Capa

Caio Hofmann Francisco Alves

Relação entre Inflamação e Transtornos Psiquiátricos na população geral: resultados do Projeto São Paulo Megacity

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Caio Hofmann Francisco Alves

Relação entre Inflamação e Transtornos Psiquiátricos na população geral: resultados do Projeto São Paulo Megacity

Relationship between Inflammation and Psychiatric Disorders in the general population: results of the São Paulo Megacity Project

	Dissertação apresentada à Faculdade de Medicina da Universidade de São Paulo, para a obtenção de Título de Mestre em epidemiologia, na Área de psiquiatria. Orientadora: Professora Dra Laura Helena Silveira Guerra de Andrade

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Orientador(a)

Dedication

To the sun,

which one day will consume everything,

making all that has ever existed futile.

Epigraph

„The brain is the last and grandest biological frontier, the most complex thing we have yet discovered in our universe. It contains hundreds of billions of cells interlinked through trillions of connections. The brain boggles the mind.“

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Abstract

A growing body of evidence has suggested a strong relationship between inflammatory processes and psychiatric disorders (PDs). Inflammatory processes, including chronic inflammation and metabolic syndrome (MS) have important systemic effects on virtually all systems of the human body, including the Central Nervous System. Inflammatory processes are related to pathologies such as: Major Depressive Disorder (MDD), Generalized Anxiety Disorder (GAD), Bipolar Affective Disorder (BAD), Schizophrenia, post-traumatic stress disorder (PTSD), among others. However, the exact mechanisms and processes by which these relationships are established have not yet been clarified.

Data are from the São Paulo Megacity Mental Health Survey, a cross-sectional study with 5,037 individuals aged 18 years and over residing in the Metropolitan Region of São Paulo (RMSP). In a subsample of 772 respondents evaluated in a hospital setting by trained psychiatrists with SCID-I we aimed to investigate: i. General inflammatory status of the sample, measured by the level of C-Reactive Protein (CRP) in the sample; ii. Inflammatory states (IS) frequency among respondents with depression, anxiety and anxiety/depression comorbidity and in subjects without psychopathology; iii. The degree of association between inflammatory states and depressive and anxiety disorders and anxiety/depression comorbidity, magnitude and significance of the association; iv. To assess the influence of sociodemographic factors, smoking, and BMI on the association between anxiety, depression and inflammation. Based on the main objective of this study, the null-hypothesis (H0) is defined as the absence of an association of depression, anxiety, and comorbid depression and anxiety with higher levels of inflammation, compared with controls (absence of psychiatric disorder).

We proceeded with a data driven approach analysis, using latent classes in order to identify subtypes of depressive phenotypes and later compare the levels of inflammatory and metabolic biomarkers of these phenotypes to those of healthy individuals in the sample. For these analyses, the total sample consisted of 653 individuals with complete data on all exposure, outcome, and covariates. To identify depressive subtypes, we conducted a latent class analysis (LCA) of the sixteen

DSM-5 individual MDD symptoms using poLCA package in R. Inflammation was investigated by high sensitivity C-reactive protein (CRP) levels. Multinomial logistic regression models were used to investigate the association of depressive subtypes and inflammatory levels, adjusted for age, gender, education, smoking and body mass index. The best LCA model of the sixteen MDD symptoms was a Four-Class model including severe depression with high somatic symptoms (16.69%), severe depression with low somatic symptoms (19.60%), mild-moderate (19.14%) depression, and non-symptomatic (44.56%) individuals. Inflammation was higher in individuals with high somatic (OR = 1.25; 1.01-1.55), lower in those with low somatic symptoms (OR = 0.68; 0.55-0.84), but not associated to inflammation in moderate/severe depression without high somatic or low somatic symptoms, when adjusted for age, gender, and education. We found that different symptomatic profile of depression are associated with different inflammatory parameters. These findings have important implications in the understanding of biological underpinnings of depression and its treatment.

Resumo

Um crescente corpo de evidências tem sugerido uma forte relação entre processos inflamatórios e transtornos psiquiátricos (TPs). Processos inflamatórios, incluindo inflamação crônica e síndrome metabólica (SM) têm importantes efeitos sistêmicos em praticamente todos os sistemas do corpo humano, incluindo o Sistema Nervoso Central. Os processos inflamatórios estão relacionados a patologias como: Transtorno Depressivo Maior (TDM), Transtorno de Ansiedade Generalizada (TAG), Transtorno Afetivo Bipolar (TAB), Esquizofrenia, Transtorno de Estresse Pós-Traumático (TEPT), entre outros. No entanto, os mecanismos e processos exatos pelos quais essas relações são estabelecidas ainda não foram esclarecidos.

Nesse estudo, utilizamos dados da Pesquisa de São Paulo Megacity, um estudo transversal com 5.037 indivíduos com 18 anos ou mais residentes na Região Metropolitana de São Paulo (RMSP). Em uma subamostra de 772 entrevistados avaliados em ambiente hospitalar por psiquiatras treinados com SCID-I, nosso objetivo foi investigar: i. Estado inflamatório geral da amostra, medido pelo nível de Proteína C-Reativa (PCR) na amostra; ii. Estados inflamatórios (EI) frequentes entre os entrevistados com depressão, ansiedade e comorbidade ansiedade/depressão e em sujeitos sem psicopatologia; iii. O grau de associação entre estados inflamatórios e transtornos depressivos e de ansiedade e comorbidade ansiedade/depressão, magnitude e significância da associação; 4. Avaliar a influência de fatores sociodemográficos, tabagismo e IMC na associação entre ansiedade, depressão e inflamação. Com base no objetivo principal deste estudo, a hipótese nula (H0) é definida como a ausência de associação de depressão, ansiedade e comorbidade depressão e ansiedade com níveis mais elevados de inflamação, em comparação com controles (ausência de transtorno psiquiátrico).

Procedemos com uma análise de abordagem orientada por dados, utilizando classes latentes para identificar subtipos de fenótipos depressivos e posteriormente comparar os níveis de biomarcadores inflamatórios e metabólicos desses fenótipos com os de indivíduos saudáveis da amostra. Para essas análises, a amostra total foi composta por 653 indivíduos com dados completos sobre todas as exposições, desfechos e covariáveis. Para identificar subtipos depressivos, realizamos uma

análise de classe latente (LCA) dos dezesseis sintomas de MDD individuais do DSM-5 usando o pacote poLCA em R. A inflamação foi investigada pelos níveis de proteína C reativa (PCR) de alta sensibilidade. Modelos de regressão logística multinomial foram utilizados para investigar a associação de subtipos depressivos e níveis inflamatórios, ajustados para idade, sexo, escolaridade, tabagismo e índice de massa corporal. O melhor modelo de LCA dos dezesseis sintomas de MDD foi um modelo de quatro classes, incluindo depressão grave com sintomas somáticos altos (16,69%), depressão grave com sintomas somáticos baixos (19,60%), depressão leve-moderada (19,14%) e uma classe de indivíduos não sintomáticos (44,56%) . A inflamação foi maior em indivíduos com sintomas somáticos altos (OR = 1,25; 1,01-1,55), menor naqueles com sintomas somáticos baixos (OR = 0,68; 0,55-0,84), mas não associada à inflamação em depressão moderada/severa sem somático alto ou baixo sintomas somáticos, quando ajustados para idade, sexo e escolaridade. Descobrimos que diferentes perfis sintomáticos de depressão estão associados a diferentes parâmetros inflamatórios. Esses achados têm implicações importantes na compreensão dos fundamentos biológicos da depressão e seu tratamento.

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1. Introduction

According to data from the *World Health Organization - World Mental Health Initiative (WMH) project,* psychiatric disorders are quite common in all countries participating in the consortium (Colombia, Mexico, United States, Nigeria, South Africa, Lebanon, Belgium, France, Germany, Israel, Italy, Netherlands, Spain, Ukraine, China, Japan, New Zealand, Brazil, among others) with lifetime prevalence estimates of any DSM-IV disorder assessed in the CIDI across these surveys of 18.1–36.1% (iinter-quartile range) , even considering high chances of underdiagnosis in underdeveloped countries, confirming that psychiatric disorders are of great importance for public health worldwide(1).

According to the same WMH data, Anxiety Disorders is the most prevalent class of psychiatric disorder in the general population, with an estimated mean lifetime prevalence of approximately 16% and a 12-month prevalence of 11% (1). Mood disorders are the second most prevalent class, with an average lifetime prevalence of approximately 12% and a 12-month prevalence of around 6%(1). In general, the prevalence of the two classes of disorders is higher in developed Western countries than in developing countries, although it is hypothesized that this difference is due to underdiagnosis in developing countries(1). The following two classes of Psychiatric Disorders are more common according to the WHO are those of externalizing disorders that include attention/hyperactivity disorder, oppositional defiant disorder, conduct disorder, intermittent explosive disorder, and substance use disorders that include alcohol and drug use and abuse(1).

When analyzing the disorders individually (without grouping them into

classes), specific phobias are the most prevalent disorder in epidemiological studies in communities with a prevalence in the range of 6 to 12% throughout life and 4 to 8% in 12 months, followed by major depressive disorder, with a lifetime prevalence in the range of 4 to 10% and a 12-month prevalence in the range of 4 to 8%(1). The authors of the project point out that the prevalence may be even higher, due to difficulties in adapting diagnostic instruments to different cultures(1).

A growing body of evidence has suggested a strong relationship between inflammatory processes and psychiatric disorders (PDs)(2). Inflammatory processes, including chronic inflammation, have important systemic effects on virtually all systems of the human body, including the Central Nervous System(2). The literature indicates that inflammatory processes are related to pathologies such as: Major Depressive Disorder (MDD) (3), Generalized Anxiety Disorder (GAD)(4), Bipolar Affective Disorder (BAD)(5,6), Schizophrenia (7), post-traumatic stress disorder (PTSD)(8), among others.

The inflammatory state is also related to disease behavior(2). These authors, specifically analyzing depression and anxiety(2), published a review in which they propose a theory of social signal transduction of depression: social and environmental factors would lead to biological changes that in turn lead to depression. The mediators of this response would be the Sympathetic Nervous System (SNS), responsible for the increase in inflammatory cytokines, and the Hypothalamic Pituitary Adrenal Axis (HPA Axis), whose imbalance would lead to a picture of resistance to endogenous corticosteroids (thus reducing their anti-inflammatory capacity).(2). Also according to these authors, the relationship between inflammation and depression could occur in 5 ways: i. Early stress associated with high levels of inflammation; ii. Stress in adulthood associated with high levels of inflammation; iii. Social stressors in a laboratory context triggering inflammatory activity; iv. Neural Mechanisms Underlying the Stress-Induced Inflammatory Response; v. Genetic and genomic mechanisms underlying the stress-induced inflammatory response; especially in the presence of somatic and neurodegenerative symptoms(2).

There is numerous evidence of the association of several physical and somatic diseases of inflammatory origin with depression, such as: Rheumatoid Arthritis, Inflammatory Bowel Disease, Metabolic Syndrome, Coronary Heart Disease and Chronic Pain(2). Additionally, the levels of multiple inflammatory markers are elevated in depressed individuals compared to healthy individuals, including plasma levels of inflammatory cytokines such as IL-1, IL-6 and TNF-α, CRP levels and several markers of cell-mediated immunity activation(2). In addition, metabolic syndrome and mood disorders share several inflammatory pathways (9). It is known that smoking, often associated with depression(10), increases oxidative stress (11).

Psychoneuroimmunology (PNI), is the study of the interaction between psychological processes and the nervous and immune systems of the human body(12,13). It may also be referred to as psychoendoneuroimmunology (PENI) or psychoneuroendocrinoimmunology (PNEI) when emphasis on the endocrine system is desired(12,13).

Immunopsychiatry, while also a discipline that studies the connection between the brain and the immune system(14), differs from psychoneuroimmunology on an hierarchical concept as it considers that behaviors and emotions are governed by peripheral immune mechanisms, while psychoneuroimmunology implies a bidirectional brain/immune system communication with no domination of one over the other with an emphasis on the notion that psychological and neural aspects can influence the immune system(14).

The possible relationship between psychiatric syndromes and/or symptoms and immune function has been a consistent area of interest since the inception of modern medicine(15).

In the mid-1800s Claude Bernard, a French physiologist of the Muséum national d'Histoire naturelle (National Museum of Natural History in English), formulated the concept of the milieu interieur (internal environment), to

describe the physiological capacity of the interstitial fluid to provide protective stability for the tissues and organs of multicellular organisms (16,17).

In 1865, Bernard described the perturbation of this internal state as protective functions of the body's organic elements, holding a reserve of living materials and maintaining conditions indispensable for vital activity such as humidity, heat and others. He defines sickness and death as simply the dislocation or perturbation of these regulating mechanisms(18,19)

In 1932. Walter Cannon, a professor of physiology at Harvard University, published his book "The Wisdom of the Body", where he coined the now common term of homeostasis, coming from the Greek word "homoios" (similar) and "stasis" (position)(20). Cannon observed, animal models, that any changes of emotional state, such as anxiety, distress, or rage, were accompanied by the total cessation of movements of the bowels(21) (Bodily Changes in Pain, Hunger, Fear and Rage, 1915). His research focused on the relationship between the effects of emotions and perceptions on the autonomic nervous system (sympathetic and parasympathetic responses) culminating with the first description of the fight or flight response (also called fight-flight-or-freeze response, called hyperarousal or acute stress response).(22).

Circa 1940, Hans Selye, a researcher at Université de Montréal, developed the concept of the General Adaptation Syndrome (later rebaptized "stress response") from his animal models of different physical and mental adverse conditions. Selye noted that the body constantly adapted to heal and recover under such stimulus, changes that included enlargement of the adrenal gland, atrophy of the thymus, spleen, and other lymphoid tissue, and gastric ulcerations(23,24). Selye was a pioneer in suggesting these adaptations as possible basis for a unified theory of modern medicine(25). His seminal work helped paved the way for modern research on the biological functioning of glucocorticoids and stress(26).

Around the mid-20th century, studies on psychiatric subjects revealed immune disturbances in psychotic individuals, including lower lymphocyte numbers(27,28), and poorer response to pertussis vaccination(29). In 1964 George Freeman Solomon and his research team in UCLA coined the term "psychoimmunology" and published the emblematic paper: "Emotions, immunity, and disease: a speculative theoretical integration."(30)

2. Project

Main Objective

To evaluate the association between the presence of an inflammatory state measured by ultra-sensitive CRP and depressive disorders, anxiety disorders, anxiety/depression comorbidity in a sub-sample part of the São Paulo Megacity Mental Health Survey, held in São Paulo Metropolitan Area (Municipality of São Paulo and 38 adjacent municipalities).

Secondary Objectives

- To assess the association between metabolic syndrome and the presence of inflammation. To assess the association of metabolic syndrome and depressive disorder and/or anxiety disorder.
- To assess the association between Inflammatory State (IS) and the occurrence of other chronic physical diseases that do not fall within the definition of metabolic syndrome (cardiovascular, respiratory, chronic pain).
- To assess the influence of sociodemographic factors, smoking, and BMI on the association between anxiety, depression and inflammation.

Hypothesis

Based on the main objective of this study, the null-hypothesis (H0) is defined as the absence of an association of depression, anxiety, and comorbid

depression and anxiety with higher levels of inflammation, compared with controls (absence of psychiatric disorder).

Expected contributions to the area

The hypothesis of inflammation as a mediator of acute and chronic conditions, not only in general clinical conditions, but also in psychiatric disorders, has been gaining momentum in the scientific environment in recent years. The majority of studies are in clinical samples. In this study, we expected to be able to investigate the level of inflammation, measured by the biomarker CRP, in different groups of subjects with psychiatric disorders in a subsample of the general population, not in patients. We can verify the variations of this marker of inflammation between different sub-groups of subjects and if there is a correlation between psychiatric symptoms and levels of inflammation. As we have information to determine the presence of metabolic syndrome in the sample subjects, we would be able to investigate the association of the different components of this syndrome with the occurrence of anxiety and/or depression.

Expected Results

As a result of the proposed project, it is expected:

- Obtain the degree of association of inflammatory states and depressive and anxiety disorders in a sample of the adult population of the Metropolitan Region of São Paulo (RMSP) as well as:
- General inflammatory status of this sample
    - Frequency of inflammatory states among subjects with depression, anxiety, anxiety/depression comorbidity and in subjects in the sample without psychopathology;

- Magnitude and significance of the association;
    - Influence of sociodemographic factors;
    - Influence of smoking;
    - Influence of the Metabolic Syndrome;
    - Influence of Physical Disorders (not included in the MS criterion).

3. Methods

Sample Description

This investigation is part of the São Paulo Megacity Mental Health Survey (SPMHS) project, a cross-sectional study of a representative sample of the general adult population residing in São Paulo Metropolitan Area (31)**.**

All data were obtained between May 2005 and December 2007. The psychiatric clinical evaluation, from which we generated the diagnostic variables and laboratory tests (blood collection) were all obtained at the same period , as part of the Clinical Phase of the SP Megacity project (see description below; Viana et al, 2009). No new collections or psychiatric interviews were carried out for this study.

Household Phase

The first phase of the SPMHS involved a complex sample selection process, in order to have a representative sample of the general population. Respondents were selected through a multi stratified probability sampling of households by area. In each household, an individual was randomly selected using a Kish table. A total of 5,237 people agreed to participate, but 200 seniors were deemed ineligible due to cognitive impairment. The overall response rate was 81.3% and the final sample was 5,037 subjects(32). These individuals were evaluated through the ***Composite International Diagnostic Interview – World Mental Health*** **(WMH-CIDI)**, a structured clinical interview applicable by laypeople that makes it possible to generate diagnoses according to the DSM-IV.version *World Mental Health* (WMH-CIDI)(33), translated into Brazilian Portuguese and adapted for use in the São Paulo Megacity project(34). The interview was divided into two parts:

A. Part I, applied to all respondents (N=5,037), included the assessment of “nuclear” psychiatric disorders: mood disorders (major depression, mania); anxiety disorders (panic disorder, specific phobia, social phobia, agoraphobia, generalized anxiety disorder, adult separation anxiety); substance use disorders; and impulse control disorders (intermittent explosive disorder, attention deficit hyperactivity disorder, oppositional defiant disorder, and conduct disorder). It also included an investigation of suicidal behavior and a sociodemographic data section. Additionally, family and childhood burden or impact, daily functioning and impairments in the last 30 days, chronic clinical conditions and non-specific symptoms in the last 30 days were evaluated(35);

B. Part II, applied to all respondents who met criteria for a “nuclear” disorder, in addition to a probabilistic subsample of “non-cases” (case-control study). In total, 2,942 subjects answered questions about less common conditions such as eating disorders, risk factors, use of services, use of psychotropic drugs, social and occupational consequences of psychiatric disorders, additional sociodemographic information, family and social support, and history of affective and offspring, in addition to less common conditions(35).

Around 42% of the sample received only the first part of the CIDI (2,095 individuals, 41.6% of the total sample of 5,037) and the complete questionnaire was applied to 2,942 individuals, divided into two groups: one formed by 2,236 individuals (44.4%) with psychiatric disorders (identified by the first part of the CIDI) and another formed by 706 individuals (14.0%) who were randomly chosen to administer the complete questionnaire even though they did not present criteria for the diagnosis of psychiatric diseases

Clinical Phase

Data collection for the clinical phase took place between June 2005 and December 2007. The sample was selected as follows: all individuals with a lifetime psychiatric disorder (2,236 participants) were invited to attend the Instituto de Psiquiatria do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo(IPq) to carry out complementary clinical and psychiatric evaluation. In addition, approximately 20% of the 2,801 (corresponding to 55.6% of the total household sample) participants without diagnosis were invited to participate in the second phase of the study, a total of 584 individuals. The selection of these individuals was carried out by simple drawing(35).

In this way, a total of 2,820 individuals were invited to participate in the second phase of the survey. Letters were sent by mail to all selected individuals, explaining the objectives of the second evaluation and inviting them to schedule an appointment by telephone to attend the Psychiatry Institute of the Hospital das Clínicas, Faculty of Medicine, University of São Paulo. If the individual agreed to participate, a date was scheduled for the consultation and the participant was asked to attend after a 12-hour fast (due to the collection of laboratory tests)(35).

It was not possible to contact 1349 individuals. Of the 1471 contacted, 780 (53%) attended the HCFMUSP (five subjects were referred to the Emergency Room, as they needed urgent care, and three withdrew from the evaluation). Thus, 772 subjects making up the sample, object of this project, were invited to attend the Psychiatry Institute of the Hospital das Clínicas of the Faculty of Medicine of the University of São Paulo (IPq) and underwent the assessments, reported below.

Anthropometric and blood pressure measurements

Four researchers performed all anthropometric measurements (Weight, Height, Abdominal Circumference and Blood Pressure). All received training before the start of field activities(35).

Weight measure was performed using a mechanical anthropometric scale according to the techniques standardized by the Center of Disease Control and Prevention (CDC)(36). The scale used was manually calibrated at the beginning of each study day(35). Participants were asked to wear only light clothing before stepping on the scale (removing coats, shoes, belts and contents of pockets) and to remain still and not communicate during the measurement. The measurement was performed in kg, recorded to one decimal place on an appropriate form(35).

Height measurement was performed with a stadiometer coupled to a mechanical anthropometric scale, according to the techniques recommended by the CDC(36). Participants were asked to remove their shoes and any headwear (clamps, headbands, caps, hats, etc.). Participants were asked to step on the scale and adopt an upright posture, with their backs to the stadiometer with feet close together, together at the heels and separated at the height of the toes, forming an angle of about 60 degrees, arms hanging at the sides of the body, with the head in the Frankfurt horizontal plane(35). In this position, the upper end of the stadiometer was supported on the individual's head, slightly compressing the hair. The participant was asked to take a deep breath and hold his breath during the measurement. The height measurement was recorded in meters with two decimal places in an appropriate form(35).

The measurement of abdominal circumference was performed using a flexible measuring tape, graduated in centimeters, according to the techniques

recommended by the CDC(36). Participants were asked to keep their abdomen free of clothing by elevating their clothing. The measurement was performed during expiration, at the height of the iliac crests, at their upper and anterior limits, ensuring that the plane formed by the measuring tape was parallel to the floor. The measurement was recorded in centimeters on an appropriate form(35).

Blood pressure measurement was performed using a calibrated portable aneroid sphygmomanometer. The participant was asked to remain in a sitting position with the arm free of clothing and supported at the precordium level. During the inflation of the cuff, the radial artery was palpated and the value of the disappearance of the pulse was observed to estimate the systolic blood pressure(35).

The cuff was then deflated and a new inflation was performed, with auscultation of the brachial artery in the antecubital fossa. The value corresponding to the appearance of the auscultated beats (first korotkoff sound) was considered as the systolic blood pressure. The value corresponding to the disappearance of beats (fifth Korotkoff sound) was considered as diastolic blood pressure(37).

Three measurements were performed using the described technique with a one-minute interval between measurements. All measurements were recorded on an appropriate form and the participant's blood pressure was considered as the average between the last two measurements(35).

Laboratory tests

Blood samples were collected in a hospital environment to analyze levels of: fasting blood glucose, lipid profile of ultra-sensitive C-reactive protein (us-CRP). Lipid profile and glycemia were considered for the classification of metabolic syndrome and the hsCRP were used to evaluate the inflammatory state of the subjects.

During telephone contact with participants that agreed to participate in the clinical evaluation, we asked them to fast for 12 hours due to the possibility of collecting blood for laboratory tests. Before collection, the participant was asked if he had fasted. If it had been done, the collection was carried out, otherwise the participant was instructed and a new collection date was scheduled. The tests performed in this collection include: Blood glucose, Total Cholesterol, HDL-Cholesterol, VLDL-Cholesterol, Ultra-Sensitive C-Reactive Protein, Thyroid Stimulating Hormone (TSH), Triglycerides (35).

After blood collection, the tubes were centrifuged and transported to two laboratories: The Laboratory of the Reference and Training Center for Sexually Transmitted Diseases and AIDS (CRT STD/AIDS), where blood glucose, lipid profile and Thyroid Hormones were analyzed, and the Laboratory of the University Hospital of the University of São Paulo (USP), where the Ultra-Sensitive PCR analysis was performed(35).

Glycemia, Total Cholesterol, HDL, VLDL and Triglycerides were measured by photometric analysis in the CRT STD/AIDS in a Konelab 60i equipment. LDL was calculated using the Fridewald formula (LDL = CT - (HDL + TG/5)). TSH was measured in the CRT STD/AIDS by the chemiluminescence method. And the us-CRP was measured at the Laboratory of the University Hospital of the University of São Paulo using the Nephelometry method(35).

Criteria for obesity

For classification purposes, male individuals with an abdominal circumference greater than 40 inches (101.6 cm) and female individuals with an abdominal circumference greater than 35 inches (88.6 cm) were considered obese (central obesity), according to the criteria of the NCP ATP III(38).

Diagnosis of metabolic syndrome

The criterion to be used for the diagnosis of metabolic syndrome was the NCP ATP III(38). According to this criterion, the subject must accumulate at least 3

of the following 5 criteria(38):

I. Abdominal circumference > 101.6cm for men or > 88.9cm for women

II. Fasting blood glucose 100mg/dl or medical prescription for the treatment of diabetes

III. Triglycerides > 150mg/dl or medical prescription for hypertriglyceridemia treatment

IV. HDL < 40mg/dl (Men) < 50mg/dl (Women) or prescription for the treatment of dyslipidemia.

V. BP > 130mmHg systolic, BP > 85mmHg diastolic or prescription for hypertension treatment

Psychiatric and other chronic conditions assessment

Psychiatric lay interview (CIDI)

Household respondents were assessed using the version developed for the World Mental Health Survey of the Composite International Diagnostic Interview of the World Health Organization (WMH) -CIDI; Kessler et AL, 2009)(33), which makes it possible to generate a diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition (DSM-IV) and the International Classification of Diseases - 10th Revision (ICD 10)(39). This version of the CIDI interview was translated and adapted into Brazilian Portuguese(34). This interview is subdivided into modules, in which the presence of nonspecific psychiatric symptoms, functioning and disability in the 30 days prior to the interview are evaluated, a screening module for self-reported chronic diseases such as chronic pain, diabetes, cardiovascular disease (hypertension, stroke and heart attack), respiratory disease, gastrointestinal disease, allergies, cancer, neurological diseases, thyroid disease, and other diseases (parasitic diseases, AIDS). The specific modules

for the so-called “core disorder” include symptoms of the disorders considered most common, according to the DSM-IV criteria: mood disorders (major depression, mania), anxiety disorders (panic disorder, specific phobia, social phobia, agoraphobia, generalized anxiety disorder, separation anxiety), substance use disorders (alcohol and other drugs), and impulse control deficit disorders (intermittent explosive disorder, attention deficit hyperactivity disorder, defiant disorder oppositional and conduct disorder). The CIDI questionnaire also included additional sections with detailed sociodemographic information.

Psychiatric Clinical Evaluation (SCID)

Psychiatric evaluation was performed by trained psychiatrists, using the Structured Clinical Interview for DSM disorders I, non-patient edition (SCID I – NP)(40). The SCID is a validated semi-structured psychiatric interview with high reliability(41–43) and is considered the gold standard of structured psychiatric assessment(44,45). It is an instrument created to assess Axis 1 psychiatric disorders, including(46):

- Delirium, dementias and other cognitive
- disorders Mental disorders secondary to clinical conditions
- Substance-related
- disorders Psychotic disorders and schizophrenia
- Mood
- disorders Anxiety
- disorders Somatoform disorders
- Disorders factitious
- Dissociative

- disorders Gender and sexual identity
- disorders Eating
- disorders Sleeping
- disorders Impulsive control
- disorders Adjustment disorders

Chronic Physical Illnesses

Chronic physical illnesses were assessed using a standard checklist, which asked: “Has a doctor or health care professional ever told you that you have or have had any of the following illnesses…”. The chronic diseases that were considered in this project were: arthritis, cardiovascular disorders (myocardial infarction, heart disease, stroke - excluding hypertension), chronic pain (chronic back or neck pain and other chronic pain), diabetes, migraines or frequent aches and pains headache, digestive disorders (stomach or intestinal ulcers) and respiratory disorders (seasonal allergy, asthma, COPD and emphysema).

Smoking

Two categories will be considered, based on self-reported tobacco use: current smokers and non-smokers (includes former smokers and those who have never smoked).

Socio-demographic variables

The following socio-demographic variables will be included in the analysis:

I. Sex: male, female;

II. Age: 18-34 years; 35-49 years; 50-64 years, 65 years and over;

III. Education, defined according to the Brazilian system, in basic (8 years or less), high school (9 -11 years) and higher education (12 years or more);

IV. Income: categorized into tertiles, due to non-linearity, such as low, low-medium, high-medium and high;

V. Marital status: single (never married), married and previously married (widowed/divorced);

VI. Occupation: work/study, retired, work from home, unemployed;

5. Analysis and Results

Exploratory Analysis

Prevalence

First, we list the prevalence of all the conditions analyzed in our sample, obtained with cross-tabulations. The complete tables of prevalence for the clinical samples can be found in Table 1, with information of both psychiatric disorders and physical illnesses. Scid assesses a present episode or the worst episode in the lifespan, so the figures could be interpreted as lifetime prevalences.

Table 1 - Disorder prevalences of the sample (n = 772) for the household and hospital samples, physical disorders included									
Disorder SCID (Clinical Sample)	**Prevalence**	**sd**	**Cases n = 771**	**Prev. ♀**	**sd**	**Cases n = 440**	**Prev ♂**	**sd**	**Cases n = 331**
Any Depression	39.30%	(35.85%-42.86%)	303	48.41%	(43.66%-53.19%)	213	27.19%	(22.54%-32.38%)	90
Any Anxiety	43.71%	(40.18%-47.30%)	337	50.91%	(46.14%-55.66%)	224	34.14%	(29.09%-39.56%)	113
Anxiety + Depression	25.03%	(22.04%-28.28%)	193	32.50%	(28.18%-37.13%)	143	15.11%	(11.52%-19.53%)	50
Major Depressive	35.15%	(31.80%-38.65%)	271	43.86%	(39.19%-48.65%)	193	23.56%	(19.17%-28.58%)	78
Minor Depressive	4.02%	(2.79%-5.73%)	31	4.32%	(2.69%-6.78%)	19	3.63%	(1.98%-6.42%)	12

To build the clinical sample, we oversampled positive cases. In this way, the prevalence of any mental disorder is higher than those in the community, with 64,3% of the sample having at least one disorder (70% of women and 58% of men). As expected, women have higher prevalence of any depressive and anxiety disorders, with the exception of social phobia which is slightly higher in the male group although not statistically significant (chi-squared p-value = 0.8519). In fact the only psychiatric disorders in our sample for which the prevalence for men is higher are substance related disorders (alcohol abuse and dependence and substance abuse and dependence). See Table S1 on page 60 for more information about the prevalence other mental disorders in the sample.

The lifetime prevalence of the physical disorders examined were higher in women than men for insomnia (42.2% vs 31.4%), migraine (41.3% vs 21.15%) and respiratory diseases (32.2% vs18.7%), to list the most prevalent in the sample. Cardiovascular problems were reported by 23% of the sample, with no sex differences.

CRP distribution in total sample

We verified that the CRP values did not follow the normal distribution. This verification was performed through the graphical analysis of the distributions

(figure 1 and figure 2), as well as the tests of normality Shapiro-Wilk (p-value < 2.2e-16) and Anderson-Darling (p-value < 2.2e- 16).

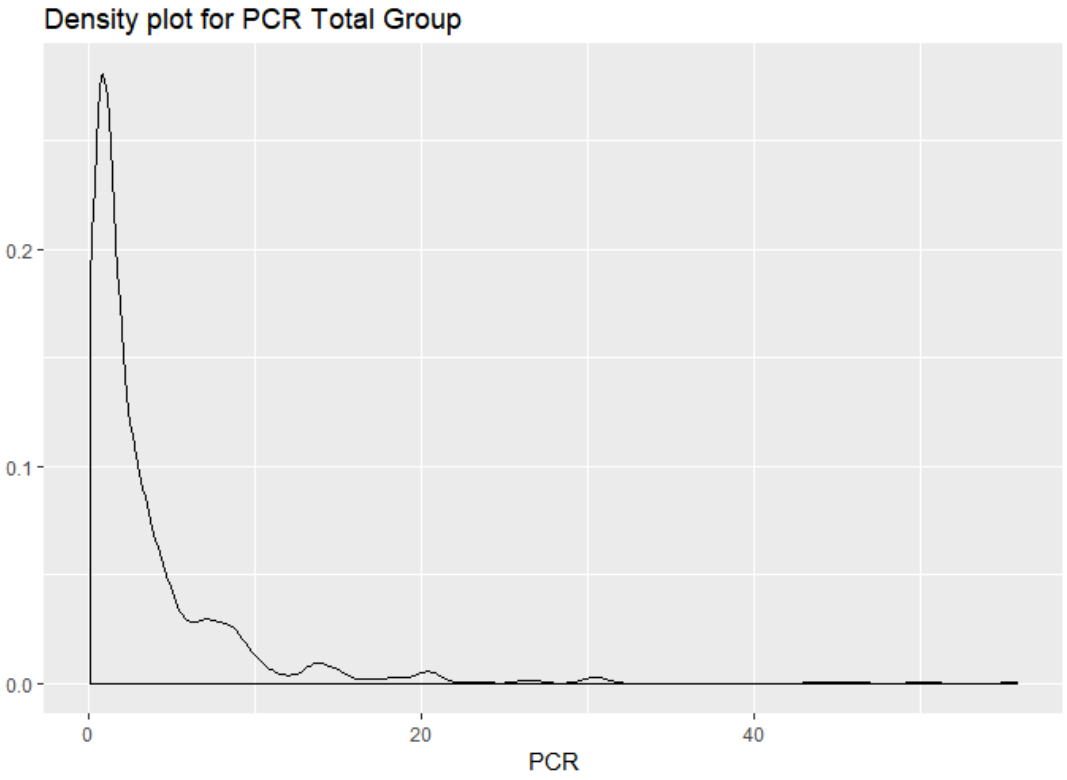

Figure 1 - CRP distribution for the total sample (770 respondents)

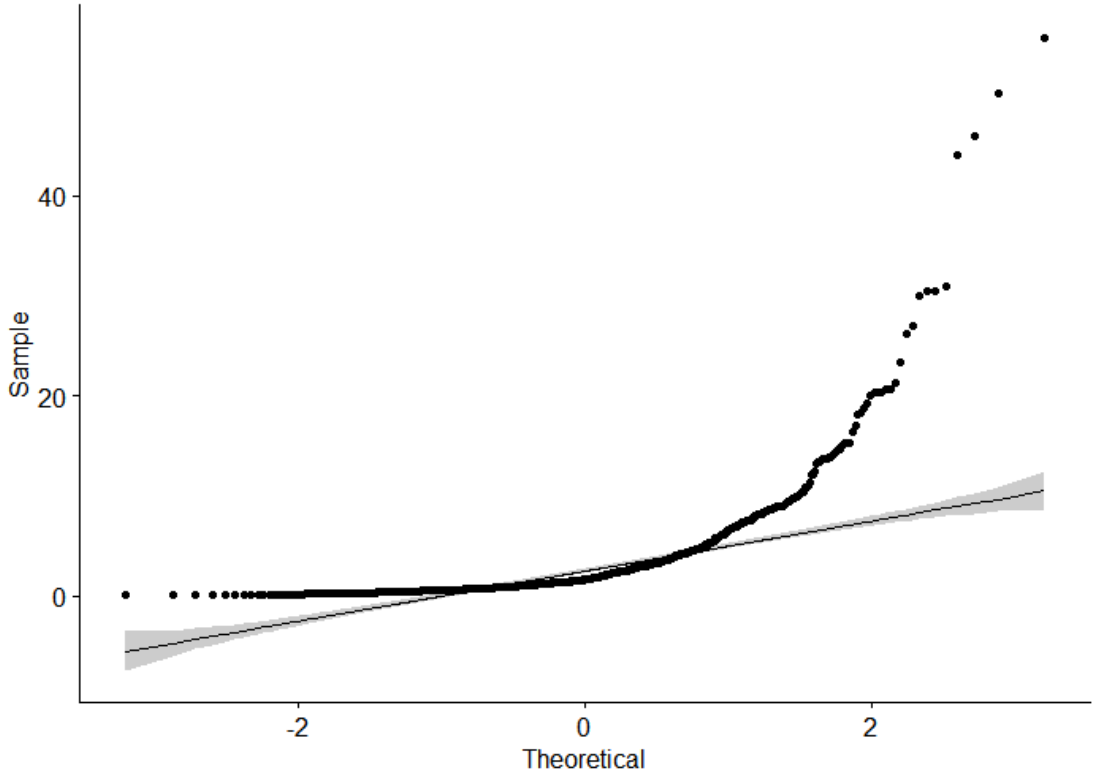

Figure 2 - QQ plot of the CRP distribution for the total sample

We also found that the CRP distributions of our sample are significantly different between the male and female groups (again verified visually and through the Shapiro-Wilk and Anderson-Darling tests).

As both PCR distributions are not normal, we verified the significance through the Wilcoxon-Mann-Whitney (p-value = 0.0001674), Kruskal-Wallis (p-value = 0.0001672) tests. In Table 2 we present the median and range for women and men, showing that the values for men are significantly higher than for women (median 2.14 vs 1.34).

Table 2 - CRP values by sex (mg/L)					
	Women		Men		
	Median	Range	Median	Range	p-value
CRP	1.34	(0.15-55.80)	2.14	(0.15-50.20)	0.0001672

Comparison of CRP medians between presence and absence of disorders

Due to the differences between sexes observed for CRP values and prevalences it was our understanding that an additional analysis considering the male and female groups separately should be carried out and that sex was an important covariate to be considered for all regression analysis..

We compared CRP medians between disorders by comparing CRP values between presence and absence of each disorder using the Kruskal-Wallis statistical test (p-value set at 0.05). Due to the large asymmetry of the distribution, we chose to report the median and range of the distribution instead of the means and standard deviations. The values obtained are described in Table S2 in Annex. We present in Table 3 only the CRP values of psychiatric disorders that showed significant differences between those with psychiatric disorders and controls. The highest levels are for dysthymia, bipolar disorder and binge eating, in the total sample. For women, the median are close to 4 mg/L particularly for bipolar and binge eating.

Table 3 - CRP values Cases Vs Controls only for psychiatric disorders with p-value below 0.05.

		Case		Control		
	Disorder	CRP Median	Range	CRP Median	Range	p-value
TOTAL	Dysthymia	3.42	(0.16-20.7)	1.59	(0.15-55.8)	0.027
	Bipolar I	3.05	(0.94-17)	1.59	(0.15-55.8)	0.016
	Social Phobia	1.45	(0.15-29.9)	1.69	(0.15-55.8)	0.05
	Binge Eating	2.97	(0.59-20.7)	1.59	(0.15-55.8)	0.01
	Tabagism	2.11	(0.16-55.8)	1.54	(0.15-50.2)	0.005
WOMEN ♀	Major Depressive	1.71	(0.15-20.7)	2.45	(0.15-50.2)	0.03
	Bipolar I	4.19	(1.89-17)	2.11	(0.15-50.2)	0.02
	Binge Eating	3.84	(0.59-20.7)	2.09	(0.15-50.2)	0.02
♂	Insomnia	1.565	(0.17-44)	1.22	(0.15-55.8)	0.02

We found higher CRP values in the presence of dysthymia (47), however we found it the relationship only for the total group, the relationship was not maintained when dividing the groups by sex. In addition, for Major Depression the median is 1.7, and again, no sex differences were found. We also found higher values for the presence of bipolar I disorder, as predicted in our model and corroborated by the literature(48,49) and the relationship remained significant for the analysis of the female group. However, we have in the sample only 45 cases of respondents in the bipolar spectrum. Significance remained in the female group also in binge eating, although high CRP values in this disorder may be associated with comorbid obesity(50). As expected, the smoking group had more extreme CRP values, with a range from 0.16 to 55.8mg/L(51–53). However, there was no difference in cases and controls by sex.

None of the anxiety disorders present differences in CRP levels between cases and controls, except for the total sample with social phobia, where CRP level was lower for cases than in controls, a result found in other studies by (54,55). Another unexpected finding was the lower CRP values for the female group with Major Depression in comparison to controls, an unexpected result by our model and our literature search(47,56–58).

We also verified if the presence of more than one psychiatric disorder increases CRP levels. As we found higher levels of CRP just for the female group, we did not proceed with further analyses. Finally, the male group only showed a significant difference for the symptom of insomnia, a result consistent with the literature (59–63).

It is important to emphasize that we did not find significant differences between levels of CRP in depression(2) and anxiety disorders(2), in the cases of comorbid anxiety and depression(61), and in those with more than one psychiatric disorders as we were expecting.

Metabolic syndrome

In this step of the analysis we aimed to investigate the association between metabolic syndrome and the presence of inflammation. We first defined its criteria. After deciding by the NCP ATP III(38) criteria, we calculated prevalences of the syndrome and for each one of its five criteria (obesity, insulin resistance, triglycerides dislipidemia, HDL dyslipidemia and high blood pressure, the presence of 3 or more of these characterizes metabolic syndrome. These results are found in table S3. We also defined an metabolic alteration criteria characterized by the presence of any of the metabolic syndrome criteria as to verify if this was enough to define inflammatory states and therefore risk groups.

Our sample presented with extremely high prevalences of both metabolic syndrome (35.61% for the whole sample, 31.90% for females and 40.58% for males) and all of its criteria with 90.36% of the whole sample (90.53% for females and 90.13% for males) having at least one of the five metabolic syndrome criteria present.

Metabolic syndrome is an inflammatory condition(64), and as such we compared the CRP levels of the whole syndrome and in any of its criteria. The results of this analysis are presented in table S4, and as is expected, both the condition and all of its components presented significantly higher levels of CRP than controls for all groups (whole sample, male and female).

In order to verify inflammatory conditions as possible risk groups and its effect sizes we calculated the odds ratios between exposure to inflammatory conditions (defined as obesity(65–71), triglyceride(58,72–74), HDL dyslipidemia(9,72,74–76), Hypertension(77–82), metabolic disorder and metabolic syndrome(54,75,83–87)) and the outcomes any depression, any anxiety and comorbid anxiety and depression. The odds ratios obtained are shown in Table S4 in the annex. All 95% confidence intervals calculated for all calculated odds ratios pass through the unit value, and therefore cannot be considered significant.

In conclusion, although metabolic syndrome is inflammatory it was not a risk factor for depression, anxiety, or depression with anxiety in total sample and by sex.

Analysis of comorbidity and effect size

For a more specific effect size analysis we performed an analysis of variance with omega squared calculation (the option for the omega square is due to the fact that an effect size measure is less biased than the eta squared or the partial eta squared(88,89) and have a similar interpretation). However, the

absence of a normal distribution in our PCR distribution excluded this possibility. We decided to perform the transformation of the PCR variable through its natural logarithm. This allowed us to obtain a distribution closer to the desirable normal distribution (figures 3 and 4).

For the purposes of the analysis, we consider that although the distribution deviates considerably from the normal (Shapiro-Wilk p-value = 0.001352, p-value = 0.00467), this approximation could be used.

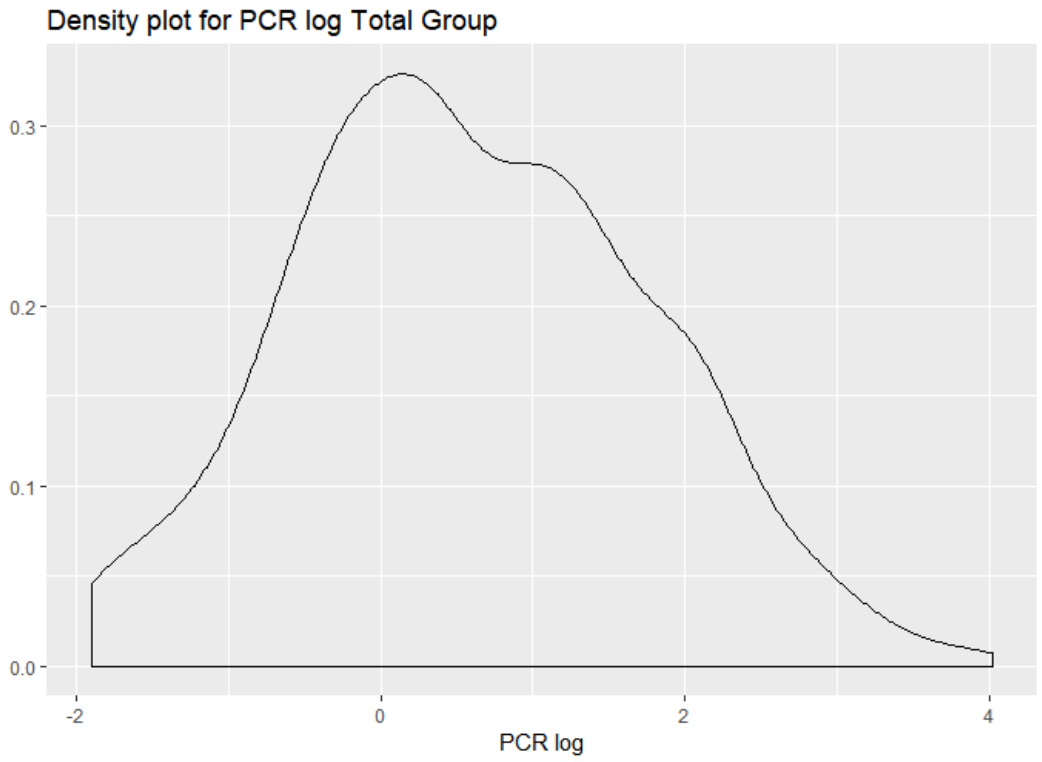

Figure 3 - Distribution of the natural logarithm of PCR for the total sample.

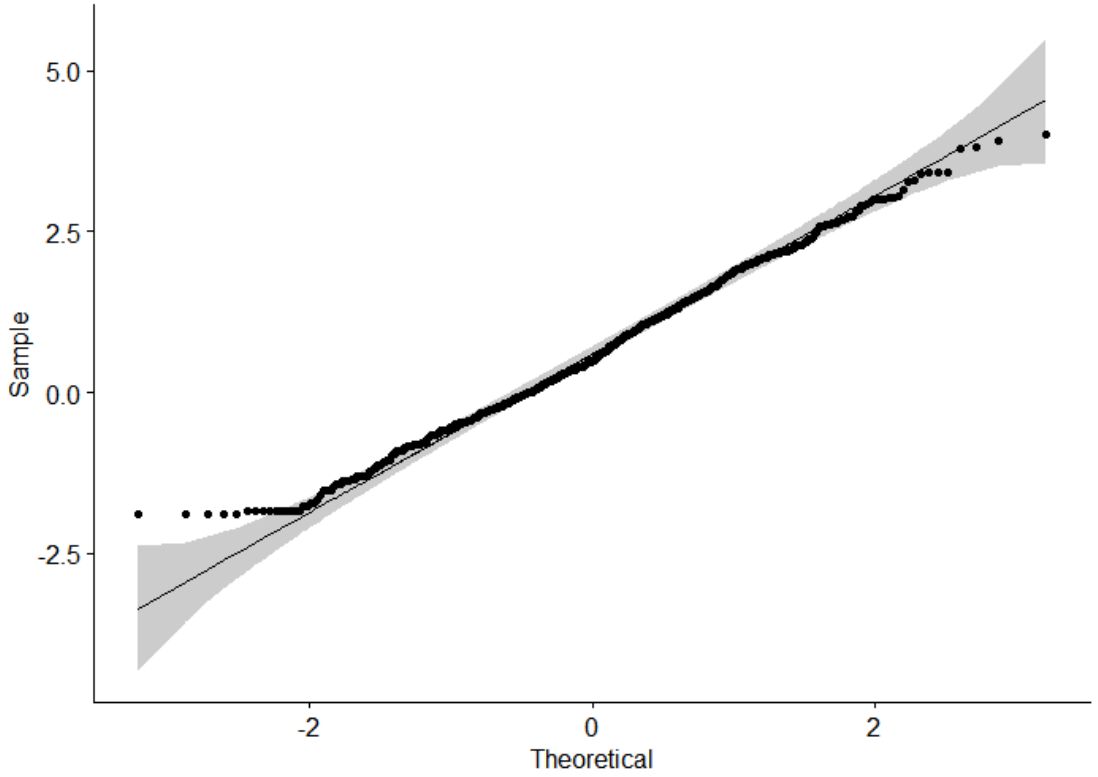

Figure 4 - Quantile - quantile plot of the natural logarithm of PCR for the total sample.

With this approximation, we performed an ANOVA analysis considering the only variables that showed significant differences in the previous analyses, any depression, any anxiety, anxiety depression comorbidity, sociodemographic variables, metabolic alteration (HDL dyslipidemia and obesity) variables and smoking. The results are compiled for each group, with the smoking covariates and both metabolic variables. The results are compiled in annex (Table S5) and we present below the data of the variables that showed significant differences (Table 4). The description of the sociodemographic variables can be found in Table S6.

Table 4 - Variance and Size effect Analysis			
Anova Variables Total Group	F value	p-value	omega²
Sex	4,307	0.03874 *	0.008
Age	9,627	0.00209 **	0.021
Occupation	6,471	0.01143 *	0,013
Obesity	53,607	1.96e- 12 ***	0.126
Dyslipidemia HDL	5.988	0.01494 *	0.012
Anova Variables Female Group	F value	p-value	omega²
Age	6.214	0.0135 *	0.019
Occupation	5.513	0.0199 *	0.016
Obesity	48.089	6.27e-11 ***	0.172
Any Depression	6.731	0.0102 *	0.021
Binge Eating	4.021	0.0464 *	0.011
Anova Variables Male Group			
Obesity	9,918	0.00209 **	0.060
Dyslipidemia HDL	7.874	0.00590 **	0.046

*Indicates values below the significance cut-off

We note that by this analysis only the depression and binge eating disorders in the female group remained significant and obesity was the only variable to

show significance in all groups. Of note, it is expected that binge eating may influence obesity(90). Depression and binge eating had modest effect sizes while obesity had a large effect size in the total and female groups and moderate in the male group. Obesity was the greatest predictor of CRP variation for all groups.

It is also important to emphasize that the interpretation of the CRP natural logarithm data, although present in the literature(63,91–94), is not as intuitive as that of the original value and is not a data frequently used in clinical practice.

6. Discussion

In this step of the analysis, we aimed to explore in the data available, how inflammation, measured by CRP and metabolic syndrome are associated with depression, anxiety and comorbid anxiety and depression. We did not find any relevant result regarding our hypothesis.

In our analyzes we found correlations previously described in the literature endorsing the possibility of using CRP as a possible marker of interest for some psychiatric disorders. However, several correlations between this marker and psychiatric disorders well described in the scientific literature were not reproduced in our analyses.

In view of these findings, we decided to focus on the subtypes of depression, using data driven approaches, which can be applied with the hope of helping navigate this “mixed bag” that is depression (27). One of such methods is latent class analysis (LCA)(28). LCA is a statistical procedure that identifies qualitatively different subgroups within a sample that share certain common characteristics(29). These subgroups are referred to as latent classes or latent groups. In order to detect these latent classes, this technique uses study participants’ responses to categorical indicator variables. Technically speaking, LCA is a method to detect latent (unobserved) heterogeneity in

samples(29). The assumption underlying LCA is that the observed patterns in the scores can be explained by membership to these latent classes(30). The method has been previously used in samples of depressed individuals, with some studies being able to find atypical and non-atypical subtypes (20,31–34). None of these studies examined the association of inflammatory markers with depressive subtypes obtained by LCA.

Our data driven approach with the latent class analysis method was successful and resulted in the paper “**Inflammation, but not metabolic parameters, differs across subtypes of depression. Results from the São Paulo Megacity Mental Health Survey”,** which has been submitted for evaluation in the Psychological Medicine medical journal.

The complete final version of the paper submitted is on page XXX

7. Supplementary Tables

Table S1 - Disorder prevalences of the sample (n = 772) for the household and hospital samples, physical disorders included

Disorder SCID (Clinical Sample)	Prevalence	sd	N=772	Prevalence ♀	sd	n = 440	Prevalence ♂	sd	n = 331
Any Depression	39.30%	(35.85%-42.86%)	303	48.41%	(43.66%-53.19%)	213	27.19%	(22.54%-32.38%)	90
Any Anxiety	43.71%	(40.18%-47.30%)	337	50.91%	(46.14%-55.66%)	224	34.14%	(29.09%-39.56%)	113
Anxiety + Depression	25.03%	(22.04%-28.28%)	193	32.50%	(28.18%-37.13%)	143	15.11%	(11.52%-19.53%)	50
Major Depressive	35.15%	(31.80%-38.65%)	271	43.86%	(39.19%-48.65%)	193	23.56%	(19.17%-28.58%)	78
Minor Depressive	4.02%	(2.79%-5.73%)	31	4.32%	(2.69%-6.78%)	19	3.63%	(1.98%-6.42%)	12
Dysthymia	3.24%	(2.15%-4.82%)	25	4.77%	(3.05%-7.32%)	21	1.21%	(0.39%-3.28%)	4
Bipolar I	1.95%	(1.13%-3.26%)	15	2.27%	(1.16%-4.28%)	10	1.51%	(0.56%-3.69%)	5
Bipolar II	2.59%	(1.63%-4.05%)	20	2.73%	(1.48%-4.85%)	12	2.42%	(1.13%-4.89%)	8
Other Bipolar	1.30%	(0.66%-2.45%)	10	1.36%	(0.56%-3.10%)	6	1.21%	(0.39%-3.28%)	4
Any Affective	40.21%	(36.74%-43.77%)	310	49.32%	(44.56%-54.09%)	217	28.10%	(23.39%-33.33%)	93
Alcohol Abuse	10.25%	(8.24%-12.66%)	79	3.86%	(2.34%-6.24%)	17	18.73%	(14.76%-23.45%)	62
Alcohol Dependence	7.52%	(5.81%-9.67%)	58	3.41%	(1.99%-5.69%)	15	12.99%	(9.66%-17.21%)	43
Substance Abuse	2.33%	(1.43%-3.74%)	18	0.45%	(0.08%-1.82%)	2	4.83%	(2.88%-7.89%)	16
Substance Dependance	3.37%	(2.26%-4.97%)	26	1.59%	(0.70%-3.40%)	7	5.74%	(3.59%-8.97%)	19
Any Substance	13.88%	(11.56%-16.57%)	107	6.14%	(4.16%-8.91%)	27	24.17%	(19.73%-29.22%)	80
Panic	6.74%	(5.12%-8.81%)	52	8.86%	(6.45%-12.02%)	39	3.93%	(2.20%-6.79%)	13

Agoraphobia	8.82%	(6.96%-11.10%)	68	10.45%	(7.83%-13.79%)	46	6.65%	(4.31%-10.03%)	22
Social Phobia	17.38%	(14.81%-20.28%)	134	17.05%	(13.72%-20.96%)	75	17.82%	(13.94%-22.47%)	59
Specific Phobia	20.36%	(17.61%-23.42%)	157	26.82%	(22.79%-31.26%)	118	11.78%	(8.61%-15.87%)	39
Post-Traumatic Stress	5.71%	(4.22%-7.65%)	44	6.59%	(4.53%-9.44%)	29	4.53%	(2.65%-7.52%)	15
Generalized Anxiety	11.93%	(9.77%-14.48%)	92	15.68%	(12.48%-19.50%)	69	6.95%	(4.55%-10.39%)	23
Disorder SCID (Clinical Sample)	**Prevalence**	**sd**	**N= 771**	**Prevalence ♀**	**sd**	**n = 440**	**Prevalence ♂**	**sd**	**n = 331**
TOC	4.41%	(3.12%-6.17%)	34	5.45%	(3.60%-8.12%)	24	3.02%	(1.54%-5.66%)	10
Any anxiety	43.71%	(40.18%-47.30%)	337	50.91%	(46.14%-55.66%)	224	34.14%	(29.09%-39.56%)	113
Anorexia	0.13%	(0.01%-0.84%)	1	0.23%	(0.01%-1.46%)	1	0.00%	(0.00%-0.00%)	0
Bulimia	0.65%	(0.24%-1.60%)	5	1.14%	(0.42%-2.79%)	5	0.00%	(0.00%-0.00%)	0
Binge eating	3.37%	(2.26%-4.97%)	26	4.09%	(2.51%-6.51%)	18	2.42%	(1.13%-4.89%)	8
Eating disorders	4.02%	(2.79%-5.73%)	31	5.23%	(3.42%-7.85%)	23	2.42%	(1.13%-4.89%)	8
Any disorder	64.33%	(60.82%-67.70%)	496	69.32%	(64.74%-73.55%)	305	57.70%	(52.17%-63.05%)	191

Physical Disorders	**Prevalence**	**sd**	**N = 772**	**Prevalence ♀**	**sd**	**n = 441**	**Prevalence ♂**	**sd**	**n = 331**
Cardiovascular	22.93%	(20.04%-26.09%)	177	23.81%	(19.97%-28.12%)	105	21.75%	(17.51%-26.67%)	72
Neurological	1.68%	(0.94%-2.94%)	13	1.81%	(0.85%-3.69%)	8	1.51%	(0.56%-3.69%)	5
Cancer	0.65%	(0.24%-1.60%)	5	0.91%	(0.29%-2.47%)	4	0.30%	(0.02%-1.94%)	1
Diabetes	4.66%	(3.33%-6.46%)	36	4.08%	(2.51%-6.50%)	18	5.44%	(3.35%-8.61%)	18
Digestive	4.53%	(3.22%-6.31%)	35	5.67%	(3.78%-8.37%)	25	3.02%	(1.54%-5.66%)	10
Respiratory	26.42%	(23.37%-29.71%)	204	32.20%	(27.90%-36.81%)	142	18.73%	(14.76%-23.45%)	62
Arthritis	8.42%	(6.60%-10.66%)	65	11.34%	(8.61%-14.76%)	50	4.53%	(2.65%-7.52%)	15
Insomnia	37.56%	(34.15%-41.10%)	290	42.18%	(37.54%-46.95%)	186	31.42%	(26.51%-36.77%)	104
Migraine	32.64%	(29.37%-36.10%)	252	41.27%	(36.66%-46.04%)	182	21.15%	(16.95%-26.03%)	70

Table S2 - Median CRP, range and p-value for Kruskal Wallis test

Total Group	Case		Control		
SCID	Median CRP	range	Median CRP	range	p-value
Any Depression	1.64	(0.15 - 50.20)	1.59	(0.15 - 55.80)	0.63930
Any Anxiety	1.64	(0.15 - 44.00)	1.59	(0.15 - 55.80)	0.91150
Anxiety + Depression	1.77	(0.15 - 20.70)	1.57	(0.15 - 55.80)	0.58940
Major Depression	1.64	(0.15 - 21.30)	0.15	(1.6 - 55.80)	0.61270
Minor Depression	1.76	(0.16 - 50.20)	1.63	(0.15 - 55.80)	0.76360
Dysthymia	3.42	(0.16 - 20.70)	1.59	(0.15 - 55.80)	0.02665*
Bipolar Disorder Type I	3.05	(0.94 - 17.00)	1.59	(0.15 - 55.80)	0.01578*
Bipolar Disorder Type II	2.165	(0.27 - 9.02)	1.625	(0.15 - 55.80)	0.85200
Bipolar Disorder Others	1.14	(0.24 - 20.40)	1.63	(0.15 - 55.80)	0.42200
Affective Disorders	1.64	(0.15 - 50.20)	1.595	(0.15 - 55.80)	0.55740
Alcohol Abuse	1.62	(0.16 - 44.00)	1.63	(0.15 - 55.80)	0.94630
Alcohol Dependance	1.43	(0.16 - 44.00)	1.64	(0.15 - 55.80)	0.19990
Substance Abuse	1.55	(0.24 - 5.81)	1.63	(0.15 - 55.80)	0.57410
Substance Dependance	1.365	(0.24 - 9.27)	1.64	(0.15 - 55.80)	0.11980
Any Substance	1.635	(0.16 - 44.00)	1.625	(0.15 - 55.80)	0.99830
Panic	1.46	(0.22 - 20.40)	1.635	(0.15 - 55.80)	0.73770
Agoraphobia	1.8	(0.16 - 44.00)	1.615	(0.15 - 55.80)	0.80520
Social Phobia	1.45	(0.15 - 29.90)	1.685	(0.15 - 55.80)	0.04893*
Specific Phobia	1.61	(0.15 - 20.70)	1.64	(0.15 - 55.80)	0.37090
PTSD	2.295	(0.15 - 13.40)	1.595	(0.15 - 55.80)	0.27190
GAD	2.24	(0.16 - 20.40)	1.595	(0.15 - 55.80)	0.22370

OCD	1.505	(0.15 - 20.40)	1.635	(0.15 - 55.80)	0.71750
SCID	Median CRP	range	Median CRP	range	p-value
Anxiety	1.64	(0.15 - 44.00)	1.59	(0.15 - 55.80)	0.94220
Bulimia	0.52	(0.25 - 7.71)	1.63	(0.15 - 55.80)	0.29950
Binge	2.97	(0.59 - 20.70)	1.59	(0.15 - 55.80)	0.009995*
Eating disorders	2.935	(0.25 - 20.70)	1.595	(0.15 - 55.80)	0.05375
Adjustment Disorder	1.675	(0.16 - 11.30)	1.625	(0.15 - 55.80)	0.87420
Multiple Disorders	1.61	(0.15 - 50.20)	1.72	(0.15 - 55.80)	0.28130
Lifestyle	Median CRP	range	Median CRP	range	p-value
Smoking	2.115	(0.16 - 55.80)	1.54	(0.15 - 50.20)	0.005184*
Insomnia	1.86	(0.15 - 50.20)	1.555	(0.15 - 55.80)	0.09097
Physical Disorders	Median CRP	range	Median CRP	range	p-value
Cardiovascular	2.71	(0.15 - 50.20)	1.435	(0.15 - 55.80)	5.01E-08*
Neurological	1.81	(0.15 - 44.00)	1.63	(0.15 - 55.80)	0.95530
Cancer	8.45	(1.13 - 20.40)	1.625	(0.15 - 55.80)	0.03129*
Diabetes	3.235	(0.39 - 46.00)	1.58	(0.15 - 55.80)	0.0003911*
Digestive	2.49	(0.31 - 30.50)	1.605	(0.15 - 55.80)	0.03657*
Respiratory	1.72	(0.15 - 30.50)	1.605	(0.15 - 55.80)	0.55360
Arthritis	2.06	(0.4 - 46.00)	1.605	(0.15 - 55.80)	0.05540
Metabolic Syndrome and Criteria	Median CRP	range	Median CRP	range	p-value

Obesity	2.31	(0.15 - 50.20)	0.855	(0.15 - 55.80)	2.20E-16*
Insulin Resistance	2.975	(0.16 - 46.00)	1.48	(0.15 - 55.80)	1.47E-05*
Dyslipidemia TGC	2.31	(0.17 - 55.80)	1.47	(0.15 - 50.20)	6.84E-06*
Dyslipidemia HDL	2.26	(0.15 - 55.80)	1.405	(0.15 - 44.00)	5.73E-07*
Hypertension	2.12	(0.15 - 50.20)	1.41	(0.15 - 55.80)	5.89E-07*
Metabolic Alteration	1.9	(0.15 - 55.80)	0.72	(0.15 - 30.50)	6.45E-09*
Metabolic Syndrome	2.565	(0.17 - 50.20)	1.22	(0.15 - 55.80)	9.18E-14*

female Group ♀					
SCID ♀	Median CRP	range	Median CRP	range	p-value

Any Depression	1.71	(0.15 - 50.20)	2.495	(0.15 - 46.00)	0.03636*
Any Anxiety	1.74	(0.15 - 29.90)	2.61	(0.15 - 50.20)	0.06433
Anxiety + Depression	1.76	(0.15 - 20.70)	2.345	(0.15 - 50.20)	0.19810
Major Depression	1.71	(0.15 - 20.70)	2.455	(0.15 - 50.20)	0.0331*
Minor Depression	1.76	(0.25 - 50.20)	2.155	(0.15 - 46.00)	0.72790
Dysthymia	3	(0.16 - 20.70)	2.115	(0.15 - 50.20)	0.16530
Bipolar Disorder Type I	4.19	(1.89 - 17.00)	2.11	(0.15 - 50.20)	0.02126*
Bipolar Disorder Type II	2.785	(0.57 - 9.02)	2.12	(0.15 - 50.20)	0.64480
Bipolar Disorder Others	2.015	(0.24 - 20.40)	2.13	(0.15 - 50.20)	0.67720
Affective Disorders	1.71	(0.15 - 50.20)	2.455	(0.15 - 46.00)	0.04476*
Alcohol Abuse	2.61	(0.16 - 10.40)	2.12	(0.15 - 50.20)	0.95670
Alcohol Dependance	1.89	(0.16 - 8.74)	2.155	(0.15 - 50.20)	0.39910
Substance Abuse	2.61	(0.16 - 10.40)	2.12	(0.15 - 50.20)	0.99770
Substance Dependance	1.61	(0.24 - 9.27)	2.155	(0.15 - 50.20)	0.75670
Any Substance	2.61	(0.16 - 10.40)	2.12	(0.15 - 50.20)	0.50930

SCID ♀	Median CRP	range	Median CRP	range	p-value
Panic	1.43	(0.22 - 20.40)	2.245	(0.15 - 50.20)	0.36670

Agoraphobia	1.91	(0.16 - 20.30)	2.16	(0.15 - 50.20)	0.98960
Social Phobia	1.6	(0.15 - 29.90)	2.25	(0.15 - 50.20)	0.06915
Specific Phobia	1.635	(0.15 - 20.70)	2.32	(0.15 - 50.20)	0.61930
PTSD	2.55	(0.15 - 13.40)	2.12	(0.15 - 50.20)	0.66120
GAD	2.485	(0.16 - 20.30)	2.06	(0.15 - 50.20)	0.62370
OCD	1.33	(0.15 - 20.40)	2.24	(0.15 - 50.20)	0.09875
Anxiety	1.74	(0.15 - 29.90)	2.61	(0.15 - 50.20)	0.07416
Bulimia	0.52	(0.25 - 7.71)	2.14	(0.15 - 50.20)	0.22850
Binge	3.845	(0.59 - 20.70)	2.09	(0.15 - 50.20)	0.02121*
Eating disorders	3	(0.25 - 20.70)	2.1	(0.15 - 50.20)	0.13950
Adjustment Disorder	2.55	(0.16 - 11.30)	2.125	(0.15 - 50.20)	0.82320
Multiple Disorders	3.661	(0.15 - 50.20)	3.18	(0.15 - 46.00)	0.01247*

Lifestyle ♀	Median CRP	range	Median CRP	range	p-value
fumante	2.27	(0.16 - 30.50)	2.12	(0.15 - 50.20)	0.24290
insonia	1.93	(0.15 - 50.20)	2.16	(0.15 - 46.00)	0.81870

Physical Disorders ♀	Median CRP	range	Median CRP	range	p-value
Cardiovascular	3	(0.15 - 50.20)	1.74	(0.15 - 30.90)	0.000046*
Neurological	2.23	(0.15 - 17.00)	2.14	(0.15 - 50.20)	0.74790
Cancer	8.515	(4.04 - 20.40)	2.12	(0.15 - 50.20)	0.01368*
Diabetes	6.47	(0.39 - 46.00)	2.075	(0.15 - 50.20)	0.003132*

Physical Disorders ♀	Median CRP	range	Median CRP	range	p-value
Digestive	1.89	(0.31 - 30.50)	2.15	(0.15 - 50.20)	0.73510

Respiratory	2.12	(0.15 - 30.50)	2.16	(0.15 - 50.20)	0.94980
Arthritis	2.195	(0.4 - 46.00)	2.14	(0.15 - 50.20)	0.22600

Metabolic Syndrome and Criteria ♀	Median CRP	range	Median CRP	range	p-value
Obesity	2.71	(0.15 - 50.20)	0.87	(0.15 - 30.50)	1.52E-11*
Insulin Resistance	4.35	(0.16 - 46.00)	1.87	(0.15 - 50.20)	3.51E-04*
Dyslipidemia TGC	3.42	(0.22 - 29.90)	1.88	(0.15 - 50.20)	8.31E-04*
Dyslipidemia HDL	2.55	(0.15 - 50.20)	1.72	(0.15 - 30.50)	1.89E-03*
Hypertension	2.48	(0.15 - 50.20)	1.86	(0.15 - 30.90)	1.46E-03*
Metabolic Alteration	2.395	(0.15 - 50.20)	0.845	(0.16 - 30.50)	6.08E-05*
Metabolic Syndrome	3.265	(0.27 - 50.20)	1.63	(0.15 - 30.90)	2.14E-07*

Male ♂					
SCID ♂	Median CRP	range	Median CRP	range	p-value
Any Depression	1.5	(0.16 - 21.30)	1.3	(0.15 - 55.80)	0.57590
Any Anxiety	1.54	(0.15 - 44.00)	1.26	(0.16 - 55.80)	0.25360
Anxiety + Depression	1.955	(0.17 - 20.40)	1.27	(0.15 - 55.80)	0.09759
Major Depression	1.47	(0.17 - 21.30)	1.32	(0.15 - 55.80)	0.54120
Minor Depression	1.755	(0.16 - 5.26)	1.32	(0.15 - 55.80)	0.95510
Dysthymia	5.055	(0.81 - 6.35)	1.32	(0.15 - 55.80)	0.12310
Bipolar Disorder Type I	2.06	(0.94 - 4.46)	1.32	(0.15 - 55.80)	0.41760
Bipolar Disorder Type II	1.41	(0.27 - 3.58)	1.34	(0.15 - 55.80)	0.78240

SCID ♂	Median CRP	range	Median CRP	range	p-value
Bipolar Disorder Others	0.965	(0.24 - 4.03)	1.38	(0.15 - 55.80)	0.42500

Affective Disorders	1.48	(0.16 - 21.30)	1.31	(0.15 - 55.80)	0.80550
Alcohol Abuse	1.46	(0.16 - 44.00)	1.295	(0.15 - 55.80)	0.28550
Alcohol Dependance	1.24	(0.16 - 44.00)	1.39	(0.15 - 55.80)	0.76550
Substance Abuse	1.55	(0.24 - 5.81)	1.32	(0.15 - 55.80)	0.99780
Substance Dependance	1.18	(0.24 - 4.68)	1.39	(0.15 - 55.80)	0.24050
Any Substance	1.46	(0.16 - 44.00)	1.295	(0.15 - 55.80)	0.49880
Panic	1.97	(0.35 - 19.30)	1.33	(0.15 - 55.80)	0.80140
Agoraphobia	1.4	(0.32 - 44.00)	1.34	(0.15 - 55.80)	0.90650
Social Phobia	1.375	(0.15 - 14.70)	1.34	(0.16 - 55.80)	0.38620
Specific Phobia	1.43	(0.46 - 20.40)	1.33	(0.15 - 55.80)	0.27770
PTSD	2.07	(0.61 - 8.66)	1.32	(0.15 - 55.80)	0.27620
GAD	1.5	(0.17 - 20.40)	1.32	(0.15 - 55.80)	0.66100
OCD	2.825	(0.76 - 10.40)	1.32	(0.15 - 55.80)	0.10190
Binge	2.06	(1.01 - 6.81)	1.33	(0.15 - 55.80)	0.27490
Eating disorders	2.06	(1.01 - 6.81)	1.33	(0.15 - 55.80)	0.27490
Adjustment Disorder	0.91	(0.58 - 4.79)	1.36	(0.15 - 55.80)	0.67120
Multiple Disorders	1.46	(0.15 - 44.00)	1.235	(0.16 - 55.80)	0.69290

SCID ♂	Median CRP	range	Median CRP	range	p-value
fumante	1.975	(0.16 - 55.80)	1.19	(0.15 - 21.30)	0.001402*
insonia	1.565	(0.17 - 44.00)	1.22	(0.15 - 55.80)	0.01984*

Physical Disorders ♂	Median CRP	range	Median CRP	range	p-value
Cardiovascular	2.035	(0.27 - 44.00)	1.19	(0.15 - 55.80)	2.93E-04*

Neurological	1.21	(0.24 - 44.00)	1.36	(0.15 - 55.80)	0.81050
Cancer	-	- - -	-	- - -	-
Diabetes	3.015	(0.43 - 6.81)	1.26	(0.15 - 55.80)	0.00960*
Digestive	5.735	(0.81 - 9.03)	1.28	(0.15 - 55.80)	0.00287*
Respiratory	1.345	(0.15 - 21.30)	1.34	(0.16 - 55.80)	0.82360
Arthritis	1.59	(0.45 - 8.90)	1.3	(0.15 - 55.80)	0.36120

Metabolic Syndrome and Criteria ♂	Median CRP	range	Median CRP	range	p-value
Obesity	1.835	(0.2 - 44.00)	0.83	(0.15 - 55.80)	5.74E-11*
Insulin Resistance	1.59	(0.17 - 15.00)	1.25	(0.15 - 44.00)	1.29E-04*
Dyslipidemia TGC	1.2	(0.16 - 9.03)	1.38	(0.15 - 55.80)	8.31E-04*
Dyslipidemia HDL	1.88	(0.16 - 55.80)	1.06	(0.15 - 44.00)	1.04E-04*
Hypertension	1.185	(0.16 - 18.20)	1.43	(0.15 - 55.80)	1.46E-03*
Metabolic Alteration	1.52	(0.16 - 55.80)	0.66	(0.15 - 20.40)	9.51E-06*
Metabolic Syndrome	1.09	(0.16 - 18.20)	1.39	(0.15 - 55.80)	2.14E-07*

*p-value below 0.05

Table S3 - Metabolic disregulation

Metabolic Syndrome and Criteria	Prevalence	sd	Cases	Total n	Prevalence ♀	sd	Cases	Total n	Prevalence ♂	sd	Cases	Total n
Obesity	69.01%	(65.59%-72.24%)	530	768	76.14%	(71.82%-79.99%)	335	440	59.45%	(53.90%-64.77%)	195	328
Insulin Resistance	19.97%	(16.97%-23.33%)	127	636	14.71%	(11.33%-18.85%)	54	367	27.14%	(22.00%-32.94%)	73	269
Dyslipidemia TGC	26.01%	(22.97%-29.29%)	200	769	19.09%	(15.59%-23.15%)	84	440	35.26%	(30.15%-40.72%)	116	329
Dyslipidemia HDL	48.95%	(45.34%-52.56%)	372	760	53.64%	(48.85%-58.36%)	236	440	42.50%	(37.05%-48.13%)	136	320
High Blood Pressure	41.95%	(38.45%-45.53%)	323	770	35.60%	(31.16%-40.29%)	157	441	50.46%	(44.93%-55.97%)	166	329
Any Criteria	90.36%	(87.96%-92.34%)	675	747	90.53%	(87.28%-93.04%)	392	433	90.13%	(86.15%-93.09%)	283	314
Metabolic Syndrome	35.61%	(32.16%-39.21%)	261	733	31.90%	(27.51%-36.63%)	134	420	40.58%	(35.13%-46.26%)	127	313

Table S4 - Odds Ratio inflammatory conditions as exposition depression and anxiety as outcomes

		Total Group			Females			Males		
Exposition	Outcome	OR	95% CI		OR	95% CI		OR	95% CI	
Obesity	Any Depression	1.14	0.83	1.56	1.16	0.75	1.80	0.75	0.46	1.23
	Any Anxiety	0.96	0.70	1.30	0.89	0.57	1.37	0.77	0.49	1.23
	Depression + Anxiety	1.03	0.72	1.47	0.90	0.57	1.44	0.77	0.42	1.41
Insulin R	Any Depression	0.91	0.61	1.36	1.18	0.66	2.11	0.97	0.53	1.80
	Any Anxiety	0.97	0.65	1.44	0.98	0.55	1.75	1.24	0.70	2.20
	Depression + Anxiety	1.10	0.70	1.74	1.36	0.74	2.50	1.29	0.61	2.71
Dyslipidemia TGC	Any Depression	0.83	0.59	1.15	1.14	0.71	1.84	0.85	0.51	1.42
	Any Anxiety	0.94	0.68	1.30	1.15	0.71	1.85	1.03	0.64	1.66
	Depression + Anxiety	0.93	0.64	1.35	1.19	0.72	1.96	1.08	0.57	2.03
Dyslipidemia HDL	Any Depression	0.95	0.71	1.27	0.71	0.48	1.03	1.19	0.73	1.94
	Any Anxiety	0.93	0.70	1.24	0.87	0.60	1.26	0.86	0.54	1.38
	Depression + Anxiety	0.96	0.69	1.33	0.82	0.55	1.22	0.98	0.53	1.80
Hypertension	Any Depression	0.84	0.62	1.13	0.89	0.60	1.31	1.07	0.66	1.74
	Any Anxiety	0.94	0.71	1.26	1.13	0.76	1.67	0.95	0.60	1.50
	Depression + Anxiety	0.95	0.68	1.33	1.00	0.66	1.00	1.37	0.74	2.53

Metalbolic Alt.	Any Depression	0.97	0.59	1.60	0.89	0.47	1.70	1.09	0.47	2.55
	Any Anxiety	1.01	0.62	1.65	1.11	0.58	2.11	0.86	0.40	1.87
	Depression + Anxiety	0.93	0.53	1.61	1.11	0.58	2.11	1.18	0.39	3.53
Met. Syndrome	Any Depression	0.93	0.78	1.61	0.97	0.64	1.47	0.85	0.51	1.43
	Any Anxiety	1.07	0.79	1.46	1.17	0.77	1.76	1.12	0.70	1.81
	Depression + Anxiety	1.01	0.71	1.43	1.13	0.73	1.75	1.04	0.55	1.96

Table S5 - Variance and Size effect Analysis			
Anova Variables Total Group	F value	p-value	omega²
Sex	4.307	0.03874 *	0.008
Age	9.627	0.00209 **	0.021
Education	0.017	0.89493	-0.002
Income	0.087	0.7677	-0.002
Marital Status	0.133	0.71522	-0.002
Occupation	6.471	0.01143 *	0.013
Tabagism	0.005	0.94221	-0.002
Obesity	53.607	1.96e-12 ***	0.126
Insulin Resistance	2.978	0.08537 .	0.005
Dyslipidemia TGC	1.957	0.16284	0.002
Dyslipidemia HDL	5.988	0.01494 *	0.012
Hypertension	1.351	0.24595	0.001
Anxiety + Depression	0.24	0.62481	-0.002
Any Anxiety	0.109	0.74195	-0.002
Any Depression	2.708	0.10084	0.004
Dysthymia	0.48	0.48886	-0.001
Bipolar Disorder Type I	0.477	0.49014	-0.001
Binge Eating	2.008	0.15747	0.002
Anova Variables female Group	F value	p-value	omega²
Age	6.214	0.0135 *	0.019
Education	1.376	0.2422	0.001
Income	0.002	0.9648	-0.004
Marital Status	0.822	0.3657	-0.001
Occupation	5.513	0.0199 *	0.016
Tabagism	0.067	0.7955	-0.003
Obesity	48.089	6.27e-11 ***	0.172
Insulin Resistance	1.579	0.2104	0.002
Dyslipidemia TGC	2.182	0.1413	0.004
Dyslipidemia HDL	1.123	0.2907	0.000
Hypertension	0.523	0.4705	-0.002
Anova Variables female Group	F value	p-value	omega²
Anxiety + Depression	0.904	0.3429	0.000
Any Anxiety	1.787	0.183	0.003
Any Depression	6.731	0.0102 *	0.021
Major Depression	0.033	0.8569	-0.004
Bipolar Disorder Type I	1.743	0.1883	0.003

Any Affective Disorder	0.787	0.3762	-0.001
Binge Eating	4.021	0.0464 *	0.011
Multiple Diagnosis	0.877	0.3502	0.000
Anova Variables Male Group	F value	p-value	omega²
Age	3.666	0.05803	0.018
Education	1.626	0.20485	0.004
Income	0.513	0.47516	-0.003
Marital Status	0.543	0.46253	-0.003
Occupation	2.84	0.09465	0.012
Tabagism	0.029	0.8648	-0.007
Obesity	9.918	0.00209 **	0.060
Insulin Resistance	1.842	0.17744	0.006
Dyslipidemia TGC	0.251	0.61722	-0.005
Dyslipidemia HDL	7.874	0.00590 **	0.046
Hypertension	0.995	0.32076	0.000
Anxiety + Depression	0.125	0.72465	-0.006
Any Anxiety	0.814	0.36894	-0.001
Any Depression	0.188	0.6655	-0.005
Dysthymia	0.313	0.57708	-0.005
Bipolar Disorder Type I	0.919	0.33965	-0.001
Binge Eating	0.004	0.95177	-0.007
Insomnia	0.803	0.37198	-0.001
Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1			

Table S6 - Sociodemographic variables description

		Total Group (n = 772)		Feminin Group (n =441)		Masculin Group (n = 331)	
Variable	Categories	n	%	n	%	n	%
Gender	-	-	-	441	57.12%	331	42.88%
Age	18 - 34	228	29.53%	133	30.16%	95	28.70%
	35 - 49	362	46.89%	207	46.94%	155	46.83%
	50 - 64	182	23.58%	101	22.90%	81	24.47%
	65 +	0	-	-	-%	-	-%
Education	Basic	355	46.47%	204	46.90%	151	45.90%
	High School	271	35.47%	149	34.25%	122	37.08%
	Higher Education	138	18.06%	82	18.85%	56	17.02%
Income	Low Class	152	19.90%	103	23.68%	49	14.89%
	Lower Middle	206	26.96%	115	26.44%	91	27.66%
	Higher Middle	193	25.26%	104	23.91%	89	27.05%
	High Class	213	27.88%	113	25.98%	100	30.40%
Marital Status	Single	492	64.40%	247	56.78%	245	74.47%
	Married	121	15.84%	93	21.38%	28	8.51%
	Prev. Married	151	19.76%	95	21.84%	56	17.02%
Occupation	Work/Study	294	67.74%	177	68.08%	117	67.24%
	Retired	90	20.74%	47	18.08%	43	24.71%
	House Work	12	2.76%	10	3.85%	2	1.15%
	Unemployed	38	8.76%	26	10.00%	12	6.90%

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9. Publication

Inflammation, but not metabolic parameters, differs across subtypes of depression.

Results from the São Paulo Megacity Mental Health Survey

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Background

Depression is a highly heterogeneous disorder likely including individuals with different disease etiologies. We investigate whether immuno-metabolic parameters are differentially implicated across depressive subtypes.

Methods

Five thousand and thirty-seven individuals from the general population participated in a mental health survey named São Paulo Megacity Mental Health Survey, part of the World Mental Health Surveys Initiative. Those who screened positive for any psychiatric diagnosis and a non-psychiatric sub-sample were reassessed using the Structured Clinical Interview for DSM Disorders, generating the final sample of 653 individuals with complete data. To identify depressive subtypes, we conducted a latent class analysis (LCA) of the sixteen DSM-5 individual MDD symptoms using poLCA package in R. Allostatic load parameters were investigated by the analysis of immuno-metabolic markers. Multinomial logistic regression models were used to investigate the association of depressive subtypes and immuno-metabolic marker levels, adjusted for age, gender, education, smoking and body mass index.

Results

The best LCA model of the sixteen MDD symptoms identified three subtypes of depression in a Four-Class model including melancholic, atypical, mild-moderate depression, and non-symptomatic individuals. Inflammation was higher in individuals with high somatic, lower in those with low somatic symptoms, and not associated with mild/moderate depression, when adjusted for age, gender, and education. High HDL was associated with low somatic symptoms. No other associations were found.

Conclusion

We found that the different symptomatic profiles of depression are associated with different inflammatory parameters. These findings have important implications in the understanding of biological underpinnings of depression and its treatment.

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Contributors

Authors IB, Y-PW, and LHA designed the study. MCV and LHA wrote protocol and created the database. BMC, DB-L, and GLV collected data. CHFA managed the literature searches and summaries of previous related work. CHFA and JMC-M undertook the statistical analysis. Authors CHFA, FCL, JMC-M, LAC, and LHA wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

None.

Keywords: symptomatology, pathophysiology, psychiatric illness, mental health, biomarker, immunometabolic dysregulation

INTRODUCTION

Major depressive disorder (MDD) is a highly prevalent mental disorder and one of the leading causes of disability worldwide (*GBD_2017_Booklet.pdf*, n.d.). The etiology of depression is not completely elucidated and shows great heterogeneity in symptom presentation. Despite the high costs and increased antidepressant prescription, morbidity of depression persists. About a third of all patients do not respond to the most widely used antidepressant drugs that act on the monoaminergic (serotonin, noradrenaline, and dopamine) system. Patients unresponsive to treatment are at-risk for poor long-term outcomes including substance abuse, mental and physical illnesses, and suicide. Uncertainty prevails and little personalization or stratification has reached clinical practice. Depression is highly comorbid to other mental illnesses, particularly with anxiety, where many constructs cut across diagnostic boundaries.

With the great heterogeneity present in depression, patients vary considerably in clinical presentation. One possible cause for this phenomenon is the polythetic definition of depression in which a patient needs to satisfy a certain number but not all symptoms (Olbert et al., 2014). Currently the diagnosis of MDD requires five of nine symptoms with at least one of two core symptoms. With such broad definitions it is possible that we are treating different diseases with diverse etiologies as one single entity. Taking these data together suggests that the current classification of DSM-5 categories include multiple different biological mechanisms underlying such dimensions Fried (Fried & Nesse, 2015). To improve diagnosis and treatment of mental illnesses, we need to move away from the current categorical diagnosis and use neuroscience to discriminate groups and subsequently inform treatment choices.

Data driven approaches have been applied with the hope of helping navigate this “mixed bag” that is depression (van Loo et al., 2012). One of such methods is latent class analysis (LCA)(McCutcheon, 1987). LCA is a statistical procedure that identifies qualitatively different subgroups within a sample that share certain common characteristics (Hagenaars & McCutcheon, 2002). These subgroups are referred to as latent classes or latent groups. To detect these latent classes, this technique uses study participants’ responses to categorical indicator variables. Technically speaking, LCA is a method to detect latent (unobserved) heterogeneity in samples (Hagenaars & McCutcheon, 2002). The assumption underlying LCA is that the observed patterns

in the scores can be explained by membership to these latent classes (Muthén & Muthén, 2000). The method has been previously used in samples of depressed individuals, with some studies being able to find atypical and non-atypical subtypes (Alexandrino-Silva et al., 2013; Lamers et al., 2010, 2012, 2013; Veltman et al., 2017).

In recent years stress related biomarkers such as inflammation and triglycerides have been implicated in the etiology of depression (Gałecki & Talarowska, 2018; Rahimian et al., 2022). Aberrant levels of pro-inflammatory cytokines or enhanced expression of their immune genes (Carvalho et al., n.d.) are observed in the periphery and in the brain of patients with severe mood disorders (Bechter et al., 2010). While the presence of inflammation is not ubiquitous in depression, many researchers report this association being causal, consequential or bidirectional (Bell et al., 2017; Berk et al., 2013; Beurel et al., 2020; Leonard, 2018; Milaneschi et al., 2021; Patel, 2013; Slavich & Irwin, 2014). Inflammation predicts the development of depressive symptoms in previously healthy individuals and Mendelian Randomization analysis suggests a probable causal link of interleukin-6 and triglycerides in depression (Khandaker et al., 2020). Anti-inflammatory drugs reduce depressive symptoms in people with or without classic inflammatory diseases (Kappelmann et al., 2018; Raison et al., 2013). The immuno-metabolic hypothesis of depression states that chronic psychological stress activates immune cells, and their counterparts in the brain (i.e. microglia) produce cytokines and chemokines impacting brain physiology and predisposing the brain in such a way that genetic and environmental influences – such as stress or trauma – are able to precipitate the symptoms of depression.

In this paper, we aimed at identifying different categorical depressive phenotypes based upon the DSM-5 criteria of Major Depressive Disorder (MDD) among participants of the São Paulo Megacity Mental Health Survey a population-based cross-sectional survey of psychiatric morbidity and investigate its association with allostatic load parameters.

METHODS

Ethics Statements

The procedures for recruitment, obtaining informed consent, and protection of

human subjects involved during field procedures of São Paulo Megacity Health Survey were approved by the Research and Ethics Committee of the University of São Paulo Medical School (Project number 792/03). Participants were interviewed after written informed consent was obtained.

Sample characteristics

The *São Paulo Megacity Mental Health Survey* is a population-based cross-sectional survey of psychiatric morbidity, designed to be representative of the general population of the São Paulo Metropolitan Area, the largest and most populated metropolitan area in Brazil. Further details are available elsewhere (Viana et al., 2009). Portuguese-speaking adults aged 18 or older who are permanent residents of non-institutionalized civilian households in Sao Paulo, were invited to participate. Data was collected between May 2005 and April 2007. Participants were selected from a stratified multistage clustered area probability sample. The survey was divided in two phases: The Household Phase and the Clinical Phase. For the household phase, social-demographic, physical and mental health data was obtained of 5,037 individuals from the general population. Data on mental health was evaluated by the World Mental Health version of the Composite International Diagnostic Interview (WMH-CIDI) (Kessler & Ustün, 2004), which was translated to Brazilian Portuguese and adapted for use in this survey (Viana et al., 2004). For the Clinical Phase, all participants with any diagnosis of mental disorder plus a sample of individuals without any mental disorders were invited to participate. The clinical phase consisted of additional attendance to a series of psychiatric and clinical assessments at the Institute of Psychiatry, School of Medicine, Universidade de São Paulo (IPq-HCFMUSP). A total of 770 individuals were evaluated by experienced psychiatrists using the Structured Clinical Interview for DSM Disorders (SCID) version I-P(16). Clinical and physical evaluation was performed by two physicians. All subjects were asked about personal history of diabetes, coronary heart disease or cerebrovascular disease, and other cardiovascular diseases. For the present study, we excluded 70 individuals who reported chronic physical illnesses. We also excluded participants with CRP levels greater than 20 mg/L (n=17), indicative of acute inflammation (Bray et al. 2016) (19–22). We restricted our analysis to subjects whose data on SCID-I depressive symptoms, CRP levels and anthropometric measures were complete, reaching a final sample size of 653. The process for

obtaining our sample is schematically described in Figure 1.

[Figure 1]

Figure 1 - Flowchart of the process employed on data collection and selection

Measures

Psychiatric Clinical Interview

The subjects composing the clinical sample were assessed through the Structured Clinical Interview for DSM Disorders (SCID) version I-P (Spitzer et al., 2002; Viana et al., 2009) by trained psychiatrists. This version of SCID was translated and adapted to Brazilian Portuguese. The Major Depressive Disorder section of the interview consisted of 27 questions, preceded by screening questions, asking the respondents about depressive symptoms of a present episode or the worst lifetime episode. At the end of the interview, subjects were evaluated with the The Clinical Global Impression – Severity scale (CGI-S) a 7-point scale that requires the clinician to rate the severity of the patient's illness at the time of assessment, relative to the clinician's past experience with patients who have the same diagnosis (Guy et al., 1976). For those who have not answered positively to the screening questions all answers were considered not present. These questions were combined to generate 27 dichotomous variables matching the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, 2013)(American Psychiatric Association, 2013) criteria, as of the three possible answers (absent, uncertain or present), none of the respondents received the score of uncertainty. Six variables were removed due to redundancy (for instance, a question about weight gain or loss followed by the specification of which of the two occurred), lasting 19 symptoms: sadness, irritable mood, loss of interest, weight gain, weight loss, insomnia, hypersomnia, psychomotor retardation, psychomotor agitation, fatigue, worthlessness, guilt, loss of concentration, indecision, death thoughts, suicidal ideation, suicide plan, suicide attempt, loss of functioning.

Allostatic load biomarkers

Blood samples were collected in the morning, during the physical examination at the IPq-HCFMUSP using standard phlebotomy techniques. Venous blood samples were obtained after a 12-hour overnight fast. The blood samples were analyzed for high-sensitive C-reactive protein (nephelometry). Allostatic load and its biomarkers have also been explored in its association with depression (Guidi et al. 2021; Scheuer et al. 2018). Biomarkers associated with the concept of allostatic load include: total cholesterol (Schnorpfeil et al. 2003), high density lipoprotein (Szanton et al. 2005), low density lipoprotein (Bruun-Rasmussen et al. 2022), and triglycerides(Bruun-Rasmussen et al. 2022).

Health and sociodemographic characteristics

The following sociodemographic correlates were considered: sex (female or male), age (in years); education (in years); height was measured using a mechanical anthropometric scale according to the techniques standardized by the Center of Disease Control and Prevention (CDC)(for Disease Control & Prevention, 2004). The height measurement was recorded in meters with up to two decimal places, in an appropriate form. Weight measurement was registered in kg up to one decimal in an appropriate form. Body mass index (BMI) was calculated, dividing the weight in kg by the height measurement in square meters.

Allostatic load markers

Venous blood samples were obtained after a 12-hour overnight fast. The blood samples were analyzed for glucose levels (hexokinase method), total cholesterol (TC) (enzymatic colorimetric assay), HDL-c (HDL - homogeneous cholesterol), and triglycerides (enzymatic colorimetric assay), high-sensitive C-reactive protein (nephelometry). Low-density lipoprotein-cholesterol (LDL-c) was obtained using the Friedewald formula (Viana et al., 2009). Blood glucose and lipid profile were obtained by photometric analysis by a Konelab 60i equipment (LDL obtained by Fridewald formula).

Statistical analysis

Latent class analysis (LCA)

We used exploratory factor analysis to identify the symptoms with lowest commonalities among the 19 symptoms, which expresses the amount of variability in the data where each item contributes to the factorial model. The following symptoms were dropped from the analyses due to poor contribution to the model: suicide ideation, suicide planning, and suicide attempt, remaining 16 symptoms.

Latent class analysis (LCA) was conducted with the poLCA R package(Linzer et al., 2011), using maximum likelihood ratio estimation. The random option in poLCA was applied to ensure convergence for the most successful LCA models, 500 sets of random starting values in the initial phase, and 10 optimizations in the final stage of convergence were used. All other parameters were set as standard. This process ensures the best log-likelihood (LL) value for each model is replicated several times. We present several statistical indices which are used to assess model fitness, including LL, Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), likelihood ratio/deviance statistics, chi-square goodness of fit and entropy. To decide on the best model, we favored the minimized values of BIC as it may reflect a better parsimonious (Muthén, 2006) and reliable (Nylund et al., 2007) method. We used Pearson's χ^2 goodness of fit and likelihood ratio chi-square (G2) statistics to determine how well the model fit the data (Goodman, 1970), without estimating excessive numbers of parameters. As a guide, no fewer than 10-20% of cells should contain fewer than 5 observations (Linzer et al., 2011).

Multinomial logistic Regression and other analysis

Once the subtypes of depression were identified as above using LCA, we conducted a multinomial logistic regression to investigate the association with inflammation. We conducted several models including non-adjusted and adjusted for age, gender, and education. All analyses were performed with R version 4.1.3. Descriptive statistics were used to characterize the sample. Specifically, counts and percentages were used to describe categorical variables.

RESULTS

Identification of depressive subtypes using LCA

We first used the LCA to identify the best depressive subtypes using the probability of the following sixteen depressive symptomatology: weight gain, weight

loss, insomnia, hypersomnia, psychomotor retardation, psychomotor agitation, fatigue, sadness, irritable mood, loss of interest, worthlessness, guilt, loss of concentration, indecision, thoughts of death and loss of functioning. We used the following parameters to estimate the best subtypes using the following fit statistics LL, AIC, BIC, likelihood ratio/deviance statistic, chi-square goodness of fit, and relative entropy. Table 1 represents the number of LCA class models and the comparison between fit statistics according to the number of latent classes based upon the 16 depressive symptoms. The higher entropy values were found in the two-class model, all the models had relatively low values of entropy (between 0.53 and 0.48). The models with 3-5 LCA classes had the lowest BIC and thus the most parsimonious. Model 5 was subsequently discarded as the percentage of smallest classes contained fewer than 10% of individuals. Amongst 3 and 4 LCA classes, we chose to continue our analysis using the 4-class model as it also had the lowest Chi-square goodness of fit, lowest entropy and clearer clinical interpretation.

The four-class LCA model included an asymptomatic class (44.56% of the subjects), a mild-moderate symptomatic class (19.14% of the subjects), and two high-moderate severity classes with similar symptom profile, which differed primarily due to symptoms related to appetite and weight. A high-moderate symptomatic class with high somatic symptoms (16.69% of subjects), and high-moderate symptomatic class with low somatic symptoms (19.60% of the subjects).

[Table 1]

Figure 2 represents the distribution of each of the sixteen symptoms on each of these Four LCA model classes shown as percentages. We found that the four-class LCA model grouped individuals according to the severity of symptoms, but within the most severe it also clearly distinguished two subgroups: weight gain and weight loss. All other symptoms had similar probabilities between these two subtypes. The high somatic group presented particularly with weight gain, and higher levels of hypersomnia and psychomotor agitation. Such a group of symptoms has been previously referred to in the literature as atypical or somatic depression.

[Figure 2]

Figure 2 – Probability of symptom profile with probability in the Four Model LCA

classes asymptomatic, mild/moderate, high/moderate with low and high/moderate with high somatic symptoms.

LCA Model Class and DSM-5 criteria for MDD

To compare the findings of the LCA class models with the traditional DSM-5 diagnostic criteria for Major Depressive Episode, we estimated which proportion of each of the Four Class models (asymptomatic, mild/moderate, low somatic and high somatic symptoms) met criteria for a DSM-5 diagnosis. We found that 78% of individuals in the high somatic, 88% of the low somatic, but only 17% of mild/moderate met criteria for a DSM-5 diagnostic of Major Depressive Episode.

LCA Model Class and Allostatic load profiling

To investigate potential differences in social, demographic, and biological characteristics between the Four Model Classes (asymptomatic, mild/moderate, high somatic and low somatic subtypes) we conducted descriptive statistics. Table 2 represents social, demographic, and biological characteristics for the total sample characteristics and for each of the Four LCA Classes. Women were overrepresented in all four classes (note that our sample has more women than men), but the difference is much more extreme in the two most severe classes. Age and education distribution did not differ across groups. Individuals from the weight loss subtype had the lowest median CRP (1.1mg/L), whereas the high somatic subtype had the highest median (2.6 mg/L). The high somatic subtype had a significantly higher proportion of overweight or obese individuals. 72.5% of individuals with high somatic were classified as overweight or obese, whereas this number reduced to 48% in individuals in the low somatic subtype. There was a higher proportion of current smokers in the higher severity weight gain or loss, compared to the asymptomatic or mild/moderate subtypes.

[Table 2]

[Table 3]

To analyze whether allostatic load parameters were differentially associated to the Four-Class LCA models of asymptomatic, mild/moderate, weight

loss or weight gain we conducted a multinomial logistic regression of different subtypes and Four-Class models (Table 3). We show that compared to the asymptomatic group, weight loss is inversely associated with lower levels of CRP when adjusted for age, gender, education, and smoking (model 1). The inverse association remains when the model is further adjusted for BMI (model 2). We also show that when compared to the asymptomatic group, weight gain is positively associated with CRP, when adjusted for age, gender, education, and smoking (model 1). BMI explains the association as the model is no longer significant for weight gain when further adjusted for BMI (model 2).

DISCUSSION

In this paper, we used latent class analysis to identify within sixteen DSM-5 individual MDD symptoms subtypes of depression and investigated whether cumulative markers of chronic stress – allostatic load – were differentially associated to depressive subtypes. The best Latent Class Model identified a Four-Class Model consisting of asymptomatic, mild/moderate, and two moderate/severe groups: a high- and a low- somatic subtypes. The symptomatic classes differed mainly by severity level and the main phenotypic differentiation of the two most severe classes occurred in psychophysiological symptoms related to appetite and weight. The high somatic subtype was particularly composed of individuals with weight gain, hypersomnia, and psychomotor agitation, whereas individuals in the low somatic subtypes comprised of those particularly with weight loss and insomnia. Individuals in the high somatic subtype showed higher levels of CRP, whereas those in the low somatic subtype had lower levels of CRP and higher levels of HDL. The observed differences were mainly explained by body mass index in those with high, but not in those with low somatic subtypes.

We believe this is the first paper to use latent class analysis to identify subtypes of depression and to associate these with parameters of the allostatic load. The subtypes of depression that were identified in this paper agree with the literature suggesting both a scale of severity and different subtypes among the more severe classes (Lamers et al., 2010, 2012; Veltman et al., 2017). Our four classes model separated our subjects in gradients of severity, which is in accordance with the literature (van Loo et al., 2012). According to (van Loo et al., 2012) the most likely

explanation for this behavior in several samples may reflect the fact that there are no subtypes of depression, or, if they exist, we are not looking at the right symptoms that would be capable of identifying them (Gaynes, 2009). Our data may also suggest that we don't have enough statistical power in our sample to identify them (Wurpts & Geiser, 2014), or that our subjects did not present symptoms enough (number or severity not severe enough) to allow the classification of these cases in clear subtypes. Our data also agrees with a previous analysis on the total sample (5,037 respondents) of the São Paulo Megacity Mental Health Survey which identified different profiles in women and men according to the melancholic and atypical symptoms and differed on somatic/vegetative symptoms (Alexandrino-Silva et al., 2013).

Our data shows that the high and low somatic symptoms of depression as important phenotypes and differentially associated with biological parameters. The high somatic subtype or atypical in the literature was mostly associated with high inflammation, whereas the low somatic phenotype, also called melancholic in the literature, associated with lower levels of inflammation and higher levels of HDL. There is already literature exploring this association in specific subtypes of depression (Lamers et al., 2020). Similar to our study, Lamers et al showed that chronic forms of the two major subtypes of depression are associated with different biological correlates with inflammatory, but they also found metabolic dysregulation in atypical depression (Lamers et al., 2013). The same group most recently showed that atypical depression is associated with immune and metabolic dysregulation (Lamers et al., 2018). Both studies contained a much bigger group of depression subtypes than our study. Some studies have suggested that inflammatory regulation, as measured by dysfunction of hypothalamic pituitary adrenal axis, as a differential biomarker for depression subtypes (Juruena et al., 2018). It is possible that in our study we were not powered enough to detect associations between metabolic dysregulation and high somatic/atypical subtype.

Our data showed that inflammation was associated with severity of depression but was highly dependent on somatic symptoms of depression and particularly important in those with weight gain. Inflammation seems to characterize those with a more severe type of depression who are unresponsive to conventional antidepressants (Carvalho et al., 2013; Cattaneo et al., 2013). Growing evidence suggests that inflammation appears to be particularly important in those more

severely-ill, with recurrent episodes (Zalli et al., 2016), with psychosocial stress or trauma and comorbid medical illnesses (Iwata et al., 2013). Our paper did not agree with the results from Frankly et al (Franklyn et al., 2022) who did not see an association with inflammation and severity of depression. Our findings reinforce the argument for the heterogeneity of depression, showing that not only there is a continuum in severity but also subtypes related to specific symptoms among the most severe cases. These subtypes are associated with marked differences in the inflammatory marker CRP, something that lends strength to the inflammatory theory of depression(Gałecki & Talarowska, 2018).

Our findings also agrees with previous literature regarding the association of obesity and low grade inflammation (Barzilay et al., 2006; Choi et al., 2013; Duncan et al., 2000; Ellulu et al., 2016; Fogarty et al., 2008; Popko et al., 2010), whether obesity is causal to inflammation, inflammation is causal to obesity, or both factors have a bidirectional relation is something that is still under debate. But there is evidence that obesity is causal to inflammation (Tuomisto et al., 2019) and Inflammatory markers are significantly higher in subjects with abnormal BMI, this difference is mediated by sex with women presenting greater levels than men (Cohen et al., 2021). Recent studies indicated that the accumulation of excessive or abnormal fat tissue in obesity trigger the release of inflammatory mediators such as tumor necrosis factor α (TNF-α) and interleukin 6 (IL-6) that stimulate the synthesis and secretion of C-reactive protein by the liver, a known risk factor for the development of cardiovascular diseases such as coagulation, atherosclerosis, metabolic syndrome, insulin resistance and diabetes, and also for non-cardiovascular ones such as depression, psoriasis, cancer and renal diseases. Managing obesity can help reduce these poor outcomes via the inhibition of these inflammatory mechanisms (Ellulu et al., 2016, 2017). It is of note that our entire sample is comprises of a high proportion of adults with overweight and obesity, conditions linked to inflammatory processes, may explain that, although the mean log of CRP levels increased with the severity of the symptoms for our moderate and weight gain classes, these differences lost significance when adjusted for BMI and smoking in our final model. Only the weight loss class retained significance after this adjustment but with a lower effect than that on the previous model. A possible explanation for this signal is the overall higher inflammatory state of our sample, which presented with higher obesity and inflammatory levels even in the subjects with no symptoms of depression.

Limitations

Our study has several strengths such as using robust statistical analysis, a relatively large population who had been thoroughly phenotypically evaluated by psychiatrists and is one of the largest mental health study with individuals from low and middle income countries where psychological stress is very relevant. Our study also has limitations. The cross-sectional design cannot establish a cause-effect relationship for the observed data. Our sample consisted of residents of a large urban area, which precludes the generalization of our findings to the general population who live in rural settings and possibly even residents of less dense urban areas. We do not have information about the time of occurrence of the episode of Major Depression. This could limit our ability to link the presence of the MDD and the inflammatory state as measured by CRP levels.

In conclusion, we have shown that individuals with low somatic symptoms had lower levels of inflammation and higher levels of HDL whereas high somatic symptoms were associated with higher levels of inflammation. These results emphasize the importance of investigating the biological etiology of depression associated with the different clinical phenotypes and will have important implications to improve future treatment.

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Table 1 - Latent Class Analysis model indexes

Model	LL	AIC	BIC	(Likelihood ratio/deviance statistic)	(Chi-square goodness of fit)	Relative Entropy	df	% smallest classes
Two-class	-3843.656	7753.312	7901.204	2488.319	77855.71	0.5319669	620	47.63%
Three-class	-3685.555	7471.109	7695.188	2172.117	47551.21	0.5105242	603	19.45%
Four-class	**-3610.956**	**7355.911**	**7656.177**	**2022.918**	**40614.38**	**0.5003702**	**586**	**16.69%**
Five-class	-3570.642	7309.284	7685.736	1942.291	56330.67	0.4950053	569	6.13%
Six-class	-3543.814	7289.628	7742.268	1888.636	59139.40	0.4950053	552	6.58%
Seven-class	-3516.572	7269.144	7797.971	1834.152	40893.32	0.4859263	535	5.36%
Eight-class	-3494.037	7258.074	7863.087	1789.081	30262.01	0.4828874	518	2.14%

Table 2 - Characteristics of participants (n = 653)

	Whole sample (n=653)	Asymptomatic (n=291)	Moderate (n=125)	HighSomatic (n=109)	Low Somatic (n=128)
CRP[1]	1.500 (0.150-19.300)	1.420 (0.150-19.300)	1.980 (0.160-16.400)	2.600 (0.160-18.100)	1.0950 (0.150-14.700)
LOGCRP[2]	0.5029 (1.100)	0.4752 (1.104)	0.661 (1.094)	0.804 (1.103)	0.155 (1.002)
Age in years[2]	39.91 (10.60)	39.86 (10.98)	40.93 (10.312)	37.98 (10.521)	40.70 (9.934)
Education in years[2]	9.182 (4.05)	9.175 (3.923)	9.089 (3.899)	9.477 (3.799)	9.032 (4.695)
Sex[3]					
Male	42.27%	46.74%	44.00%	24.77%	30.47%
Female	57.73%	53.26%	56.00%	75.23%	69.53%

BMI[1]	26.30 (16.24-44.79)	26.62 (16.85-44.55)	26.02 (16.40-40.51)	27.29 (18.34-44.79)	24.89 (16.24-39.90)
BMI[2]	26.89 (4.91)	27.13 (4.92)	27.02 (4.89)	28.21 (5.33)	25.09 (3.95)
Smoking[3]					
Non-Smoker	83.15%	87.29%	85.60%	78.90%	75.00%
Current Smoker	16.85%	12.71%	14.40%	21.10%	25.00%
HDL[2]	47.43 (11.94)	46.09 (11.14)	47.44 (12.12)	47.67 (12.64)	50.18 (12.49)
LDL[2]	122.20 (35.36)	122.10 (34.03)	122.47 (32.58)	122.9 (36.46)	121.62 (39.96)
Total cholesterol[2]	193.50 (46.44)	193.3 (50.34)	194.10 (39.95)	194.20 (41.84)	192.60 (47.29)
Fasting glucose[2]	89.10 (14.80)	90.66 (17.36)	90.18 (12.64)	86.43 (12.66)	86.29 (10.22)
Triglycerides[3]	95.00 (81.00)	94.00 (82.50)	99.00 (93.00)	103.00 (74.00)	84.5 (72.75)

Continuous variables with non-normal distribution are presented as median (range)[1] or median (interquartile range)[3], continuous variables with normal distribution are presented as mean (SD)[2], and categorical variables are presented as percentage[3]. Education level was modeled as a continuous variable that represents years of education

Table 3 - Multinomial logistic models for C-Reactive Protein levels, HDL, LDL, Total Cholesterol, Fasting Glucose and Triglycerides and Four-Class LCA Models.

Variable	Latent Class	Logistic Model 1*		Logistic Model 2**	
		OR	CI	OR	CI
CRP (log adjusted)					
	Low Somatic	**0.678**	**(0.551-0.836)**	**0.768**	**(0.612-0.965)**
	High Somatic	**1.255**	**(1.013-1.555)**	1.195	(0.943-1.513)
	Mild/Moderate	1.132	(0.926-1.385)	1.163	(0.933-1.449)
HDL					
	Low Somatic	**1.023**	**(1.004-1.042)**	1.017	(0.998-1.037)
	High Somatic	1.000	(0.980-1.021)	1.003	(0.983-1.024)
	Mild/Moderate	1.007	(0.988-1.026)	1.008	(0.988-1.027)
LDL					
	Low Somatic	0.999	(0.992-1.005)	1.000	(0.993-1.007)
	High Somatic	1.003	(0.996-1.010)	1.002	(0.995-1.009)
	Mild/Moderate	0.999	(0.993-1.006)	0.999	(0.993-1.006)
Total Cholesterol					
	Low Somatic	0.999	(0.994-1.004)	1.000	(0.995-1.006)

	High Somatic	1.002	(0.997-1.007)	1.001	(0.996-1.007)
	Mild/Moderate	1.000	(0.995-1.005)	1.000	(0.995-1.005)
Fasting glucose					
	Low Somatic	0.976	(0.955-0.997)	0.986	(0.964-1.008)
	High Somatic	0.987	(0.965-1.010)	0.983	(0.960-1.007)
	Mild/Moderate	0.998	(0.982-1.014)	0.999	(0.983-1.016)
Triglycerides (log adjusted)					
	Low Somatic	0.704	(0.473-1.049)	0.944	(0.613-1.452)
	High Somatic	1.336	(0.904-1.975)	1.168	(0.762-1.789)
	Mild/Moderate	0.984	(0.682-1.421)	0.996	(0.670-1.480)

*Adjusted for age, sex, education, and smoking

*Adjusted for age, sex, education, smoking, and BMI