Universitat de Girona
Facultat de Medicina

The effects of SARS-CoV-2 infection on Major Depressive Disorder symptomatology

Final Degree Project

Acute Psychiatry Department
Hospital Santa Caterina
Girona, November 2020

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I would like to express my gratitude to Domènec Serrano Sarbosa for transmitting to me his passion for psychiatry and for giving me his time and his help.

In addition, I would like to thank all the team of Acute Psychiatry Department Hospital Santa Caterina for their warm welcome and Rafael Marcos Gragera for helping me with the methodological part.

Per últim, també vull donar les gràcies a la meva família i als meus companys de pis pel seu suport i la seva confiança.

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1. ABSTRACT

Background: Major Depressive Disorder (MDD) has a Spanish prevalence of 1.363.200 people. Regarding MDD pathophysiology, even though there are various hypothesis, the exact cause isn't known. SARS-CoV-2 infection is causing a worldwide pandemic with more than 40 million cases and more than 1,5 million of deaths all over the World. It is known that is transmitted via small droplets and aerosols, and that while there's a proportion of people that is asymptomatic, others suffer from Sever Acute Respiratory Syndrome and other severe complications. Regarding the pathophysiology, it is discovered that the virus interacts with the immune system producing a cytokine release syndrome contributing to tissue damage. Previous studies indicate that since the pandemic begin, there has been an increase on depressive symptomatology and MDD. Linking with previous data that indicates that one of the most accepted and studied theory of the MDD aetiology is the proinflammatory hypothesis, the virus may cause depressive symptoms via inflammatory pathways.

Main objective: to demonstrate that infection with SARS-CoV-2 aggravates MDD symptomatology in previously-diagnosed patients from *Xarxa de Salut Mental i Addiccions de Girona* (XSMA).

Secondary objective: to study if patients with higher inflammatory parameters suffer from a major worsening of the MDD symptomatology.

Study design: An observational prospective cohort study with matching carried out from August 2020 to October 2022 in the XSMA of Girona region. The patient's follow-up will take 1 year.

Participants: The study will be formed by adults with a previous MDD diagnosis of the XSMA of Girona region which had been diagnosed according DSM-5 diagnosis criteria. They will be selected by a consecutive non-probabilistic model, in the

Centres of Mental Health of Girona region, *Centres de Salut Mental d'Adults* (CSMA), and included in the study when their informed consent will be signed.

Key words: Depressive Major Disorder, SARS-CoV-2 infection, Hamilton Rating Scale for Depression, IL-6, CRP

2. ABBREVIATIONS

MDD	Major depressive disorder
XSMA	Xarxa de Salut Mental i Addicions de Girona
CSMA	Centre de Salut Mental Adults
CNS	Central Nervous System
HPA axis	Hypothalamic Pituitary Adrenal Axis
NGF	Nerve Growth Factor
BDNF	Brain Derived Neurotrophic Factor
IL-2	Interleukina-2
HVB	Hepatitis B Virus
HVC	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
5-HT	5-Hidroxi-Triptamina
IL-6	Interleukin-6
CSF	Cerebrospinal fluid
GABA	Gamma-Aminobutyric Acid
HDRS	Hamilton Depression Rating Scale
ICD-11	International Classification of Diseases
DSM-5	Diagnostic and Statistical Manual of Mental Disorders 5
WHO	World Health Organization
SARS-CoV-2	Sever Acute Respiratory Syndrome Coronavirus-2
COVID-19	Coronavirus Disease 2019

SARS-CoV-1	Sever Acute Respiratory Syndrome Coronavirus-1
ACE-2	Angiotensin Converting Enzyme 2
G-CSF	Granulocyte-Colony Stimulating Factor
IL-10	Interleukin-10
MCP1	Monocyte Chemoattractant Protein 1
MIP-1α	Macrophage Inflammatory Protein 1α
TNF	Tumour Necrosis Factor
CRS	Cytokine Release Syndrome
IL-1β	Interleukin-1β
CRP	C-Reactive Protein
SNS	Sympathetic Nervous System
PAMPs	Pathogen Associated Molecular Patterns
DAMPs	Damage Associated Molecular Patterns
IL-18	Interleukin-18
HSP	Heat Shock Proteins
IL-4	Interleukin-4
BBB	Blood-Brain Barrier
RT-PCR test	Reverse Transcription Polymerase Chain Reaction test
ESCA	Enquesta de Salut de Catalunya
SMAQ	Simplified Medication Adherence Questionnaire
MARS	Medication Adherence Rating Scale
BHS	Beck's Hopelessness Scale

GAF	Global Assessment of Functioning Scale
CEIC	Comité Ètic d'investigació Clínica
CINP	Collegium Internationale Neuro-Psychopharmacologicum
IdibGi	Institut d'Investigació Biomèdica de Girona
IAS	Institut d'Assistència Sanitaria
UHA	Unitat d'Hospitalització d'Aguts
URPIJ	Unitat de Referència en Psiquiatria Infantil i Juvenil
CSMIJ	Centres de Salut Mental Infantil i Juvenil
EIPP	Equips d'Intervenció Precoç en la Psicosi

3. INTRODUCTION

3.1 MAJOR DEPRESSIVE DISORDER

3.1.1 PREFACE

"Depression is different from usual mood fluctuations and short-lived emotional responses to challenges in everyday life. Especially when long-lasting and with moderate or severe intensity, depression may become a serious health condition. It can cause the affected person to suffer greatly and function poorly at work, at school and in the family. At its worst, depression can lead to suicide. Close to 800 000 people die due to suicide every year. Suicide is the second leading cause of death in 15-29-year-olds" (1).

MDD is characterize for depressive disorders that have a minimum duration of two weeks and cause clear affectivity, cognition and neurovegetative functions changes (2).

3.1.2 EPIDEMIOLOGY

"Depression is a common illness worldwide, with more than 264 million people affected" (1). Moreover, depression is one of the most common psychiatric disorder.

The MDD prevalence in Spain is of 1.363.200 people (2014) (3). MDD is three times more frequent from 18 to 29 years old and 1,5-3 times more frequent in women (2).

It is expected that for 2030 depression will be the leading cause of disability in developed countries. Approximately 20% of all depressed patients develop a chronic depression (4).

Even though it has a high prevalence and it represents an important health and social issue, MDD is underdiagnosed and undertreated as many patients doesn't consult their doctor (5).

3.1.3 PATHOPHYSIOLOGY

MDD has a complex etiological relationship between genetic and environmental factors in which early childhood adversity and stressful life events are recognized environmental risk factors.

Monoamines hypothesis proposes that depression is caused by a functional lack of norepinephrine and serotonin in the limbic cerebral region. Because of this dysfunction, there are the behavioural and visceral symptoms of the MDD. On the one hand, the lack of serotine causes sleep alterations, motor activity, sensorial perception, appetite, sexual behaviour, thermic regulation and nociception and hormone secretion. On the other hand, the norepinephrine lack can cause disorders in motivation, wakefulness and alertness state, consciousness level, sensitive perception, sleep regulation, appetite, sexual behaviour, reward mechanism, learning and memory.

Chronic stress hypothesis suggests that chronic stress modifies the central nervous system (CNS), since stress is an important factor of vulnerability for MDD. It has been observed that in some patients, chronic stress produces a pathological interaction between the CNS, the innate immune system and the hypothalamic pituitary adrenal (HPA) axis. The hyperactivity of HPA axis has been associated with depression and other neuropsychiatric disorders because its negative effects that produce on the brain (it reduces neurogenesis and neuroplasticity and increase the neuronal death).

Neurotrophic hypothesis states that the reduction of neurotrophins [nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF)] affects the limbic area which is involved in the mood and the cognitive functions.

Proinflammatory hypothesis is based on the depressive effects produced by immune therapies [interferon alfa and interleukin-2 (IL-2)] in Hepatitis B Virus (HVB) and Hepatitis C Virus (HVC), Human Immunodeficiency Virus (HIV) and cancer. Moreover, cytokine analysis before and after antidepressant treatment have demonstrate a decrease in those cytokine levels. The hypothesis is supported by neuroimaging studies and animal experimental models which shows that cytokine produce neuroplasticity changes, causing atrophy and neuronal death, developing depressive symptoms, such as anhedonia, fatigue, appetite changes and psychomotor alteration. The depressive symptoms are caused by the raised activity of the corticotrophins induced by cytokines, which hyperactivate the HPA axis, with the consequent increasing level of glucocorticoids. Those glucocorticoids increase the broken of 5-hidroxi-triptamina (5-HT), the receptors of serotonin. Moreover, the Interlukin-6 (IL-6) has been associated with the sleep disorders of the patients with depression.

Gamma-Aminobutyric acid (GABA) deficit hypothesis: there is evidence of GABA reduction levels in blood plasma, cerebrospinal fluid (CSF) and cortical tissue. Interestingly, patients with melancholically symptoms and treatment resistance shows the lowest GABA levels.

Glutamate hypothesis: exacerbation of the glutamate system, causing spine remodulation, synapsis reduction and volumetric reduction (6).

3.1.4 RISK FACTORS

TABLE 1: Risk factors for MDD

PERSONAL FACTORS	SOCIAL FACTORS	COGNITIVE FACTORS
More frequent in female	Low socioeconomic status (5)	Automatic thoughts
More disability in female	Poor social support (4)	Cognitive distortion
Chronic disease (physical and mental) and association with alcohol and tobacco use	Unemployment	Cognitive reactivity
Psychiatric disorder: anxiety disorder, dysthymia (5), borderline personality disorder, substance use disorder (2), panic attacks (male), postpartum depression (4)	Marital status (unmarried, divorced, widower)	Ruminate answers (5)
Migraine	Life adversities (5)	**FAMILIAR AND GENETIC FACTORS**
Dementia	Childhood experiences (physical, sexual and/or emotional abuse) (7)	Four times more at risk if first degree relative (2)
Diabetes, hypothyroidism and hyperthyroidism, Cushing Syndrome, Addisson disease and amenorrhea hyperprolactinemia (5)	Chronic stress (5)	Increased in second-degree relative (5)

3.1.5 RISK FACTORS FOR RECURRENCE

Risk factors in patients with previous MDD diagnosis:

- **No self-efficacy:** self-efficacy describe the patient's confidence in their ability to control behaviours to prevent and being aware of future depressive episodes (8)
- **Previous recurrences**: higher if long duration (9)
- **Residual symptoms of depression:** based on the 17-item Hamilton Depression Rating Scale (HDRS) (4)

- **High intensity of previous MDD episodes** (4)
- **Early age of onset** (10)
- **Disorders of personality cluster B and C** (11)
- **Dysthymia and/or social phobia** (4)
- **Poor social support:** assessed using the Social Support Survey (4)
- **Child abuse:** it causes an effect on physical and psychological health. Moreover, it is associated with earlier age of onset and poor functional status (4) (9)
- **High stress factors or repeated stress periods** (4)
- **Family story of anxiety** (4)
- **Poor medication adherence** (8)

3.1.6 CLINICAL PRESENTATION

The nucleus of MDD clinical presentation is the deep sadness experienced by patient invading all the parts of their life, intra and interpersonally (12). Moreover, the depressive clinical can be explained in five big areas, represented in table 2:

TABLE 2: MDD symptoms (12)

Affectivity	Cognition and thoughts	Behaviour	Biological rhythm	Somatic disorder
▪ Sadness ▪ Apathy ▪ Anxiety ▪ Irritability ▪ Anhedonia ▪ Numbness	▪ "slowing down" ▪ Negativity ▪ Low self-esteem ▪ Hopelessness ▪ Suicidal ideas ▪ Sense of guilt, sense of failure and hypochondria ideas (Cotard Syndrome as a most negative expression) ▪ Attention deficit	▪ Self-care difficulty ▪ Hypotony ▪ Nervousness/ Inhibition ▪ Isolation ▪ Suicidal attempts	▪ Early awakening ▪ Worse mood in the morning ▪ Spring or autumn onset	▪ Anorexia ▪ Weight loss ▪ Insomnia/ hypersomnia ▪ Digestive disorders ▪ Constipation ▪ Asthenia ▪ Algia ▪ Sexual dysfunction ▪ Cephalea ▪ Amenorrhea

An important MDD issue is the suicidal risk, as during an MDD episode, suicidal behaviour can be 20 times more frequent with respect to health population. The suicidal behaviour goes from suicidal thoughts to suicidal threats, suicide attempts and suicide. Another important issue is the risk factors for suicidal behaviour: male, familiar history of mental disorder, previous suicidal attempt, serious depression, comorbid disorders

(especially anxiety and drug and alcohol use), hopelessness, Borderline Personality Disorder, high levels of impulsivity and aggressivity and loneliness (5).

3.1.7 DIAGNOSIS

Although MDD diagnose is clinical, by recognizing the symptoms explained before by clinical interview, there are scales made with the objective of standardise the diagnose criteria. The most commonly used classifications are the International Classification of Diseases (ICD-11) and the Classification of The American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5). This protocol will use the DSM-5 criteria (5). Considering the DSM-5 criteria (table 3), criteria A to C confirm the MDD diagnosis. Therefore, the physician has to obtain information of the patient's mood and its effect on their functioning in social, occupational and other important areas (2).

TABLE 3: Diagnosis criteria for Major Depressive Disorder to DSM-5 (2)

A	Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1.) depressed mood or (2.) loss of interest or pleasure. **Note:** Do not include symptoms that are clearly attributable to another medical condition
	1. Depressed most of the day, nearly every day as indicated by subjective report (e.g., feels sad, empty, hopeless) or observation made by others (e.g., appears tearful) **Note:** In child and adolescent the mood could be irritability
	2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by subjective account or observation)
	3. Significant weight loss when not dieting or weight gain (e.g., change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day **Note:** On child, considering the failure for not increasing the hoped weight
	4. Insomnia or hypersomnia nearly every day
	5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)
	6. Fatigue or loss of energy nearly every day
	7. Feelings of worthlessness or excessive or inappropriate guilt (which could be delusional) nearly every day (not merely self-reproach or guilt about being sick)
	8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)
	9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide
B	The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
C	The episode is not attributable to the physiological effects of a substance or to another medical condition. **Note:** The A-C criteria represent a major depressive episode. **Note:** Responses to a significant loss (e.g., bereavement, financial ruin, losses from a natural disaster, a serious medical illness or disability) may include the feelings of intense sadness, rumination about the loss, insomnia, poor appetite, and weight loss noted in Criterion A, which may resemble a depressive episode. Although such symptoms may be understandable or considered appropriate to the loss, the presence of a major depressive episode in addition to the normal response to a significant loss should also be carefully considered. This decision inevitably requires the exercise of clinical judgment based on the individual's history and the cultural norms for the expression of distress in the context of loss.
D	The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.
E	There has never been a manic episode or a hypomanic episode. **Note:** This exclusion does not apply if all the manic-like or hypomanic-like episodes are substance-induced or are attributable to the physiological effects of another medical condition.

3.1.8 PROGNOSIS AND EVOLUTION

MDD evolution has a wide range of possibilities; some patients rarely have remission periods and others have remission periods of years with few or non-symptoms between episodes. There are some factors that determine a major risk of recurrence (mentioned before).

The recovery after MDD episode takes place after three months of the onset in 2/5 patients, and after one year in 4/5 patients. Long duration, psychotic characteristics, high anxiety, personality disorders and symptoms severity are associated with worst recovery rate.

Even though the prevalence is different between the sexes (women are more likely to suffer from MDD), this difference has not been demonstrated in the disorder's evolution and neither in the treatment's response.

The suicide behaviour and attempts decrease proportionally with the patient age, in contrast, the consummate suicide maintain the risk rates (2).

Apart from the personal variety of the recurrences and remission, there are some factors that modify the evolution and course of MDD. Having another mental disorder normally implicate a refractory course. Moreover, the disability and chronic diseases increase the risk of MDD episodes. Additionally, some prevalent diseases as diabetes mellitus, morbid obesity and cardiovascular pathology are related with MDD chronification. Some other predictors have been described as a predictor of bad response: high severity, social difficulties persistence, low educational level, early age of onset, onset of depression in elderly adults (13).

Regarding the MDD functional consequences, the deterioration may be minimum, or could reach a level of complete incapacity leading the patient to not being able to self-care, or even to mutism and catatonic state. Moreover, MDD patients consult more because of pain episodes, psychical diseases and dysfunction in physical, social and personal areas (2).

3.1.9 TREATMENT

The MDD treatment involves non-pharmacological and pharmacological strategies depending on the stage of the episode. Mild MDD episodes may receive non-pharmacological therapies, and moderate and sever MDD episodes may require antidepressant treatment as well as non-pharmacological treatment. The choice of the drug will depend on the previous response, the familiar history of response, the security, the secondary effects and the cost and use commodity (14).

Moreover, sleep disorder and/or anxiety treatments are sometimes needed. Regarding the use of the antidepressant drugs, they are administrated in the acute phase and a subsequent period of maintenance is needed with the aim of avoiding recurrences. During the maintenance period, antidepressants are associated with other additional physiotherapy and other non-pharmacological strategies. In addition, the following up of the MDD patients who are taking antidepressant drugs is essential as the risk of suicide attempt increases in the first two weeks of treatment.

3.2 SARS-CoV-2

On 31st December 2019, the Chinese Govern reported that a group of 27 causes of unknown cause of pneumonia had been detected in a food market in Wuhan, China. On 7th January a new coronavirus was detected as the infection aetiology, named Sever Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). Afterwards, the World Health Organization (WHO) named the epidemic disease as coronavirus disease 2019 (COVID-19). On 11th March 2020, WHO declared the SARS-CoV-2 a worldwide pandemic. On 15th March the Spanish government declared a lockdown period with the aim of reducing the COVID-19 transmission (15).

3.2.1 EPIDEMIOLOGY

	CATALONIA (30/10)	SPAIN (30/10)	EUROPE (2/11)	WORLD (2/11)
CASES	228,000 (16)	1,185,678 (16)	7,569,075 (17)	46,166,182 (18)
DEATHS	5,991 (16)	35,878 (16)	222,701 (17)	1,196,362 (18)

Regarding the SARS-CoV-2 infection prevalence, the Spanish government developed a seroprevalence study which analysed the Spanish seroprevalence in three periods. The last period, from 8th June 2020 to 22th June 2020, showed a 5,2% of seroprevalence in all Spain and 5,9% in Catalonia (19).

3.2.2 VIRUS INFORMATION

SARS-CoV-2 is a coronavirus, a family of virus which causes human and other animal infections. It's a zoonotic disease. The coronavirus that infects humans can cause from a common cold in winter to a sever acute respiratory syndrome as SARS-CoV-1 which was detected on 2003 and caused more than 8.000 cases in 27 countries with a mortality of 10% (15).

3.2.3 TRANSMISSION

The disease transmission is from person to person through small droplets and aerosols coming from the mouth and nose, which are expelled by coughs, sneezes or when speaking. Aerosol transmission occurs in specific settings, particularly in indoor, inadequately ventilated and crowed spaces, where infected persons spend long periods of time with others. Moreover, droplets can lead on surfaces, so people can become infected by touching them and then touching their own mouth, nose or eyes. Due to the way of transmission, WHO recommendations are: regular hand-washing, maintaining at least 1 meter distance, avoiding crowed places, avoiding touching eyes, nose and mouth, wearing masks, opening windows and staying home in cases of symptoms such as cough, headache, mild fever, … (20).

3.2.4 INFECTION

The incubation period is around five and six days with a ranging from 1 to 14 days. Regarding infective period, patients with low SARS-CoV-2 infection have presented the maximum viral load during the 5-6 first days after onset of symptoms, and it practically disappear on the tenth day. In contrast, in patients with severe SARS-CoV-2 infection seems to be present longer infective periods (20).

3.2.5 PATHOPHYSIOLOGY

INTERACTION WITH RENIN-ANGIOTENSIN-ALDOSTERONE AXIS

It has been discovered that SARS-CoV-2 penetrate the cells with the angiotensin converting enzyme 2 (ACE-2). The studies show high levels of Angiotensin II in cases of sever SARS-CoV-2 infection, which have been related with the viral load and the pulmonary damage, as ACE-2 is highly expressed in lung. Therefore, this disequilibrium could be associate with a virus inhibition of the ACE-2. This effect was also found in the SARS-CoV-1 (15).

INTERACTION WITH THE IMMUNE SYSTEM

SARS-CoV-2 activates the innate immune system leading to an exaggerate response against the virus infection which aggravates the pulmonary lesion and the disease evolution. The immune response is initiated by antigen presentation via dendritic cells and macrophage to lymphocytes CD4+ and CD8+. CD4+ produces IL-6 which is increased in patients with severe infection (15). Moreover, other increases of cytokine as Interleukin-10 (IL-10), granulocyte-colony stimulating factor (G-CSF), monocyte chemoattractant protein 1 (MCP1), macrophage inflammatory protein (MIP) 1α, and tumour necrosis factor (TNF) α, have been noticed (21). Nonetheless, the hyperactivation, named cytokine release syndrome (CRS), isn't efficient for the infection control and lead to a lymphocyte decrease which is associated to a major tissue damage, SARS and other clinical (15).

INTERACTION WITH THE COAGULATION AND MICROVASCULAR SYSTEM

The hyperactivation of the innate immune system cause coagulation and microvascular system damage. Consequently, disseminated intravascular coagulopathy lead to generalized microvascular damage which contribute to multiorgan failure. Regarding to antithrombin levels, a decrease has been observed, while dimer D and fibrinogen increase (15).

3.2.6 SYMPTOMS

The most common symptoms are fever, dry cough and tiredness. And less frequently: aches, nasal congestion, conjunctivitis, sore throat, headache, diarrhoea, loss of smell

and taste, cutaneous rash and finger or toes discoloration. Even though these symptoms usually are mild and about 80% of patients recover from the disease without hospital treatment, 1 out of 5 have severe consequences with breath difficulty and other complications such neurological, cardiological, ophthalmological, otolaryngology, dermatological and haematological symptoms. Older people and those who have other medical problems like immunodepression (cancer, diabetes, …), heart and lung diseases or high blood pressure, are at risk of suffering more severe symptoms and complications. Moreover, there are people that become infected without having any symptom, which indirectly can contributes to transmit the virus (20).

3.2.7 DIAGNOSIS

Recently, the Ministry of Health validate two tests for the active infection detection; rapid antigen test and the RNA detection by Reverse Transcription Polymerase Chain Reaction (RT-PCR) test. The recommended sample has to be taken from the superior and inferior respiratory system. On the other hand, antibody tests are done to check if the person was infected by the virus in the past (22).

RT-PCR test: due to its sensibility and specificity and the fact that is a test which has been standardized by the microbiology laboratories for a lot of infections diagnosis, it is the reference test for the active SARS-CoV-2 infection detection in symptomatic and asymptomatic patients.

Antibodies test: it looks for the presence of antibodies produced by the immune system in response to a threat, such as a specific virus. Antibodies can take days or weeks to develop after the infection and can stay several weeks in blood after recovery. For that reason, antibody tests cannot be used to diagnose the active infection, but to determine if the person was infected by the virus in the past. Currently, it is not known if a positive serology means that this person is immune to the SARS-CoV-2.

3.2.8 TREATMENT

Even though many worldwide countries are studding and publishing about the virus treatments, there is no proven treatment available (23). However, there are many studies in progress around the world.

3.3 INFECTION AND MAJOR DEPRESSIVE DISORDER

As mentioned in the pathophysiology of MDD section, the immune response is an important contributor for the development of MDD. When human is under stress the person experiences a fight or flight response which is represented by an increase of heart rate, blood pressure and cortisol and catecholamines release. Moreover, it has been discovered that laboratory stressor activates immune responses. So, this immune response is not against the pathogen, but against the stressor. In addition, those individuals that have experienced an early-life trauma show higher immune response against the same stimulus (24). Regarding the explanation of the origin of these immune response against stressors, recent theories explain this fact as a protection for the survival response; those individuals that presented MDD were less exposed to pathogenic environment (25). See figure 1.

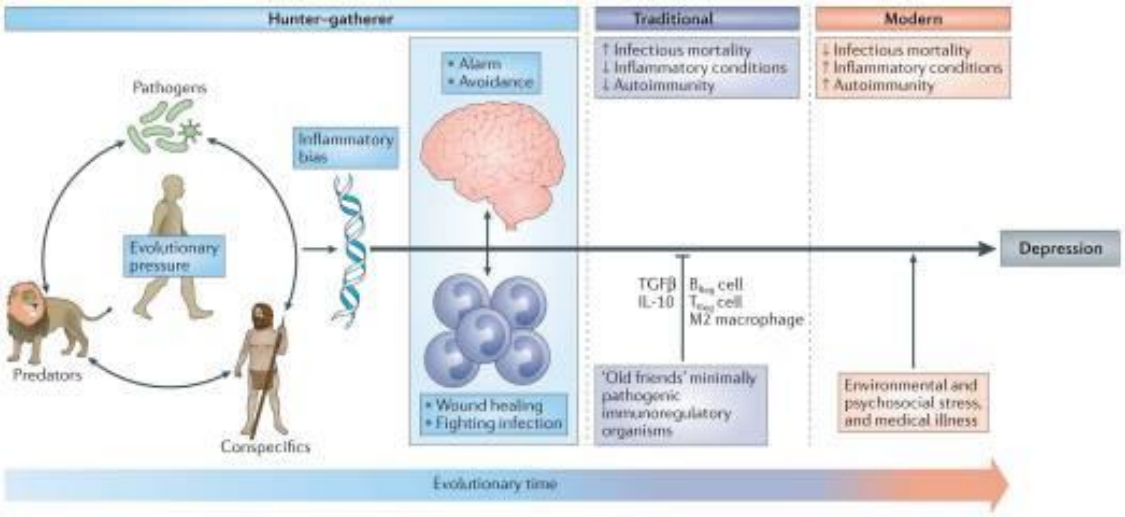

Figure 1: Evolutionary legacy of an inflammatory bias (24)

The higher MDD prevalence in women can also be explained by the proinflammatory theories, some studies demonstrated a major sensitivity to the behavioural effects of the inflammation. With the exposure to endotoxin, women showed higher increase in depressed mood (26).

Nowadays in modern life where there is less exposure to pathogens and more sanitary measures, this exacerbated inflammatory biases do not represent an advantage (24).

Regarding the MDD relation with the inflammatory response, patients with this disorder have an increased expression of acute phase reactants, chemokines and soluble adhesion molecules in peripheral blood and CSF, and proinflammatory cytokines and their receptors, as shown in figure 2. The most reliable inflammatory biomarkers are interleukin-1β (IL-1β), IL-6, tumour necrosis factor (TNF) and C-reactive protein (CRP) (27). Moreover, the inflammatory parameters have been associated with poor treatment response to antidepressant drugs.

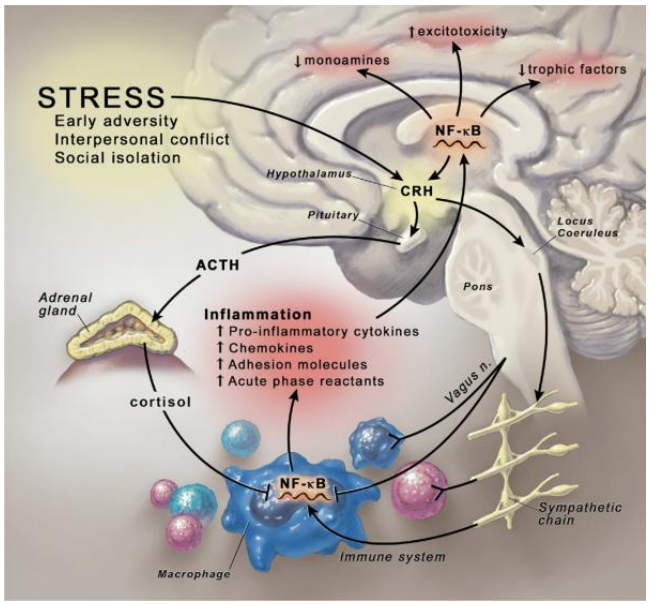

Figure 2: Stress-induced activation of the inflammatory response (27)

3.3.1 IMMUNE PATHWAYS

INFLAMMASOMES

The exposure to psychosocial stress activates neuroendocrine pathways, sympathetic nervous system (SNS) and HPA axis, which have been associated with the inflammasomes activity. Inflammasomes are a group of complexes of proteins which are formed in myeloid cells in response to pathogens and stress. They recognize pathogen associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) and control the production of pro-inflammatory cytokines such as Interleukin-18 (IL-18) and IL-1β (28). DAMPs include ATP, heat shock proteins (HSPs), uric acid and other molecules linked with oxidative stress.

TRANSMISSION INFLAMMATORY SIGNALS TO THE BRAIN

Some studies demonstrate an inflammation activation in the depressive brain so that the inflammatory response produced in peripherical blood by psychosocial stress may produce brain inflammation that cause a depression. The studies describe the following pathways:

- Humoral pathway: cytokine go through blood-brain barrier (BBB) by leaky regions.
- Neural pathway: cytokine enter the brain by peripheral afferent nerve fibres.

- Cellular pathway: activated immune cells, monocytes typically, enter the brain by parenchyma and vasculature (24).

BRAIN INFLAMMATORY EFFECT

Cytokines reduce the synaptic availability of the monoamines, which links with the monoamine hypothesis, one of the most accepted pathophysiological MDD hypothesis. Pro-inflammatory cytokines type I and II, IL-1β and TNF reduce the synaptic serotonin, dopamine and noradrenaline availability by the potentiation of the presynaptic transporters. Furthermore, activated microglia can lead to excessive glutamate which can be linked with glutamate hypothesis. Regarding the representation of these facts to the regional brain activity, the dopamine has been shown to decrease in basal ganglia, associated with the reduce of motivation and reward circuit (24). See figure 3.

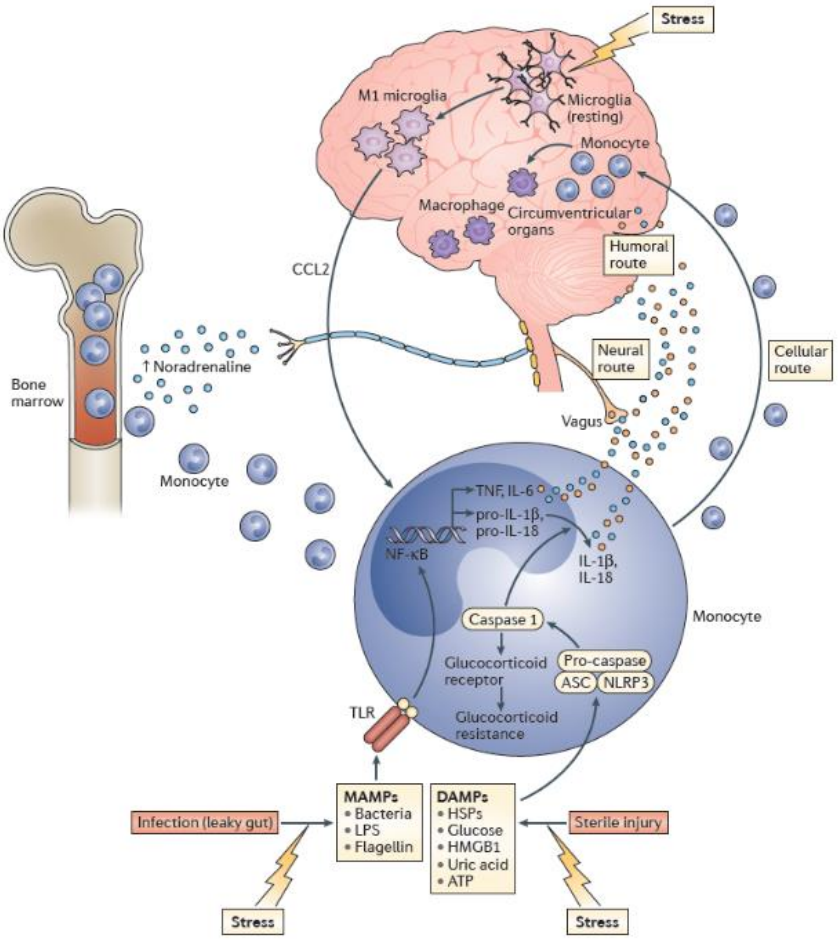

Figure 3: Transmitting stress-induced inflammatory signals to the brain (24)

3.3.2 DEPRESSIVE RISK AND RESILIENCE

Some studies have demonstrated an association between increased CRP in peripheral blood and the risk of cognitive depressive symptoms (29). In addition, childhood and adult trauma are associated with inflammatory increasing and have shown to be predictive of higher risk of depressive disorders development (30).

Regarding resilience, studies shows a protection against stress and depression produced by T cells, in vitro. It is believed that T cells produce Interleukin-4 (IL-4) which stimulate BDNF, so T cells may have an implication in inflammatory reduction and supporting neuronal integrity. Some studies have demonstrated a reduce of T cells $CD4^+$ and $CD25^+$ in peripherical blood in MDD patients (31).

3.4 SARS-CoV-2 PANDEMIC AND DEPRESSION

3.4.1 MENTAL EFFECTS OF THE PANDEMIC

Meta-analysis and systematic reviews demonstrated an increase of physiological and psychiatric disorders due to SARS-CoV-2 pandemic. The most common indicators were anxiety and depression, and patients with pre-existing psychiatric condition showed an increased prevalence compared to general population. Regarding risk factors, studies coincide on: being women, being nurses, with a high risk of infection, social isolation, low socioeconomic status, spending a lot of time reading and watching SARS-CoV-2 pandemic news (32), also adults with multi comorbidities and children and women that suffer from domestic violence (33). In addition, other risk factors have been found such as unemployment, high number of people living in the same house or flat, having children at school, stressful events, loss of income, having a good income, big houses without paying mortgage and a great amount of savings, protective factors for mental health (34). Moreover, major risk of depression and anxiety has been associated with the 21-40 age group, due to their concerns over future consequences and economic challenges. The impact of SARS-CoV-2 pandemic is not only is affecting health and mental health population, but also the economy of countries and their individuals (35).

Finally, the lockdown has increased social distancing which can cause poor social support. In addition, the concern of being infected and concern about a family member loss, etc, can be considered a life adversity and also, can increase the stress.

3.4.2 SARS-CoV-2, INFLAMMATION AND DEPRESSION

Some studies have demonstrated a correlation between the SARS-CoV-2 infection and depression, explained by the immune activation that the virus produced. This fact links the SARS-CoV-2 pathophysiology of the CRS and the MDD proinflammatory hypothesis. Although there is an association observed, the causality could also be explained by other factors: stressors such as social isolation, concern about infecting others, the dangerous consequences of the infection and stigma, can lead to an inflammatory response which links with the MDD proinflammatory hypothesis. In fact, on this study the hospitalization time was inversely correlated with depression which suggests that less care support can increase the psychiatric disorders (36). Regarding the invasion of the CNS by the virus, researchers confirmed the presence of SARS-CoV-2 in the CSF. This fact supports the inflammation of the CNS that explains the inflammatory hypothesis of the depression (37).

4. JUSTIFICATION

MDD represents an important health issue due to its high prevalence, 264 million people affected and its impact on patient's quality of life. In addition, it has an important impact on family and social structure, as it is associated with a major use of the healthcare resources. Moreover, it has an elevated morbidity and mortality due to suicide and its elevated association with physical diseases (13). On the other hand, it is one of the most frequent mental disorder as well as one of the major suicidal risk factors. Another argument that support that high impact is the early onset and its chronic and recurrently pattern, representing one of the main causes of disability and its high disease burden. As a result, it not only represents an important issue for the countries' health system, but also for society (5). That's why investigation on MDD is important.

The discovery of the inflammation effects caused by the SARS-CoV-2 in MDD patients will bring us the following benefits:

- Knowledge improvement about the SARS-CoV-2 infection in mental health

Considering that SARS-CoV-2 infection is one of the major health problems scientific society is facing nowadays and that it is causing thousands of death per day in all over the world it is important to improve the knowledge about infection with the aim of preventing and treating the effects of the virus. Due to the emergent pandemic situation, although many countries are making a big effort in studying SARS-CoV-2 infection, it's important taken into consideration that studies have been done in a few periods of time, which could affect the scientific evidence. Furthermore, they cannot represent the long term impact of the pandemic. Therefore, the development of a long-term study will contribute to increase the scientific knowledge and evidence.

- Relationship between inflammation caused by virus and MDD

Even though the inflammatory hypothesis has been studied for long time, the SARS-CoV-2 pandemic is offering a great opportunity to study the relationship between the inflammation caused by the virus and MDD, which may be explained by the proinflammatory hypothesis of MDD, as there is a great number of MDD patients

exposed to the virus and a big need of information regarding the effects of the virus in the human body.

Indirectly, although the existence of hypothesis, the exact causes of MDD are still unknown which impedes the application of specific preventive measures. This fact links with the MDD underdiagnosis and undertreatment; it is estimated that 28% of the MDD patients in Spain are not diagnosed (5). Therefore, the expansion of MDD knowledge will lead future studies about the prevention and the detection of MDD patients, focusing on the proinflammatory pathophysiology.

In addition, the demonstration of a direct correlation between SARS-CoV-2 and the worsening of MDD symptoms will entail and improvement for the recurrence risk factors which would include the infection as a risk factor.

Finally, the ampliation of knowledge about the proinflammatory hypothesis, can bring information for new projects that apart from leading to more information for the MDD prevention and detection, may result in the development of novel antidepressant therapies, by demonstrating the therapeutic potential of targeting the immune system to treat depression (24).

5. HYPOTHESIS

The SARS-CoV-2 infection aggravates MDD symptomatology on previously-diagnosed patients from *Xarxa de Salut Mental I Addiccions de Girona*.

6. OBJECTIVES

Main objective: to demonstrate that infection with SARS-CoV-2 aggravates MDD symptomatology in previously-diagnosed patients from *Xarxa de Salut Mental i Addiccions de Girona*.

Secondary objective: to study if patients with higher inflammatory parameters suffer from a major worsening of the MDD symptomatology.

7. METHODOLOGY

7.1 STUDY PROTOCOL

At the beginning of the study any of the patients will be exposed to SARS-CoV-2 infection, as it is an exclusion criteria. During the study and once the results are obtained, two groups will be established: the exposed group to virus infection and the unexposed group.

7.2 STUDY DESIGN

This study is designed as an observational prospective cohort study with matching carried out from August 2020 to October 2022 in the XSMA of Girona region. The patients' follow-up will take 1 year.

7.3 STUDY POPULATION

The study population will be formed by adults with a previous MDD diagnosis of the XSMA of Girona region which have been diagnosed by DSM-5 diagnosis criteria. They will be selected in the CSMAs, and included in the study once their informed consent is signed.

7.3.1 INCLUSION CRITERIA

- Individuals with previous MDD diagnosis of the XSMA of Girona which have been diagnosed by DSM-5 diagnosis criteria.
- Individuals with 18 years old or more.
- Individuals who agree to participate in the study by understanding and signing the informed consent.
- Individuals who are able to cooperate in the study

7.3.2 EXCLUSION CRITERIA

- Individuals who have or have had SARS-CoV-2 infection
- Individuals with another psychiatric diagnosis

- Individuals with substance use disorder
- Individuals with inflammatory diseases (cancer, systemic inflammatory disease, chronic infection)
- Individuals who did not achieve infection's resolution one week before the study begun (38)

7.3.3 MATCHING CRITERIA

- Sex: female/male
- MDD evolution time: less than 2 years/more than 2 years
- MDD severity: no depression or mild depression (0 - 18 in HDRS) / moderate or severe depression (19 -53)
- Employment situation: employed/unemployed

7.4 SAMPLE

7.4.1 SAMPLE SELECTION

Participants will be selected by their psychiatrist in their follow up visits, so the selection will be done following the non-probabilistic consecutive model. Patients will be chosen applying the inclusion and exclusion criteria. They will be given the information document of the study (Annex 1) and they will be informed of the study objective. After receiving the information, those who want to participate in the study will be given the informed consent (Annex 2).

7.4.2 SAMPLE SIZE

We have not found similar studies to make the sample calculation. For this reason, we have considered the study as a pilot study. For the sample selection the dependent variable will be included as a discrete quantitative variable.

We will analyse 20 patients of each exposure group and with the data obtained we will calculate the final sample with the following parameters: alpha risk of 0.05 and a beta risk of 0.2 in a two-side test. The common standard deviation assumed will be 8.4 (39) and an anticipated a drop-out rate of 10% will be assumed.

According to data, the prevalence of MDD in Spain is 1.363.200 (3). Taking into consideration that Spain has 47.329.981 habitants (40) and the XSMA region of Girona has 750.000 habitants (41), it can be estimate that are 21.601 people with MDD in the Girona region. Additionally, the SARS-CoV-2 prevalence is estimated at 5,9% in Catalonia region (19). With this data we can estimate the current seroprevalence of the MDD patients of XSMA, which will be 1.275 MDD patients that have been infected by SARS-CoV-2. Therefore, one-year follow-up of patients will be enough for obtaining two groups patients based on the virus exposure.

7.5 STUDY VARIABLES AND DATA COLLECTION

7.5.1 INDEPENDENT VARIABLE

Infection for SARS-CoV-2

The SARS-CoV-2 infection will be tested via RT-PCR test (gold standard) for the detection of the active infection and the antibody test for demonstrating that the person was infected by the virus in the past (22).

RT-PCR test

The sample is collected from:

- The upper respiratory tract: preferably from nasopharynx and oropharynx.

- Lower respiratory tract: preferably from bronchoalveolar lavage, bronchial aspiration, sputum and/or endotracheal aspiration, especially in patients with severe respiratory disease.

It will be analysed in the hospital laboratory.

Test limitations: as its sensibility depends on the viral load in the airway, a negative test in a patient with symptoms does not exclude infection. Moreover, the sample extraction requires trained professionals. Even tough, the results are obtained within 12 to 24 hours, for our study it is not going to represent a disadvantage (22).

Antibody test

The sample is collected from the patient's blood and sent to the hospital laboratory and the result is obtained in 20 minutes (42) (43).

Test limitations:

- False positives: antibody tests may detect other coronavirus.
- False negative: when the patient is tested too early (before the body have created the immune response against the virus infection) or if it is done when the antibody levels have already decrease (44).

The results will be represented as a dichotomous qualitative variable:

- SARS-CoV-2 infection: it includes those people with active infection (positive RT-PCR test) and those who were infected in the past (positive Antibody test).
- No SARS-CoV-2 infection: it includes those people with negative results in both tests.

When a positive result is found, physicians have to fulfil a SARS-CoV-2 register which is standardized and globalized in all Catalan hospitals.

7.5.2 DEPENDENT VARIABLE

MDD symptomatology

The MDD symptomatology aggravation will be analysed by HDRS (Annex 3) (5)**.**

The variable could be presented as a discrete quantitative variable (from 0 to 53) or as an ordinal qualitative variable (no depression: 0-7 / subclinical depression: 8-13 / mild depression: 14-18 / moderate depression: 19-22 / severe depression: >23).

7.5.3 COVARIATE

The covariables included have been related with the risk of MDD and the risk of recurrence of MDD episodes. Moreover, previous infection is added because can be a misleading SARS-CoV-2 association with MDD. MDD data can also influence, as well as severity of the infection. The inflammatory parameters are analysed has a secondary objective.

SOCIODEMOGRAPHIC FACTORS:

- Sex: will be presented as a dichotomous qualitative variable (male / female).
- Age: will be a continuous quantitative variable.
- Marital state: will be presented as a nominal qualitative variable (married / divorced / single / widower).
- Employment situation: will be presented as a dichotomous qualitative variable (employed / unemployed).
- Socioeconomic status: will be presented as 3 ordinal qualitative variable based on the *Enquesta de Salut de Catalunya* (ESCA)(45):
    - Studies level: no studies or primary studies, secondary studies, university degree.
    - Social class: class I (managers, university professionals, directors), class II (intermediate occupations, self-employed workers), class III (manual workers).
    - Employment situation: housework, unemployed, active worker.

MEDICAL INFORMATION:

- Familiar psychiatric history: presented as a dichotomous qualitative variable (yes / no).
- Drugs use: presented as a dichotomous qualitative variable (drug use during the last year / no drug use during the last year).
- Frequency of drug use: it evaluates cannabis, alcohol, cocaine, opiates and amphetamines, and it is expressed as an ordinal qualitative variable with five categories: (Absence of drug use / Daily use / Once a week use / Once a month use / Once a year use)

MDD DATA:

- Disease evolution time: represented as a discrete quantitative variable measured by years.
- Number of hospitalizations: represented as a discrete quantitative variable.

- MDD treatment: represented with the following variables:
    - Treatment changes because of inefficacy: presented as a dichotomous qualitative variable (yes / no).
    - Increase of the drug/s dose because of inefficacy: presented as a dichotomous qualitative variable (yes / no).
    - Treatment adherence: measured by Simplified Medication Adherence Questionnaire (SMAQ) (Annex 4) (46). The questionnaire results will be expressed as a dichotomous qualitative variable (adherence / non-adherence).
- Suicidal behaviour: each suicidal behaviour type will be represented by a discrete quantitative variable: suicidal thoughts, suicidal threats, suicide attempts.
- Suicidal risk scale: it will be measured with the Beck's Hopelessness Scale (BHS) (Annex 5) (47) and expressed as an ordinal qualitative variable [minimal (0-3) / mild (4-8) / moderate (9-14) / severe (15-20)].
- Functionality scale: it will be measured with the Global Assessment of Functioning Scale (GAF) (Annex 6) (48) and expressed as a discrete quantitative variable [1-100 (major punctuation represents a major functionality)].

SOCIAL SUPPORT: measured with MOS Social Support Survey (Annex 7) (49) and expressed as a discrete quantitative variable [19-95 (major punctuation represents a major social support)].

STRESSORS: measured with The Holmes-Rahe Life Stress Inventory (Annex 8) (50). It will be exposed as ordinal qualitative variable [mild (≤150) / moderate (150-300) / severe (≥300)].

INFECTIONS: it will be represented as a dichotomous qualitative variable; individuals who have had an infection have achieved infection's resolution one week before the blood sample collection (yes /no).

INFLAMATORY PARAMETERS: All the parameters are quantitative continuous; however, CRP and IL-6 levels will be categorized:

- White blood cells: quantitative continuous variable.

- CRP: ordinal qualitative variable: [low inflammation (<1.0 mg/L) / moderate inflammation (1.0 – 3.0 mg/L) / high inflammation (>3.0mg/L)] (51).
- IL-6: presented as a dichotomous qualitative variable: (levels above 5 pg/mL / levels under 5pg/mL). Levels above 5pg/mL have been associated with more depression (52).

SARS-CoV-2 INFECTION SEVERITY:

The severity of the infection will be expressed as an ordinal qualitative variable with the following categories obtained from WHO SARS-CoV-2 disease severity classification (Annex 9) (53): [Asymptomatic / Mild disease / Moderate disease (pneumonia) / Sever disease (sever pneumonia) / Critical disease (acute respiratory distress syndrome) / Critical disease (sepsis) / Critical disease (septic shock)].

7.6 MEASURING INSTRUMENTS

7.6.1 HAMILTON DEPRESSION RATING SCALE

The HRSD was designed for evaluate the intensity or severity of the depression. It is one of the most used scales to monitor the depressive symptom's evolution in clinics and investigation.

The total punctuation of the scale is 53 points and inform of the severity of the depressive symptoms regarding 17 items: no depression (0-7), subclinical depression (8-13), mild depression (14-18), moderate depression (19-22), severe depression (>23).

Moreover, it can be obtained three factors punctuation with the addition of the items that conform the factor: melancholia (items 1, 2, 7, 8, 10 y 13); anxiety (items 9-11) and sleep (items 4-6).

7.6.2 SIMPLIFIED MEDICATION ADHERENCE QUESTIONNAIRE

Designed for evaluate the treatment adherence via 6 direct questions. The last question is semiquantitative and indicates the percentage of therapeutic compliance.

The following items answer are considered in the non-adherence category:

1: yes / 2: no / 3: yes / 4: yes / 5: C, D or E / 6: more than 2 days

With only one answer that indicate no adherence, the questionnaire result will be considered non-adherence.

The semiquantitative question is represented in the following adherence percentages; A: 95-100% of adherence, B: 85-94% of adherence, C: 65-84% of adherence, D: 30-64% of adherence, E: < 30% of adherence.

7.6.3 BECK'S HOPELESSNESS SCALE

The BHS was created to asses pessimism in patients with suicidal risk. The scale is confirmed by 20 items in which patients must answer true or false. The items that indicate hopelessness are scored with 1 point in contrast with those that do not indicate, which are scored with 0 points. It has 4 categories, described in the covariates section.

7.6.4 GLOBAL ASSESSMENT OF FUNCTIONING SCALE

The GAF is a scale which evaluates the functioning level of a patient. It is administrated by professionals and consist in one punctuation from 1 to 100. It is important to no include alterations of the activity caused by physic limitations.

7.6.5 MOS SOCIAL SUPPORT SURVEY

A 19-item survey of functional social support that represents multiple dimensions of support: emotional/informational, tangible, affectionate, and positive social interaction.

7.6.6 THE HOMES-RAHE LIFE STRESS INVENTORY

A scale designed for predict the health effects of the life stressors happened during the previous year. Conformed by 43 items, it used 3 categories described in the covariates section.

7.6.7 WHO SARS-CoV-2 DISEASE SEVERITY CLASSIFICATION

The WHO SARS-CoV-2 disease severity classification is a classification set by the WHO for helping physicians with the SARS-CoV-2 patient classification with the aim of organize and decide the health care facility and measures needed for each patient. The scale includes 7 categories described in the covariates section.

8. STATISTICAL ANALYSIS

8.1 DESCRIPTIVE ANALYSIS

The qualitative variables will be summarized by proportions in the exposed and unexposed groups.

The quantitative discrete variables will be summarized using the median and the interquartile rang, stratifying in exposed and non-exposed groups.

The analysis will be stratified by covariates.

8.2 BIVARIATE INFERENCE

The relationship between the SARS-CoV-2 infection and the MDD symptoms aggravation, explored by the HRSD, will be checked by the Mann Whitney test taking the HRSD results as a discrete quantitative variable, and by the X^2 test taking the HRSD results as an ordinal qualitative variable.

This analysis will be repeated for the rest of variables. The covariables will be analysed by the X^2 in case of qualitative variables, by the Mann-Whitney test in case of quantitative discrete variables and quantitative non-normal variables, and by the Student's t test in case of quantitative normal variables.

8.3 MULTIVARIATE ANALYSIS

The relationship between SARS-CoV-2 infection and the worsening of MDD symptoms will be adjusted in a logistic regression controlling for all other explanatory variables.

9. WORK PLAN AND CHRONOGRAM

9.1 WORK PLAN

The research will include the following stages:

9.1.1 STAGE 1: Protocol design and acceptance (5 months)

Protocol writing with wide literature review and presentation to Comité Ètic d'investigació Clínica (CEIC). The study will be carried out from August 2020 to October 2022. The patients' follow-up will take 1 year.

9.1.2 STAGE 2: Coordination and organization (2 months)

As the standardization of the data collection is very important, three coordination meetings will take place in the Santa Caterina Hospital:

- First meeting: presentation of the study design and explanation of the criteria used in sample selection.
- Second meeting: looking over the data collection items with the objective of standardize the process, focusing on the scales collection.
- Third meeting: recap on previous issues and help with any doubts before the participants recruitment.

These meetings will be attended by the main investigators, the psychiatrist and the nurses who will collect the data.

During the data collection, two meetings will be held for the data collection report; one after six-months period and another one when the data collection process ending.

Moreover, nursery staff who are not used to carry RT-PCR tests as a habitual procedure will be taught by an experienced nurse in the collection procedure.

9.1.3 STAGE 3: Participants recruitment (3 months)

The recruitment will be done by psychiatrist from the 7 CSMA's in the region (Annex 11). Patients who attend CSMA for their follow up visits and meet inclusion and exclusion criteria will be informed of the clinical, legal and ethical aspects of the study and will be

given the information sheet (Annex 1). If they are interested in participating in the study, they will be asked to sign the informed consent (Annex 2).

9.1.4 STAGE 4: Data collection and sample analysis (1 year and 3 months)

After having signed the informed consent, the participants will be scheduled for the data collection, which will take place in the same CSMA. In these appointments they will be given the data collection sheet (Annex 10) and will answer the scales (Annex 3, 4, 5, 6, 7, 8, 9) asked by physiatrists. Additionally, blood analysis and the SARS-CoV-2 test will be conducted by nurses and sent to the hospital laboratory. If needed, information will be collected from the medical history of the patients. The same procedure will be repeated once every 3 months during the follow-up year, except for the RT-PCR test and the Antibody test, which won't be collected if a positive results have been obtained so that the patient will already be in the group of exposed to the SARS-CoV-2. During the participants follow-up, the two exposure groups will be created considering the SARS-CoV-2 test results.

9.1.5 STAGE 5: Data analysis (2 months)

The results will be obtained by univariate, bivariate and multivariate analysis and analysed by a statistician.

9.1.6 STAGE 6: Results interpretation and writing (2 months)

The results of the analysis will be interpreted by the investigators and conclusions will be extracted. After that, the results and conclusions will be written in the final article.

9.1.7 STAGE 7: Publication and dissemination

Once the main researches will have the written report, it will be published it in several scientific journals and the study will be presented at the *Congreso Nacional de Psiquiatria* and at the Collegium Internationale Neuro-Psychopharmacologicum (CINP) international meeting.

9.2 STUDY CHRONOGRAM

STAGE	TASK	STAFF	CALENDAR								
			2020		2021			2022			
			Aug to Oct	Nov and Dec	Jan and Feb	Mar to May	Jun to Dec	Jan to Jun	Jun and Aug	Sep and Oct	From Nov
Stage 1	Protocol design	Main investigators									
	Protocol acceptance	CEIC									
Stage 2	Coordination and organization	All research team									
Stage 3	Participants recruitment	Referring psychiatrists									
Stage 4	Data collection and sample analysis	Referring psychiatrists, nurses and laboratory staff									
Stage 5	Data analysis	Main investigators and statistician									
Stage 6	Results interpretation and writing	Main investigator									
Stage 7	Publication and dissemination	Main investigators									

10. ETHICAL AND LEGAL CONSIDERATIONS

This study will take place in compliance with the ethical principles established by The World Medical Association in the Declaration of Helsinki, signed in 1964 and last revised in October 2013.

The study protocol will be sent to the CEIC of *Institut d'Investigació Biomèdica de Girona* (IdibGi) for evaluation and approval. It may be initiated after receiving its approval.

Articles included in the *Ley 41/2002, de 14 de Noviembre, Básica reguladora de la autonomía del paciente y de derechos y obligaciones en materia de información y documentación clínica*, will be considered. Therefore, before including the patients in the study, they will be informed of the ethical, legal and clinical aspects (Annex 1). Moreover, the informed consent will be given to them (Annex 2). It is important to explain to the individuals that they are free to accept or decline participation in the study.

According to the *Ley Orgánica 15/1999, de 13 de Diciembre, de protección de Datos de Carácter Personal* and in accordance with the *recent Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016*, the study will guarantee the confidentiality of the data obtained during the investigation of the study.

As biological samples will be collected during the study investigation, the *Ley 14/2007, de 3 de Julio, de investigación biomédica*, will be implemented.

No conflict of interest has been declared by the authors.

11. STUDY LIMITATIONS

There are some limitations that may interfere with the study results. Consequently, they should be considered:

Regarding the SARS-CoV-2 infection it is important to highlight, as mentioned before, that the recent discovery of that type of coronavirus, even though it is the focus of a lot of recent studies, the obtained information can have some scientific evidence limitations because of the short-term studies. Therefore, the descriptive information of the SARS-CoV-2 infection in this study can have some bias. Moreover, it is important to point out that the study design is based on the current information data, which leads to the possibility of not including some important factors regarding the disease. Another important issue is that, even we have done a deep research on the seroprevalence and the epidemiological tendency of the infection, there could be many unknown factors that can change the tendency of the infection complicating the study results obtention. One of these factors could be the discovery and application of an effective vaccine which can imply small expose group. Last but not least, the exposition variable of the study, the SARS-CoV-2 infection, can cause patient's death. The mortality is markedly different in the different populational groups, for instance, older patients and those who have more medical comorbidities have major taxes of mortality. That is why in the sample selection we will contemplate the risk of losing participants because of this fact.

As explained in the study introduction, the MDD pathophysiology is not well known and one of its negative effects is included in the knowledge of the MDD risk factors. As a consequence, even we have contemplated the known risk factors as a covariate, there could be some other unknown factors creating confusion and bias.

In addition, the sample selection can have some limitations. As the selection sample will be done by non-probabilistic consecutive model, selecting the participants that are going to the follow-up visits, it would imply a selection bias. For that reason, we will apply a matching with the aim of reducing this bias.

Regarding the exclusion criteria, results will not represent all the MDD patients as patients who have an additional psychiatric disorder apart from the MDD diagnosis will be excluded from the study. It is important to mention that fact because the MDD is frequently associated with other disorders. However, exclusion criteria are needed because the main objective of the study is demonstrating the association between the MDD and de SARS-CoV-2 infection, therefore, including patients with another psychiatric disorder will bring confusion.

Furthermore, some of the study variables are collected via scales and even though all of them are validated scales, the results can depend on the observer who performs the interviews. In order to reduce this bias, the professionals will be instructed at the beginning of the study to create a consensus in the collection of each scale. Moreover, we will minimize the number of professionals that will perform the obtaining of results.

Finally, as the study design is a prospective cohort study, it will have the limitations of an elevated cost and a long period of study which can increase the risk of participants loss. To avoid that, the physicians will use motivational interviewing. Despite the described limitations, the choice of this model of study has been done with the objective of observing the evolution of exposed and unexposed patients to the temporal sequence, and reducing the elevated probability of bias, cause by a case-control study design.

12. FEASIBILITY

The XSMA of the *Institut d'Assistència Sanitaria* (IAS) is the public network specialized in mental health of the Girona region population (750.000 inhabitants). It is involved in two areas: community care and hospital care. One of the community care facilities is the CSMA (Annex 11). It is formed by 7 centres which have a permanent contact.

In addition, we have the participation of different psychiatrists working at the IAS, who already have a great deal of experience in this field. They will combine their healthcare work with the active participation of this study, at no additional cost.

As XSMA is the reference unit for the whole Girona Province population, the collaboration of other institutions won't be needed.

Regarding the budget, we can add that it has been adjusted as much as possible considering that it is a long follow-up study and that the laboratory study is expensive.

Consequently, we consider that this study is feasible regarding the sample availability, the professionals involved and the estimated budget.

13. BUDGET

STAFF		
Statisticians	35€/h x 70h	2.450€
MATERIAL		
Documents printing (study information and informed consent)	0,05€/page (3 pages per person)	Will depend on the final sample size
Blood analysis (inflammatory parameters)	50€ per person each time	Will depend on the final sample size
SARS-CoV-2 RT-PCR test	93€ per person each time	Will depend on the final sample size
Antibody test	36,54€ per person each time	Will depend on the final sample size
PUBLICATION		
Publication in open access journal		2.000€
CONFERENCES		
C*ongreso Nacional de Psiquiatria*		1.000€
CINP		2.000€
TOTAL		€

Material such as computers and sites for the coordination meetings and the patients interviews are not included in the budget as are already available in the different CSMAs.

On the other hand, psychiatrists and nurses involved in the study are from the XSMA and will not receive financial compensation for their work.

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15. ANNEXES

ANNEX 1. Information sheet

FULL INFORMATIU PER ALS/LES PARTICIPANTS

Principals investigadors/es: Joana Díaz i Font i Domènec Serrano Sarbosa

Títol de l'estudi: The effects of SARS-CoV-2 infection on Major Depressive Disorder symptomatology

Benvolgut/uda,

Agraïm el seu interès i participació a l'estudi al qual el/la convidem a participar. La seva col·laboració és de gran ajuda per a poder desenvolupar de manera adient el projecte ideat. A continuació li exposarem detalladament els motius del present estudi, així com els detalls que en necessita conèixer. Si us plau, llegeixi atentament tota la informació, i no dubti en consultar qualsevol aspecte amb la persona que li entrega el present document, quan ho consideri necessari.

GENERALITATS DEL PROJECTE

L'estudi serà dut a terme per psiquiatres de la Xarxa de Salut Mental i Addiccions de Girona amb una durada d'un any. El projecte de recerca ha estat avaluat i aprovat pel Comitè Ètic d'investigació Clínica de Institut d'Investigació Biomèdica de Girona.

QUINS SÓN ELS OBJECTIUS I FINALITAT DE L'ESTUDI?

El principal objectiu de l'estudi és valorar si es produeix un empitjorament de la clínica depressiva, en pacients amb diagnòstic de Trastorn Depressiu Major previ, en aquells/es pacients que pateixen la infecció del virus SARS-CoV-2.

De manera secundaria, mitjançant l'obtenció de mostres sanguínies, es vol valorar si aquells/es pacients amb paràmetres inflamatoris més elevats pateixen un major empitjorament dels símptomes.

QUÈ HE DE FER AL PARTICIPAR A L'ESTUDI?

Primerament, és important remarcar que la seva participació a l'estudi és totalment voluntària i que és lliure d'abandonar la seva participació en qualsevol moment, sense necessitat de justificar-se i sense que la seva assistència mèdica es vegi perjudicada per aquest fet. També remarcar que la participació a l'estudi és gratuïta i no remunerada.

Pel que fa a la part pràctica, la seva funció serà assistir a les visites que se li assignin, de manera acordada, amb els professionals del seu Centre de Salut Mental d'Adults. Durant les visites, que es realitzaran cada 3 mesos durant 1 any, se li faran una sèrie de preguntes per omplir un formulari, se li passaran unes escales i se li realitzaran una analítica de sang, un test PCR i una serologia per la detecció de la infecció del SARS-CoV-2. Aquestes últimes proves seran realitzades per el personal d'infermeria del centre.

UN COP FINALITZAT L'ESTUDI, TINDRÉ ACCÉS A LES MEVES DADES?

Sí, tots i totes les participants a l'estudi tindran dret a accedir a la informació i conclusions que se'n derivin, així com a rebre una explicació de les dades pròpies, sempre que així ho desitgin.

PUC SORTIR PERJUDICAT/ADA AMB LA MEVA PARTICIPACIÓ EN L'ESTUDI?

En el present estudi s'aplicaran mesures per garantir la confidencialitat de les seves dades en compliment de la *Ley Orgánica 15/1999, de 13 de Diciembre, de protección de Datos de Carácter Personal* i també, *Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016.* Per aquest motiu les dades seran recollides de forma anònima i utilitzades només per a finalitats investigadores. També es garantiran els articles de la *Llei 14/2007* d'investigació biomèdica.

QUINS BENEFICIS S'OBTINDRAN AMB AQUEST ESTUDI?

El principal benefici que s'espera obtenir és conèixer la relació que tenen el virus SARS-CoV-2 i el Trastorn Depressiu Major per tal de poder fer actuacions en aquest nivell, i a més a més avançar en el coneixement del trastorn en relació a la teoria inflamatòria. Per tant els resultats podran beneficiar a les persones afectades i serviran de base per a investigacions futures.

ANNEX 2. Informed consent

CONSENTIMENT INFORMAT

Títol de l'estudi: The effects of SARS-CoV-2 infection on Major Depressive Disorder symptomatology

Jo (Nom i Cognoms)_____

- He llegit la fulla informativa sobre l'estudi que se m'ha entregat.
- He pogut fer totes les preguntes necessàries respecte l'estudi.
- He rebut suficient informació sobre l'estudi.
- He estat informat per l'investigador/a _____ _____de les implicacions i finalitats de l'estudi.
- Entenc que la meva participació és voluntària.
- Entenc que es respectarà la confidencialitat de les meves dades.
- Entenc que puc revocar el meu consentiment de participació a l'estudi, sense haver de donar justificacions i sense afectar la meva assistència sanitària.

Accepto participar de forma voluntària a l'estudi.

Accepto que els investigadors i investigadores principals de l'estudi puguin contactar amb mi si en un futur es considera oportú.

En cas afirmatiu; telèfon o correu electrònic: _____

Signatura del/la participant,

Signatura investigador/a,

Data: _____, _____ de_____ de l'any_____

ANNEX 3. Hamilton Rating Scale for Depression

ESCALA DE HAMILTON PARA LA DEPRESIÓN

Versión de JA Ramos-Brieva y A Cordero-Villafáfila

1- ESTADO DE ÁNIMO DEPRIMIDO_____[ ]

0 *Ausente*
1 *Ligero*: actitud melancólica; el paciente no verbaliza necesariamente el descenso del ánimo
2 *Moderado*: llanto ocasional, apatía, pesimismo, desmotivación....
3 *Intenso*: llanto frecuente (o ganas); introversión; rumiaciones depresivas; pérdida del gusto por las cosas
4 *Extremo*: llanto frecuente (o ganas); frecuente tendencia al aislamiento; contenidos depresivos exclusivos en el pensamiento o la comunicación verbal; pérdida de la capacidad de reacción a estímulos placenteros

2- SENTIMIENTOS DE CULPA_____[ ]

0 *Ausente*
1 *Ligero*: autorreproches, teme haber decepcionado a la gente
2 *Moderado*: ideas de culpabilidad; sentimiento de ser una mala persona, de no merecer atención
3 *Intenso*: la enfermedad actual es un castigo; meditación sobre errores, malas acciones o pecados del pasado; merece lo que padece
4 *Extremo*: ideas delirantes de culpa con o sin alucinaciones acusatorias

3- SUICIDIO_____[ ]

0 *Ausente*
1 *Ligero*: la vida no vale la pena vivirla
2 *Moderado*: desearía estar muerto o piensa en la posibilidad de morirse
3 *Intenso*: ideas o amenazas suicidas
4 *Extremo*: serio intento de suicidio

4- INSOMNIO INICIAL (si toma hipnóticos y no puede evaluar, puntúe 1)_____[ ]

0 *Ausente*
1 *Ocasional*: tarda en dormir entre media y una hora (<3 noches/semana)
2 *Frecuente*: tarda en dormir más de una hora (3 ó más noches /semana)

5- INSOMNIO MEDIO (si toma hipnóticos y no puede evaluar, puntúe 1)_____[ ]

0 *Ausente*
1 *Ocasional*: está inquieto durante la noche; si se despierta tarda casi una hora en dormirse de nuevo (<3 noches/semana)
2 *Frecuente*: está despierto durante la noche, con dificultades para volver a conciliar el sueño; cualquier ocasión de levantarse de la cama (excepto para evacuar), o necesidad de fumar o leer tras despertarse debe puntuar 2 (3 ó más noches seguidas por semana)

6- INSOMNIO TARDÍO (si toma hipnóticos y no puede evaluar, puntúe 1)_____[ ]

0 *Ausente*
1 *Ocasional*: se despierta antes de lo habitual (<2 horas antes; <3 días por semana)
2 *Frecuente*: se despierta dos o más horas antes de lo habitual 3 ó más días por semana)

7- TRABAJO Y ACTIVIDADES_____[ ]

0 *Ausente*
1 *Ligero*: ideas o sentimientos de incapacidad o desinterés. Distíngalo de la fatiga o pérdida de energía que se puntúan en otra parte.
2 *Moderado*: falta de impulso para desarrollar las actividades habituales, las aficiones o el trabajo (si el paciente no lo manifiesta directamente, puede deducirse por su desatención, indecisión o vacilación ante el trabajo y otras actividades).
3 *Intenso*: evidente descenso del tiempo dedicado a sus actividades; descenso de su eficacia y/o productividad. En el hospital se puntúa 3 si el paciente no se compromete al menos durante tres horas/día a actividades (Trabajo hospitalario o distracciones) ajenas a las propias de la sala. Notable desatención del aseo personal.
4 *Extremo*: dejó de trabajar por la presente enfermedad. No se asea o precisa de gran estímulo para ello. En el hospital se puntúa 4 si el paciente no se compromete en otras actividades más que a las pequeñas tareas de la sala o si precisa de gran estímulo para que las realice.

8- INHIBICIÓN_____ [ ]
0 *Ausente*
1 *Ligera*: ligera inhibición durante la entrevista; sentimientos ligeramente embotados; facies inexpresiva.
2 *Moderada*: evidente inhibición durante la entrevista (voz monótona, tarda en contestar las preguntas).
3 *Intensa*: entrevista difícil y prolongada; lentitud de movimientos al caminar.
4 *Extrema*: estupor depresivo completo; entrevista imposible.

9- AGITACIÓN_____ [ ]
0 *Ausente*
1 *Ligera*: mueve los pies; juega con las manos o con los cabellos
2 *Moderada*: se mueve durante la entrevista, se agarra a la silla; se retuerce las manos; se muerde los labios; se tira de los cabellos; mueve ampliamente los brazos, se muerde las uñas, las manos...
3 *Intensa*: no puede estarse quieto durante la entrevista; se levanta de la silla.
4 *Extrema*: la entrevista se desarrolla "corriendo", con el paciente de un lado para otro, o quitándose la ropa, o arrancándose los cabellos; el paciente parece desconcertado y "desatado".

10- ANSIEDAD PSÍQUICA_____ [ ]
0 *Ausente*
1 *Ligera*: tensión subjetiva e irritabilidad.
2 *Moderada*: tensión objetiva, evidente; preocupación por trivialidades.
3 *Intensa*: actitud aprensiva evidente en la cara y el lenguaje.
4 *Extrema*: crisis de ansiedad observadas, la ansiedad forma la mayor parte del contenido de su comunicación espontánea, verbal o no verbal.

11- ANSIEDAD SOMÁTICA_____ [ ]
0 *Ausente*
1 *Ligera*: un solo síntoma o síntoma dudoso o varios síntomas de un mismo sistema.
2 *Moderada*: varios síntomas de distintos sistemas.
3 *Intensa*: múltiples síntomas de varios sistemas simultáneamente.
4 *Extrema*: numerosos síntomas persistentes e incapacitantes la mayor parte de las veces.

12- SÍNTOMAS SOMÁTICOS GASTROINTESTINALES_____ [ ]
0 *Ausentes*:
1 *Ligeros*: pérdida de apetito, pero come sin necesidad de estímulo; sensación de pesadez en el abdomen.
2 *Intensos*: pérdida de apetito, no come aunque se le estimule, o precisa de gran estímulo para comer; precisa o solicita laxantes o medicación para sus síntomas gastrointestinales.

13- SÍNTOMAS SOMÁTICOS GENERALES_____ [ ]
0 *Ausentes*:
1 *Ligeros*: fatigabilidad, pérdida de energía, pesadez en extremidades, espalda, cabeza; algias en el dorso, cabeza, músculos.
2 *Intensos*: fatigabilidad y pérdida de energía la mayor parte del tiempo; cualquier síntoma somático bien definido o expresado espontáneamente.

14- SÍNTOMAS GENITALES (preguntar siempre)_____ [ ]
0 *Ausentes*: o información inadecuada o sin información (emplear lo menos posible estas dos últimas).
1 *Ligeros*: descenso de la líbido; actividad sexual alterada (inconstante, poco intensa).
2 *Intensos*: pérdida completa de apetito sexual; impotencia o frigidez funcionales.

15- HIPOCONDRÍA_____ [ ]
0 *Ausente*:
1 *Ligera*: preocupado de sí mismo (corporalmente).
2 *Moderada*: preocupado por su salud.
3 *Intensa*: se lamenta constantemente. Solicita ayuda, etc.
4 *Extrema*: ideas hipocondríacas delirantes.

16- PÉRDIDA DE INTROSPECCIÓN_____ [ ]

0 *Ausente*: se da cuenta de que está enfermo, deprimido.

1 *Ligera*: reconoce su enfermedad, pero la atribuye a la mala alimentación, al clima, al exceso de trabajo, a una infección viral, a la necesidad de descanso, etc.

2 *Moderada*: niega estar enfermo o el origen nervioso de su enfermedad.

17- PÉRDIDA DE PESO_____ [ ]

0 *Ausente*:

1 *Ligera*: probable pérdida de peso asociada a la enfermedad actual; pérdida superior a 500 gr/semana ó 2,5 kg/año (sin dieta).

2 *Intensa*: pérdida de peso definida según el enfermo; pérdida superior a 1 kg/semana ó 4,5 kg/año (sin dieta).

PUNTUACIÓN TOTAL_____ [ ]

ANNEX 4. Simplified Medication Adherence Questionnaire

Cuestionario adherencia SMAQ	
1. ¿Alguna vez olvida tomar la medicación?	Sí ❑ No ❑
2. ¿Toma siempre los fármacos a la hora indicada?	Sí ❑ No ❑
3. ¿Alguna vez deja de tomar los fármacos si se siente mal?	Sí ❑ No ❑
4. ¿Olvidó tomar la medicación durante el fin de semana?	Sí ❑ No ❑
5. En la última semana, ¿cuántas veces no tomó alguna dosis?[2]	A: ninguna B: 1 - 2 C: 3 - 5 D: 6 - 10 E: más de 10
6. Desde la última visita, ¿cuántos días completos no tomó la medicación?	Días: ....

[1]Se considera no adherente: 1: sí, 2: no, 3: sí, 4: sí, 5: C, D o E, 6: más de dos días. El cuestionario es dicotómico, cualquier respuesta en el sentido de no adherente se considera no adherente. [2]La pregunta 5 se puede usar como semicuantitativa: A: 95-100% adhesión; B:85-94%; C:65-84%; D:30-64%; E: < 30%.

ANNEX 5. Beck's Hopelessness Scale

Se trata de una escala **autoadministrada**

Instrucciones para el paciente: Por favor, señale si las siguientes afirmaciones se ajustan o no a su situación personal. Las opciones de respuestas son verdadero o falso.

	V	F
1. Espero el futuro con esperanza y entusiasmo		
2. Puedo darme por vencido, renunciar, ya que no puedo hacer mejor las cosas por mí mismo		
3. Cuando las cosas van mal me alivia saber que las cosas no pueden permanecer tiempo así		
4. No puedo imaginar como será mi vida dentro de 10 años		
5. Tengo bastante tiempo para llevar a cabo las cosas que quisiera poder hacer		
6. En el futuro, espero conseguir lo que me pueda interesar		
7. Mi futuro me parece oscuro		
8. Espero más cosas buenas de la vida que lo que la gente suele conseguir por término medio		
9. No logro hacer que las cosas cambien, y no existen razones para creer que pueda en el futuro		
10. Mis pasadas experiencias me han preparado bien para mi futuro		
11. Todo lo que puedo ver por delante de mí es más desagradable que agradable		
12. No espero conseguir lo que realmente deseo		
13. Cuando miro hacia el futuro, espero que seré más feliz de lo que soy ahora		
14. Las cosas no marchan como yo quisiera		
15. Tengo una gran confianza en el futuro		
16. Nunca consigo lo que deseo, por lo que es absurdo desear cualquier cosa		
17. Es muy improbable que pueda lograr una satisfacción real en el futuro		
18. El futuro me parece vago e incierto		
19. Espero más bien épocas buenas que malas.		
20. No merece la pena que intente conseguir algo que desee, porque probablemente no lo lograré		
PUNTUACIÓN TOTAL		

ANNEX 6. Global Assessment of Functioning Scale

[Hay que considerar la actividad psicológica, social y laboral a lo largo de un hipotético *continuum* de salud-enfermedad. No hay que incluir alteraciones de la actividad debidas a limitaciones físicas (o ambientales).]

100 91	**Actividad satisfactoria en una amplia gama de actividades, nunca parece superado por los problemas de su vida, es valorado por los demás a causa de sus abundantes cualidades positivas. Sin síntomas.**
90	**Síntomas ausentes o mínimos** (p. ej., ligera ansiedad antes de un examen), **buena actividad en todas las áreas, interesado e implicado en una amplia gama de actividades, socialmente eficaz, generalmente satisfecho de su vida, sin más preocupaciones o problemas que los cotidianos** (p. ej., una discusión ocasional con miembros de la familia).
80	**Si existen síntomas, son transitorios y constituyen reacciones esperables ante agentes estresantes psicosociales** (p. ej., dificultades para concentrarse tras una discusión familiar); **sólo existe una ligera alteración de la actividad social, laboral o escolar** (p. ej., descenso temporal del rendimiento escolar).
70	**Algunos síntomas leves** (p. ej., humor depresivo e insomnio ligero) **o alguna dificultad en la actividad social, laboral o escolar** (p. ej., hacer novillos ocasionalmente o robar algo en casa), **pero en general funciona bastante bien, tiene algunas relaciones interpersonales significativas.**
60	**Síntomas moderados** (p. ej., afecto aplanado y lenguaje circunstancial, crisis de angustia ocasionales) **o dificultades moderadas en la actividad social, laboral o escolar** (p. ej., pocos amigos, conflictos con compañeros de trabajo o de escuela).
50	**Síntomas graves** (p. ej., ideación suicida, rituales obsesivos graves, robos en tiendas) **o cualquier alteración grave en la actividad social, laboral o escolar** (p. ej., sin amigos, incapaz de mantenerse en un empleo).
40	**Una alteración de la verificación de la realidad o de la comunicación** (p. ej., el lenguaje es a veces ilógico, oscuro o irrelevante) **o alteración importante en varias áreas como el trabajo escolar, las relaciones familiares, el juicio, el pensamiento o el estado de ánimo** (p. ej., un hombre depresivo evita a sus amigos, abandona la familia y es incapaz de trabajar; un niño golpea frecuentemente a niños más pequeños, es desafiante en casa y deja de acudir a la escuela).
30	**La conducta está considerablemente influida por ideas delirantes o existe una alteración grave de la comunicación o el juicio** (p. ej., a veces es incoherente, actúa de manera claramente inapropiada, preocupación suicida) **o incapacidad para funcionar en casi todas las áreas** (p. ej., permanece en la cama todo el día; sin trabajo, vivienda o amigos).
20	**Algún peligro de causar lesiones a otros o a sí mismo** (p. ej., intentos de suicidio sin una expectativa manifiesta de muerte; frecuentemente violento; excitación maníaca) **u ocasionalmente deja de mantener la higiene personal mínima** (p. ej., con manchas de excrementos) **o alteración importante de la comunicación** (p. ej., muy incoherente o mudo).
10	**Peligro persistente de lesionar gravemente a otros o a sí mismo** (p. ej., violencia recurrente) **o incapacidad persistente para mantener la higiene personal mínima o acto suicida grave con expectativa manifiesta de muerte.**
0	Información inadecuada.

ANNEX 7. MOS Social Support Survey

Aproximadamente, ¿cuántos amigos íntimos o familiares cercanos tiene Ud.? (Personas con las que se encuentra a gusto y puede hablar acerca de todo lo que le ocurre)

N.º de amigos íntimos o familiares ... ☐

La gente busca a otras personas para encontrar compañía, asistencia u otros tipos de ayuda. ¿Con qué frecuencia dispone Ud. de cada uno de los siguientes tipos de apoyo cuando lo necesita?
(Marque con un círculo uno de los números de cada fila)

PREGUNTA	NUNCA	POCAS VECES	ALGUNAS VECES	LA MAYORÍA DE VECES	SIEMPRE
Alguien que le ayude cuando tenga que estar en la cama	1	2	3	4	5
Alguien con quien puede contar cuando necesita hablar	1	2	3	4	5
Alguien que le aconseje cuando tenga problemas	1	2	3	4	5
Alguien que le lleve al médico cuando lo necesita	1	2	3	4	5
Alguien que le muestre amor y afecto	1	2	3	4	5
Alguien con quien pasar un buen rato	1	2	3	4	5
Alguien que le informe y le ayude a entender una situación	1	2	3	4	5
Alguien en quien confiar o con quien hablar de sí mismo y sus preocupaciones	1	2	3	4	5
Alguien que le abrace	1	2	3	4	5
Alguien con quien pueda relajarse	1	2	3	4	5
Alguien que le prepare la comida si no puede hacerlo	1	2	3	4	5
Alguien cuyo consejo realmente desee	1	2	3	4	5
Alguien con quien hacer cosas que le sirvan para olvidar sus problemas	1	2	3	4	5
Alguien que le ayude en sus tareas domésticas si está enfermo	1	2	3	4	5
Alguien con quien compartir sus temores y problemas más íntimos	1	2	3	4	5
Alguien que le aconseje cómo resolver sus problemas personales	1	2	3	4	5
Alguien con quien divertirse	1	2	3	4	5
Alguien que comprenda sus problemas	1	2	3	4	5
Alguien a quien amar y hacerle sentirse querido	1	2	3	4	5

ANNEX 8. The Holmes-Rahe Life Stress Inventory

Escala de Acontecimientos Vitales Estresantes (2) (Continuación)

Acontecimientos vitales estresantes: este cuestionario es autoadministrado y se trata de que el encuestado rellene con un círculo el número o números que corresponde/en al/los acontecimiento/os que haya padecido en el último año. La puntuación del test se realiza sumando la puntuación que corresponde a cada suceso según la siguiente tabla:

1. Muerte del cónyuge: 100
2. Divorcio: 73
3. Separación matrimonial: 65
4. Encarcelación: 63
5. Muerte de un familiar cercano: 63
6. Lesión o enfermedad personal: 53
7. Matrimonio: 50
8. Despido del trabajo: 47
9. Paro: 47
10. Reconciliación matrimonial: 45
11. Jubilación: 45
12. Cambio de salud de un miembro de la familia: 44
13. Drogadicción y/o alcoholismo: 44
14. Embarazo: 40
15. Dificultades o problemas sexuales: 39
16. Incorporación de un nuevo miembro a la familia: 39
17. Reajuste de negocio: 39
18. Cambio de situación económica: 38
19. Muerte de un amigo íntimo: 37
20. Cambio en el tipo de trabajo: 36
21. Mala relación con el cónyuge: 35
22. Juicio por crédito o hipoteca: 30
23. Cambio de responsabilidad en el trabajo: 29
24. Hijo o hija que deja el hogar: 29
25. Problemas legales: 29
26. Logro personal notable: 28
27. La esposa comienza o deja de trabajar: 26
28. Comienzo o fin de la escolaridad: 26
29. Cambio en las condiciones de vida: 25
30. Revisión de hábitos personales: 24
31. Problemas con el jefe: 23
32. Cambio de turno o de condiciones laborales: 20
33. Cambio de residencia: 20
34. Cambio de colegio: 20
35. Cambio de actividades de ocio: 19
36. Cambio de actividad religiosa: 19
37. Cambio de actividades sociales: 18
38. Cambio de hábito de dormir: 17
39. Cambio en el número de reuniones familiares: 16
40. Cambio de hábitos alimentarios: 15
41. Vacaciones: 13
42. Navidades: 12
43. Leves transgresiones de la ley: 11

Con esta información se completa el impreso anterior.
En la casilla superior se introduce el número del AVE.
En la casilla inferior se introduce la puntuación sumada.
En algunos acontecimientos como "Vacaciones" o "Navidades" surgirán posiblemente dudas, a lo que se responderá diciendo que lo marquen si es que supuso o ha supuesto algún tipo de estrés, sin más.

ANNEX 9. WHO SARS-CoV-2 Disease Severity Classification

Table X: SARS-CoV-2 disease severity: adapted from (53)	
Asymptomatic	Positive test without any symptoms.
Mild disease	Symptomatic patients meeting the case definition for COVID-19 without evidence of viral pneumonia or hypoxia.
Moderate disease (pneumonia)	Clinical signs of pneumonia (fever, cough, dyspnoea, fast breathing) but no signs of severe pneumonia, including SpO2 ≥ 90% on room air. While the diagnosis can be made on clinical grounds; chest imaging (radiograph, CT scan, ultrasound) may assist in diagnosis and identify or exclude pulmonary complications.
Sever disease (severe pneumonia)	Clinical signs of pneumonia (fever, cough, dyspnoea, fast breathing) plus one of the following: respiratory rate > 30 breaths/min; severe respiratory distress; or SpO2 < 90% on room air. While the diagnosis can be made on clinical grounds; chest imaging (radiograph, CT scan, ultrasound) may assist in diagnosis and identify or exclude pulmonary complications.
Critical disease (acute respiratory distress syndrome)	Onset: within 1 week of a known clinical insult (i.e. pneumonia) or new or worsening respiratory symptoms. Chest imaging: (radiograph, CT scan, or lung ultrasound): bilateral opacities, not fully explained by volume overload, lobar or lung collapse, or nodules. Origin of pulmonary infiltrates: respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g. echocardiography) to exclude hydrostatic cause of infiltrates/oedema if no risk factor present. Oxygenation impairment in adults: • Mild ARDS: 200 mmHg < PaO2/FiO2a ≤ 300 mmHg (with PEEP or CPAP ≥ 5 cmH2O). • Moderate ARDS: 100 mmHg < PaO2/FiO2 ≤ 200 mmHg (with PEEP ≥ 5 cmH2O). • Severe ARDS: PaO2/FiO2 ≤ 100 mmHg (with PEEP ≥ 5 cmH2O).
Critical disease (sepsis)	Acute life-threatening organ dysfunction caused by a dysregulated host response to suspected or proven infection. Signs of organ dysfunction include; altered mental status, difficult or fast breathing, low oxygen saturation, reduced urine output, fast heart rate, weak pulse, cold extremities or low blood pressure, skin mottling, laboratory evidence of coagulopathy, thrombocytopenia, acidosis, high lactate, or hyperbilirubinemia.
Critical disease (septic shock)	Persistent hypotension despite volume resuscitation, requiring vasopressors to maintain MAP ≥ 65 mmHg and serum lactate level > 2 mmol/L.

Abbreviations: BP blood pressure; bpm beats per minute; CPAP continuous positive airway pressure; CT computed tomography; FiO2 fraction of inspired oxygen; MAP mean arterial pressure; NIV non-invasive ventilation; OI Oxygenation Index; OSI Oxygenation Index using SpO2; PaO2 partial pressure arterial oxygen; PEEP positive end-expiratory pressure; SBP systolic blood pressure; SD standard deviation; SIRS systemic inflammatory response syndrome; SOFA sequential organ failure assessment; SpO2 oxygen saturation.

ANNEX 10. Data Collection Sheet

DATA COLLECTION SHEET

CODI DEL PARTICIPANT ___ ___ ___ ___ DATA: ___ /___ /___

Telèfons de contacte: Participant: _____ Familiar 1 (especificar relació familiar): _____Familiar 2 (" " "): _____

DADES PERSONALS:

Sexe: ☐ Femení ☐ Masculí

Data de naixement (DD/MM/AAAA): ___ / ___ / ___

ANTECEDENTS FAMILIARS:

El seu pare o mare presenten diagnòstic de Trastorn Depressiu Major?

Mare ☐ SÍ ☐ NO

Pare ☐ SÍ ☐ NO

ANTECEDENTS PATOLÒGICS:

Historial mèdic i psiquiàtric:

_____

Fàrmacs que pren:

_____

ANTECEDENTS TÒXICS:

De les drogues que apareixen a continuació, quines ha consumit durant l'últim any?

Alcohol: ☐ SÍ ☐ NO

Cànnabis: ☐ SÍ ☐ NO

Opiacis: ☐ SÍ ☐ NO

Cocaïna: ☐ SÍ ☐ NO

Amfetamines: ☐ SÍ ☐ NO

(En cas de que la resposta a la pregunta anterior sigui afirmativa) Quin ha estat el seu consum?

Alcohol: ☐ Un cop/dia ☐ Un cop/Setmana ☐ Un cop/mes ☐ Un cop/any

Cànnabis: ☐ Un cop/dia ☐ Un cop/Setmana ☐ Un cop/mes ☐ Un cop/any

Opiacis: ☐ Un cop/dia ☐ Un cop/Setmana ☐ Un cop/mes ☐ Un cop/any

Cocaïna: ☐ Un cop/dia ☐ Un cop/Setmana ☐ Un cop/mes ☐ Un cop/any

Amfetamines: ☐ Un cop/dia ☐ Un cop/Setmana ☐ Un cop/mes ☐ Un cop/any

DADES SOCIODEMOGRÀFIQUES:

Estat civil: ☐ Casat/ada ☐ Divorciat/ada ☐ No casat/ada ☐ Vidu/a

Estatus socioeconòmic:

Nivell d'estudis (marqui el nivell més alt d'estudis assolit):

☐ No estudis o estudis de primària ☐ Estudis de secundaria ☐ Grau universitari

Ocupació:

☐ Gestor/a, professional universitari, director/a

☐ Autònom/a, ocupació intermèdia (ocupació que no apareix nombrada a les opcions)

☐ Treballador/a manual

Situació laboral: ☐ Treballador/a actiu/va ☐ Treballador/a de la llar ☐ Aturat/ada

DADES DEL TRASTORN DEPRESSIU MAJOR:

Anys d'evolució de la malaltia:

Nombre d'ingressos:

Tractament:

- Escrigui quin tractament pren pel trastorn:

  _____

  _____

- Canvis de tractament/s per ineficàcia: ☐ SÍ ☐ NO
- Augments de dosi per ineficàcia: ☐ SÍ ☐ NO

Comportament suïcida: respondre numèricament

- **Pensaments suïcides:**
- **Amenaces suïcides:**
- **Intents de suïcidi:**

INFECCIONS:

- **Primer cop que respon al qüestionari:**

Ha patit alguna infecció recent (que hagi curat fa menys d'una setmana)? ☐ Sí ☐ NO

- **A partir del segon cop que respon el qüestionari (segon inclòs):**

Ha patit alguna infecció durant els últims 3 mesos? ☐ SÍ ☐ NO

Si la resposta anterior és afirmativa; aquesta infecció ha curat fa més d'una semana?

☐ SÍ ☐ NO

ESCALA DE HAMILTON PER LA DEPRESSIÓ:

Resultat:

QÜESTIONARI D'ADHERÈNCIA A LA MEDICACIÓ:

Resultat:

ESCALA DE DESESPERANÇA DE BECK:

Resultat:

ESCALA DE FUNCIONAMENT GLOBAL:

Resultat:

ESCALA DE SUPORT SOCIAL:

Resultat:

ESCALA D'ESTRESSORS VITALS DE HOLMES-RAHE:

Resultat:

TESTS SARS-CoV-2:

Resultats RT-PCR test:

Resultats Antibodies test:

SEVERITAT DE LA INFECCIÓ PER SARS-CoV-2 (si l'ha patit):

Resultat:

ANNEX 11. Xarxa de Salut Mental i Addiccions

The IAS Mental Health and Addictions Network is the public network specialized in mental health care of the Girona region population (approximately 750,000 inhabitants).

It is constituted by hospital care and community care:

Hospital care:

- ***Unitat d'Hospitalització d'Aguts*** **(UHA):** it deals with the treatment of acute psychiatric episodes in patients over 18 years old.
- ***Unitat de Referència en Psiquiatria Infantil i Juvenil*** **(URPIJ):** it deals with the treatment of acute psychiatric episodes in patients under 18 years old.

Community care:

- ***Centres de Salut Mental d'Adults*** **(CSMA):** outpatient specialized care in psychiatric disorders in patients over 18 years old.
- ***Centres de Salut Mental Infantil i Juvenil*** **(CSMIJ):** outpatient specialized care in psychiatric disorders in patients under 18 years old.
- ***Equips d'Intervenció Precoç en la Psicosi*** **(EIPP):** its main objective is early detection of those people who present a psychosis or risk of developing it, in addition to carrying out a comprehensive treatment depending on the needs of the person.

These community care facilities are distributed in 7 areas: Selva interior and Selva marítima, Ripollés, La Garrotxa, Baix empordà, Alt Empordà, Gironès-Pla de l`Estany.

"The Mental Health and Addictions Network of the Girona Counties has become a national and international reference model according to a study called REFINEMENT". (41)

With the following remarkable data:

- Minor use of hospital resources in Europe
- The highest rate of continuity of care in Europe
- The lowest percentage of readmissions in Europe

- And the highest proportion of community versus hospital resources in Europe
- One of the best access systems to health centres