Universidade do Minho
Escola de Medicina

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Metabolic syndrome in inpatients with schizophrenia and major depressive disorder: case studies in the Casa de Saúde do Bom Jesus

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Metabolic syndrome in inpatients with schizophrenia and major depressive disorder: case studies in the Casa de Saúde do Bom Jesus

Dissertação de Mestrado
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Trabalho efetuado sob a orientação da
Professora Doutora Joana Almeida Pacheco Palha
e da
Doutora Nadine Correia Santos

junho de 2017

A minha mãe por ter-me entendido.

Ao meu esposo Marques Olece Nhamonga pelo carinho, insistência e encorajamento no processo de candidatura do curso e consequente conclusão desse trabalho.

Aos meus filhos; Melvio & Melton, meus companheiros de todos momentos, e ao Marques jovem Jú, o último homem pela compreensão dos momentos de ausência que passaram.

A minha família pela coragem e apoio prestado.

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Abstract

Introduction: Metabolic syndrome (MetS) is a disorder with high prevalence in patients with mental illness. This is of importance since it can lead to increased morbidity and mortality due to metabolic causes and cardiovascular disease. More so, it associates with the prognosis of mental illness by reducing adherence to therapy and increasing functional limitation. **Objective:** To determine the prevalence of MetS in female inpatients with Schizophrenia and Major depressive disorder in the Casa de Saúde do Bom Jesus, between September 2016 and March 2017. **Materials and methods**: The work was a case study, with a consecutive sampling approach. A final sample of 80 (n= 40 SZ; n=40 MDD). Main inclusion criteria included being female over 18+ years old with a diagnosis of SZ or MDD, according to the international statistical classification of diseases (ICD-10), with treatment with antipsychotic or/and antidepressive drugs. The study parameters included anthropometric measures, blood pressure and biochemical variables [fasting glucose, high density lipoprotein (HDL), cholesterol and triglycerides]. **Results:** The overall mean age was of 51.5 years (SD=13.3; range 24-75 years). MetS was found in 46% of the inpatients considered; 38% in MDD patients and 55% in SZ patients. Of the components of the MetS, increased waist circumference was the most prevalent (73% for MDD and 85% for SZ), followed by low HDL< 50 mg/dl (65% in both groups). When considering for the number of Mets components, 94% of patients had at least one (1) criterion, with 35% of MDD having two (2) criteria and 25% of the SZ patients having three (3). MetS was associated with increased age and lower adherence of Mediterranean diet in MDD patients, and with higher body mass index in SZ patients. In SZ patients' antipsychotic was associated with increased waist circumference. **Conclusions:** Patients with mental illness have a high prevalence of MetS independently of the diagnosis. Current findings may emphasize the critical need of care, with precise and detailed longitudinal monitoring. As such, it is important to monitor patients in any clinical setting regarding metabolic issues.
Keywords: Metabolic syndrome; schizophrenia; major depressive disorder; prevalence; case study.

Resumo

Introdução: A síndrome metabólica (SM) é uma perturbação com alta prevalência em pacientes com doença mental. Como consequência aumento da morbidade e da mortalidade devido a causas metabólicas e doenças cardiovasculares. ***Objetivo:*** Determinar a prevalência de SM em pacientes internados com esquizofrenia e perturbação depressiva Major na Casa de Saúde do Bom Jesus entre Setembro de 2016 e Março de 2017. ***Materiais e métodos:*** O trabalho foi um estudo de caso, com uma amostra de 80 pacientes (n = 40 esquizofrenia, n = 40 perturbação depressiva major). Critérios de inclusão foram: mulheres com mais de 18 anos de idade com diagnóstico de esquizofrenia ou perturbação depressiva major, de acordo com a classificação estatística internacional de doenças (CID-10), tratamento com antipsicóticos e/ou antidepressivos. Os parâmetros do estudo incluíram: medidas antropométricas, pressão arterial e variáveis bioquímicas [glicemia de jejum, lipoproteína de alta densidade (HDL), colesterol e triglicéridos]. ***Resultados:*** média da idade foi de 51,5 anos (DP = 13,3; variando de 24 a 75 anos). A SM foi encontrada em 46% dos pacientes internados; 38% em pacientes com perturbação depressiva major e 55% em pacientes com esquizofrenia. Dos componentes da SM, o aumento da circunferência da cintura foi o mais prevalente (73% para perturbação depressivo major e 85% para esquizofrenia) seguido de baixo HDL <50 mg / dl (65% nos dois grupos). Quanto ao número de critérios de SM, 94% dos participantes teve pelo menos um (1), com 35% dos doentes com depressão com dois (2) e 25% dos doentes com esquizofrenia com três (3). A SM foi associada com maior idade e menor aderência da dieta mediterrânea em doentes com depressão, e com maior índice de massa corporal em doentes com esquizofrenia. Em doentes com esquizofrenia, os antipsicóticos foram associados ao aumento da circunferência da cintura. ***Conclusão:*** Na doença mental encontramos uma alta prevalência de SM, independente do diagnóstico. Os achados enfatizam a necessidade de abordagem crítica e monitorização dos problemas metabólico em qualquer ambiente clínico e dentro duma abordagem holística.

Palavras-chave: Síndrome metabólica; esquizofrenia; perturbação depressiva major; Prevalência; estudo de caso

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List of Abbreviations

HDL High density lipoprotein

MDD Major depressive disorder

MetS Metabolic syndrome

SZ Schizophrenia

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CHAPTER I

1. Introduction

Metabolic Syndrome (MetS) is defined by a cluster of clinical features that include increased abdominal and/or visceral adiposity, dyslipidemia, hypertension and glucose dysregulation or diabetes mellitus (DM) (1). Different studies and systematic reviews have shown that the prevalence of MetS is quite high among both treated and untreated psychiatric patients [reaching 25-59% in the USA and Europe (1)]. This is also the case for patients with schizophrenia (SZ) and those with major depressive disorder (MDD), affecting both sexes, albeit with predominance in women (2–4). The quality of life of these patients may be quite low (5) and multiple comorbidities are associated with increased mortality in these patients, predominantly cardiovascular disease and the risk factors associated with it (6–8). In fact, morbidity and mortality are about 2 or 3 times higher as compared with that in the general population (6).

The most useful predictor of high rate of MetS in mental illness is waist size, illness duration and older age (1). Many studies point to the use of psychiatric drugs, predominantly second generation antipsychotics and tricyclic antidepressants, as a possible cause, but also polypharmacy and duration of treatment are associated risk/causative factors (9–12). Furthermore, MetS can relate to an unhealthy lifestyle, such as smoking, alcohol consumption, unhealthy diet and physical inactivity (13,14). Finally, among factors associated with of SZ and MDD, hypothalamic pituitary-adrenal and mitochondrial dysfunction, and neuro-inflammation, may also contribute (1,11).

It is important to determine the prevalence of MetS and associated risk factors, across populations and community settings, as its identification is required for recommendations and possible interventions on lifestyle and/or pharmacological treatment (15). More so, such need is particularly relevant in patients with severe mental illness, if considering that MetS is also important for the prognosis of mental illness in itself, since it may lead to reduced adherence to therapy and to functional limitation. Here, following a case study design approach, the goal was to conduct an epidemiological study on the prevalence of MetS in severe mental illness patients, namely with SZ and MDD, in the Casa de Saúde do Bom Jesus (Braga, Portugal).

1.1. Problem statement

MetS is now considered a worldwide epidemic (16) with high socioeconomic cost (17). It is estimated that around 20-25% of adults worldwide have MetS (18), and in Europe the prevalence ranges from 4.7 to 18.3% (19). The prevalence is similar across continents, ranging from about 20% in Asia, to 25% in Latin America and 33% in the USA. These estimates are expected to increase due to the parallel rise in the prevalence of obesity (16). However, the prevalence varies according to sex, countries and ethnic groups, with lifestyle being a strong determinant (17). In Portugal, the prevalence of MetS adjusted for gender, age and region size, is 27.5% and presents regional variations, being highest in the Alentejo region (30.9%) and the lowest in the Algarve (24.4%). More so, it is more common among women and increases with age, body mass index and waist circumference (20).

Different studies and systematic reviews have shown that the prevalence of MetS is quite high in patients with severe mental illness, compared to the rest of the population. The overall prevalence of MetS in severe mental illness is around 32.5 % (21), ranging from 25-59% in the USA and Europe, to 20-40% in the Asian population, 14-30% in South America, 20-30% in Australia (1) and 23.2% in South Africa (22). The overall prevalence of MetS in MDD patients worldwide is estimated around 36 % (3), and in SZ is of about 38% (3), affecting both sexes, albeit with predominance in women (21). Multiple comorbidities are associated with increased mortality in these patients, predominantly cardiovascular disease and the risks factors associated with it (23). In fact, patients with severe mental illness have a 2 to 3 times higher mortality rate compared to the general population, and 60% of excess mortality is due to physical comorbidities, predominantly cardiovascular disease (2) and type 2 diabetes, some types of cancer and all-cause mortality (24). SZ and MMD patients also have an increased risk for cardiovascular and related diseases (1).

1.2. Metabolic syndrome

MetS is a complex disorder broadly defined by the presence of abdominal obesity, high blood pressure, low high density lipoprotein (HDL) cholesterol, elevated triglycerides, and hyperglycemia (18). The study of metabolic abnormalities has been conducted for several years, but the term “metabolic syndrome” was only coined in 1950 and became more commonly used after the 1970s (25). MetS has been also been referred to as plurimetabolic syndrome, X syndrome, X plus Syndrome, X metabolic syndrome, cardiovascular metabolic syndrome, insulin-resistance-dyslipidemia syndrome, atherogenic metabolic syndrome, and syndrome of atherogenic factor (26). Briefly, in 1947, Vague, a French physician, described that android obesity (adiposity of the superior part of the body) was mostly related with diabetes mellitus and cardiovascular disease, kidney stones and gout (25). After that, in 1977, Herman Haller used the term metabolic syndrome in reference to the association between obesity, diabetes mellitus, high blood lipid, high uric acid level and fatty liver disease (26). In the late 80s, Gerald Reaven hypothesized that insulin resistance could be the underlying factor linking this constellation of abnormalities, and this association was called X syndrome. Thereafter, Ferranini and collaborators, resumed this idea, confirming that this group of “disturbances” can have a causal link in insulin–resistance, thus terming it “insulin – resistance syndrome” (26).

In 1998, the World Health Organization gave the first “official/consensual” definition of MetS as the presence of type 2 diabetes mellitus, or the altered tolerance to glucose combined with at least two other factors (hypertension, increased level of blood lipids, obesity and microalbuminuria) (25). In 2001, the National Cholesterol Education Program Adult Treatment Panel III (USA) added a more updated concept, important for clinical use, which does not require confirmation of resistance to insulin. Specifically, this panel defined MetS as the coexistence of at least 3 of the following parameters (26):

- Waist circumference > 102 cm for men >88 cm for women;
- Plasma triglycerides ≥ 150 mg/dl (> 1.7 mmol/l);
- Plasma HDL cholesterol < 40 mg/dl (1.0 mmol/l) in men < 50 mg/dl (1.3 mmol/l) in women;

- Blood pressure ≥ 130/85 mmHg;
- Plasma glucose ≥ 110 mg/dl (> 6.1 mmol/l).

In 2005, the International Diabetes Federation modified this definition, indicating that the key element is the central obesity (25), and that the presence of any other two of the listed factors establishes the MetS diagnostic. The International Diabetes Federation definition is based on the presence of central obesity (defined by the waist circumference ≥ 94 cm for men and ≥ 80 cm for women, of European origin, with characteristics values for various ethnic groups) and ≥ 2 of the following parameters:

- High level of the triglycerides ≥ 1.7 mmol/l (150 mg/dl) or drug treatment for hyperlipidemia;
- Low level of the HDL – cholesterol < 1.03 mmol/l (40 mg/dl) in men and < 1.29 mmol/l (50 mg/dl) in women or drug treatment for dyslipidemia;
- Arterial hypertension, systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg or cure for hypertension that was previously diagnosed;
- The increased levels of the venous glycaemia ≥ 5.6 mmol/l (100 mg/dl) or previously diagnosed type 2 diabetes mellitus (with values > 5.6 mmol/l or 100 mg/dl.

In addition, the International Diabetes Federation recommends an oral test of tolerance to glucose, but that is not needed for defining MetS (18).

Despite the total of six definitions of the MetS from the various organizations, all are consensual in that the definition includes the four major components: hyperglycemia, hypertension, dyslipidemia and obesity. The definitions differ in how they value obesity or diabetes, definition and extent of pre-diabetes or pre-hypertension and, finally, on the choice of measurement criteria for obesity (such as body mass index, waist circumference or waist to hip ratio) (18,25). Table 1 summarizes the definitions.

Table 1 – Criteria for the metabolic syndrome definition (adapted from Cornier et al. 2008, International Diabetes Federation, 2006).

WHO (1998)	**EGIR (1999)**	**NCEP-ATP III (2001, modified in 2003)**	**AACE (2003)**	**IDF (2006)**
(A) and any two of (B), (C), (D) or (E)	***(A) and any two of (B),(C), (D), (E) or (F)***	***Three or more of (A), (B), (C), (D) or (E)***	***(A) and any two of (B), (C) or (D)***	***(A) and any two of (B), (C), (D) or (E)***
(A) High insulin levels, impaired glucose tolerance or impaired fasting glucose	(A) Top 25% of the fasting insulin values among individuals without diabetes		(A) Impaired glucose tolerance	
(B) Abdominal obesity: waist-to-hip ratio >0.9, BMI ≥ 30 kg/m², waist circumference > 94 cm	(B) Waist circumference: ≥94 cm for men, ≥80 cm for women	(A) Waist circumference: >102 cm for men, >88 cm for women		(A) Abdominal obesity: BMI ≥ 30 kg/m², waist circumference ≥ 94 cm for men, ≥ 80 cm for women (of European descent)
(C) Raised triglycerides: >150 mg/dl	(C) Raised triglycerides: ≥177 mg/dl	B) Raised triglycerides: ≥150 mg/dl	(B) Raised triglycerides: ≥150 mg/dl	(B) Raised triglycerides: ≥150 mg/dl
D) Reduced HDL cholesterol: <35 mg/dl	(D) Reduced HDL cholesterol: <38.6 mg/dl	(C) Reduced HDL cholesterol: <40 mg/dl for men, <50 mg/dl for women	(C) Reduced HDL cholesterol: <40 mg/dl for men, <50 mg/dl for women	(C) Reduced HDL cholesterol: <40 mg/dl for men, <50 mg/dl for women
(E) Raised BP: >140/90 mmHg	(D) Raised BP: ≥140/90 mmHg or antihypertensive medication	(D) Raised BP: ≥130/85 mmHg	(D) Raised BP: ≥130/85 mmHg	(D) Raised BP: systolic BP ≥ 130 mmHg or diastolic BP ≥ 85 mmHg
	(F) Raised fasting plasma glucose: ≥110 mg/dl	(E) Raised fasting plasma glucose: ≥110 mg/dl; from 2003 onwards ≥100 mg/dl		(E) Raised fasting plasma glucose: ≥100 mg/dl or previously diagnosed type II diabetes

AACE, American Association of Clinical Endocrinologists; BMI, body mass index; BP, blood pressure; EGIR, European Group for the Study of Insulin Resistance; HDL, high-density lipoprotein; IDF, International Diabetes Federation; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III; WHO, World Health Organization.

As indicated by the difficulty in defining it, the pathophysiology of MetS is not yet fully understood. There are several conditions contributing to the pathogenesis of MetS; among these, obesity and insulin resistance remain the principal ones. Furthermore, a number of other factors, such as chronic stress and dysregulation of the hypothalamic-pituitary adrenal axis and the autonomic nervous system, increased cellular oxidative stress, renin-angiotensin aldosterone system activity, and intrinsic tissue glucocorticoid actions, have been proposed to underlie the pathology (1,3,27). Of relevance, and as stated, when considering preventive strategies, there are several risk factors related to unhealthy lifestyle (smoking, alcohol consumption, unhealthy diet, physical inactivity) also to consider. Of interest in the context of the present thesis, severe mental illnesses such as SZ, MDD and bipolar disorder have also been reported to increase the risk of MetS, by changes in eating behavior and medication (3,4).

1.2.1. Obesity, insulin resistance and metabolic syndrome

The most accepted hypotheses to describe the pathophysiology of MetS is insulin resistance, which is related with an overabundance of circulating fatty acids, released from an expanded adipose tissue mass (27,28). Free fatty acids reduce insulin sensitivity in muscle, and increase the level of circulating glucose, pancreatic insulin secretion (resulting in hyperinsulinemia) and the production of glucose, triglycerides and secretion of very low density lipoproteins in the liver. The overall consequence is the reduction in glucose transformation to glycogen and increased lipid accumulation as triglyceride (27–29). Obesity is related to increased level of leptin, resistin, tumor necrosis factor alpha, interleukin-6 and angiotensin II (which induce insulin resistance), along with plasminogen activator inhibitor 1 (which is related to thermogenic vascular disease) (29). Also, obese individuals have decreased level of adiponectin, an important adipocytokine suggested to protect against the development of type 2 diabetes mellitus, hypertension, inflammation and other vascular disease (27,28).

1.2.2. Dysregulation of hypothalamic-pituitary adrenal axis

Dysregulation of the hypothalamic-pituitary adrenal axis is typically associated with chronic stress and, as such, with depression and other mental illness, all associated with high level of cortisol. This hypercortisolemic trait leads to development of both MDD and metabolic syndrome components (such as abdominal obesity and glucose intolerance) (30). High levels of cortisol inhibits lipid mobilization and directly affects dyslipidemia (31), also lead to increased activity of lipoprotein lipase, an enzyme responsible for fat deposition especially in intra-abdominal fat, which may explain central obesity (30–32).

1.2.3. Physical inactivity

Physical activity is considered as the major intervention component, in terms of treatment and prevention, of MetS and of many other diseases (including cardiovascular diseases and depression). In fact, inactivity is considered one of the major risk factor for both MetS and for its contributing components (obesity, hypertension and hyperlipidemia) (33). It has been shown that physical activity decreases the risk to develop MetS by 35% to 50 % (34). The association between inactivity and MetS seems to rely on the imbalance of reduced energy expenditure and increase energy intake, which is inversely associated with body weight, blood pressure and blood concentrations of triglycerides and glucose (33). It is considered a major modifiable risk factor that can significantly contribute to the reduction of MetS and other chronic diseases (33).

1.2.4. Age and sex

Many studies reported that age and sex are also determinant factors in developing MetS. With age the risk increases, with females having an higher chance to develop the syndrome (27). The peak of MetS seems to occur in the fifth decade of life (27). There are many mechanisms of aging in MetS.

One of them is related with oxidative stress in which higher levels of reactive oxygen species are related to insulin resistance, visceral obesity, hypertension, hyperglycemia and dyslipidemia (23). Also, it is known that with aging the intraabdominal fat accumulates more rapidly than total fat, and that happens even in the absence of obesity. In females, this is aggravated by the reduction of estrogen at menopause which, independently, may induce intra-abdominal fat (23). Finally, aging is also associated with an increase in proinflammatory cytokine profile, which interferes with insulin action (35,36).

1.2.5. Diet

Diet should include a balanced intake of nutrients. An excess (non moderated) consumption/food intake can lead to weight gain/obesity which, ultimately, can underlie some aspects of the metabolic disturbances that contribute to MetS (37). Interestingly, several nutrients may, on the other hand, be protective for MetS, such as unsaturated fats and high fiber diets (38).

1.2.6. Smoking

Smoking is among the behavior components associated with MetS (and/or some of its components), being also considered as risk factor for cardiovascular disease (39), even though the mechanism is not clear. It may be due to several alterations induced by smoking, such as the circulating levels of catecholamine, cortisol, growth hormone, circulating levels of free fatty acids, and increased level of multiple inflammatory markers including interleukin- 6, C-reactive protein, and tumor necrosis factor alpha (39,40).

1.2.7. Alcohol consumption

Alcohol consumption has also been associated with MetS. However, the precise influence seems to depend on the type of consumption (24), and can possibly be a protector of cardiovascular disease when at moderate levels

(41). Excess alcohol consumption is more correlated with abdominal obesity and increased risk for obesity. Interestingly, normal weight individuals with heavy beer alcohol consumption have increased risk of larger waist circumference when compared to obese individual who are light- to moderate-drinkers; the biological mechanism of this difference remains unclear (24). Regarding the type of drink, wine consumption shows better overall metabolic profile compared to other drinks. Beer consumption is predominately related to higher hypertriglyceridemia, and can be explained by the higher carbohydrate content of beer (41).

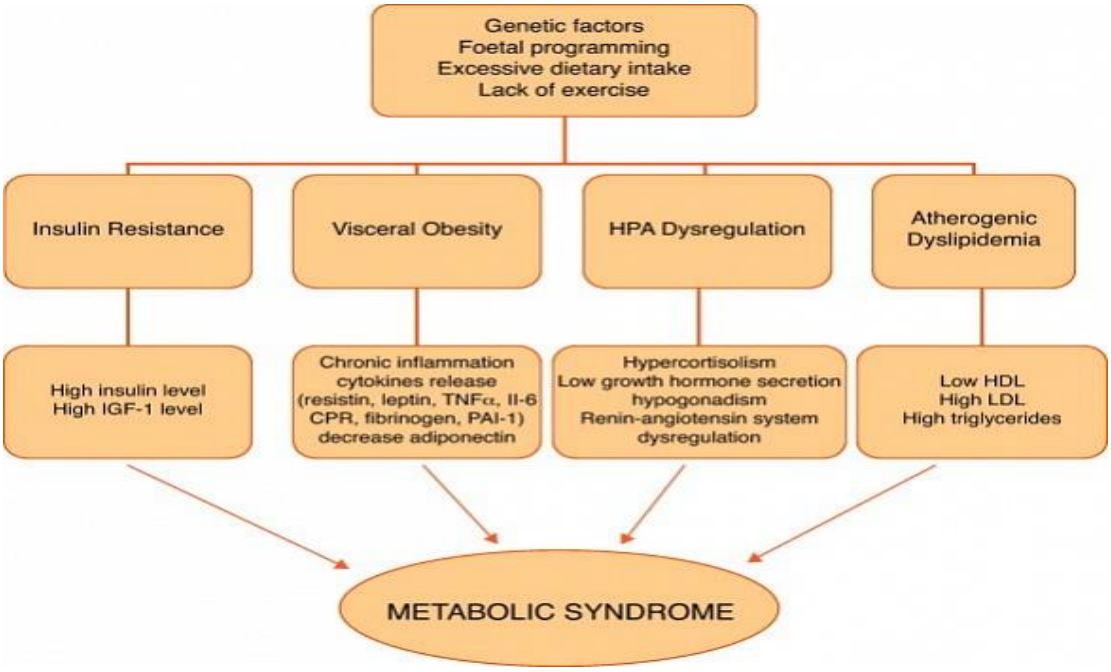

Figure 1 - Pathophysiology of metabolic syndrome. Adapted from Nunzio, Cosimo et al, 2012. *HPA=hypothalamic–pituitary adrenal axis; IGF-1=insulin like growth factor 1; TNF-α=tumour necrosis factor 1; IL-6=interleukin-6; CRP=C-reactive protein; PAI-1=plasminogen activator inhibitor 1; HDL=high-density lipoprotein; LDL=low-density lipoprotein.*

1.3. Mental illness

Today, about 450 million people worldwide suffer from a mental or behavioral disorders (42), and it is estimated that 1 in 6 individuals experience mental problems, such as mental distress, depression or stress, at any one time in life (43). In Europe, it is estimated that every year 38.2% of all adults are affected by a mental disorder (44). MDD is generally found to be the second most prevalent disorder, with lifetime prevalence estimates usually in the 4–10% range and 12-month prevalence estimates in the 3–6% range (45) . SZ affects just under 1% of the population (46).

The number of individuals with mental problems is likely to further increase if taking into account the ageing of the world population (43). Mental problems lead to an higher number of individuals living with disability, and it must be considered as a chronic disease (42). Numerous studies show that mortality among people with severe mental illness, including SZ, MDD, bipolar disorder, and schizoaffective disorder is 2–3 times higher than that in the general population, while life expectancy is between 13–30 years shorter (42). In Portugal, based on the data from the global burden of disease study 2010, depressive disorder is the second cause of disability, representing 8.72 % of total years lived with disability; while, SZ is in the seventeenth position with representing 1.68 % of total years live with disability (47).

1.3.1. Major depressive disorder

MDD is a psychiatric condition characterized by persistent sadness, or loss of interest in enjoyable activities, and includes other symptoms such as disturbance of appetite, sleep disturbance, fatigue, difficult concentration, feelings of hopelessness, or agitation that significantly interfere with daily life (48). It affects more individuals in the age group 50-69 years, and it is more prevalent among females than males (between 1.5–3 times higher prevalence rates) (49). Worldwide it is considered the 4th leading cause of disability, and the leading cause of nonfatal disease burden, accounting for almost 12% of total year lived with disability (42). MDD is projected to become the 2nd leading

cause of disability adjusted life year in developing and developed nations by the year 2020 (47). Its etiology is unknown, can be spontaneous, can follow a traumatic emotional experience, can be triggered or precipitated by pharmacological agents or drugs of abuse, and can share symptoms of other chronic disease (49,50).

There are several environmental risk factors related to MDD. Among these are pre-natal factors, deprivation, grief stress, natural disaster, war, low social support, drug effects and medical illness such as cancer (49), marital problems, divorce and childhood sexual abuse (50). There are several theories that can explain the etiology or pathophysiology of MDD, such as genetic factors that may explain 30-40% of the etiology (50), but no single gene has been found as causal to depression. As in SZ, and other mental illnesses, the interplay of genes and environment is the likely trigger of disease. Based on the target of action of currently used antidepressants, the major theories of the disease suggest that deficiency of neurotransmitters underlies the pathology. The so-called “monoamine deficiency theory” states that depression is related to the depletion of the neurotransmitters serotonin, norepinephrine or dopamine in the central nervous system. Other theories have related neurotrophic factors, inflammatory mediators and the hypothalamus-pituitary-adrenal axis with depression (51).The interplay of these systems, challenged by environmental factors and psychological stressors, is considered to predispose for the disease.

The treatment of MDD has two components: the pharmacological and the psychological (psychodynamic and compartmental cognitive psychotherapy) (23). There are several group of antidepressant drugs used in MDD treatment, such as selective serotonin reuptake inhibitor, dopamine norepinephrine reuptake inhibitor, serotonin norepinephrine reuptake inhibitor, serotonin modulators, norepinephrine serotonin modulator and tricyclics anti depressive and monoamine oxidase inhibitors (52). These antidepressant drugs have several side effects mainly related with inducing and worsen of MetS (23) as will be discussed next.

1.3.2. Schizophrenia

SZ is a chronic, severe and disabling psychiatric disorder, affecting thoughts, feelings and acts. It is characterized by symptoms that appear progressively or abruptly, with cycles of remission and relapse (53). The principal symptoms consist of separation from reality with delusion formation, hallucination, emotional dysregulation and disorganized behavior, which are considered positive symptoms; and negative symptoms such as affective flattening, apathy, social withdrawal, loss of motivation, deficits in communication, lack of initiative, cognitive symptoms, motor retardation and changes in mood (54).

SZ affects about 1% of the individuals worldwide (55)**,** usually with onset in late adolescence/early adulthood, being generally more aggressive in men. In women, another peak of onset is observed later close to the age of menopause (56). It is estimated to be the 5th leading worldwide cause of global disease burden (42,45) and the 8th leading cause of disability, adjusted worldwide, in the age group 15-44 year (46). The etiology of SZ remains to be fully elucidated. Predisposition to the disease increases as the number of shared genes with an affected individual increase, which points for a genetic cause. However, the lack of concordance of monozygotic twins clearly indicates that the environment is fundamental. Several genome wide studies have associated multiple chromosomal regions and genes with increased odds of developing SZ (55,56)**.**

It is currently accepted that SZ results from environmental “insults” during development of the central nervous system in genetically predisposed individuals. Because the development of the central nervous system in humans is completed in early adulthood, several periods of life are susceptible. When considering embryonic development, factors such as infections in the mother or malnutrition have been associated with disease development (55). The precise mechanisms through which the immune system is involved is not known, but it may relate with the release of cytokines that cross the placenta (55). Regarding the perinatal period, conditions such as fetal hypoxia have been implicated. During childhood, SZ can be related with trauma, head injury and also infection (55). Finally in adolescence, the better studied risk factor is exposure to cannabis (55,56).

Older paternal age at conception, which is considered a risk factor, increases twice as much the risk for SZ, because of impaired spermatogenesis can lead to an increase likelihood of *de novo* mutation and also the aberrant epigenetic regulation. Other sociodemographic factors have been studied, among which the month of birth, which again may be related with the risk of infection and exposure to vitamin D, or factors such as living in cities which may be related to exposure to stress (55,56). Altogether, current knowledge has implicated several moments in life and particular conditions that may contribute to developing of SZ. Consequently, several mechanisms have been proposed, including almost all neurotransmitter pathways (56,57). Most evidence originates from the knowledge of the molecular targets of traditional antipsychotics. As such, the dopaminergic hypothesis is the most popular and it is based on pharmacological evidence that the clinical potency of antipsychotics correlates with their affinity for dopamine receptors and that high doses of stimulus increases the release of brain dopamine which may cause psychosis (56). The glutamatergic hypothesis is related with hypoactive of N-Methyl-D-aspartate which is the receptor of glutamate (57). The current knowledge reveals that most pharmaceuticals target, directly or indirectly, more than a single metabolic pathway.

While there is no definitive treatment for SZ, patients can have a mostly normal life when well accompanied. Treatment options include administration of drugs and psychosocial intervention. First generation antipsychotics are the first option, but their secondary effects, have led that actually the most commonly used are second generation antipsychotics. These display low extrapyramidal side effects (46). Still, the second generation antipsychotics also have side effects, among which weight gain (58) and can, therefore, be classified according to the risk for inducing weight gain and increasing body mass index. Among these, clozapine and olanzapine have higher risk, quetiapine and risperidone have medium risk and ziprasidone and aripiprazole have low risk (58). Also important is the psychosocial counseling; this is important not only to rehabilitate patients, aiding in and preventing relapse, but also in both helping their reintegration in the community and families, friends and/or caregivers in coping with the illness (46).

1.4. Metabolic syndrome and mental illness

The association of metabolic disturbance and mental illness has been alluded to for a long time. At the end of the XIX century, Sir Henry Maudsley, a English psychiatrist, noted that diabetes is more frequent in families with a history of mental illness (59). Nowadays, for example, it is known that diabetes and SZ may share familiar risk factor or common genetic predisposition (29). Actually, this association has further raised the interest to study metabolic abnormalities in these patients, given both its serious impact on the quality of life and the known association with higher levels of morbidity and mortality (59).

Different studies and systematic reviews have shown that the prevalence of MetS in patients with mental disorders is 2 to 3 times higher than that in the general population; with an overall worldwide prevalence of MetS in severe mental illness being estimated to be around 32.5% (21). Estimation of the prevalence of MetS in patients suffering from severe mental illness encounters the same difficulties as those in the group of healthy individuals. The results, and reported differences depend on the diagnostic criteria, as well as on considerations such as ethnicity and years of disease duration (2). Thus, the reported prevalence of MetS ranges from 38-60%, in various studies in different countries (60–62).

In SZ it has been shown that the prevalence of MetS in first episode patients treated with antipsychotic varies from 10.1 a 31%, while in patients with longer duration of illness is of 60% (63). Nonetheless, the elevated prevalence of MetS in serious mental illness is thought to be multifactorial, relating to the disease in itself, as well as with its treatment(s) and the unhealthy lifestyle that characterizes some of the patients (and their interplay, since lifestyle factors are influenced by aspects of disease such as negative symptoms and vulnerability of stress in SZ and MDD patients as well as their reduced likelihood to receive standard levels of medical care) (64,65).

When considering MDD, the interplay between MDD and MetS is also bidirectional in that people with established MetS have higher rate of

depression than that in the general population. Depression is also generally associated with a more unhealthy lifestyle, which, in itself, is a risk factor for the development of MetS; and, individuals with MetS, and a negative self-perception, are at higher risk of depression (66). Some additional aspects are of interest when considering the various aspects of MetS in individuals suffering from severe mental illness, which will be next presented.

1.4.1. Specific risk or causative factors associated with MetS in MDD and SZ patients

The evidence estimates that the overall prevalence of MetS in worldwide is of around 36 % in MDD patients, and of about 38% in SZ patients. Also to consider in relation with risk of MetS, 40–60% of individuals with SZ and 55–68% of individuals with MDD are overweight or obese, possibly due to a combination of illness-related factors and use of psychiatric medication, albeit the exact mechanisms not being fully understood. We will next discuss factors related with MetS to be considered also in the context of mental illness.

1.4.1.1. Obesity

It has been estimated that 55–68% of individuals with MDD and 40–60% of individuals with SZ are overweight or obese (67,68). Several parameters have been considered to define obesity and their contribution as risk factor for several diseases. Among these are central obesity and body mass index. Central obesity is defined by waist circumference while body mass index is a ration that takes into consideration the weight and the height. Nowadays, central obesity is considered as a potentially more valid and reliable predictor of risk for cardiovascular disease, type 2 diabetes mellitus, and other metabolic risk-related conditions, than body mass index (69). In general, both measures are associated with lifestyles factors (e.g., lack of exercise, poor diet) which is aggravated in patients with severe mental illness by the illness-related characteristics (negative symptoms, disorganized and depressive symptoms such as decrease motivation and limit social interactions and activities) and treatment options (which may increase appetite, produce fatigue, and sedation (70).

In case of depression the relationship between depression and obesity may be bidirectional (67,68).

1.4.1.2. Diabetes

It is estimated that between 10% and 15% of people with severe mental illness have diabetes, and have a 2 to 3 times higher prevalence compared to those without mental illness. More so, it is thought that approximately 70% of cases of type 2 diabetes Mellitus may be undiagnosed (71). In MDD the prevalence is of about 6.4%, higher than in the general population. In SZ 11.5% of patients have type 2 diabetes of which 3% already at the time of disease onset; this number increases to 16.5% when the disease is established for more than 20 years (72) and may be differentially influenced by antipsychotic medication. Both in MDD and in SZ this increased prevalence must result from a combination of genetic, lifestyle and/or environmental risk factors including medication (72).

1.4.1.3. Dyslipidemia

Dyslipidemia consists of elevated levels of triglyceride, low concentration of HDL and greater concentration of small and dense LDL. The major lipid abnormalities seen in people with severe mental illness are lower levels of HDL cholesterol and hypertriglyceridemia; overall, dyslipidemia is reported in 25-70% of people with severe mental illness (73,74). A meta-analysis on comparisons between patients with SZ first episode and long duration show that there are differences in the levels of triglyceride and of HDL. The rate of hypertriglyceridemia in first episode was 16.9% and increased to 41.1% in long duration. Also the proportion of those with low HDL in first episode was 20.4% compared to 44.7% for long duration illness (21). The higher levels of triglycerides are mainly related with antipsychotic drugs with recognized impact on weight gain, such as clozapine and olanzapine (74).

1.4.1.4. Hypertension

Considered one of the key components of MetS it is in itself related with other factors such as obesity, glucose intolerance and resistance to insulin and it is

an important risk factor for the development of cardiovascular disease. Hypertension is a “silent symptom” which may remain undetected for long time (75). A meta-analysis with 41 studies show the prevalence of hypertension in MDD to range from 21.3-26.8% (76); while, the prevalence of hypertension in SZ ranges from 36.3% to 41.1%, and in drug-naıve the prevalence is reported at 31.6% (2,21).

After briefly presenting the mental illnesses under study and defining the concept of MetS, a final note on specific factors that may contribute to the appearance of MetS in patients with SZ and MDD.

1.5. Lifestyle

Individuals with serious mental illness are indicated as more at risk to have unhealthy lifestyles, including higher alcohol consumption, smoking, unhealthy diet and physical inactivity, compared to the general population. Part of these lifestyle factors are influenced by aspects of the disease such as negative symptoms and vulnerability of stress in MDD and SZ patients (28).

1.5.1. Diet

Different studies have demonstrated that MDD and SZ patients tend to have an unhealthy diet, rich in saturated fats, excess carbohydrate and poor in fiber and fruit. This diet does not ensure an adequate intake of B vitamins, folic acids, and essential fatty acids for vascular, inflammatory and metabolic balance, and may induce weight gain, obesity, diabetes and hypertension (77).

1.5.2. Smoking

Being a risk factor for cardiovascular disease, smoking may contribute to MetS irrespectively of any other medical condition. Of interest, however, is the higher percentage of smokers found among psychiatric patients (32.4% to 66.7%) compared with the general population (22.5%) (78). For MDD, data indicates that 39.8 % of patients with MDD are smokers, which may similarly relate with “self-medication”; of note, smoking in itself has been reported to

increased risk of depression (78). Of particular relevance are those suffering from SZ, where exceptionally high smoking rates (60–90%) are reported(2,78,79). It has been hypothesized that smoke functions may represent a form of 'self-medication' to improve memory, reduce symptoms, and to alleviate medication-related side effects such as sedation and neuroleptic-induced Parkinsonism, which is yet to be clearly understood (79,80).

1.5.3. Physical inactivity

Exercise can be beneficial in mental illness, as it is in the general population, and it has even been considered as a protective factor in depression. In fact, inactivity can contribute to both MetS and mental illness (81). People with severe mental illness often have poor physical activity and this sedentary behavior leads to increased risk of developing diabetes and heart disease (81). How physical activity/inactivity impacts in the brain, contributing to behavior, is not fully understood, but it may be mediated by changes in blood flow to the brain and modulation of the hypothalamus-pituitary-adrenal axis, neurotransmitter release, among others (82). Regular aerobic physical activity such as jogging, swimming, cycling, walking and dancing, for 20-30 minute, 2-3 times per week, is the current recommendation and has been associated to reduce anxiety and depression, and to contribute to longer antidepressant effects (82). It has also been shown that specific physical activity programs improve the quality of life, the emotional state and alleviate secondary symptoms of SZ such as depression, low self-esteem, and social withdrawal (83).

1.5.4. Alcohol consumption

Among psychiatric patients alcohol is the most common substance of abuse, when compared with the general population, being the prevalence almost twice higher. The reasons of higher level of alcohol consumption in mental illness are not fully understood. Again, it may be related with the decrease of psychiatric symptoms or side effect of medication (84).

1.6. Antipsychotics and antidepressant drugs

The mechanisms through which psychiatric medications contribute to MetS is likely related with their targets of action, particularly neurotransmitter receptors, also present in peripheral tissues. They may also indirectly influence the brain orexigenic centers or induce prolactin secretion (8,85). Through these pathways, still not fully understood, there are changes in feeding behavior, alterations in lipid composition, and hormonal changes that further contribute to risk factors of MetS (86). Given the evidence that psychiatric medication may, in itself, cause MetS, psychiatrist and health care professionals must take it into consideration when the management of patients is planned (11,86). For instance, there are concerns that antipsychotics contribute to cardiovascular risk by inducing weight gain and worsening the lipid profile, affecting between 15% and 72% of psychiatric patients. Patients treated with any antipsychotic drug are at higher risk for MetS, but the prevalence of MetS and its components is three times higher with second generation antipsychotic as compared with first generation antipsychotic (11). The effect of antipsychotic on metabolic indices is evident after 2 weeks and reaches maximum at around 3 months of treatment (63). Mean weight gain is highest with clozapine and olanzapine; while there is an intermediate risk of weight gain with quetiapine and risperidone. Aripiprazole, amisulpride and ziprasidone have little effect on weight (63).

Some first generation antipsychotics, such as chlorpromazine, and other psychotropic medication, such as the tricyclic antidepressants and mirtazapine, are also associated with a high risk of inducing weight gain (87,88) . Polypharmacy is common practice in patients with mental illness and it is considered independently associated with a further increased risk for MetS (88). Data from five studies, totaling n=51,364 demonstrated lower pooled MetS prevalence in participants receiving monotherapy (30.4%) versus polytherapy (35.2%). The prevalence of MetS was lowest in antipsychotic-naıve participants (10.2%). Among those receiving antipsychotics, participants taking aripiprazole had the lowest MetS prevalence (19.4 %,), whilst those taking clozapine had the highest (47.2%). For other drugs, MetS frequencies were reported to be with amisulpride

22.8%, typical antipsychotics 28.0%, risperidone 30.7%, olanzapine 36.2% and quetiapine 37.3% (2).

Finally, tricyclic drugs (predominantly amitriptyline) and monoamine oxidase inhibitor are associated with weight gain (87). Tricyclics cause insulin resistance and increase serum lipids, independently from their effect on weight, which is also related with dose and duration of medication. The risk of MetS is 11.7% and is equal for serotonin noradrenalin reuptake inhibitors and selective serotonin reuptake inhibitors (23). Regarding the selective serotonin reuptake inhibitor; paroxetine is related to higher prevalence of weight gain, and affects all parameters of MetS except serum HDL level and BP (87) and fluoxetine, fluvoxamine and sertraline are mostly associated with abdominal obesity and hypercholesterolemia (89), while bupropion, and nefazodone are considered to have low effect on weight gain and MetS (87).

In this background, several guidelines (e.g. Belgian consensus group, the British Association of Psychopharmacology, The European Psychiatric Association and the Maudsley Prescribing Guidelines) carefully consider the interactions between the various variables enumerated in this introduction. Care, with precise and detailed (longitudinal) monitoring is of need (90). As such, it is important to monitor patients in any clinical setting, for raising awareness and for proper monitoring and intervention in the patients. A first step is to investigate prevalence in each setting. This is the reason for the project presented next.

CHAPTER II

2. Aims

2.1. General objective

To determine the prevalence of MetS in female inpatients with MDD or SZ in the Casa de Saúde do Bom do Jesus (Braga, Portugal).

2.2. Specific objectives

In patients with MDD or SZ that meet the inclusion criteria:

- Evaluate the central obesity;

- Assess the blood pressure;

- Determine the triglycerides, HDL and fasting plasma glucose circulating levels in peripheral blood samples;

- Evaluate the intake of psychiatric medication;

- Assess the dietary intake and lifestyle behaviors via questionnaire.

CHAPTER III

3. Material and methods

3.1. Subjects

The study followed a case study design, with consecutive sampling. The calculated sample size was 190 patients, 135 for SZ and 55 for MDD, to be recruited throughout a six-month period (September to March 2016). The sample size was calculated using the software OpenEpi version 3.03, calculate IC of 0.95 and significance level 0.05, for a recorded number of 374 patients (266 from SZ and 108 from MDD) admitted over 6 months (base year 2015); hypothetical proportion factor results in the population (p): 50% + / - 5; effect of study design of 1.

In total, the study comprised patients hospitalized in the CSBJ, on the acute ward due to clinical relapse. The inclusion criterion was: females, 18+ years of age, with a MDD or SZ diagnosis, according to ICD-10, resorting to pharmacologic mental health treatment with antipsychotic or antidepressive drugs. Subjects were excluded if pregnant, unable to provide the informed consent, or with concomitant SZ and MDD diagnosis. After inclusion and exclusion criteria, of the 190 patients approached, a final sample of n= 80 patients were included in the analysis, n= 40 MDD and n= 40 SZ patients.

The study was compliant with ethical standards, and free informed consent was obtained from all potential study participants prior to study enrollment. Submission to ethics committees was conducted prior to any data collection and/or analysis. The author was committed to ensuring ethical principles during the research and the study was conducted in compliance with good clinical and research practices.

3.2. Assessments

A standardized data collection form was used. A socio-demographic questionnaire was used for data collection including: socio-demographic (age, occupation, educational level, marital status); clinical data (age at onset, age of diagnosis and duration of illness); data on current therapy (from medical records); lifestyle behaviors [alcohol consumption, smoking (number of cigarettes per day, and age at start of smoking), and physical activity and dietary habits. The methodology is next described:

3.2.1. Physical activity assessment

The Adaptation of the Modified Habitual Physical Activity Questionnaire (Baecke) to the Portuguese population was used. The questionnaire consists of eight items, grouped into two dimensions: AF-sport (4 items) - seeks to assess the physical activity performed in sports or planned exercise practiced during leisure time and AF-laser (4 items) - seeks to assess physical activity in activities other than sport, practiced in leisure time (eg, walking, cycling) (91). Independent self-reports of activities that the individual did over the past 12 months were identified and recorded.

The respondent was asked to remember and put a tick on the list given of any of the physical activities (PA) which she had done during the last 12 month, how many days in a week and time spent on each activity per week. All answers are scored on a five point scale, except for the question regarding sports practice. The higher the score of each item, the higher the level of physical activity. For each of the two groups or dimensions of physical activity results in a partial index, the total physical activity calculated by summing the two partial values. Then the different physical activities were categorized into light, moderate and vigorous levels of physical activities respectively. The categories of physical activities were assigned intensity levels based on the rate of energy expenditure as MET's. Light physical activities were those activities with score of <3 MET's, moderate physical activities those with the score of 3-6 MET's and vigorous physical activities those with score of >6 MET's (91).

3.2.2. Dietary habits assessment

Dietary habits were assessed via a food frequency questionnaire. The questionnaire aims to identify food consumption over the last year. The basic structure of the questionnaire consists of two components: a list of foods and a response section to the frequency with which individuals ingest these foods; a semi quantitative food frequency questionnaire with 86 items, divided into 8 groups of foods, including: (i) First group: Dairy; (ii) Second group: eggs, meat and fish; (iii) Third group: oils and fats; (iv) Fourth group: bread, cereals and similar; (v) Fifth group: sweets and crayons, (vi) Sixth group: vegetable; (vii)

Seventh group: fruits; and, (viii) Eighth group: drinks and miscellaneous. Information is provided on how many times, on average, per day, week or month each specific food is consumed over the last year (92). The Mediterranean Diet score was calculated based on food frequency questionnaire described. Specifically, we first grouped the food in seven categories, namely dairy products, cereals, vegetables, fruits, vegetables, meat and fish. The value found we divide with caloric intake, and calculated the mean of the 7 categories. A value of 0 or 1 was assigned to each of the 7 groups using mean as cutoffs. For beneficial components (fruits, vegetables, legumes, cereals, and fish), each subject whose consumption was below the mean was assigned a value of 0, and each subject whose consumption was at or above the mean was assigned a value of 1. For meat and dairy products, each subject whose consumption was below the mean was assigned a value of 1, and each subject whose consumption was at or above the mean was assigned a value of 0. For fat intake, we used the ratio of daily consumption of monounsaturated lipids to saturated lipids (again using mean cutoffs for assignment values of 0 for low and 1 for high). For alcohol intake, each subject was assigned a score of 0 for either no consumption (0 g/d) or more than moderate (30 g/d) consumption and a value of 1 for mild to moderate alcohol consumption (0 to 30 g/d). Finally the Mediterranean diet score was generated for each participant by adding the scores in the food categories (ranging 0-9) with a higher score indicating higher adherence (93,94).

3.2.3. Anthropometric Measurement

The following anthropometric measures were assessed: bodyweight, height, skinfolds, abdominal circumference, body mass index and percentage of fat mass. The methodology is next described.

3.2.3.1. Weight and height measurements

Bodyweight or body mass was measured using a Seca weighing scale, with the subjects using minimal clothing and standing in the Centre of the scales without support and with the weight distributed evenly on both feet. Height was measured with a stadiometer, the patient standing, barefoot, with heels

together, arms extended along the body and back straight (95). Calibration was done every morning before starting the work using a standard weight. BMI for each respondent was calculated by dividing weight (kilograms) with height squared (meter). BMI of 30kg/m2 and over was taken as obesity (95).

3.2.3.2. Circumference measurements

Waist circumference was taken using a non-stretchable tape measure, at the midpoint between the iliac crest and the lower rib when the patient is relaxed, assuming standing position (95). The measurement above 88cm in women was considered as central obesity. This was according to the criteria of IDF (18). Hip was taken using a non-stretchable tape measure, with the subject assumes a relaxed standing position with the arms folded across the thorax. The subject's feet should be together and the gluteal muscles relaxed. The girth is taken at the level of the greatest posterior protuberance of the buttocks which usually corresponds anteriorly to about the level of the symphysis pubis. Calf was taken using a non-stretchable tape measure, with the subject assumes a relaxed Standing position with the arms hanging by the sides. The subject's feet should be separated with the weight evenly distributed. The maximum girth of the calf is at the marked Medial calf. Arm was taken using a non-stretchable tape measure with the subject assumes a relaxed standing position with the arms hanging by the sides. The subject's right arm is abducted slightly to allow the tape to be passed around the arm. The girth of the arm is measured at the marked level of the medial-acromial- radial. The tape should be positioned perpendicular to the long axis of the arm (95). The cardiovascular risk was calculated with the Waist / hip ratio (WHR). It was calculated from the division of the waist circumference by the value of the circumference of the hip. The ratio of waist to hip circumference greater than 0.82 for women, which characterize the central distribution of fat, has been used to identify individuals with increased cardiovascular risk (96).

3.2.3.3. Skinfolds measurements and % fat mass

Skinfolds was measured with the patient assuming a relaxed standing position, with the arms hanging by the sides, the measurement sites were the

triceps, subscapular, biceps, and supra iliac (95). Triceps skinfold was measured while the subject assumed a relaxed standing position with the left arm hanging by the side. The right arm should be relaxed with the shoulder joint slightly externally rotated and elbow extended from the side of the body (95). For the subscapular skinfold the subject must assume a relaxed standing position with the arms hanging by the sides. For the biceps skinfold the subject must assume a relaxed standing position with the left arm hanging by the side. The right arm should be relaxed with the shoulder joint slightly externally rotated and elbow extended from the side of the body and finally the supra-iliac was measured with the subject assumes a relaxed position with the left arm hanging by the side and the right arm abducted to the horizontal (95). Body fat was calculated from density using Siri's (1956) equation: % fat = (4.95/ density -4.50) x 100. Where Density =1,1567-0,0717$\log_{10}$ (skinfold triceps + biceps+ subscapular + supra-iliac), Durnin equation (97).

3.2.4. Blood pressure measurements

Blood pressure was measured with a standard apparatus, digital sphygmomanometer, with values presented in mm Hg; the patient was seated and at rest. It was measured twice, with a minimum interval of one minute, calculating the average values of the systolic and diastolic pressures obtained. The systolic pressure of above or equal to 140 mmHg and diastolic pressure above or equal to 90 mmHg was regarded as a high blood pressure (18).

3.2.5. Biochemical tests

Fasting blood sample was drawn to evaluate glucose, high density lipoprotein (HDL) cholesterol and triglycerides. Laboratory tests were performed at the Hilario de Lima Laboratory following established accredited protocols.

3.3. Diagnosis criteria for the metabolic syndrome

Metabolic syndrome was diagnosed according to the criteria of the International Diabetes Federation (IDF) summarized below (18):

1) Central obesity (defined as waist circumference, for European woman over 80 cm);
2) The presence of any two of the four following factors:
    a. raised triglyceride levels ≥ 1.7 mmol / L (150mg / dL);
    b. reduced HDL cholesterol: <29.01 mmol / l (50mg / dl) in females (or treatment for specific These lipid abnormalities);
    c. raised blood pressure (systolic BP ≥ 130 or diastolic BP ≥ 85 mmHg) (or treatment of previously diagnosed with hypertension);
    d. raised fasting plasma glucose [FPG ≥ 5.6 mmol / L (100mg / dL)]; (or previously diagnosed with type 2 diabetes);

3.4. Statistical analysis

The data analyses were done using the Statistical Package for Social Sciences (SPSS) v23. Parametric and non-parametric tests were performed. For the variables that follow the normal distribution the mean, median, standard deviation were calculated; comparisons were made with the T-test and correlations assessed through the Pearson correlation coefficient. Variables that did not follow the normal distribution were compared by the Mann-Whitney test. Percentages were compared with the Chi-square test.

CHAPTER IV

4. RESULTS

4.1. General characteristics of the study sample

The characterization of the study population is summarized in Table 1. The socio-demographic profile of the subjects was assessed with the use of descriptive statistics. During the study period, 80 female patients were included (50% MDD and 50% SZ). The overall mean age of the participants was of 51.5 years (SD=13.3; range 24 - 75 years). The mean age between the two groups was not statistically different (MDD and SZ mean age was 49.1±11.9 and 53.5 ±13.2 respectively; $t_{(78)} = 1.5$; $p = 0.127$). But as for age according the group (< 50 and > 50), and age of biological note due to menopause considerations, the groups were different [$\chi^2_{(1)} = 4.05$; $p = 0.044$]. The majority of the MDD patients were below the 50 years (n = 24, 60%), while the majority of the SZ patients were above 50 years (n=25, 61%). Regarding the educational level, there were no differences between groups [$\chi^2_{(3)} = 5.5$; $p = 0.137$], but in MDD the majority had between five and nine years of school (n = 17, 42%) followed by less than five years 10 (25%), while although in SZ patients the majority had less than 5 years of school year (n = 16, 40%) followed by between nine and twelve years of school (n = 12, 30%). As for the working status, the groups were different [$\chi^2_{(2)} = 7.3$; $p = 0.025$]; the majority of MDD was employed 17 (43%) and the SZ patients were mainly pensioners (n = 21, 53%). Both MDD and SZ patients were predominantly married, but there a statically significant differences in marital status between the two groups [$\chi^2_{(3)} = 9.1$; $p = 0.027$], with a higher percentage of SZ patients being single and of MDD divorced. Finally, in both groups the majority of participants were currently living with a partner or a relative (all sample, 83%).

Table 2 - Sociodemographic characteristics

Variable	Participants		
	MDD (N=40)	SZ (N=40)	*p*
Age (mean ±SD)	49.1±11.9	53.5 ±13.2	0.127[a]
Age group N (%)			0.044*[b]
< 50	24(62)	15(39)	
>50	16(39)	25(61)	
Education level N (%)			0.137[b]
<5 years	10(25)	16(40)	
5-8 years	17(42)	8(20)	
9-12 years	8(20)	12(30)	
>12 years	5(13)	4(10)	
Marital status N (%)			0.027*[b]
Single	5(13)	15(38)	
Married	23(58)	17(43)	
Divorced	11(28)	5(13)	
Widowed	1(3)	3(8)	
Working status N (%)			0.025*[b]
Unemployed	9(23)	13(33)	
Employed	17(43)	6(15)	
Pensioner	14(35)	21(53)	
Living With N (%)			
Single	7(18)	7(18)	
Other people	33(83)	33(83)	

*p < 0.05 was statistically significant [a] Independent –t test [b] chi-square test

4.2. Characterization of lifestyle and of clinical variables

Table 3 summarizes the health indicators of the participants. Both MDD and SZ patients were predominantly nonsmokers and non-alcoholic beverages drinkers, with less than 25% reporting smoking or drinking habits. There were no differences on the level of physical activity between the groups [MDD (2.4 ±0.57) and SZ (2.5 ±0.62); $t_{(78)} = 0.55$; $p = 0.579$]. All participants currently preformed some physical activity, even though mostly light (<3 MET's) in both groups [MDD 34 (85%) and SZ 32 (80%)]. Diet habits evaluated were by Mediterranean diet score (range 0 to 9, higher scores means high adherence), with no differences noted between groups [MDD (3.9±1.5) and SZ (3.8± 1.8); $t_{(78)} = 0.2$; $p = 0.842$]. The score ranged from 0 to 7 and the majority of the inpatients had moderate adherence (MDD 47% and SZ 50%).

The median duration of illness was identical between groups [U=716.5, p=0.421; median = 12 years (15) in MDD and 14 years (24) in SZ], as was the number of admissions [U = 662, $p = 0.179$; median = 3 (3) in MDD and 4 (5) in SZ]. The main comorbidity in both groups was hypertension (SZ 22% and

MDD 18%), followed by diabetes mellitus (12% in MDD and 15% in SZ). All patients were in polypharmacy. The median number of psychiatric medication was identical [U = 683.5, *p* = 0.238); 3 (1) in MDD and 3 (2) in SZ]. All patients were taking benzodiazepines, all MDD patients were taking antidepressants and all SZ patients were taking antipsychotics. In addition, 48% of MDD were also given antipsychotics and 42% of SZ individuals were taking antidepressants. Regarding antipsychotic medication the majority of both SZ patients and MDD patients were taking atypical or second generation antipsychotic (75% SZ and 33% MDD). Regarding antidepressive medication, MDD patients were taking combined antidepressive (48%) and SZ patients were taking selective serotonin reuptake inhibitor (18%). As for the comorbidities, patients were receiving medication for reduce blood pressure and for diabetes when appropriate.

Table 3 - Characterization of lifestyle and clinical variable

Variable	**Participant**		***p***
	MDD	**SZ**	
Smoking N (%)	10(25)	7(18)	0.412[a]
Alcohol drinks N (%)	9(23)	5(13)	0.283[a]
Mediterranean diet score(mean ±SD)	3.8±1.5	3.8±1.8	0.842[a]
Low adherence (0-3) N (%)	15(38)	15(38)	
Moderate adherence (4-5) N (%)	19(47)	20(50)	
Higher adherence (6-9) N (%)	6(15)	5(12)	
Physical activities (mean ±SD)	2.4±0.5	2.5± 0.6	0.579[b]
Light (<3METs) N (%)	34(85)	32(80)	
Moderate (3-6 METs) N (%)	6(15)	8(20)	
Duration of illness(median, IQR)	12(15)	14(24)	0.421[c]
Number of admission(median,IQR)	3(3)	4(5)	0.179[c]
Comorbid diagnoses N (%)			
History of hypertension	7(18)	9(23)	0.576[a]
History of diabetes	5(13)	6(15)	0.745[a]
History of dyslipidemia	4(10)	6(15)	0.499[a]
Number of psychiatric medication (median, IQR)	3(1)	3(2)	0.238[c]
Antipsychotics medication N %	18 (45)	40 (100)	
Atypical	13(33)	30(75)	
Typical	4(10)	2(5)	
Combined	1(3)	8(20)	
Antidepressants medication N %	40 (100)	16 (40)	
SSRIs	13(33)	7(18)	
SNRIs	8(20)	6(15)	
Combined	19(48)	3(8)	
Benzodiazepine	40 (100)	40 (100)	
Others medication N (%)			
Antidiabetic	5(13)	6 (15)	
Blood pressure-lowering	7(18)	9 (23)	
Lipid-lowering	5(13)	5 (13)	

[a] chi-square test [b] Independent –t test [c] Mann-Whitney

SSRI, selective serotonin reuptake inhibitor; *SNRI*, serotonin noradrenaline reuptake inhibitor.

4.3. Descriptive statistic of the main cardiovascular risk factors

Both patient groups displayed abnormal waist circumference/hip ratio, which was more pronounced and statistically significantly higher in the SZ [mean = 0.88 (0.09) in MDD and 0.93 (0.1) in SZ patients, $p = 0.009$]. Of notice, 92% of SZ and 70% of the MDD presented ratios above the normal cut-off of 0.80. No differences were observed among groups with respect to body mass index or to the WHO corresponding classifying categories ($p = 0.177$). Most were overweight [MDD (30%) and SZ (40%)] or obese [MDD (28%) and SZ (38%)]. The mean of % fat mass index was 38 for MDD and 40 for SZ, which is identical ($p = 0.102$). A descriptive analysis was done for each of the components of MetS. Measurement of abdominal circumference was elevated (> 80 cm) in both groups, higher in SZ patients ($p = 0.032$). The medians of the HDL values were inferior to the cutoff point (< 50 mg/dl) in both groups. The median triglyceride levels, blood pressure and fasting glucose were normal for patients in both diagnostic categories. Table 4 summarizes the data.

Table 4 - Descriptive statistic of the main cardiovascular risk factors

Variable	Participant		*p*
	MDD	SZ	
Waist / hip(mean ±SD)	0.88± 0.09	0.93± 0.1	0.009[a]*
Waist/hip >0.80 N (%)	28(70)	37(92.5)	0.01[b]*
Body mass index(mean ±SD)	27.1± 5.4	28.8± 5.3	0.177[a]
Underweight N (%)	3(7.5)	1(2.5)	0.281[b]
Normal N (%)	14(35)	8(20)	
Overweight N (%)	12(30)	16(40)	
Obesity N (%)	11(27.5)	15(37.5)	
% fat mass (mean ±SD)	37.8± 6.1	40± 5.8	0.102[a]
Systolic blood pressure (mean ±SD)	117.3± 11.2	121.1± 17.1	0.410[a]
Diastolic blood pressure (mean ±SD)	74.3±19.9	73.4± 9.8	0.715a
Waist circumference (mean ±SD)	89.9± 15	97.3± 15.6	0.032*[a]
Fasting Glucose (median, IQR)	89(18)	90(22.8)	0.592[c]
HDL- C (median, IRQ)	47(17.5)	46(14.3)	0.114[c]
Total cholesterol(median, IQR)	196(40.8)	199.5(41.3)	0.447[c]
Triglycerides(median, IQR)	124(60)	130(78.5)	0.393[c]

*p < 0.05 was statistically significant [a] Independent –t test [b] Chi-square test [c] Mann-Whitney
HDL-C, high density lipoprotein cholesterol

4.4. Prevalence of metabolic syndrome and number of components

Table 5 lists the components used by the various scientific organizations to define metabolic syndrome, as well as the % of individuals, in both patient

groups fulfilling the criteria for being classified with metabolic syndrome. The prevalence was always higher in the SZ group, even though reaching statistical significance only when considering the definition by the NCEP ATP III. Thirty eight percent up to 55% of the individuals with SZ fulfilled criteria for metabolic syndrome, while in the case of MDD the levels varied from 20-38%, depending on the classification system. When decomposing for the numbers of Mets components, 94% of participants had at least one or more criteria, being the presence of the presence of 2 the most abundant in MDD (35%) and 3 criteria in SZ (25%).

Table 5 - Prevalence of metabolic syndrome and number of its components

	N (%)	**Diagnostic**		**p**
Metabolic syndrome		MDD	SZ	
Prevalence by IDF	37(46)	15(38)	22(55)	0.116
Prevalence by NCEP ATP III	33(41)	11(28)	22(55)	0.012*
Prevalence by WHO	23(29)	8(20)	15(38)	0.084
Number of components				
0	5(6.3)	3(8)	2(5)	
1	15(19)	8(20)	7(18)	
2	23(29)	14(35)	9(23)	
3	17(21)	7(18)	10(25)	
4	11(14)	6(15)	5(13)	
5	9(11)	2(5)	7(18)	

*p < 0.05 was statistically significant

4.5. Prevalence of metabolic syndrome components

In overall terms, the most common MetS component was central obesity (> 80), found in 79% (n = 63) of all patients, followed in decreasing order by reduced HDL cholesterol (or treatment for specific lipid abnormalities) 65% (n = 52), hyperglycemia (or treatment and previously diagnosis) 41% (n = 33), hypertriglyceridemia (or treatment) 38% (n=38), and hypertension (or treatment) 29% (n = 29). No differences were observed between the groups. Table 6 summarizes the data.

Table 6 - Prevalence of metabolic syndrome components according IDF criteria

Variable	All frequency (%)	MDD (%)	SZ (%)	*p*
Central obesity (WC > 80)	63(79)	29(73)	34(85)	0.172
Higher Blood pressure; ≥ 130 /85mmHg (or treatment)	23(29)	10(25)	13(33)	0.459
Reduced HDL:< 50 mg/dl (or treatment)	52(65)	25(65)	26(65)	0.999
Triglycerides ≥ 150 mg/dl (or treatment)	30(38)	11(28)	19(48)	0.065
Glucose ≥ 100 mg/dl (or treatment)	33(41)	15(38)	18(45)	0.496

Chi-square

4.6. Prevalence of metabolic syndrome, by sociodemographic and clinical characteristics

The prevalence of MetS is by sociodemographic, clinical and lifestyle characteristics of participants are shown in Table 7 and 8. Regarding de sociodemographic characteristics it was observed a progressive rise in prevalence with increasing age in both groups, but only reached significance in MDD patients (p = 0.04). Other characteristics were not significantly associated with MetS. In both groups the prevalence was increased in overweight patients, but was more pronounced, reaching statistical significance, in SZ patients (p = 0.03). Diet habits, as evaluated by the Mediterranean diet score, associated with MetS presence only in MDD patients (p = 0.04). Others lifestyle factors such as smoking, physical activities, and alcohol consumption were not found to have a significant association with presence of the MetS. Antipsychotics and antidepressive in general, were not associated with MetS. Regarding the MetS components only increased waist circumference (central obesity) was associated with antipsychotic medication (p = 0.02).

Table 7 - Prevalence of metabolic syndrome, by sociodemographic, lifestyle and clinical characteristics

Variable	*MDD*	*p*	*SZ*	*p*
Age group		0.04*		0.87
<50 years	6(25)		8(53)	
>50 years	9(56)		14(56)	
Marital status		0.17		0.64
Single	1(20)		8(53)	
Married	7(30)		11(65)	
Divorced	7(63)		2(40)	
Widowed	1(0)		1(33)	
Working status		0.65		0.12
Unemployed	4(44)		8(62)	
Employed	5(29)		1(16.7)	
Pensioner	6(43)		13(62)	
Education level		0.59		0.89
<5 years	4(40)		10(63)	
5-8 years	8(47)		4(50)	
9-12 years	2(25)		6(50)	
> 12 years	1(20)		2(50)	
Living With		0.04*		0.12
Single	5(71)		2(29)	
Other people	10(30)		20(61)	
Smoking		0.71		0.99
No	12(40)		18(55)	
Yes	3(30)		4(57)	
Alcohol use		0.70		0.64
No	11(35)		20(57)	
Yes	4(44)		2(40)	
Mediterranean diet score		0.04*		0.45
Low (0-3)	6(40)		8(53)	
Moderate (4-5)	9(47)		10(50)	
Higher (6-9)	0		4(80)	
Physical activities		0.99		0.99
Light (<3METs)	13(38)		18(56)	
Moderate (3-6 METs)	2(33)		4(50)	
Duration of illness		0.86		0.14
<10 years	5(36)		5(39)	
>10 years	10(39)		17(63)	
BMI		0.08		0.03*
Normal	4(25)		2(22)	
Overweight	8(67)		12(75)	
Obesity	3(27)		8(53)	

*p < 0.05 was statistically significant Chi-square test
BMI, body mass index

Table 8 - Associations of metabolic syndrome and its individual components with the psychotropic medication.

Psychopharmacological Treatment	MetS		Increased Waist circumference		Raised blood pressure		Raised fasting blood glucose		Reduced HDL cholesterol		Raised triglycerides	
	N %	*p*	N %	*p*	N %	*p*	N %	*p*	N %	*p*	N %	*p*
Antipsychotic		0.77		0.02*		0.96		0.12		0.79		0.39
No (n=22)	9(41)		14(63)		2(10)		7(33)		12(57)		5(24)	
Atypical (n=43)	21(49)		34(79)		5(12)		17(41)		28(67)		16(38)	
Typical (n=6)	2(33)		6(100)		1(17)		-----		3(50)		2(33)	
Combined (n=9)	5(56)		9(100)		1(11)		3(33)		5(56)		5(56)	
Antidepressive		0.37		0.52		0.92		0.67		0.71		0.61
No (n=24)	12(50)		20(83)		3(13)		8(33)		17(71)		11(46)	
SSRI (n=20)	8(40)		17(85)		2(10)		5(29)		11(61)		6(33)	
SNRI (n=14)	9(64)		11(79)		1(11)		7(50)		9(64)		5(36)	
Combined (n=22)	8(36)		15(68)		3(14)		7(32)		12(55)		6(27)	

Chi-square test Fischer exact test *p < 0.05 was statistically significant

SSRI, selective serotonin reuptake inhibitor; *SNRI*, serotonin noradrenaline reuptake inhibitor

4.7. Relationship of number of Mets components with socio-demographic, lifestyle and clinical date

Correlation analysis was carried out using the Spearman Correlation Coefficient. A positive correlation between number of Mets components and age was observed, but reached statistically significance only in the MDD group (r = **.**47; $p < 0.01$). Both groups had a positive and significant correlation with the % fat mass. In the SZ group, a positive significant correlation was also observed for the waist/hip ratio (r = **.**517; $p < 0.01$). The duration of illness was positively associated only in SZ patients (r = .327; $p < 0.05$). Number of admissions, number of psychiatric medication, Mediterranean diet score and physical activity were not statistically significantly correlated. Table 9 summarizes the data.

Table 9 - Relationship of number of Mets components, with socio-demographic, lifestyle clinical date.

Variable	Number of MetS criteria	
	MDD	SZ
Age	.479**	.122
Weight	.218	.373*
Physical activity	-.209	-.128
Mediterranean diet score	-.290	.029
Illness duration	.101	.327*
Number of admissions	.027	.044
Number of psychiatric medication	.155	.029
Body mass index	.372*	.287
%fat mass	.428**	.547**
Waist/hip	.538**	.339*

*Correlation is significant at 0.05 level **Correlation is significant at 0.01 level

4.8. Correlations of MetS components, Mediterranean diet, clinical characteristics

Correlation analysis was carried out using the Spearman Correlation Coefficient. A positive correlation between systolic blood pressure and number of admission was observed, but reached statistically significance only in the SZ group ($r = .425$, $p < 0.01$). Diastolic blood pressure and waist circumference had positive correlation with number of admission and illness duration but reached statistically significance only in SZ group. A negative and

significant correlation between Mediterranean diet score and waist circumference was observed only in SZ patients ($r = -.448$, $p < 0.01$) and positive association with fasting blood glucose and HDL-cholesterol in MDD patients (r = .363 and r = .410, $p < 0.05$).

Table 10 - Correlations of MetS components, Mediterranean diet score clinical characteristics

Variable	Fasting blood glucose	Triglycerides	HDL-cholesterol	Systolic blood pressure	Diastolic blood pressure	Waist circumference
MDD Patients						
Number of admissions	-.029	-.131	-.139	.086	.093	.126
Illness duration	-.070	-.261	.204	.136	.o81	.114
Number of psychiatric medication	-.277	.094	-.296	.048	.016	.166
Mediterranean diet score	363*	-.207	.410*	-.259	-.199	-.195
SZ patients						
Number of admissions	-.024	.123	-259	.425**	.402*	.447**
Illness duration	.216	.186	-.317*	.251	.371*	.449**
Number of psychiatric medication	-.12	.171	.028	.038	.049	.228
Mediterranean diet score	.049	.156	.229	-.152	-.139	-.448**

*Correlation is significant at 0.05 level; **Correlation is significant at 0.01 level

CHAPTER V

5. DISCUSSION AND CONCLUSION

5.1. Prevalence of metabolic syndrome and its components

Different studies and systematic reviews have shown the large variations in MetS prevalence in severe mental illness worldwide according to geographical area, gender and ethnic group, suggesting that genetic and environmental factors play an important role in the risk for MetS (1,3). It is important to determine the prevalence of MetS and associated risk factors, across populations and community settings, as its identification is required for recommendations on lifestyle changes and/or pharmacological treatments (16). More so, such need is particularly relevant in patients with severe mental illness, if considering that MetS is also important for the prognosis of mental illness in itself, since it may lead to reduced adherence to therapy and to functional limitations. To date, to our knowledge, there had been no epidemiological studies conducted on the prevalence and associated risk factor of MetS in the inpatients of the "Casa de Saúde do Bom Jesus". Thus, here the purpose of this case study was to determine the prevalence of MetS, and its associated risk factors, in the female inpatients with SZ or with MDD.

Summarily, we found a prevalence of MetS of 46% by IDF and the 41% ATP III criteria, respectively. This prevalence is both higher than that reported for the general population (which ranges from 4.7 to 18.3%) (19), and the mental illness population (32%) in Europe (1). Albeit here the prevalence being within the range reported across populations (25 and 59%) (1), the prevalence is rather high compared to the international data on severe mental illness, which places the mean prevalence at 34% among mental illness patients, as indicated in a recent meta-analysis (2). The data does follow studies in specific countries where concern has been raised. In Australia, where the overall prevalence is 54% with IDF criteria and 49% with NCEP ATP III criterion (2003) (61), researchers indicate that such high prevalence among patients who use public mental health services warrants urgent attention from service provider. Regarding specifically females, a study in Brazil reported a prevalence of MetS of 48.1% using the NCEP ATP III criteria 2003 definition (59), and a study in menopausal women, also in Brazil, indicates a prevalence of 50.6% (98).

In Portugal, in the general population MetS it is found at 27.5% (adjusted for gender, age and size of region) and in females at 28.7% (20).

Here, the prevalence of MetS was higher in SZ patients (55% compared to 37.5% in MDD), but the difference as only significant with NCEP ATP III criteria, which is in line with a recent systematic review and meta-analysis (2). Among studies that directly compared patients with schizophrenia, bipolar disorder and major depressive disorder, no significant differences in the prevalence of MetS among groups was noted when using the IDF and the NCEP ATP III criteria, with no statistical difference in both man and female (2). Here, the MetS prevalence in SZ patients (55% IDF and NCPT ATT III) was high compared to rates reported worldwide in meta-analyses that considered only SZ patients (62). It was reported an overall 35.3% prevalence rate by IDF and 28.6% by NCPT ATT III. In psychiatric inpatients the prevalence has been reported at 30.4%, and in female at 34.8% (2,21). Regarding MDD patients, the prevalence was relatively close to the reported in a meta-analysis (36%) (2), but high when compared to some studies [e.g. 24.8% in a German female population (19) and 20.2% in the Netherlands (99)]..

When considering the MetS components, increased waist circumference (central obesity) was the most prevalent of metabolic changes. The results are in agreement with the findings in a recent meta-analysis, where, overall, the proportion of patients with abdominal obesity was 50.3% by the ATP definitions and 63.2% according to IDF (2). This data, may indicate for lifestyle factors such as diet, inactivity, alcohol consumption and smoking, but also the effect of the use of psychotropic drugs cannot be overlooked (1,31,100). In severe mental illness patients weight gain induced by psychoactive drugs is a main factor leading to the metabolic dysfunctions. Atypical antipsychotics, such as clozapine and olanzapine, and some antidepressants, especially tricyclics, and noradrenaline serotonin reuptake inhibitors, are recognized to increase appetite (23,87,88,101). Mores so, the secondary sedation of the some drugs leading to sedentary lifestyle is also a recognized problem (23,87,88,101). This places the population under study with higher risk of

diabetes mellitus, cardiovascular disease (since central obesity is considered a reliable predictor of risk for cardiovascular disease) and other metabolic risk-related conditions (69).

Here, a more puzzling finding was the HDL-cholesterol, where a higher rate of low HDL-cholesterol was found (65 %) compared to results of a meta-analysis (44.7%) (2). HDL-cholesterol is of importance in the prevention of cardiovascular disease, in that it decreases the relative risk. It plays a role in reversing cholesterol transport, and preventing oxidation and aggregation of LDL-c particles in the arterial wall, thereby decreasing the atherogenic potential of this lipoprotein (102)**.** We also found a high prevalence of hyperglycemia in our study population (25% in MDD and 43% in SZ patients). The prevalence of hyperglycemia in recent meta-analysis was reported to be approximately 18.8% in patients with severe mental illness (2). Higher central obesity, as was here found, is associated with insulin resistance and consequently hyperglycemia (27,28). The high prevalence of diabetes in mental illness should lead us to pay more attention to mental illness patients, as they are at increased risk for a high prevalence of hyperglycemia. A genetic component may also play a role. Diabetes and SZ may share familiar risk factor or common genetic predisposition (5). This is important, showing that it should improve screening in these patients, given its serious impact on quality of life and the known association with higher levels of morbidity and mortality. Here, hypertriglyceridemia (overall prevalence in our sample 38%) was similar to that in other studies (2,21,103). Of note, this is a marker/indicator of insulin resistance, further aggravating hyperglycemia in these patients (28,104). Hypertension in both groups was similar compared to other studies (2,76), including a study in the Portuguese general population, where the data for the year 2015 showed a frequency of prior diagnosis of hypertension of 29.5% in adult female adult (105).

Overall, the findings indicate that notwithstanding the 46% of overall prevalence of MetS in the sample, when decomposing for the numbers of MetS components 94% of participants had at least one which indicates that these patients are at elevated risk for developing MetS in the future. Finally, in

our study no differences were observed related with the prevalence of MetS individual components between the disease groups. There are several possible explanations for that, including that patients in both groups have similar lifestyle risk factors such as smoking, alcohol drinking, inactivity and use of the same psychotropic medication.

5.2. MetS: Clinical, lifestyle and sociodemographic characteristic

In respect to comorbidities, systemic hypertension was found to be the most prevalent comorbidity in both groups (18% in MDD and 23% in SZ patients), followed by diabetes and dyslipidemia. Our result was different from many studies in severe mental illness in which the most frequent comorbid was dyslipidemia (48.7% - 70%) (21,54,106)**.** One of the reasons may be related to the fact that there is already a high prevalence of hypertension amongst the Portuguese female population (29%) (105).

In general, polypharmacy is very common within the mental health population ranging from 13% to 90%, and it is reported that in inpatients with SZ more than 50% are on polypharmacy (107,108). In our study, all patients were on polypharmacy, with a mean of three different medications per patient. Forty percent of SZ patients on antipsychotic therapy were also being treated with antidepressants. This is similar to the prevalence rate reported in other studies (107–109). Forty five percent of MDD patients on antidepressants were also taking antipsychotic this is also in line with other studies (110). In contrast, the use of benzodiazepines (100%) was higher compared to other studies (111,112), and perhaps it is due to being a female population. Studies show that a greater number of benzodiazepines and other psychotropic medications are prescribed in women (108). Still, surprisingly, albeit the literature indicates that patients using antipsychotics in general, especially clozapine and olanzapine, and also some antidepressants, are consistently found to have a higher rate of MetS and its components (2,3,10,113), here this association was not found. This is puzzling since while the risk of MetS increases with the duration of medication and in our sample does not have the same duration of consumption of medication, we did find an association of

increased waist circumference with antipsychotic medication as also indicated in the literature (21,52,70,88)**.**

Increased body mass index and its association with MetS has been reported (2). Here, similarly, we found a high rate in both MDD and SZ patients (30% overweight and 28% obese and 40% overweight and 38% obese, respectively). The finding is of clinical relevance. Body mass index is an easily obtainable measurement and if it is routinely measured it might inform clinicians of the potential risk of MetS and the consequent risks of cardiovascular morbidity and mortality and help in the choice of medication and patient management (11, 59). A positive association of the number of criteria with percentage of % fat mass, waist/hip ratio, duration of disease (only SZ) and weight (only SZ) was also found, furthering indicating for the need of a an holistic approach in patient care (11,59).

Different studies report factors such as, illness duration, number of admissions and number of medication taken as associated with the individual components of the metabolic syndrome (2,19), but in our study this was not the case. This lack of association may be explained by a recall bias as these measures are, in part self-reported. More so, albeit the higher intake of alcohol and smoking on mental health patients, and its effect, MetS having been largely studied (24,40), here in both groups smoking rates were lower than those reported (25% vs 39.8 % in MDD vs and 17.5% vs 60-90% in SZ) (53, 56, 72). However, the all-female characteristic of the sample is of note. We did not find studies done only in SZ and MDD female patients, considering for smoking rate and/or prevalence, although here the noted prevalence of smoking is higher when compared to the Portuguese female population (overall 11%, and >55 years old decreased to 5%) (114). Similarly, alcohol consumption in our study the rate was low (MDD 22.5% and SZ 12.5%) even when compared with Portuguese women (65%) (115). Again, a response bias (self-report) is of note.

Of consideration is also physical activity. People with severe mental illness often have poor physical activity and this sedentary behavior can lead to

increased risk of developing diabetes and heart disease (57,76). In our study sample, both groups were characterized by light physical activity/ sedentary behavior (80 to 85%).

Different studies report favorably association of Mediterranean diet with reduction in the risk of death, including deaths from cardiovascular disease , and a possible role in improving mental health and protecting against MetS (116–118). Here, we observed that consuming a Mediterranean-style dietary pattern was favorably associated with avoiding metabolic syndrome traits, such as less abdominal obesity in SZ patients, and increase the HDL-cholesterol and lower prevalence of MetS in MDD patients.

Finally, the variability of MetS among psychiatric patients by socio-demographic characteristics has been studied extensively. A progressive rise in prevalence was observed with increasing age, from 25% in those aged below 50 to 56 % in those over 50 years old (2,19,21). In the Portuguese general population, higher prevalence varies according to age, showing a higher prevalence in females over 50 years of age (reported as 39.2%) (20). This increase with age can have several explanations, one of them being that the advanced age in itself has physiological changes that are implicated in the pathophysiology of MetS. More so, if mental illness arises at a younger age, the individual will have a longer exposure to MetS risk factors, such as antipsychotics, by the time he/she reaches an older age. Again, the full medication history was here impossible to assess, preventing such analysis. Finally, here, an association with MetS was also found in MDD patients living alone (presented a higher MetS rate, range from 30% to 71%). However, despite these findings, in general weak associations were found between MetS and sociodemographic factors; confirming that the pathophysiology of the syndrome is multifactorial.

5.3. Limitations

Some study limitations should be addressed. First, because of the small sample size, and its all-female inpatient characteristic, the results should not be generalized to males, to the general population or to other contexts. Still,

by working with a more homogeneous group, the effects of variability between groups to consider in analysis were reduced. Second, in addition, patients took different types of psychiatric medication, drug combinations, in both groups, including that all were taking benzodiazepines. This precludes a rigorous analysis on the effect of medication type. Finally, self-reporting was used to assess physical activities and dietary habits, alcohol consumption and cigarette smoking. Patients may omit information on purpose, since most of them know the disadvantages of these unhealthy life styles, or may not recall. The use of dietary data that derived from a food frequency questionnaire to calculate the Mediterranean diet score is another potential limitation. The questionnaire aims to identify food consumption over the last year, and is also self-report. In these cases it would have been an advantage if they were filled by caregivers so that verification could take place. Clinical variables, such as illness duration and number of admission, also require further methodological considerations. For instance, even if based on self-report with clinical history confirmation via medical records, some patients may have forgotten and, in some cases, the clinical process may lack this information. This would allow to more exploring correlations between these and other variables of interest. This work should, therefore, be considered as the pilot of a larger study.

5.4. Conclusions

The results of the study suggest that the prevalence of MetS and its components among patients with severe mental illness is high irrespective of the diagnoses of MDD or SZ, with a consequent risk of developing diabetes, hypertension and cardiovascular disease and lead to increase mortality. A total of 94% of the patients presented at least one criterion of the MetS, being an increased waist circumference (central obesity) the most prevalent component of MetS. Important hemodynamics alterations were also of note, emphasizing the need of screening before starting the treatment with psychotropic drugs (antidepressants and antipsychotics), assisting in the correct choice of medication, looking for risk and benefit, and have particular attention to these aspects in patient follow-up. These data help to think about strategies for the management and prevention of the MetS. Strategies may be

based on lifestyle changes, which may be of particular relevance due to their modifiable nature as factors with great impact on MetS. On the other hand, health professionals should look at the mentally patient as a whole and not simply look at the mental illness and carefully evaluate the medication and give what is really necessary. Again, the current findings may emphasize the critical need for metabolic screening and management especially among patients with severe mental illness and principally with long duration of disease. Further prospective studies are needed to confirm our findings. Care, with precise and detailed longitudinal monitoring is of need. As such, it is important to monitor patients in any clinical setting, for raising awareness and for proper monitoring and intervention in the patients.

5.5. Final remarks and future research perspectives

Improved patient care in what regards lifestyle advice could be a health plan and policy to implement at the Casa de Saúde do Bom Jesus, strengthening good health habits in all patients regardless of diagnosis. It would be useful to design longitudinal studies with a higher sample size and devise small doable intervention studies.

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Supplementary information

PARECER DA COMISSÃO DE ÉTICA

A Comissão de Ética da Casa de Saúde do Bom Jesus, após analisar o pedido de Protocolo de estudo intitulado "Síndrome metabólico em utentes internados com esquizofrenia e perturbação depressiva major", na Casa de Saúde do Bom Jesus de **Domingas da Luz Rosário Ferrão**, médica em pós-graduação em psiquiatria do Curso de Mestrado em Ciências da Saúde da Universidade do Minho, deu parecer positivo.

Na realização deste estudo deverão ficar salvaguardados a confidencialidade e o anonimato das informações recolhidas.

Braga, 12 de setembro de 2016

O Presidente

Dr. António Guimarães

Termo de Consentimento Livre e Esclarecido para Estudo de Investigação

Título da Pesquisa: "Síndrome Metabólica em doentes internados na Casa de Saúde do Bom Jesus"

Investigadora: Domingas da Luz Rosário Ferrão. **Orientadoras:** Prof. Joana Almeida Palha, PhD; Nadine Santos, PhD.

1. **Natureza** da pesquisa: convidamo-la a participar nesta pesquisa que tem como finalidade avaliar a prevalência da síndrome metabólica em doentes internados na Casa de Saúde do Bom Jesus, Braga
2. **Envolvimento e participação na pesquisa:** Tem a liberdade de recusar participar ou interromper a qualquer momento a sua participação no estudo, sem nenhum tipo de penalização. Iremos- lhe pedir para preencher um formulário de dados demográficos (idade, estado civil, escolaridade, situação profissional), antropométricos (peso, altura, circunferência da cintura, pregas cutâneas, % massa gorda, Índice de massa corporal), pressão Arterial, exames bioquímicos (Glucose em jejum, HDL, Triglicerídeos) e os medicamentos utilizados. O preenchimento será feito na Casa de Saúde, terá duração máxima de 1hora.
3. **Risco e Desconforto**: A participação não infringe as normais legais e éticas. Poderá ter algum desconforto ao serem efectuadas as medidas antropométricas, na colheita de sangue ou durante o preenchimento do formulário, similar a uma consulta/exame de rotina. As suas respostas serão mantidas anónimas e confidenciais, e as informações obtidas serão, somente para uso deste projeto de investigação.
4. **Benefícios**: Não terá nenhum benefício directo. No entanto espera-se que o estudo traga informações importantes sobre a síndrome metabólica e, dessa forma, possa contribuir na prevenção e tratamento da síndrome.
5. **Pagamento**: Não terá nenhum tipo de despesa na participação neste projeto de investigação, e não será paga pela sua participação.

Se tiver qualquer dúvida sobre a pesquisa por favor pode contactar o investigador principal: Domingas da Luz Rosário Ferrão pelo telefone celular numero 934609291 ou pelo e-mail: daluzferrao@gmail.com, ou ainda Casa de Saúde do Bom Jesus-Braga.

Compreendi a informação que me foi dada, tive oportunidade de fazer perguntas e as minhas dúvidas foram esclarecidas.

Foi- me dado o tempo necessário para decidir participar de forma livre e informada.

Aceito participar de livre vontade no estudo acima mencionado.

Concordo que sejam efectuados os exames e a colheita de amostras de sangue para realizar as análises que fazem parte deste estudo.

Também autorizo a divulgação dos resultados obtidos no meio científico, garantindo o anonimato.

Tomei conhecimento que posso recusar participar e/ou desistir a qualquer momento sem qualquer tipo de prejuízo, incluindo na minha relação com a equipe de clínicos e/ou investigadores.

Nome do Participante no estudo

Data Assinatura

___/___/____ _____

Nome do Investigador Responsável

Data Assinatura

___/___/____ _____

O estudo foi devidamente submetido para aprovação das comissões de Ética responsáveis, recebendo a devida aprovação.

Este consentimento consiste de duas páginas e é feito em duplicado, uma cópia para o investigador e uma cópia para quem consente.

Caracterização demográfica e clínica

Síndrome metabólica em doentes internados na casa de Saúde do Bom Jesus

NÚMERO DO QUESTIONÁRIO:				
DATA				

I. IDENTIFICAÇÃO/DEMOGRAFIA

Data de nascimento:	

II. ESTADO CIVIL

- ◯ Solteira
- ◯ Casada ( )
- ◯ Divorciada ( )
- ◯ Viúva ( )
- ◯ União de facto/vive junto ( )
- ◯ Companheiro ( )
- ◯ Separado ( )
- ◯ Outro ( )

III. ESCOLARIDADE

- ◯ Analfabeto
- ◯ Sabe ler e escrever
- ◯ 1ª Ciclo / Ensino Básico
- ◯ 2ª Ciclo
- ◯ 3ª Ciclo/ 12ª Ano
- ◯ Curso Profissional
- ◯ Curso superior
- ◯ Outro

IV. SITUAÇÃO PROFISSIONAL/ OCUPACIONAL

- ◯ Trabalha por conta de outrem
- ◯ Trabalha por conta própria
- ◯ Pensão /Invalidez
- ◯ Estudante
- ◯ Outra
- ◯ Actividades Profissionais anteriores

V. COM QUEM VIVE ACTUALMENTE

- ◯ Mãe /Pai
- ◯ Cônjuge
- ◯ Companheiro
- ◯ Filho(a)
- ◯ Irmão(a)
- ◯ Sozinha
- ◯ Neto(a)
- ◯ Com outras pessoas

VI. EM RELAÇÃO AO HÁBITO DE FUMAR É:

- ◯ Não fumador
- ◯ Fumador
- ◯ Há quanto tempo consome:_____
- ◯ Quantos cigarros ao dia:_____

VII. EM RELAÇÃO AO HÁBITO DE CONSUMO DE BEBIDAS ALCOÓLICAS CONSIDERA-SE:

- ◯ Não consumidor
- ◯ Consumidor
- ◯ Que tipo de bebida consome:_____
- ◯ Quanto consome diariamente/semanalmente:_____
- ◯ Há quanto tempo consome:_____

VIII. HISTORIAI CLINICA

- ◯ Ano da primeira consulta de psiquiatria_____
- ◯ Idade do diagnóstico psiquiátrico_____
- ◯ Duração da doença_____
- ◯ Número de internamentos_____
- ◯ Possui Hipertensão Arterial: ☐ Sim ☐ Não ☐ Não sabe
- ◯ Possui Diabetes: ☐ Sim ☐ Não ☐ Não sabe
- ◯ Possui Doença Renal: ☐ Sim ☐ Não ☐ Não sabe

IX. MEDICAÇÃO

Nome do medicamento	Dose	Função

X. DADOS CLÍNICOS E ANTROPOMÉTRICOS

	Data		
TA sistólica			
TA Diastólica			
Altura			
Peso			
Circunferência abdominal			
Circunferência anca			
Circunferência meio braço			
Circunferência perna			
Prega bicipital			
Prega tricipital			
Prega sub-escapular			
Prega supra-ilíaca			
% MG			

XI. EXAMES LABORATORIAIS

	Data da análise	Dosagem
Glicemia em jejum		
Colesterol total		
HDL		
Triglicerídeos		

Habitual Physical Activity Questionnaire (Baecke), versão modificada, para a população portuguesa

1. Pratica desporto ou exercício físico programado?

- ◯ Sim
- ◯ Não

a) Se sim, qual o desporto que pratica mais frequentemente?

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b) Quantas horas por semana?

- ◯ <1h;
- ◯ 1-2h;
- ◯ 2-3h;
- ◯ 3-4h;
- ◯ >4h

c) Quantos meses por ano?

- ◯ < 1;
- ◯ 1-3;
- ◯ 4-6;
- ◯ 7-9;
- ◯ > 9

d) Se pratica um segundo desporto. Qual o desporto que pratica?

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e) Quantas horas por semana?

- ◯ <1h;
- ◯ 1-2h;
- ◯ 2-3h;

◯ 3-4h;

◯ >4h

f) Quantos meses por ano?

◯ < 1;

◯ 1-3;

◯ 4-6;

◯ 7-9;

◯ > 9

2. **Em comparação com outras pessoas da sua idade, considera que a atividade física que realiza nos tempos livres é:**

◯ Muito menor

◯ Menor

◯ Igual

◯ Maior

◯ Muito maior

3. **Por dia, quantos minutos costuma andar a pé ou de bicicleta (para ir e vir do trabalho, da escola ou fazer compras)?**

◯ 1 <5m

◯ 5 a 15m

◯ 15 a 30m

◯ 30 a 45m

◯ > 45m

4. Nos tempos livres, com que frequência costuma transpirar (devido às atividades que realiza?)

◯ Nunca

◯ Raramente

◯ Algumas vezes

◯ Frequentemente

◯ Muito frequentemente

5. Nos tempos livres, com que frequência costuma praticar desporto ou exercício físico programado?

◯ Nunca
◯ Raramente
◯ Algumas vezes
◯ Frequentemente
◯ Muito frequentemente

6. Nos tempos livres, com que frequência costuma ver televisão?

◯ Nunca
◯ Raramente
◯ Algumas vezes
◯ Frequentemente
◯ Muito frequentemente

7. Nos tempos livres, com que frequência costuma andar a pé?

◯ Nunca
◯ Raramente
◯ Algumas vezes
◯ Frequentemente
◯ Muito frequentemente

8. Nos tempos livres, com que frequência costuma andar de bicicleta?

◯ Nunca
◯ Raramente
◯ Algumas vezes
◯ Frequentemente
◯ Muito frequentemente

1. Pratica desporto ou exercício físico programado? Sim Não	Intensidade ligeira: <3 METS (0,76) Intensidade moderada: ≥ 3 e ≤ 6 METS (1,26) Intensidade vigorosa: > 6 METS (1,76)				
Se sim, qual o desporto que pratica mais frequentemente?	Intensidade: 0,76 – 1,26 – 1,76				
Quantas horas por semana? <1h; 1-2h; 2-3h; 3-4h;> 4h	Tempo: 0,5 – 1,5 – 2,5 – 3,5 – 4,5				
Quantos meses por ano? < 1; 1-3; 4-6; 7-9; > 9	Proporção: 0,04 – 0,17 – 0,42 – 0,67 – 0,92				
Se pratica um segundo desporto. Qual o desporto que pratica?	Intensidade: 0,76 – 1,26 – 1,76				
Quantas horas por semana? <1h; 1-2h; 2-3h; 3-4h;> 4h	Tempo: 0,5 – 1,5 – 2,5 – 3,5 – 4,5				
Quantos meses por ano? < 1; 1-3; 4-6; 7-9; > 9	Proporção: 0,04 – 0,17 – 0,42 – 0,67 – 0,92				
Cálculo do item 1: desporto 1 (intensidade x tempo x proporção) + desporto 2 (intensidade x tempo x proporção)	1 0	2 0,01 < 4	3 ≥ 4 < 8	4 ≥ 8 < 12	5 ≥12
2. Em comparação com outras pessoas da sua idade, considera que a atividade física que realiza nos tempos livres é:	1 muito menor	2 menor	3 igual	4 maior	5 muito maior
3. Por dia, quantos minutos costuma andar a pé ou de bicicleta (para ir e vir do trabalho, da escola ou fazer compras)?	1 < 5m	2 5 a 15m	3 15 a 30m	4 30 a 45m	5 > 45m
4. Nos tempos livres, com que frequência costuma transpirar (devido às atividades que realiza?)	1 nunca	2 raramente	3 algumas vezes	4 Frequentemente	5 muito frequentemente
5. Nos tempos livres, com que frequência costuma praticar desporto ou exercício físico programado?	1 nunca	2 raramente	3 algumas vezes	4 Frequentemente	5 muito frequentemente
6. Nos tempos livres, com que frequência costuma ver televisão?	1 nunca	2 raramente	3 algumas vezes	4 frequentemente	5 muito frequentemente
7. Nos tempos livres, com que frequência costuma andar a pé?	1 nunca	2 raramente	3 algumas vezes	4 frequentemente	5 muito frequentemente
8. Nos tempos livres, com que frequência costuma andar de bicicleta?	1 nunca	2 raramente	3 algumas vezes	4 frequentemente	5 muito frequentemente

Fórmulas de cálculo:
Índice de Desporto (AF-desporto) = $(I_1 + I_2 + I_4 + I_5) / 4$
Índice de Lazer (AF-lazer) = $[I_3 + (6 - I_6) + I_7 + I_8] / 4$
Atividade Física Habitual Total = AF-desporto + AF-lazer

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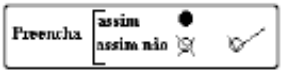
INSTRUÇÕES (PARA ENTREVISTADOR)

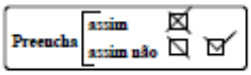
• As questões devem ser "neutras", isto é, não devem influenciar de qualquer forma o tipo de respostas

• O questionário pretende identificar o consumo de alimentos do ano anterior. Assim para cada alimento, deve assinalar, preenchendo o respectivo círculo, quantas vezes, em média, por dia, semana ou mês o inquirido consumiu cada um dos alimentos referidos nesta lista, **ao longo do último ano**. Não se esqueça de assinalar no círculo respectivo os alimentos que o inquirido nunca come, ou come menos de 1 vez por mês.



• Na coluna correspondente à quantidade assinale se a porção que habitualmente o inquirido come é igual, maior ou menor do que a referida como porção média.

• Para os alimentos que só são consumidos, em determinadas épocas do ano (por ex: cerejas, diospíros, etc.), assinale as vezes em que o inquirido consumiu o alimento nessa época, e coloque uma cruz (x) na última coluna (Sazonal).



• Não se esqueça de ter em conta as vezes que o alimento é consumido sozinho e aquelas em que é adicionado a outros alimentos ou pratos (ex: café com leite, os ovos das omeletas, etc).

• No grupo III - **Óleos e Gorduras** - pergunte apenas os que **são adicionados** em saladas, no prato, no pão, etc, e **não** aos utilizados para cozinhar

• No grupo VI - **Hortaliças e Legumes** - pergunte pensando nos que são consumidos no prato (cozidos ou em saladas) e **não** nos que entram na confecção da sopa.

• No item nº 86, anote a frequência com que o inquirido come sopa de legumes. No caso da sopa consumida ser caldo verde, canja ou sopa instantânea, com uma frequência de **pelo menos 1 vez por semana**, deve assinalar este consumo separadamente no quadro existente para outros alimentos, tendo o cuidado em o subtrair à frequência que foi referida anteriormente para a sopa de legumes.

• Se houver algum alimento não mencionado na lista de alimentos e que consuma pelo menos 1 vez por semana, assinale, no quadro que existe para **outros alimentos**, a respectiva frequência e indique ainda a porção média de consumo. ***Por ex: frutos tropicais, sumos de fruta natural, bebidas espirituosas, café de mistura, alheiras, farinheiras, frutos secos (figo, ameixa, damasco), produtos dietéticos, rebuçados, etc.***

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Por favor, **antes de iniciar o questionário leia as instruções da página anterior.**
Pense durante o último ano quantas vezes por dia, semana ou mês, em média, consumiu cada um dos alimentos referidos. Na coluna referente à quantidade deverá assinalar se sua porção é igual, menor ou maior do que a referida como porção média. Para os alimentos consumidos só em determinadas épocas do ano, anote a frequência com que o alimento é consumido nessa época e assinale com uma cruz (**x**) na última coluna (Sazonal).

I. P. LÁCTEOS	Frequência alimentar									Quantidade				Sazonal
	Nunca ou <1 mês	1-3 por mês	1 por sem	2-4 por sem	5-6 por sem	1 por dia	2-3 por dia	4-5 por dia	6 + por dia	Porção Média	A sua porção é: Menor	Igual	Maior	
1. Leite gordo	○	○	○	○	○	○	○	○	○	1 chávena = 250 ml	○	○	○	□
2. Leite meio-gordo	○	○	○	○	○	○	○	○	○	1 chávena = 250 ml	○	○	○	□
3. Leite magro	○	○	○	○	○	○	○	○	○	1 chávena = 250 ml	○	○	○	□
4. Iogurte	○	○	○	○	○	○	○	○	○	Um =125g	○	○	○	□
5.Queijo (de qualquer tipo incluindo queijo fresco e requeijão)	○	○	○	○	○	○	○	○	○	1 fatia = 30g	○	○	○	□
6. Sobremesas lácteas: pudim, aletria e leite creme , etc	○	○	○	○	○	○	○	○	○	Um ou 1 prato sobremesa	○	○	○	□
7. Gelados	○	○	○	○	○	○	○	○	○	Um ou 2 bolas	○	○	○	□

II. OVOS, CARNES E PEIXES	Frequência alimentar									Quantidade				Sazonal
	Nunca ou <1 mês	1-3 por mês	1 por sem	2-4 por sem	5-6 por sem	1 por dia	2-3 por dia	4-5 por dia	6 + por dia	Porção Média	A sua porção é: Menor	Igual	Maior	
8.Ovos	○	○	○	○	○	○	○	○	○	Um	○	○	○	□
9.Frango	○	○	○	○	○	○	○	○	○	1 porção ou 2 peças=150g	○	○	○	□
10.Peru, coelho	○	○	○	○	○	○	○	○	○	1 porção ou 2 peças=150g	○	○	○	□
11.Carne vaca, porco,cabrito	○	○	○	○	○	○	○	○	○	1 porção =120g	○	○	○	□
12. Fígado de vaca, porco, frango	○	○	○	○	○	○	○	○	○	1 porção = 120g	○	○	○	□
13 Língua, mão de vaca, tripas, chispe, coração, rim	○	○	○	○	○	○	○	○	○	1 porção =100g	○	○	○	□
14.Fiambre, chouriço, salpicão, presunto, etc	○	○	○	○	○	○	○	○	○	2 fatias ou 3 rodelas =20g	○	○	○	□
15. Salsichas	○	○	○	○	○	○	○	○	○	3 médias	○	○	○	□
16. Toucinho, bacon	○	○	○	○	○	○	○	○	○	2 fatias=50g	○	○	○	□
17. Peixe gordo: sardinha, cavala, carapau, salmão,	○	○	○	○	○	○	○	○	○	1 porção =125g	○	○	○	□
18. Peixe magro: pescada, faneca, dourada, etc	○	○	○	○	○	○	○	○	○	1 porção =125g	○	○	○	□
19.Bacalhau	○	○	○	○	○	○	○	○	○	1 porção =125g	○	○	○	□
20.Peixe conserva: atum, sardinhas,etc	○	○	○	○	○	○	○	○	○	1 lata	○	○	○	□
21.Lulas, polvo	○	○	○	○	○	○	○	○	○	1 porção =100g	○	○	○	□
22.Camarão, amêijoas, mexilhão, etc	○	○	○	○	○	○	○	○	○	1 prato sobremesa =100g	○	○	○	□

III. Óleos e Gorduras	Frequência alimentar									Quantidade				Sazonal
	Nunca ou <1 mês	1-3 por mês	1 por sem	2-4 por sem	5-6 por sem	1 por dia	2-3 por dia	4-5 por dia	6 + por dia	Porção Média	A sua porção é: Menor	Igual	Maior	
23. Azeite	○	○	○	○	○	○	○	○	○	1 colher sopa	○	○	○	□
24. Óleos: girassol, milho, soja	○	○	○	○	○	○	○	○	○	1 colher sopa	○	○	○	□
25. Margarina	○	○	○	○	○	○	○	○	○	1 colher chá	○	○	○	□
26. Manteiga	○	○	○	○	○	○	○	○	○	1 colher chá	○	○	○	□

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IV.PÃO, CEREAIS E SIMILARES	Frequência alimentar									Quantidade				Anotações
	Nunca ou <1 mês	1-3 por mês	1 por sem	2-4 por sem	5-6 por sem	1 por dia	2-3 por dia	4-5 por dia	6 + por dia	Porção Média	A sua porção é: Menor	Igual	Maior	
27. Pão branco ou tostas	○	○	○	○	○	○	○	○	○	Um ou 2 tostas = 40g	○	○	○	□
28. Pão (ou tostas), integral,centeio, mistura	○	○	○	○	○	○	○	○	○	Um ou 2 tostas= 50g	○	○	○	□
29. Broa, broa de avintes	○	○	○	○	○	○	○	○	○	1 fatia = 80g	○	○	○	□
30. Flocos cereais (muesli, corn-flakes, chocapic,etc.)	○	○	○	○	○	○	○	○	○	1 chávena =40g	○	○	○	□
31. Arroz	○	○	○	○	○	○	○	○	○	½ prato = 100g	○	○	○	□
32. Massas: esparguete, macarrão, etc.	○	○	○	○	○	○	○	○	○	½ prato = 100g	○	○	○	□
33. Batatas fritas caseiras	○	○	○	○	○	○	○	○	○	½ prato = 100g	○	○	○	□
34. Batatas fritas de pacote	○	○	○	○	○	○	○	○	○	1 pacote pequeno =30g	○	○	○	□
35. Batatas cozidas, assadas, estufadas e puré	○	○	○	○	○	○	○	○	○	2 batatas médias =160 g	○	○	○	□

V.DOCES E PASTÉIS	Frequência alimentar									Quantidade				Anotações
	Nunca ou <1 mês	1-3 por mês	1 por sem	2-4 por sem	5-6 por sem	1 por dia	2-3 por dia	4-5 por dia	6 + por dia	Porção Média	A sua porção é: Menor	Igual	Maior	
36. Bolachas tipo maria, água e sal ou integrais	○	○	○	○	○	○	○	○	○	3 bolachas	○	○	○	□
37. Outras bolachas ou biscoitos	○	○	○	○	○	○	○	○	○	3 bolachas	○	○	○	□
38. Croissant, pastéis, bolicao, doughnut ou bolos	○	○	○	○	○	○	○	○	○	Um; 1 fatia = 80g	○	○	○	□
39.Chocolate (tablete ou em pó)	○	○	○	○	○	○	○	○	○	3 quadrados; 1 colher sopa	○	○	○	□
40. Snacks de chocolate (Mars, Twix, Kit Kat, etc)	○	○	○	○	○	○	○	○	○	Um	○	○	○	□
41. Marmelada, compota, geleia, mel	○	○	○	○	○	○	○	○	○	1 colher sobremesa	○	○	○	□
42. Açúcar	○	○	○	○	○	○	○	○	○	1 colher sobremesa; 1 pacote	○	○	○	□

VI. HORTALIÇAS E LEGUMES	Frequência alimentar									Quantidade				Anotações
	Nunca ou <1 mês	1-3 por mês	1 por sem	2-4 por sem	5-6 por sem	1 por dia	2-3 por dia	4-5 por dia	6 + por dia	Porção Média	A sua porção é: Menor	Igual	Maior	
43. Couve branca, couve lombarda	○	○	○	○	○	○	○	○	○	½ chávena =75g	○	○	○	□
44. Penca, Tronchuda	○	○	○	○	○	○	○	○	○	½ chávena = 65g	○	○	○	□
45. Couve galega	○	○	○	○	○	○	○	○	○	½ chávena =65g	○	○	○	□
46. Brócolos	○	○	○	○	○	○	○	○	○	½ chávena =85g	○	○	○	□
47. Couve-flor, Couve-bruxelas	○	○	○	○	○	○	○	○	○	½ chávena =65g	○	○	○	□
48. Grelos, Nabiças, Espinafres	○	○	○	○	○	○	○	○	○	½ chávena =72g	○	○	○	□
49. Feijão verde	○	○	○	○	○	○	○	○	○	½ chávena =65g	○	○	○	□
50. Alface, Agrião	○	○	○	○	○	○	○	○	○	½ chávena =15g	○	○	○	□
51. Cebola	○	○	○	○	○	○	○	○	○	½ média=40g	○	○	○	□
52. Cenoura	○	○	○	○	○	○	○	○	○	1 média=80g	○	○	○	□
53. Nabo	○	○	○	○	○	○	○	○	○	1 médio=78g	○	○	○	□
54. Tomate fresco	○	○	○	○	○	○	○	○	○	½ médio=63g	○	○	○	□
55. Pimento	○	○	○	○	○	○	○	○	○	½ médio=68g	○	○	○	□
56. Pepino	○	○	○	○	○	○	○	○	○	¼ médio=50g	○	○	○	□
57. Leguminosas: feijão, grão de bico	○	○	○	○	○	○	○	○	○	1 chávena	○	○	○	□
58. Ervilha grão, Fava	○	○	○	○	○	○	○	○	○	½ chávena	○	○	○	□

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VII. FRUTOS	Frequência alimentar									Quantidade				
	Nunca ou <1 mês	1-3 por mês	1 por sem	2-4 por sem	5-6 por sem	1 por dia	2-3 por dia	4-5 por dia	6 + por dia	Porção Média	A sua porção é: Menor	Igual	Maior	
59. Maçã, pêra	○	○	○	○	○	○	○	○	○	uma média	○	○	○	□
60. Laranja, Tangerinas	○	○	○	○	○	○	○	○	○	1 média; 2 médias	○	○	○	□
61. Banana	○	○	○	○	○	○	○	○	○	uma média	○	○	○	□
62. Kiwi	○	○	○	○	○	○	○	○	○	um médio	○	○	○	□
63. Morangos	○	○	○	○	○	○	○	○	○	1 chávena	○	○	○	□
64. Cerejas	○	○	○	○	○	○	○	○	○	1 chávena	○	○	○	□
65. Pêssego, Ameixa	○	○	○	○	○	○	○	○	○	1 médio; 3 médios	○	○	○	□
66. Melão, Melancia	○	○	○	○	○	○	○	○	○	1 fatia média = 150g	○	○	○	□
67. Diospiro	○	○	○	○	○	○	○	○	○	1 médio	○	○	○	□
68. Figo fresco, Nêsperas, Damascos	○	○	○	○	○	○	○	○	○	3 médios	○	○	○	□
69. Uvas frescas	○	○	○	○	○	○	○	○	○	1 cacho médio	○	○	○	□
70. Frutos conserva pêssego, ananás	○	○	○	○	○	○	○	○	○	2 metades ou rodelas	○	○	○	□
71. Amêndoas, avelãs, nozes, amendoins, pistachio, etc.	○	○	○	○	○	○	○	○	○	½ chávena (descascado)	○	○	○	□
72. Azeitonas	○	○	○	○	○	○	○	○	○	6 unidades	○	○	○	□

VIII. BEBIDAS E MISCELANEAS	Frequência alimentar									Quantidade				
	Nunca ou <1 mês	1-3 por mês	1 por sem	2-4 por sem	5-6 por sem	1 por dia	2-3 por dia	4-5 por dia	6 + por dia	Porção Média	A sua porção é: Menor	Igual	Maior	
73. Vinho	○	○	○	○	○	○	○	○	○	1 copo=125ml	○	○	○	□
74. Cerveja	○	○	○	○	○	○	○	○	○	1 garrafa ou 1 lata=330 ml	○	○	○	□
75. Bebidas brancas: whisky, aguardente, brandy, etc	○	○	○	○	○	○	○	○	○	1 cálice = 40 ml	○	○	○	□
76. Coca-cola, pepsi-cola ou outras colas	○	○	○	○	○	○	○	○	○	1 garrafa ou 1 lata=330 ml	○	○	○	□
77. Ice-tea	○	○	○	○	○	○	○	○	○	1 garrafa ou 1 lata=330 ml	○	○	○	□
78.Outros refrigerantes, sumos de fruta ou néctares embalados	○	○	○	○	○	○	○	○	○	1 garrafa ou 1 copo = 250 ml	○	○	○	□
79.Café (incluindo pingo, meia de leite e outras bebidas com café)	○	○	○	○	○	○	○	○	○	1 chávena café	○	○	○	□
80. Chá preto e verde	○	○	○	○	○	○	○	○	○	1 chávena	○	○	○	□
81. Croquetes, rissóis, bolinhos de bacalhau, etc.	○	○	○	○	○	○	○	○	○	3 unidades	○	○	○	□
82. Maionese	○	○	○	○	○	○	○	○	○	1 colher sobremesa	○	○	○	□
83. Molho de tomate, ketchup	○	○	○	○	○	○	○	○	○	1 colher sopa	○	○	○	□
84. Pizza	○	○	○	○	○	○	○	○	○	Meia pizza-normal	○	○	○	□
85. Hambúrguer	○	○	○	○	○	○	○	○	○	Um médio	○	○	○	□
86. Sopa de legumes	○	○	○	○	○	○	○	○	○	1 prato	○	○	○	□

Existe algum alimento ou bebida que eu não tenha mencionado e que tenha consumido pelo menos 1 vez por semana mesmo em pequenas quantidades, ou numa época em particular. Por ex: **frutos tropicais, sumos de fruta natural, bebidas espirituosas, café de mistura, alheiras, farinheiras, frutos secos (figo, ameixa, damasco), produtos dietéticos, rebuçados, etc.**

Outros Alimentos	Frequência alimentar									Quantidade	
	Nunca ou <1 mês	1-3 por mês	1 por sem	2-4 por sem	5-6 por sem	1 por dia	2-3 por dia	4-5 por dia	6 + por dia	Porção Média	
	○	○	○	○	○	○	○	○	○		□
	○	○	○	○	○	○	○	○	○		□
	○	○	○	○	○	○	○	○	○		□