-life factors. Adverse social factors in early-life are associated with a higher risk for the development of both PSD and metabolic disease. Given their important prevalence in PSD, social factors are potential etiological sources linking these conditions. As one of the earliest links in the chain of events leading to metabolic disease, adipose tissue dysregulation is potentially a main pathophysiological promoter of metabolic impairment in PSD.

Objective: To determine the presence of adipose tissue dysregulation in FEP, and if present, examine the influence of adverse social factors in its appearance.

Methods: Adipose tissue function, as indicated by blood levels of adipokines (leptin, adiponectin, resistin, chemerin), was compared between 45 FEP patients with negligible exposure to antipsychotics and 38 controls. Further uni– and multivariate models tested the effects of social factors (childhood trauma, ethnic minority, SES) and covariates (tobacco smoking, depression, sex, waist-to-height ratio) on adipokine levels.

Results: All tested adipokine levels were significantly altered in cases compared to controls, before and after controlling for social factors. Childhood physical abuse was associated with higher resistin, and ethnic minority status with lower chemerin.

Conclusion: Prominent adipose tissue dysregulation is already present at the onset of PSD. Some social factors are associated with these anomalies.

INTRODUCTION

Severe mental illnesses, particularly psychosis-spectrum disorders (PSD), increase the risk for the development of cardiovascular disease (CVD)[20], which largely contributes to the disproportionate comorbidity burden and premature mortality observed in this population [209]. The origin of this relationship is complex and multifactorial, and the hypothesized underlying pathophysiological substrates still remain unproven.

Predominant theories explaining the PSD-CVD association point to medication adverse effects and lifestyle changes. Second-generation antipsychotics, the prevailing pharmacotherapeutic agents for the treatment of PSD especially in its early course, induce metabolic side-effects (e.g., insulin resistance, weight gain) leading to pathophysiological processes associated with CVD (e.g., diabetes). However, the relationship between schizophrenia and hyperglycemia was already documented more than five decades before the introduction of the first antipsychotic [2]. Furthermore, studies with first-episode psychosis (FEP) patients who are young, relatively unexposed to antipsychotics, and not chronically affected by cardiovascular risk factors such as tobacco smoking and sedentary behaviours, have demonstrated the presence of clinical disorders of energy metabolism (e.g., pre-diabetes). Altogether, these findings suggest that metabolic dysregulation may already be present at the FEP stage, and is likely independent of antipsychotic side-effects.

The nature of such intrinsic metabolic anomalies at this early stage could be either genetic or environmental. Genetic studies have often been unsuccessful in finding common variants explaining cardiometabolic comorbidity in psychosis [285,286]. Moreover, if present, the effect size of gene variants

could not easily account for the magnitude of comorbidity reported in epidemiological studies. The influence of environmental insults on the other hand is pervasive enough to explain this relationship. For instance, social determinants of health are ubiquitous and have proven to be developmental risk factors, not only for the manifestation of metabolic disorders [287], but also for CVD [288]and PSD [289].

Given that patients with PSD are typically burdened by a cluster of psychosocial strains [131,290,291], this might explain the high incidence of diverse comorbid conditions in PSD, particularly in the cardiometabolic sphere. Among the most prominent social determinants of health linked to a higher risk for both CVD and PSD, are childhood trauma [119,144], social and material deprivation [120,292], visible minority status [213,293], and migrant background [134,294] (the latter two importantly involving experiences of discrimination). We have previously documented associations between visible minority status and physical abuse with glycated hemoglobin (after controlling for BMI) [263], and between social deprivation and blood lipids in FEP (See previous chapter).

The documentation of clinically detectable changes of metabolic homeostasis in FEP implies the presence of well-established underlying processes at the pathophysiological level, as well as a developmental component. Considering the young age of FEP patients, and the decades-long evolution of cardiovascular disease, it is thus necessary to explore the pathophysiological origins of CVD. One of the foundational pathophysiological processes in the etiology of metabolic and CVD disorders is adipose tissue dysregulation [67]. Adipose tissue dysregulation promotes insulin resistance [79], dyslipidemia [69], and inflammation [295], all of which contribute to endothelial dysfunction and atherosclerosis.

The adipose tissue is a functional endocrine organ [93], exerting paracrine and endocrine actions via adipokines and cytokines. Among the most prominent adipokines at the core of adipose tissue function

(and dysfunction), are leptin, adiponectin, resistin, and chemerin [296]. These mediators are central to some pathophysiological processes key to adipose tissue dysregulation such as adipocyte differentiation and proliferation [297], insulin resistance [298] and lipid metabolism [299] among others. Unsurprisingly, adipokines have also been associated with CVD risk [300].

The present study has two main objectives. First, to demonstrate the presence of adipose tissue dysregulation in FEP as indicated by changes in adipokine levels. We hypothesize that FEP patients will have altered levels of adipokines that would connote metabolic dysregulation, presumptively higher levels of leptin, resistin or chemerin, or lower levels of adiponectin when compared to controls without a mental health diagnosis. Second, to test if social determinants of health: childhood trauma, visible minority status, and socioeconomic status, are associated with the development of adipose tissue dysregulation, and examine their relationship with FEP. We hypothesize that some of these determinants potentially explain part of the adipokine changes associated with FEP, if present.

METHODS

Participants and Setting

This project was conducted using data from the Signature project. The Signature project is a data bank of functional dimensions of mental health, i.e., signatures, at the biological, psychological and social levels [301]. Participants are first recruited at the emergency department of the Institut Universitaire en Santé Mental de Montréal (IUSMM), a specialized mental health care institution. Participants who grant (written) consent to participate in the project provide blood samples, are interviewed and assessed by a research nurse, and complete a battery of questionnaires assessing mental and physical health issues, as well as psychosocial dimensions. Subsequent visits allow for a longitudinal collection of

signatures. The present project uses data from the initial visit (first contact) at the emergency department. Data was collected from February 2013 to January 2018 and allowed for a case-control design.

An initial screening of Signature's database identified potential patients by diagnosis (schizophrenia-spectrum, first contact). This was followed by a confirmation of FEP diagnosis through review and evaluation of clinical files by one of the investigators (FVL). Criteria for inclusion were: a first-episode of psychosis, i.e., no previous contact with mental health providers for psychotic symptoms, plus subsequent confirmation of psychosis-spectrum diagnosis by treatment team (e.g., schizophrenia, affective psychosis, or psychosis NOS), minimal exposure to antipsychotics or antidepressants (i.e., less than 7 days from day of first prescription to the day of blood sampling), and ages between 18 and 40 years. Exclusion criteria were: substance-induced psychosis, unclear or unconfirmed psychosis-spectrum diagnosis, and diabetes mellitus. Controls were recruited by Signature from the same community as the case group. In addition to the exclusion criteria used for patients (above), controls had no history of mental health disorders, which was ascertained with a clinical evaluation by a psychiatrist (Signature). The research ethics board of the IUSMM approved the present study, and oversees the Signature project.

Outcome Variables

The main outcome variables are blood levels of the following adipokines: leptin, adiponectin, resistin and chemerin. Blood samples were collected by Signature's research nurse at the time of recruitment, and stored (serum) until processing at -80°C. Adipokine levels were measured with commercial ELISA kits, following manufacture's protocols (insert-manufacturer) by a dedicated

laboratory technician from Signature. Adipokine levels were computed from the mean of two individual ELISA measurements.

Predictor Variables

The main variable, as indicated by the case-control design of the study, is the presence of a diagnosis of FEP. Childhood trauma, visible minority background, and socioeconomic status represent the primary psychosocial predictors of metabolic function based on current evidence. Childhood trauma was assessed with the Childhood Experiences of Violence Questionnaire (CEVQ). The CEVQ is a seven-question instrument exploring a history of physical (victim and/or witness), and sexual abuse in childhood. Both CEVQ questions and categorizing algorithms have been validated [302]. Total scores were used as the main trauma variable. Visible minority background was self-reported, and obtained from Signature's demographic questionnaire. Participants were asked to select which ethnic group or groups they belong to. The variable was then dichotomized: participants who identify themselves as belonging to an ethnic group other than "white" were classified as coming from a visible minority background. Income was also self-reported, and acquired from Signature's demographic questionnaire.

Three clinical variables with potential confounding effects were included: depression, physical activity and current tobacco smoking. The total score from the depression scale from the Patient Health Questionnaire (PHQ-9) was used to assess the level of depressive symptoms. The PHQ-9 consists of nine DSM IV-based items, and has been validated and frequently used as a screening, measuring, and diagnostic tool for depressive symptoms [303]. The World Health Organization Disability Assessment Schedule (WHODAS) [304] provided an assessment of physical activity. The question on the ability to walk long distances (~1Km) was used as a proxy measure of physical activity. This item was rated in a 5-point Likert scale. Likewise, Signature followed the same questionnaires used by Statistics Canada to

appraise tobacco smoking (Canadian Community Health Survey: CCHS). Current tobacco consumption was dichotomized classifying participants as smokers (daily or intermittent), versus non-smokers.

In addition, the influence of the participant's sex was tested given the sexually dimorphic character of physiologic responses at the endocrine level [229], and marked differences in exposure to childhood trauma [305]. Similarly, the effect of age was considered as the risk for metabolic disease increases with it. Finally, the participant's waist-to-height ratio (WHeR) was included to control for body fat mass. Adipose tissue mass is one of the main determinants of leptin [306] and adiponectin [307] levels, and varies with ethnicity. Thus, this measure was included to control for genetic differences in adiposity (thus allowing the appraisal of other factors associated with ethnicity).

Statistical Analyses

Demographical comparisons between participants with a FEP and controls were conducted with Student's t or chi-square tests. Leptin levels increased exponentially [308], and indeed a logarithmic distribution was observed in our sample. Thus, this variable was treated with a logarithmic transformation. Other adipokines followed a normal distribution. The first objective, to determine the effect of a FEP diagnosis on adipokine levels, was tested using Student's t-tests (2-sided, equal variances). The second objective, to test the influence of psychosis-associated factors on metabolic function, including social determinants of health, was conducted first by exploring the univariate relationships between these predictors and adipokine levels. Those predictors with significant influence were further tested together in a multiple regression model. This model was tested using a hierarchical procedure in order to assess the distinct contribution of different groups of variables to the total adipokine variance. As such, the first block contains inherent individual characteristics including FEP

diagnosis, sex, and WHeR. The second block tests for the effect of social determinants of health, i.e., visible minority status, and childhood trauma. The final block gauges the influence of behavioral factors, namely tobacco smoking and depression.

An analysis of the differences between the final models and univariate results was used to guide post-hoc analyses. All analyses were conducted with the R statistical environment (version 3.2.3) [309].

RESULTS

Sample Characteristics

A comparison of the sample characteristics by diagnosis is illustrated in Table 1. Patients tended to be younger, have less income and lower levels of BMI, but these differences were not statistically significant. The patient group had a significantly higher proportion of male participants. This group also had a greater proportion of individuals from visible minority backgrounds but the difference did not reach statistical significance. Finally, controls had borderline significant higher WHeRs (Table 1).

Adipokines by FEP diagnosis

All tested adipokine levels were significantly different between FEP patients and controls (Figure 1). Patients had significantly lower levels of log-transformed leptin ($t = -3.84$, $df = 83$, $p<0.01$) and chemerin ($t = -6.72$, $df = 85$, $p<0.01$), and higher levels of adiponectin ($t = 3.23$, $df = 85$, $p<0.01$) and resistin ($t = 2.54$, $df = 85$, $p=0.01$).

Univariate Analyses

Univariate analyses consisted of correlations (Pearson) for continuous variables, and Student's t-tests for categorical variables. These are illustrated in tables 2 and 3. Total trauma showed a significant positive correlation with resistin, and a negative correlation with chemerin. Among the trauma components, physical violence was the variable most closely associated with the measured adipokines, having significant associations with higher levels of resistin and lower levels of chemerin, and with lower levels of leptin, albeit with a non-significant trend. Depression was significantly associated with higher levels of resistin, and lower levels of chemerin. A higher income was correlated with higher levels of leptin, and age had a marginal negative association with chemerin levels. There were no significant associations between level of activity and adipokines, but activity was significantly correlated with higher levels of depression and marginally with physical abuse. Regardless of diagnosis, females had significantly lower levels of leptin and chemerin, and near-significant lower levels of adiponectin. Participants belonging to a visible minority group had significantly higher levels of chemerin. Participants who smoked had significantly lower levels of leptin, and borderline significant higher levels of adiponectin.

Multivariate Models

In the first two steps of the hierarchical model, after controlling for sex, WHeR, childhood trauma and visible minority background, all differences in adipokine levels seen in the univariate models between cases and controls remained significant (Table X). In the last step, after adding smoking and depression, differences by diagnosis were still significant for adiponectin and chemerin, which had demonstrated larger effects in univariate analyses. Leptin and adiponectin levels were significantly higher in women, and increased in proportion to WHeR. Taken together, FEP diagnosis, sex and

WHeR significantly explained 69% of the variability of leptin, and 28% in the case of adiponectin. None of the social determinants of health, smoking or depression had significant influences on these adipokines after multivariate comparison. Resistin levels significantly increased in association with childhood trauma scores after taking into account all other variables. Replacing total scores of trauma with those of physical violence resulted in a similar picture, but this was not the case when testing for the influence of sexual violence, indicating that the former was the main driver of the effects of trauma in this sample (Ancillary table Y). After controlling for sex and WHeR, FEP diagnosis significantly explained 9% the variance of resistin, with an additional 5% being explained by childhood trauma. When accounting for the effect of all selected predictors, chemerin levels increased in proportion with WHeR, were significantly lower in participants belonging to an ethnic visible minority, and higher in smokers. In contrast, this adipokine was not significantly predicted by sex, trauma or depression. The complete model explained 57% of the variance of this adipokine.

Post-hoc Analyses

An additional exploration of the data was conducted after examining the differences between the univariate and multivariate predictions. Smoking increased leptin levels in patients, but decreased them in controls, while non-smokers had similar levels regardless of diagnosis (Figure 2). The diagnosis by smoking interaction was statistically significant (Table 6). Other suspected interactions were not statistically significant (Supplementary table 1).

DISCUSSION

A growing body of evidence indicates that clinical metabolic dysregulation in psychosis is already present upon first diagnosis. The present study explores the pathophysiological substrate of this phenomenon by comparing levels of four adipokines (leptin, adiponectin, resistin, chemerin) in first-episode psychosis patients with negligible exposure to antipsychotics and age-matched controls without a psychiatric diagnosis. All four tested adipokine levels were significantly different in FEP patients when compared to controls, and this remained true after controlling for individual traits and social determinants of health. The inclusion of two more covariates in the model decreased the magnitude of some effects however (but not their direction). Females tended to have higher adipokine levels, and except for resistin, strong associations were observed between adipokine levels and adipose mass as indicated by WHeR. Being part of a visible minority group, and exposure to childhood trauma were found to independently contribute to adipokine dysregulation. The initial associations with depression seem to depend on other factors, as these were lost in the multivariate analysis. In addition, smoking interacted with diagnosis leading to opposite changes in leptin. Given that participants were young (~25yr patients, ~27yr controls), and that the patient group had a negligible exposure to antipsychotic medication, abnormal adipokine levels indicate that adipose tissue dysregulation is already established before the first diagnosis of psychosis. Moreover, these changes also indicate the involvement of the immune system to a considerable extent, as adipokines are important regulators of its function [310]. Indeed, changes in adipokine secretion are widely being documented in association with immune disorders such as allergies and autoimmune disease [311]. Taken together, these findings indicate that patients with a PSD diagnosis already bear alterations in the regulation of energy metabolism, some of which are only partially explained by psychosocial factors. This implies an innate susceptibility for the development of metabolic disease, i.e., a diathesis, which would in turn explain (in part) the increased risk for cardiometabolic comorbidity and mortality observed in this population.

Leptin acts as a negative feedback signal controlling energy balance by promoting appetite reduction when adipose mass increases, while at the immune level, it prompts inflammation. Thus, after controlling for WHeR, the lower levels of leptin found in the patient group suggest that, at the same level of adiposity, leptin responses are impaired in this group. Leptin's failure to rise with adipose mass gain would leave the input of energy obtained from food unopposed. The resulting positive shift in energy balance would lead to increased weight gain, insulin resistance, etc. Such impairment might be partially explained by our post-hoc results indicating an antipodal effect of tobacco smoking in patients versus controls, i.e., smoking increases leptin in non-psychotic controls but decreases it in FEP patients.

Adiponectin enhances insulin action, glucose uptake, and oxidation of fatty acids [84], resulting in lower insulin resistance. In the cardiovascular system, adiponectin has anti-inflammatory and anti-atherogenic effects [312], but a recent meta-analysis reported higher levels in patients with rheumatoid arthritis [86]. The increased adiponectin levels found in FEP patients might reflect a counter-regulatory response to the increase in resistin and the decrease in leptin. However, the relatively higher effect size of the difference found in adiponectin levels in our sample suggests that other pathophysiological mechanisms associated with increased insulin resistance, or other chronic metabolic and immune processes might be already in play. This is even more relevant taking into account that this variable was controlled for in the final model, and that controls had a small but significantly higher difference in WHeR ratios, implying a higher percentage of visceral fat, the main stimulus for adiponectin production [313].

Resistin contributes to insulin resistance in specific situations [89], hinders adipocyte differentiation (negative feedback control of adipogenesis [314]), and promotes inflammation and vascular disease [315].

However, resistin actions are more prominent at the immune level. Resistin has a bidirectional relationship with pro-inflammatory cytokines, which stimulate resistin secretion (e.g. TNFα, IL-6), and resistin in turn activates NF-kB in macrophages, a quintessential molecular inflammatory pathway [316]. Resistin exerts chemoattractant effects on monocytes (explaining its role in atherosclerosis), and shifts macrophage differentiation towards a classical pro-inflammatory phenotype, which support its role as a central link between obesity and inflammation [89]. At the FEP stage, pathophysiological changes (such as insulin resistance) might be still compensated by adiponectin upregulation. While blood levels of resistin are not different between patients with rheumatoid arthritis and controls, increased production has been documented at inflammatory loci (e.g. synovia) in this autoimmune condition adding evidence of its pro-inflammatory potential [317].

Chemerin is a versatile molecule with multi-systemic functions. In adipose tissue it is an essential promoter of adipocyte differentiation, and in mature adipocytes is associated with adipogenesis and lipolysis in an autocrine fashion. Moreover, it modulates the expression of core metabolic genes such as leptin and adiponectin [318]. Chemerin affects glucose metabolism by promoting insulin resistance in muscle cells [319]. At the immune level, chemerin has chemotactic properties on macrophages and dendritic cells, and both pro-inflammatory and anti-inflammatory effects have been described [320]. Given such a repertoire of functions, it is hard to hypothesize the repercussions of the reduction of chemerin levels reported in the present study. However, it is reasonable to consider consequences on the quantity and quality of adipocyte differentiation, the type and proportions of immune cell populations recruited into the adipose tissue, and the interplay of leptin and adiponectin secretory responses. Interestingly, chemerin levels are increased in multiple autoimmune disorders such as rheumatoid arthritis, psoriasis, and inflammatory bowed disease [310]. Schizophrenia has an inverse relationship with rheumatoid arthritis [321], but has a positive association with psoriasis [322].

The inferences described above were based on our results and thus still need to be confirmed given the complex relationships between adipokines, the cross-sectional nature of the study, and the fact that these changes potentially reflect the mobilization of compensatory mechanisms. Nevertheless, the findings of the present study allow postulating that: 1) psychotic disorders bear inherent metabolic anomalies that are present before exposure to antipsychotic medication; 2) the adipose tissue plays a central role in this phenomenon; 3) phenomena such as insulin resistance, adipose tissue development, lipid metabolism, and inflammation could be impacted, possibly explaining the increased susceptibility for disorders of energy metabolism in PSD; 4) the crosstalk between the immune and the adipose tissue is altered in FEP; and 5) some of the examined psychosis-associated clinical and psychosocial factors independently contribute to adipose dysregulation.

Altogether, the current findings are highly suggestive of adipocyte dysregulation in FEP arising from aberrant adipocyte maturation, abnormal recruitment of immune cells, and enhanced activation of pro-inflammatory pathways (high resistin and leptin, low chemerin,). Systemic control of energy metabolism would be unbalanced via unopposed appetite control (impaired leptin), and increased insulin resistance (elevated resistin). Finally, the documented adipokine changes could contribute, or make part of, the pro-inflammatory imbalance described in early psychosis [323]. It is important to note however that the effect sizes of the adiponectin increase and the chemerin reduction (which would prevent insulin resistance) are disproportionate to the decrease in leptin and rise in resistin (which would promote insulin resistance). This directional imbalance suggests that the former would be either the main affected subsystems or are compensating for the effect of other factors promoting insulin resistance or inflammation. Broadly, the findings of the present study are consistent with recent advances in the understanding of physical health in psychosis, i.e., that psychosis is a multi-systemic disorder in which the immune system has a central role [324].

Most studies measuring adipokines in FEP examine their change in association with antipsychotic pharmacotherapy, but few test these parameters without this influence. A meta-analysis of FEP studies concluded that there was no difference in adiponectin levels between patients and controls [325]. However, included studies greatly differed in the average age of their cohorts, and indeed some reported significant but contradicting findings [326,327]. Still, a study with drug-naive patients in a similar age range as our cohort concurred with our finding of increased adiponectin [328]. A different study found increased leptin and no differences in resistin levels, but some patients had up to three months of antipsychotic treatment [329]. It would seem, therefore, that the amount of exposure to antipsychotic medication was an important determinant of the results of such studies.

Strengths of the present study include a very meticulous review and selection of cases through strict inclusion criteria. This led to the exclusive selection of confirmed FEP cases with minimal exposure to antipsychotics. While this procedure restricted the number of participants, it reduced noise in the data, and perhaps was responsible for the observed effect sizes. In addition, the collection of clinical and psychosocial data, blood sampling, and processing of biological specimens were conducted by dedicated professionals from the Signature bank. Using the waist-to-height ratio, which better estimates the proportion of visceral fat compared to BMI [330], was a more accurate way to control for adiposity. Lastly, to our knowledge, this is the first study exploring chemerin levels in FEP.

The main limitation of the present study was the number of participants, which required limiting the number of variables in the final models. Ideally, all theoretical predictors of metabolic dysfunction should be included in the regression models. However, this would have had unfavourably reduced the number of participants per group. However, the selection of the final predictors to construct the main multivariate model was based on the univariate results, which allowed keeping an adequate variable-to-observation ratio, and constructing parsimonious models. While in the final model including seven

predictors, the coefficients of FEP diagnosis for leptin and resisitin were not significant, the fact that these were in the previous steps indicates that this was likely due to a loss of power. In spite of these limitations, the number of participants was considerable taking into account the depth of biological, clinical and psychosocial phenotyping. Moreover, the effect sizes of the adipokine effects were substantial even after controlling for other predictors. The proportion of male vs female participants was significantly uneven between patients and controls. Nevertheless the documented effects remained significant after this variable was controlled for in the multivariate models. In addition, it would have been optimal to have a continuous measure of tobacco smoking (e.g. number of cigarettes smoked per day), particularly to test a dose-response relationship. Similarly, only a proxy variable was available to estimate the influence of physical activity, and information on dietary behaviors and habits was not available. Finally, a slightly better measure of body mass composition such as the waist-to-hip ratio could have been used, but hip circumference was not available in the database. More specific measures might have provided more efficient models, and broader insights on our findings.

In conclusion, the present study documents the presence of substantial changes in adipokine production associated with a diagnosis of psychosis. Such changes signal the presence of adipose tissue dysregulation in PSD, and suggest the possibility of abnormal adipocyte differentiation and deviant recruitment of immune cells to the adipose organ. The manifestation of such changes at first diagnosis, prior to exposure to antipsychotic medication, indicates the presence of a diathesis, i.e., a constitutional susceptibility for the development of metabolic disease in psychosis. This is congruent with the high levels of comorbidity observed in these patients, and is likely worsened by antipsychotic side effects. The reported findings could redirect the search for genetic variants and epigenetic changes, and underscore the importance of environmental risk factors. In addition, these findings could help clarify the paradoxical association between PSD and autoimmune disorders, where sometimes PSD confers a protective effect (e.g., rheumatoid arthritis) while increasing the risk for others (e.g., psoriasis). Further

confirmation with larger samples is needed, as identifying those individuals with higher metabolic liability would importantly aid in guiding pharmacotherapy. Finally, adipokines have the potential to be used as ancillary laboratory markers profiling the secretome of patients with PSD, making them ideal tools to gauge the state of metabolic control in FEP.

Table 1. Demographic Comparison Between FEP Cases and Controls

Demographic	FEP		Controls		Test Statistic		
	Mean	SD	Mean	SD	*t*	df	*p* (2-tail)
Age	25.73	6.30	27.54	7.97	-1.18	85	0.24
Income	17294.35	18529.17	21660.53	22900.83	-0.95	79	0.35
BMI	24.13	5.54	25.25	3.97	-1.06	85	0.29
WHeR	0.48	0.11	0.52	0.06	-1.95	85	0.05
	N	%	N	%	x^2	df	*p* (2-tail)
Sex (male)	41	85.4%	23	59.0%	7.74	1	0.01
Minority (yes)	19	40.4%	8	21.1%	3.64	1	0.06

Table 2. Correlation matrix, adipokines and continuous variables

	lptn.ln	adpn	rstn	chmr	age	income	cevq.t	cevq.pv	cevq.pa	cevq.sv	cevq. count	depression	activity	WHeR
lptn.ln	1	-0.173	-0.047	0.498**	0.110	0.236*	-0.092	-0.199†	-0.142	0.209†	-0.036	-0.062	0.050	0.464**
adpn		1	0.021	-0.303**	-0.177	-0.154	0.068	-0.036	-0.060	0.180†	0.034	0.081	0.020	-0.239*
rstn			1	-0.071	-0.097	0.010	0.249*	0.248*	0.168	0.028	0.191†	0.225*	-0.037	-0.081
chmr				1	0.205†	0.161	-0.200†	-0.239*	-0.225*	0.010	-0.187†	-0.298**	-0.156	0.437**
age					1	0.435**	-0.058	-0.022	0.025	-0.088	0.013	-0.123	0.004	0.328**
income						1	0.143	0.157	0.176	0.016	0.261*	-0.039	-0.110	0.363**
cevq.t							1	0.889**	0.869**	0.446**	0.817**	0.051	0.112	0.043
cevq.pv								1	0.970**	-0.005	0.735**	0.081	0.140	-0.008
cevq.pa									1	0.025	0.637**	0.109	0.197†	0.026
cevq.sv										1	0.377**	0.032	0.011	0.143
cevq.count											1	0.034	0.136	0.175
Depression												1	0.286**	-0.067
Activity													1	-0.007
WHeR														1

Table 3. Adipokines by grouping variables: sex, minority status and smoking status

	Sex			Minority			Smoker		
	t	DF	*p*	*t*	DF	*p*	*t*	DF	*p*
Leptin (log)	5.61	83	<0.01	0.74	81	0.46	-2.39	83	0.02
Adiponectin	1.91	85	0.06	-0.22	83	0.82	1.91	85	0.06
Resistin	0.35	85	0.73	-0.70	83	0.48	1.07	85	0.29
Chemerin	1.96	85	0.05	3.79	83	<0.01	-1.53	85	0.13

Table 4a. Hierarchical Multiple Linear Regression Model: Leptin (log-transformed)

Leptin (n-log)	Step 1		Step 2		Step 3	
N= 81	**Demographic**		**SDH**		**Confounders**	
Coefficient Statistics	**β**	**p**	**β**	**p**	**β**	**p**
FEP	0.14	0.04	0.16	0.03	0.15	0.10
Sex	-0.48	<0.01	-0.47	<0.01	-0.47	<0.01
WHeR	0.59	<0.01	0.60	<0.01	0.60	<0.01
Minority			0.06	0.41	0.05	0.44
CEVQ.total			0.02	0.73	0.02	0.77
Smoker (yes/no)					0.03	0.66
Depression					0.02	0.86
Step Statistics	**ΔR2**	**Δp**	**ΔR2**	**Δp**	**ΔR2**	**Δp**
	0.69	<0.01	<0.01	0.66	<0.01	0.90
Model Statistics	**R2**	**p**	**R2**	**p**	**R2**	**p**
	0.69	<0.01	0.69	<0.01	0.69	<0.01

Abbreviations at the end of the table

Table 4b. Hierarchical Multiple Linear Regression Model: Adiponectin

Adiponectin	Step 1		Step 2		Step 3	
N= 83	**Demographic**		**SDH**		**Confounders**	
Coefficient Statistics	**β**	**p**	**β**	**p**	**β**	**p**
FEP	-0.41	<0.01	-0.43	<0.01	-0.54	<0.01
Sex	-0.29	0.01	-0.31	<0.01	-0.35	<0.01
WHeR	-0.25	0.01	-0.29	0.01	-0.26	0.01
Minority			-0.16	0.12	-0.13	0.20
CEVQ.total			0.02	0.86	0.01	0.96
Smoker (yes/no)					-0.04	0.73
Depression					-0.20	0.10
Step Statistics	**ΔR2**	**Δp**	**ΔR2**	**Δp**	**ΔR2**	**Δp**
	0.28	<0.01	0.02	0.30	0.03	0.25
Model Statistics	**R2**	**p**	**R2**	**p**	**R2**	**p**
	0.28	<0.01	0.30	<0.01	0.32	<0.01

Abbreviations at the end of the table

Table 4c. Hierarchical Multiple Linear Regression Model: Resistin

Resistin	Step 1		Step 2		Step 3	
N= 83	**Demographic**		**SDH**		**Confounders**	
Coefficient Statistics	**β**	**p**	**β**	**p**	**β**	**p**
FEP	-0.32	0.01	-0.26	0.03	-0.20	0.19
Sex	-0.11	0.31	-0.13	0.26	-0.11	0.35
WHeR	0.04	0.70	0.04	0.69	0.03	0.77
Minority			0.03	0.77	0.02	0.87
CEVQ.total			0.22	0.05	0.23	0.05
Smoker (yes/no)					-0.02	0.86
Depression					0.09	0.51
Step Statistics	**ΔR2**	**Δp**	**ΔR2**	**Δp**	**ΔR2**	**Δp**
	0.09	0.05	0.05	0.14	0.01	0.78
Model Statistics	**R2**	**p**	**R2**	**p**	**R2**	**p**
	0.09	0.05	0.14	0.04	0.14	0.10

Abbreviations at the end of the table

Table 4d. Hierarchical Multiple Linear Regression Model: Chemerin

Chemerin	Step 1		Step 2		Step 3	
N= 83	**Demographic**		**SDH**		**Confounders**	
Coefficient Statistics	**β**	**p**	**β**	**p**	**β**	**p**
FEP	0.48	<0.01	0.42	<0.01	0.50	<0.01
Sex	-0.10	0.25	-0.12	0.14	-0.13	0.13
WHeR	0.39	<0.01	0.35	<0.01	0.37	<0.01
Minority			-0.21	0.01	-0.22	0.01
CEVQ.total			-0.06	0.46	-0.04	0.58
Smoker (yes/no)					-0.18	0.04
Depression					<0.01	0.98
Step Statistics	**ΔR2**	**Δp**	**ΔR2**	**Δp**	**ΔR2**	**Δp**
	0.50	<0.01	0.04	0.03	0.03	0.12
Model Statistics	**R2**	**p**	**R2**	**p**	**R2**	**p**
	0.50	<0.01	0.54	<0.01	0.57	<0.01

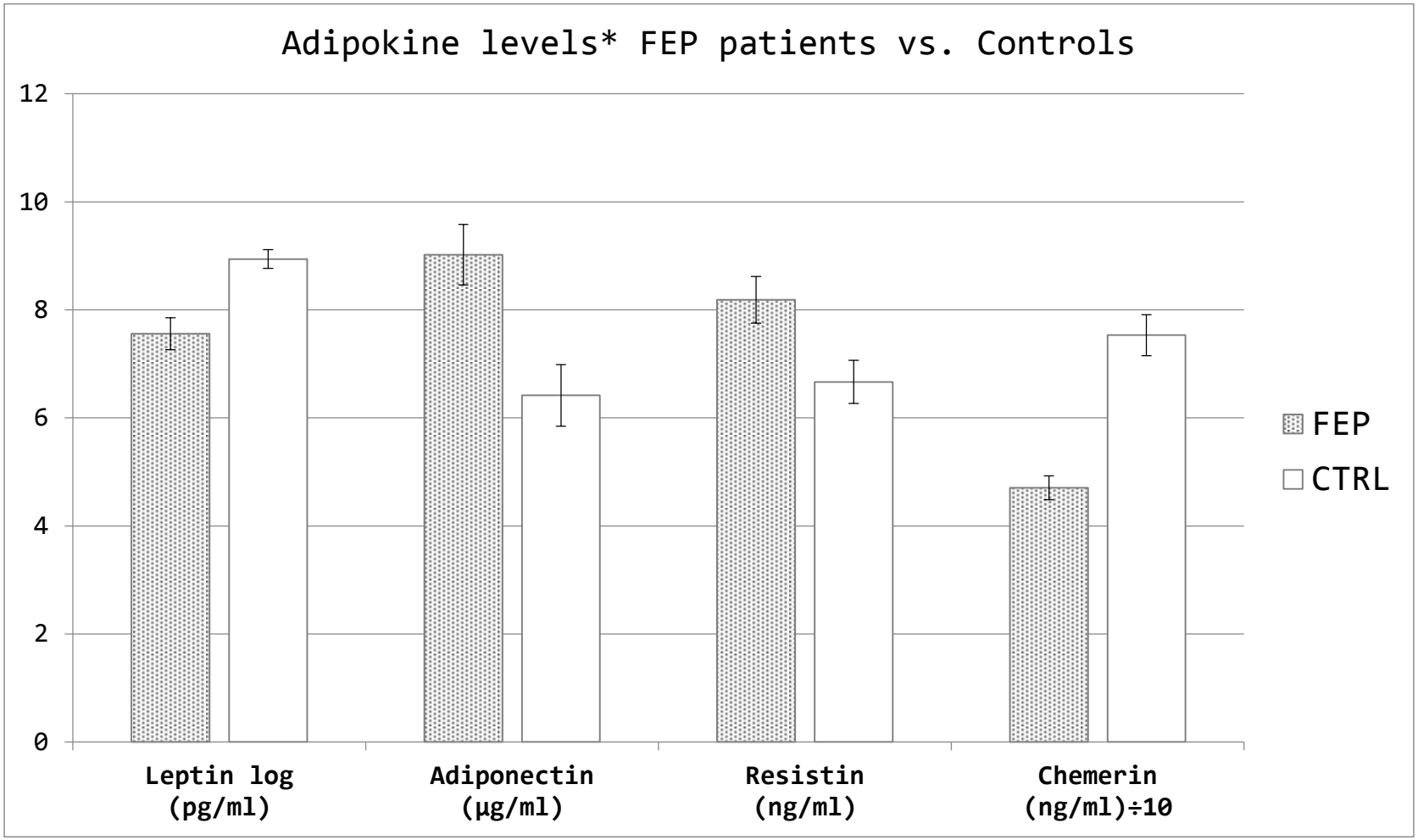
Abbreviations at the end of the table

Table 4 abbreviations:
CEVQ.total: Childhood Experiences of Violence Questionnaire total score; FEP: First-episode psychosis diagnosis; SDH: Social determinant of health;
Guide: FEP: 1=fep, 2=ctrl; Sex: 1=male, 2=female; Minority 1=white, 2=minority; Smoker:1=yes, 2=no.

Table 5. Interaction Between FEP diagnosis and Smoking

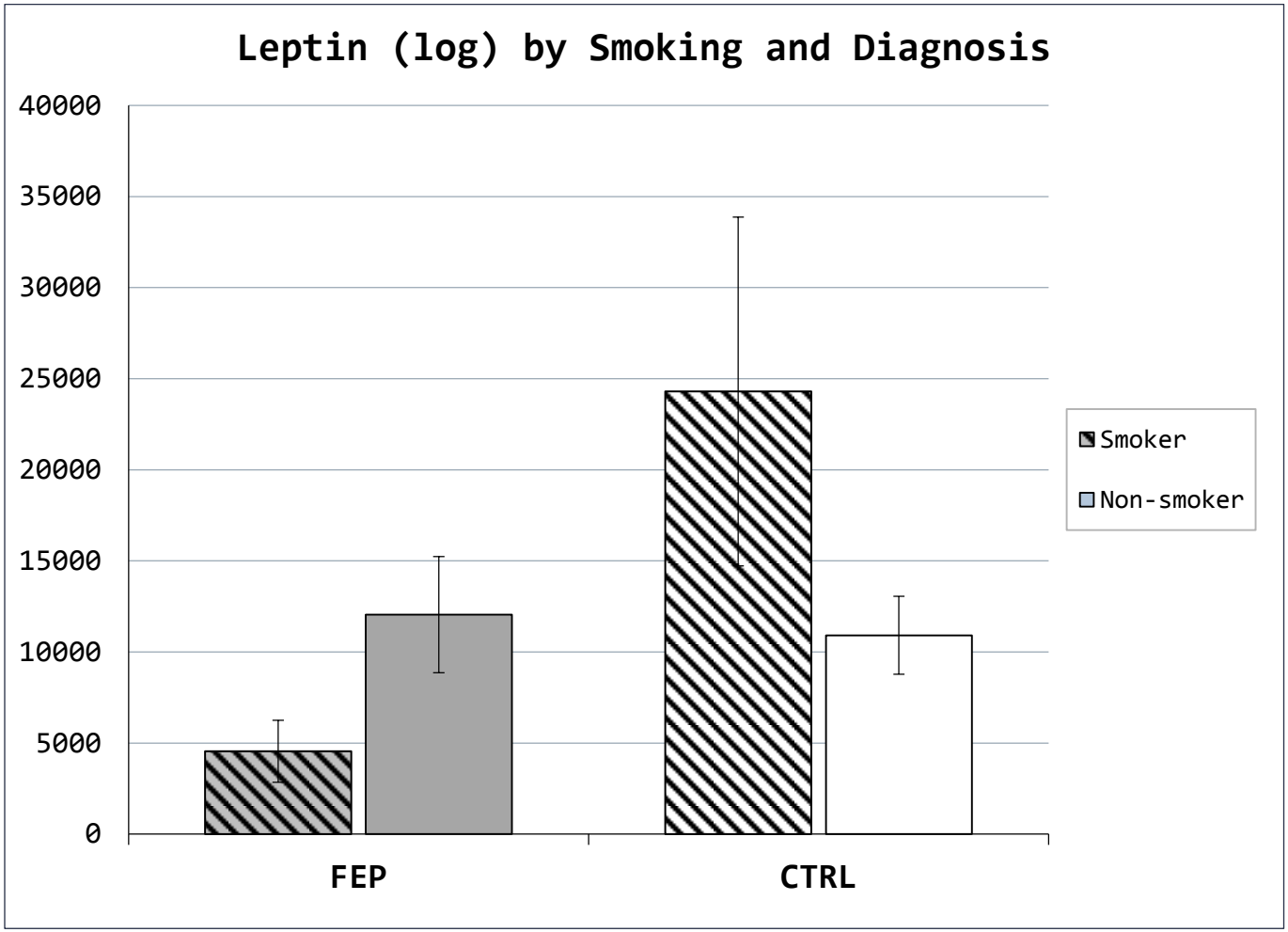
COEFFICIENTS		
Leptin (log)	**Std. β**	***p***
Intercept		<0.01
FEP	-0.47	<0.01
Smoker (dichotomous)	<0.01	0.97
FEP * Smoker	-0.26	0.02
MODEL		
R^2	**F**	***P***
0.21	7.31	<0.01

Figure 1. Adipokines by FEP diagnosis



*Please note that the measurement units of each adipokine are different and adjusted to fit in the graph.

Figure 2. Leptin levels by FEP diagnosis and Smoking



CHAPTER VI

DISCUSSION AND CONCLUSIONS

VI.A Discussion of Global Objectives and Results

Most of the efforts aimed towards the improvement of the quality of life of patients suffering from psychosis-spectrum disorders (PSD) seem to have been geared towards the alleviation of psychotic symptoms and the recovery of function at the personal, social, and occupational levels. Consequently, efforts towards the improvement of physical health in this population have received considerably less attention [331]. This might stem from the difficulties in the implementation of measures such as diet and exercise in the context of some psychosis-associated behavioral changes (e.g., loss of motivation), and the unavoidable lack of pharmacological options without considerable side-effects. The latter has a substantial influence on medical practice, and seems to have led to the acceptance of this dilemma as a "necessary evil" [332]. Such a mindset has shifted the focus away from understanding pathophysiological phenomena in PSD, and has put an excessive emphasis in finding novel therapeutic agents to solve this problem. In other words, it seems that we are waiting for the arrival of a third generation of antipsychotics devoid of side effects, an almost two decade-long promise [333] that has failed to materialize [334]. This position is unsustainable especially considering that metabolic dysregulation, and the associated cardiovascular diseases (CVD) that largely stem from it, are the main causes of morbidity and mortality in patients with PSD. On the other hand, since a growing body of evidence has documented the presence of important clinical anomalies of metabolic homeostasis at the onset of psychosis, a different approach can be proposed. Understanding the physiological divergence of metabolic function in this population is critical for the delineation of potential interventions at multiple levels (e.g., pharmacological, nutritional, exercise), as well for the advancement of the understanding of underlying molecular processes.

The raison d'être of the present study is thus to begin filling this theoretical gap and to contribute to the knowledge on cardiometabolic health in PSD. An evaluation of the meaning of the above-mentioned evidence led to the formulation of the main hypothesis of the present study, i.e., that patients with PSD bear an intrinsic vulnerability for the development of metabolic alterations, a diathesis. Thus, the first objective was to demonstrate the existence of such diathesis through the documentation of metabolic anomalies leading to a higher risk of developing metabolic disorders in these patients. A deeper reflection guided by a thorough examination of the literature on the potential origins of such vulnerability pointed to two main directions: genetics and the environment. Since finding gene polymorphisms that are universally associated with each of these disorders has already been proven to be elusive, the presence of common allelic variants that simultaneously increase the risk for psychosis and metabolic disease seems remote. On the other hand, some environmental factors have proven to increase the risk for the onset of diverse pathologies, and are present in all societies. Among these, social determinants of health are prime candidates given their high prevalence, and their capability to act as risk factors for metabolic disease, CVD and PSD. This led to the formulation of the second leading hypothesis of the study, i.e., that social determinants of health are central elements in the etiology of metabolic dysregulation in psychosis.

The present endeavor was possible through the study of these phenomena in patients with a first episode of psychosis. At this point, the diagnosis of psychosis is certain, while exposure to antipsychotic medication is minimal, and the influence of unhealthy behaviors is relatively limited. This allowed appraising for other factors potentially associated with the origins of

metabolic dysregulation. As such, all the data employed to test the hypotheses was obtained from cohorts of patients diagnosed with a first episode of psychosis. Early intervention services not only provide a multifaceted therapeutic environment supporting clinical, functional and social recovery, but their clinical research infrastructure may be an optimal platform to launch, test, and develop endeavors such as my project, and at the same time expeditiously translate into clinical practice the knowledge arising from it.

This project was conducted in three different but complementary components, each one embodied in a manuscript, and represented in a chapter of this monograph. Each component focused on one major aspect of metabolic homeostasis. The first one examined the clinical dimension of glycemic control as reflected by the levels of glycated hemoglobin (HbA1C). The second component measured the levels of clinically relevant lipid fractions (total cholesterol, LDL, HDL, and triglycerides). The last component plunged into understanding the physiology of adipose tissue by examining the main endocrine mediators of its function: adipokines. In all three studies, the effects of social determinants of health on these outcomes were tested.

The first study leveraged the utilization of glycated hemoglobin (HbA1C) since it is less affected by day-to-day changes (as opposed to fasting glucose), providing a reliable estimation of glycemic control in the three preceding months. Thus, HbA1C is an indirect indicator of insulin resistance. While none of the patients reached the threshold for diabetes, 11% of the sample already had levels consistent with a pre-diabetic state, as defined by the American Diabetes Association (HbA1c = 5.7%–6.4% [335]). This is startling since the estimated prevalence of diabetes in the 18-34 year population is 1.3% for Canada, and only 1.0% for the province of

Quebec where the study was conducted [336]. A more conclusive picture emerged from the second study, where average values and confidence intervals of blood lipid levels from the Canadian general population within a similar age range were obtained from the Statistics Canada website. When comparing the means and confidence intervals from the first-episode psychosis (FEP) cohort against those of the Canadian population, it became clear that patients had lower levels of total cholesterol and HDL. This finding seems paradoxical since low total cholesterol denotes lower cardiovascular risk, but lower HDL indicates higher risk. However, animal models studying the physiological processes underlying lipid homeostasis had found a similar pattern in association with social isolation. Furthermore, the same animal study pinpointed the origin of these changes to an impairment of reverse cholesterol transport. Altogether, these findings point towards a deficit in cholesterol clearance via HDL, which hypothetically favours atherosclerosis, although this needs confirmation. Since the first two components of this project were conducted exclusively in a clinical cohort (i.e., without controls), the evidence of the presence of metabolic dysregulation in FEP patients, while compelling, was still indirect. This limitation was addressed by the third study, which directly compared adipokine levels between patients and controls. These hormones are not only mediators of endocrine function and are involved in inflammation, but are being tested as potential markers of cardiovascular risk. All the tested adipokines were significantly different between the two groups (medication-naive FEP patients and controls), even after controlling for sex, WHeR, minority background, and childhood trauma. In my study I have shown that adiponectin and chemerin further maintained a statistically significant influence after accounting for the effects of depression and tobacco smoking, while leptin and resistin showed trends without a change in the direction of the effects. The latter suggested a lack of adequate power due to their smaller effect sizes (rather than a lack of effect). Collectively, these

findings suggest that patients with PSD may present with important alterations in energy homeostasis even before the use of antipsychotics, and that these changes are probably rooted in the adipose tissue. Such alterations would include impaired adipose-hypothalamic negative feedback signaling, allowing a higher-than-normal accumulation of fat (low leptin, worsened by tobacco smoking, and low chemerin); overshot or hypersensitive compensatory responses (high adiponectin, low chemerin) that would imbalance other systems (local inflammation); abnormal adipocyte maturation (high resistin); and anomalous recruitment and activation of immune cells in the adipose tissue (high resistin, low chemerin). While these latter conjectures are still speculative as the biology of adipokine regulation is extremely complex and has not been completely deciphered, an important effort was put to include the most up-to-date knowledge on this topic in the analyses. Moreover, some of the documented adipokine changes have been described elsewhere in relation with insulin resistance in clinical samples, which is compatible with the findings of the first study.

In sum, the first two studies pointed towards the presence of metabolic dysregulation in FEP patients, already detectable at the clinical level, even before substantial exposure to antipsychotic pharmacotherapy. These results guided the design of the third study, in which I included controls and tested these changes in an essentially drug-naive cohort of FEP patients. This allowed documenting the presence of antipsychotic-independent metabolic anomalies at the onset of psychosis and in association with it. These pathophysiological alterations are compatible with a nascent metabolic syndrome. Thus, it is possible to conclude with a good degree of confidence that patients with a diagnosis of PSD indeed bear a metabolic diathesis.

The influence of social determinants of health was explored in all three studies. In the first study, the levels of HbA1C were significantly higher in participants with an ethnic minority background, which held true after controlling for personal characteristics (age, sex, BMI), social and material deprivation, depression, and physical activity. This effect was strong, and its standardized coefficient was higher than those for age or BMI. A history of self-reported physical abuse predicted higher HbA1C after accounting for the effects of personal characteristics, and was marginally significant after including the effects of depression and physical activity, although its standardized coefficient was comparable to the minority background one. As mentioned above, in the second study, social but not material deprivation was found to be significantly associated with lower total cholesterol and HDL. Finally, the third study documented significant effects for the same social determinants of health that were associated with higher HbA1C. In this case, a history of self-reported physical abuse increased resistin, and chemerin was lower in participants belonging to a visible minority group. In both instances, the effects were significant after controlling for multiple covariates.

When considering on the influence of ethnicity on these outcomes, the first thing that comes to mind is the presence of genetic differences. However, three facts suggest that such contrast in metabolic function was not dependent on genetic variation. First, ethnic minority status was important in two different FEP cohorts, reducing the possibility of a selection bias. Second, in both samples, all persons from a visible minority ethnic background (i.e., not white) were grouped together. This means that this group was composed of participants from populations with considerable genetic differences, and risk profiles. For instance, while East-Asian populations usually have better metabolic profiles and overall lower CVD risk compared to

Caucasians, the opposite can be said for Latino-Americans, who have a higher burden of CVD. Thus, mixing participants from diverse ethnic backgrounds substantially reduced the influence of genetics. Finally, most of the associations between metabolic risk and ethnicity depend on variations in the proportion of adipose tissue mass, particularly abdominal fat. This is why it is recommended that waist circumference cut-offs are tailored for specific populations when calculating CDV risk, and assessment guidelines already reflect it. Furthermore, abdominal adiposity is correlated with insulin resistance. Body fat composition was controlled for with BMI in the HbA1C study, and with the waist-to-height ratio in the adipokine assessment, further reducing ethnicity-associated constitutional differences. Hence, if such disparities did not originate from genetic differences, it means that the minority variables were appraising differences in environmental exposures. Belonging to an ethnic minority implies a multitude of circumstances and factors beyond genetic differences and the obsolete concept of race. The most salient environmental factor associated with belonging to a visible minority is racial discrimination, which pours onto many predictors of health, including chronic stress exposure, access to healthcare, housing and employment opportunities, and socioeconomic disadvantage [337,338]. This last part is speculative as it was beyond the scope of the project, and as such, no measure of discrimination that could support this claim was included.

Childhood trauma is perhaps one of the most pervasive and noxious determinants of mental and physical health, including psychosis. The effects of childhood abuse on health are mediated by multiple factors such as the age and sex of victims, their kinship with the perpetrator, its duration, the cumulative effects of exposure to different forms of abuse, as well as specific outcomes linked to the type of trauma. The latter has a higher relevance in the context of the

findings of this project, since metabolic parameters associated with glycemic control seemed to be mostly affected by physical abuse (although data on neglect was not available for the adipokine study). The concurring effects of childhood physical abuse on HbA1C and resistin are intriguing, since both are at the core of insulin resistance. These findings point towards the presence of a specific molecular pathway associated with insulin that could be particularly affected by physical abuse. Confirmation of such results is warranted.

Social deprivation affects an important proportion of the population, and is possibly one of the aspects behind the association between urbanicity and psychosis risk, one of the most consistently replicated findings in this field [339]. In addition, the geographical measures such as the one tested in the second study have proven to be reliable indicators of health. The lack of influence of material deprivation on lipid levels contradicts most reports from the literature [340], as this measure has been associated with factors such as unhealthy diets (e.g., energy-rich, low-fiber). However, this might be a reflection of egalitarian policies in Canada such as its universal healthcare and economic safety nets that may relieve the population from some of these burdens, which in some countries can be insurmountable. In contrast, social adversity is a growing problem, and its influence on health should not be surprising. The measure of social adversity used by my project is an important indicator of social isolation, which has a strong association with psychological stress, and is a proven predictor of cardiovascular health. The parallel between animal studies of social isolation and the findings of the present study is thus an indication that the project's hypotheses pointed in the right direction, but also speaks of the complexity of these interactions. Indeed, an important lesson from the second study is that the

type of diagnosis (schizophrenia-spectrum versus schizoaffective) determined the influence of the social environment on metabolic health in PSD.

The data from the present study suggests that noxious social factors known to be highly prevalent in PSD, and to determine cardiovascular health, make part of the elements contributing to the high rate of the metabolic comorbidity in psychosis. However, it is important to underscore that the data cannot unmistakably confirm or deny such a claim. In the third project, the influence of diagnosis on resistin and chemerin was slightly reduced after the inclusion of childhood physical abuse and visible minority background in the multiple regression models respectively. Discerning how much the impact of social factors on adipokine regulation ultimately contributes to increase cardiometabolic comorbidity in PSD, will require testing these phenomena in large-scale longitudinal studies. Despite this, the weight of the findings of the present study cannot be disregarded. The clinical significance of these changes has to be understood with the lens of time. For instance, the impact of relatively minor changes in well-known risk factors is substantially higher at younger ages, and their cumulative effects over subsequent decades lead indeed to pathological changes such as atherosclerosis [341]. In addition, the alterations in resistin and chemerin induced by social factors will also have repercussions on the immune system. In fact, inflammation has been linked to stress and recognized as an important component of a multitude of conditions including endocrine [342], cardiovascular [343], oncologic [344], and psychiatric disorders [345].

The potential magnitude of these social determinants of health on metabolic health in PSD becomes more evident when looking at their prevalence in the present study (PEPP population).

The proportion of patients from a visible minority background was 38%, which is almost double the 20% estimate for the city of Montreal based on the 2011 census [346]. Half of the cohort reported having a history of considerable exposure to any form of childhood trauma, which is higher than some estimates (38%) for the Canadian population [347]. Finally, 50% of the patients lived under high levels social deprivation (living alone, without a partner, and in single-parent households), which contrasts with the 24% for the whole population in the PEPP catchment area where patients live. Thus, the patient population likely had a higher social burden than the rest of the population. Given this context, and the decades of evidence supporting the effects of social factors on health, it may be prudent to not ignore the present findings.

VI.B Implications

Determining that patients with a PSD have an increased vulnerability for the development of metabolic disorders, that such changes are not associated with previous medication exposure, and that there is a potential involvement of social factors in its origins has implications at multiple levels.

At the etiological level, these findings add to the literature on social determinants of health in psychosis, but also raise some questions. For instance, some well-known determinants of health seemed to have no influence on the examined metabolic parameters. Two explanations are suggested. First, the Canadian social context is indeed unique, and the impact of these determinants might have been minimized by the way societal needs are met or addressed in this country. Second, some of the tools that measure social factors were initially developed in other

populations, and further refinements might be needed to capture the nuances of the Canadian context. Future Canada-focused research on the sensitivity and the impact of social determinants on health will be able to solve these questions. On the other hand, those social determinants that proved to have an impact did not explain all the variance of metabolic change in FEP. Since it was argued that genetic variants with such potential would be rare, it can be proposed that other environmental factors should also be promoting this phenomenon. Events occurring during developmental periods have proven potentials to induce substantial physiological changes, and have been associated with higher rates of these disorders as well [348-350]. The programming of disease occurs as early as in intrauterine life [351,352], and perhaps this is when the impact of environmental insults is consequential. A multitude of early-life factors such as prenatal stress, maternal undernutrition, obstetric immune activation (e.g., infection), and perinatal complications have also a proven potential to fill this etiological void [353-355].

In the context of physiology, the present results advance the current state of the knowledge by identifying some of the pathophysiological processes responsible for metabolic disease in FEP patients. Three main physiological elements need to be considered. First, since the brain is the primary anatomic location of psychosis, it will be important to ascertain other changes in the neuroendocrine integration in psychosis beyond the stress response. In particular, the dysregulation of hypothalamic responses involved in energy balance targeted by leptin and adiponectin, such as appetite control and energy expenditure [356], are first-line candidates as potential anomalies in the nervous system. The differential response of leptin to tobacco smoking is an additional important piece of this puzzle. Second, the proposed anomalies of adipose tissue guided by the findings of the present study need to be confirmed, as these point to constitutional

changes derived from abnormal adipocyte differentiation and impaired endocrine (i.e., adipokine) responses. The findings from the present study already point towards the dysregulation of molecular pathways such as the AMP-activated protein kinase pathway [357]. Finally, this is the first study to identify changes chemerin in FEP, which can provide a link between metabolic function and inflammation in psychosis. This is of particular importance since anomalies in adipokine function have increasingly been identified in immune disorders such as cancer and autoimmune conditions. Thus, documenting adipokine dysregulation in psychosis could help explaining the multiple epidemiological and often paradoxical relationships between schizophrenia and other chronic disorders.

Regarding clinical implications, recognizing that some patients might be at a higher risk for developing metabolic anomalies such as obesity, dyslipidemia and insulin resistance should be a priority. As documented by the present study, and the wealth of data on which its hypotheses stand on, social factors are powerful determinants of health. As such, active measures should be universally implemented, and the social context of patients must be routinely assessed using a personalized medicine framework. In addition, the biochemical markers analyzed in the third project might represent future avenues of clinical diagnosis, particularly as tools to understand metabolic function before –and in association with– the use of antipsychotics.

At the social level, this project adds to the literature on social determinants of health, but documents these associations in a new context. These results emphasize that the considerable social burden carried by patients suffering from psychosis has additional repercussions on their physical health, quality of life, and longevity. Thus, social interventions are also relevant for the

physical health of this population. While loneliness is a complex phenomenon that depends on internal and external factors, in PSD, loneliness importantly depends on social factors such as lack of social support and internalized stigma [358]. Social support is indeed recognized by early intervention programs as a vital element in the process of recovery in psychosis, and hence the important emphasis put on family involvement and community engagement. However, the impact of collective factors on physical health such as structural stigma, which has been correlated with increased mortality in sexual minority populations [359], has not been explored in the context of psychosis. Such factors from cultural and institutional levels need to be well-understood and approached from multiple levels. Even though there is no shortage of reasons to advocate for a stronger promotion of societal interventions against stigma and discrimination in general, the results from the present study provide an additional argument to advocate for the delineation of policies, and the allocation of resources to tackle this problem.

Globally, the present study demonstrates that there is a need for the study of the biology of disease within the psychosocial context. While animal and human studies provide invaluable insights from the molecular to the population levels, and advancements in the understanding of complex disorders such as PSD and DM2 keep going further, it seems that the determination of their causes has reached an impervious wall. As these conditions have multiple etiologies, only by taking into account all aspects associated with their development, the interactions between the genes and the environment that give rise to them will be unveiled. As such, only multidisciplinary approaches will break this barrier. This seems like an insurmountable task, but the present study proves that even with a small sample, if the rationale is pointed in the right direction, some of these interactions can be established. Overall, the present study is thus an

important advancement towards the integration of developmental, immune, metabolic, and environmental theories to address the comorbidity puzzle of PSD.

VI.C Future Directions

Given that this project has documented different links between the social environment and adipose physiology in psychosis, a deeper exploration of this phenomenon is needed to confirm these findings and expand the knowledge on this issue. Testing other elements of the physiology of adipose tissue in PSD, including other adipokines, would be rational. The next logical step would be to unravel the underlying processes responsible for this association. A reasonable path might be testing for epigenetic changes in the molecular pathways regulating adipokine production, secretion and their receptors, adipocyte maturation, and differentiation of adipose-resident immune cells, among others. However, epigenetic changes alone would not determine the origins of the metabolic diathesis of psychosis, and this might prove to be as complex as disentangling the puzzle of psychosis. Hence, an even deeper understanding of genetic processes, and especially a clear mapping of the social landscape of this disease will be needed to articulate more accurate models of disease. Multidisciplinary collaboration might help advancing the knowledge through the integration of different views, as it is been proposed for complex issues such as obesity [360].

The results from this study should also be considered by pharmacological researchers, as these findings could complement some theoretical proposals and animal models on the effects of antipsychotics on the adipose tissue [39], immune cells [361], and thalamic nuclei [362]. For instance,

antipsychotics might have differing side-effects in patients than in controls. This could potentially explain the failure to achieve pharmacological agents that have minimal metabolic side-effects in practice, despite initial promising results during the first steps of drug development.

Finally, my project demonstrates that embracing contemporary paradigms on the etiopathogenesis of disease has the potential to provide a newer angle to explain complex medical phenomena such as comorbidity in PSD. For instance, the high frequency of metabolic disease in this population might result in part from the exposure to adverse social factors that are independently associated with these disorders, known to act throughout development, and promote or trigger the onset of these conditions. These paradigms need to keep evolving however, so as to provide a deeper understanding of the origins of disease, and speak to the need for collaborative interdisciplinary approaches.

The presence of metabolic alterations early in the natural history of PSD, and which precede the use of antipsychotic medication, strongly suggests that psychotic and metabolic disorders may have shared etiological roots acting throughout development. The present doctoral project incorporated newer theories on the emergence of disease to explore this phenomenon. Among the cluster of possible common etiological roots, it was hypothesized that social determinants of health might play an important role, given their known influence on the risk for psychotic and metabolic disorders, and their pervasive influence throughout the development of the individual. Some of the examined social factors were indeed found to promote metabolic changes in patients undergoing a first episode of psychosis. In addition, the adipose organ was identified as one of

the impaired systems harboring the pathophysiology of metabolic dysregulation in PSD. The findings of this dissertation are an additional step towards building the necessary knowledge to improve the physical health of patients with PSD, not only with the purpose of reducing cardiovascular mortality, but also to improve the quality of life of this population.

APPENDICES

APPENDIX A. ANCILLARY TABLES

Chapter III — Manuscript 1

Supplementary Table 1: Red blood cell levels by analyzed subpopulations

Sample	Ethnicity Subsample				Physical Abuse Subsample			
Variable	**Mean**	**SD**	**95% C.I.**	**N**	**Mean**	**SD**	**95% C.I.**	**N**
Hemoglobin	14.65	1.23	14.85–14.44	139	14.45	1.20	14.75–14.16	66
Hematocrit	43.14	3.57	43.74–42.54	139	42.65	3.52	43.51–41.78	66
Mean Corpuscular Volume	89.59	5.33	90.48–88.70	140	89.37	5.22	90.65–88.10	67
Mean Corpuscular Hemoglobin	30.48	2.01	30.82–30.14	140	30.38	1.98	30.86–29.89	67
Mean Corpuscular Hemoglobin Concentration	34.01	0.79	34.15–33.88	140	33.98	0.82	34.18–33.78	67

Supplementary Table 2: HbA1c Levels by Substance abuse diagnosis at admission

Sample	Ethnicity Subsample	Physical Abuse Subsample
N	137	66
R^2	0.000123	0.000986
F	0.0165	0.0632
p-value	0.8978	0.8023
Mean(SD) No abuse Dx	0.0518 ± 0.0039	0.0517 ± 0.0040
Mean(SD) Abuse Dx	0.0519 ± 0.0038	0.0515 ± 0.0040

Supplementary Table 3**:** HbA1c Levels by Hollingshead SES index

Sample	**Main HbA1c Subsample**	**Ethnicity Subsample**	**Physical Abuse Subsample**
N	159	109	57
R^2	0.051	0.015	0.009
F	0.80	1.65	0.54
p-value	0.37	0.20	0.46

Chapter IV — Manuscript 2

Supplementary Table 1: Average Lipid Levels at Similar Age Ranges, General Canadian Population versus Study Participants

Blood Lipids	Group	StatCan Mean (C.I.) 20-39 years	PEPP Mean (C.I.) 16-35 years
Total Cholesterol	All	4.6 (4.5-4.7)	4.2 (4.0-4.3)
	Male	4.7 (4.5-4.8)	4.2 (4.0-4.3)
	Female	4.6 (4.4-4.7)	4.1 (4.0-4.3)
LDL	All	2.6 (2.5-2.7)	2.5 (2.4-2.6)
	Male	2.7 (2.6-2.9)	2.5 (2.4-2.7)
	Female	2.5 (2.4-2.7)	2.5 (2.3-2.6)
HDL	All	1.40 (1.33-1.47)	1.16 (1.11-1.20)
	Male	1.24 (1.17-1.31)	1.11 (1.06-1.16)
	Female	1.56 (1.48-1.65)	1.27 (1.19-1.35)
Triglycerides	All	1.06 (0.98-1.16)	1.06 (0.96-1.17)
	Male	1.20 (1.07-1.34)	1.13 (1.00-1.26)
	Female	0.94 (0.85-1.05)	0.90 (0.71-1.09)

C.I.: Confidence Interval; HDL: High-density Lipoprotein; LDL: Low-density Lipoprotein; StatCan: Statistics Canada.

Supplementary Table 2: t-tests Outcomes and Main Predictors by Diagnostic Category

VARIABLE	Diagnosis	N	Mean	SEM	DF	*t*	*p*
Total Cholesterol	SSD	146	4.16	0.077	199	0.09	0.93
	Affective Psychosis	55	4.17	0.126			
HDL	SSD	147	1.16	0.026	200	-0.12	0.90
	Affective Psychosis	55	1.15	0.042			
LDL	SSD	144	2.54	0.063	197	-0.45	0.65
	Affective Psychosis	55	2.48	0.102			
Triglycerides	SSD	147	1.02	0.063	200	1.21	0.23
	Affective Psychosis	55	1.17	0.103			
Material Deprivation	SSD	147	63.11	2.531	200	-1.51	0.13
	Affective Psychosis	55	55.76	4.139			
Social Deprivation	SSD	147	75.28	1.600	200	0.05	0.96
	Affective Psychosis	55	75.42	2.616			
Physical Anergia	SSD	147	2.52	0.124	200	-3.34	<0.01
	Affective Psychosis	55	1.73	0.204			
Medication Exposure	SSD	147	9.08	1.536	200	2.33	0.02
	Affective Psychosis	55	15.95	2.512			

DF: Degrees of Freedom; HDL: High-density Lipoprotein; LDL: Low-density Lipoprotein; N: number in group; p: test statistic significance; SEM: Standard Deviation of the Mean; SSD: Schizophrenia Spectrum Disorder; t: t-test value.

Supplementary Table 3: Collinearity Statistics Main Multiple Regression Models

	All Patients		SSD		Affective Psychosis	
Total Cholesterol	**Tolerance**	**VIF**	**Tolerance**	**VIF**	**Tolerance**	**VIF**
Sex	0.987	1.013	0.976	1.024	0.965	1.036
Age at entry	0.926	1.080	0.963	1.038	0.787	1.271
Material Deprivation Score	0.954	1.048	0.942	1.062	0.977	1.024
Social Deprivation Score	0.952	1.051	0.936	1.068	0.832	1.202
Medication Exposure Index	0.932	1.073	0.957	1.045	0.861	1.162
Physical Anergia	0.978	1.022	0.975	1.025	N/A	N/A
LDL	**Tolerance**	**VIF**	**Tolerance**	**VIF**	**Tolerance**	**VIF**
Sex	0.986	1.015	0.970	1.031	0.965	1.036
Age at entry	0.928	1.077	0.965	1.036	0.787	1.271
Material Deprivation Score	0.951	1.051	0.939	1.065	0.977	1.024
Social Deprivation Score	0.952	1.051	0.935	1.069	0.832	1.202
Medication Exposure Index	0.936	1.069	0.960	1.042	0.861	1.162
Physical Anergia	0.974	1.027	0.968	1.033	N/A	N/A
HDL	**Tolerance**	**VIF**	**Tolerance**	**VIF**	**Tolerance**	**VIF**
Sex	0.986	1.014	0.970	1.031	0.965	1.036
Age at entry	0.928	1.078	0.962	1.039	0.787	1.271
Material Deprivation Score	0.956	1.046	0.946	1.058	0.977	1.024
Social Deprivation Score	0.952	1.050	0.935	1.069	0.832	1.202
Medication Exposure Index	0.934	1.071	0.957	1.045	0.861	1.162
Physical Anergia	0.976	1.024	0.972	1.029	N/A	N/A
Triglycerides	**Tolerance**	**VIF**	**Tolerance**	**VIF**	**Tolerance**	**VIF**
Sex	0.985	1.015	0.974	1.027	0.965	1.036
Age at entry	0.927	1.079	0.963	1.038	0.787	1.271
Material Deprivation Score	0.956	1.046	0.946	1.057	0.977	1.024
Social Deprivation Score	0.952	1.050	0.936	1.069	0.832	1.202
Medication Exposure Index	0.932	1.072	0.957	1.045	0.861	1.162
Physical Anergia	0.978	1.023	0.976	1.024	N/A	N/A

HDL: High-density Lipoprotein; LDL: Low-density Lipoprotein; SSD: Schizophrenia Spectrum Disorder; VIF: Variance Inflation Factor.

APPENDIX B. COVER PAGE ACCEPTED MANUSCRIPT

Original Research

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Social Determinants of Health and Preclinical Glycemic Control in Newly Diagnosed First-Episode Psychosis Patients

Déterminants sociaux de la santé et contrôle glycémique préclinique chez des patients ayant reçu un diagnostic de premier épisode de psychose

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Abstract

Background: The abnormally high incidence of disorders of glucose metabolism (DGM) in psychotic-spectrum disorders (PSD) has often been attributed to the side effects of antipsychotics and unhealthy lifestyles. The influence of social determinants of health has been largely ignored, despite ample evidence linking social adversity with both PSD and DGM. The aim of this study is to examine the influence of well-established social determinants of health on preclinical levels of glycated hemoglobin (HbA1c) in a sample of first-episode psychosis (FEP) patients.

Methods: In a sample of newly admitted FEP patients, univariate analyses were used to select the main predictors of HbA1c levels from the following social determinants of health: childhood trauma, immigrant background, visible minority status, and indices of social and material deprivation. The predictors identified in the univariate analyses were tested in multivariate linear regression models including age, sex, BMI, depression, and physical anergia (proxy of sedentary behaviour) as covariates.

Results: Univariate analyses identified visible minority status and childhood physical abuse as predictors of HbA1c. After controlling for covariates, minority status significantly predicted higher levels of glycated hemoglobin ($\beta = 0.23$; $P = 0.01$), and physical abuse had a marginally significant effect ($\beta = 0.23$; $P = 0.06$). Other predictors were not significantly associated.

Conclusion: FEP patients from a visible minority or who were victims of childhood physical abuse have higher levels of HbA1c at admission compared with other patients. This might suggest an increase in risk for the development of future DGM. If confirmed, preventive strategies could be tailored for these groups.

Abrégé

Contexte : L'incidence anormalement élevée des troubles de métabolisme du glucose (TMG) dans les troubles du spectre de la psychose (TSP) a souvent été attribuée aux effets secondaires des antipsychotiques et à un mode de vie médiocre. L'influence des déterminants sociaux de la santé a été largement ignorée, malgré amplement de données probantes liant l'adversité sociale au TSP et aux TMG. Cette étude vise à examiner l'influence des déterminants sociaux de la santé bien établis

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