BLOOD BIOMARKERS AS AN INDEPENDENT PREDICTOR OF PSYCHOSIS IN AT-RISK MENTAL STATES FOR PSYCHOSIS

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" El conocimiento descansa no solo sobre la verdad, sino también sobre el error."

C. G. Jung

"¿Tan lejos anda la locura de la sabiduría?"

George R. R. Martin

ACKNOWLEDGEMENTS

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1. ABREVIATIONS

APO E   Apolipoprotein E

APS   Attenuated Psychotic Symptoms

ARMS   At-Risk Mental State for psychosis

BDNF   Brain-Derived Neurotrophic Factor

BLIPS   Brief Limited Intermittent Psychotic Symptoms

BMI   Body Mass Index

CAARMS   Comprehensive Assessment of At-Risk Mental State

CEIC   "Comitè Ètic d'Investigació Clínica"

CNS   Central Nervous System

DSM-5   Diagnostic and Statistical Manual of Mental Disorders

DUP   Duration of Untreated Psychosis

EIPP   "Equip d' Intervenció Precoç de Psicosis"

GAF   Global Assessment of Functioning Scale

ICD-10   International Classification of Diseases

IAS   "Institut d'Assistència Sanitària"

IL-6   Interleukin 6

PANNS   Positive and Negative Syndrome Scale

RPS   at-Risk of Psychosis State

TNF-α α-Tumour Necrosis Factor

UHR   Ultra High Risk of psychosis

2. ABSTRACT

TITLE: Blood Biomarkers as an Independent Predictor of Psychosis in At- Risk Mental States for Psychosis.

BACKGROUND: Psychosis is a severe mental disorder that impairs the patient's entire behaviour and psychosocial functioning; it is characterized by delusions, hallucinations, thought and behaviour disorganization, and negative symptoms.
Psychotic disorders affect a 3% of population, beginning before 25 years of age. Psychosis supposes high costs for Health Care System and a worse quality of life and life expectancy for the affected population.
It is known that psychosis prognosis is related to diagnoses and treatment delay. Because of this, early intervention programmes are very important, thus improving the burdens of psychotic disorders. The problem is that, nowadays, early intervention tools detect a huge number of high risk patients which may never suffer psychotic disorders in the future.
Psychotic disorders can be understood as neurodevelopment disorders, this fact is because of the evidence in new research which shows that some biomarkers can appear altered before psychosis develops. Therefore, an abnormal maturation of the brain in combination with the presence of known risk factors could interact modifying these biomarkers (BDNF, ApoE and IL-6) levels.
In accordance to all of the above, more specific instruments are needed for early psychosis detection. Biomarkers are a promising path of researching.

OBJECTIVE: To analyse if BDNF, ApoE and IL-6 serum levels are different between high risk of psychosis patients which develop a first episode of psychosis to those who do not.

DESIGN: This project is a pilot multicentre prospective cohort study.

METHOD: Blood samples collection and psychopathological interview evaluation will be done every 6 months during 3 years to patients that are considered by their physicians as at-risk mental state for psychosis (ARMS).
We will follow up a cohort of 100 ARMS, monitoring biomarkers plasma levels since the beginning of the project and, the absence or presence of a first episode of psychosis (FEP) (using The Positive and Negative Syndrome Scale: PANNS).
Thus, we can know if there is some relation between biomarkers blood levels and the development of a FEP.

KEYWORDS: *Psychosis, ARMS, BDNF, ApoE, IL-6, early intervention, FEP*

3. INTRODUCTION

3.1. PSYCHOSIS

DSM 5 includes psychosis into *"Schizophrenia and other psychotic disorders"*. Psychotic disorders are characterized by the presence of delusions, hallucinations without insight, thought and behaviour disorganization and catatonia. All of these, in different combinations, severity and duration (1,2). These conditions occur along a spectrum in primary psychotic disorders (3). Although psychosis is the defining feature of schizophrenia spectrum disorders (schizophrenia, schizoaffective disorder, delusional disorder, schizophreniform disorder, and brief psychotic disorder), it also occurs in some people with bipolar disorder during maniac or depressive episodes. Additionally, in the context of a major depressive disorder, some individuals have depressive episodes with psychotic characteristics.

Delusions are fixed beliefs that individuals are not willing to change despite the existence of evidence against them. There are different types: persecutory, referential, somatic, religious, delusions of greatness, erotic, nihilistic (4).

Hallucinations are perceptions that happen without the presence of an external stimulus, being not under voluntary control. They can occur in any sensory modality, being auditory hallucinations the most common in schizophrenia and related disorders. They are clear and vivid (4).

Disorganized thinking is formal thought disorder which is deduced through the speech of individuals. It has different forms: derailment (individual switching from one topic to another), tangentiality (answers to questions are oblique or completely unrelated), or incoherence (speech is nearly incomprehensible), making sometimes an impossible communication (4).

Grossly disorganized or abnormal motor behavior (including catatonia) is characterized by variability of motor movements. Catatonic behaviour is a significant reactivity decrease to environmental stimuli (4).

Negative symptoms decrease emotional expression. For example: avolition (reduction in motivated self-initiated purposeful activities), alogia (decline speech output), anhedonia (decreased ability to experience pleasure from positive stimuli), and a-sociality (lack of interest in social interactions) (4).

Nowadays, there is a dimensional approach regarding hallucinations and delusions as disturbances in the neural systems involved in perception and information processing. Therefore, both symptoms in primary psychotic disorders and psychosis associated with other neurologic conditions are aligning in the same neurobiological framework (3).

3.1.1. <u>EPIDEMIOLOGY</u>

Schizophrenia and other psychosis forms are one of the leading causes of disability in the world and are important social and health burdens. The point prevalence in the general population is approximately 3% (5). The lifetime prevalence of psychosis is estimated to be between 0.2 and 3.5% and the annual incidence between 0.01 and 0.035%. In addition, there are some risk factors which increase these rates, such as masculine sex, race and ethnicity, and percentage of owner-occupied houses (6,7).

Recent epidemiological studies show that 75% of mental disorders begin before 25 years of age (5). Besides, more than half of young people have at least a psychotic experience, many of them developed in childhood. Also, 5-10% of the general population live through attenuated or subthreshold psychotic symptoms (for example: reference and bizarre delusional ideas; school, university or work absence and, changes in family and friends relations) (8). In addition, some incidence studies about chronic health problems indicate that psychotic disorders are the most important health problem between 14 and 25 years of age, decreasing life expectancy in15 years compared with general population. Nonetheless, the relation between psychotic symptoms and developing psychotic disorder is somewhat controversial. Psychotic symptoms can have wide progressions (9–11).

3.1.2. <u>MORBIDITY AND COSTS</u>

Hospitalization morbidity dates indicate the high cost that mental diseases, specially psychosis, have on health care systems. Mental disorders present the major hospital stay average (26-28 days), highlighting schizophrenic disorders particularly (12). In Spain, the hospital morbidity rate of mental disorders is 2,5% of all discharges, increasing in ages 15-24 up to 6%. Between 15 to 34 years of age, mental disorders are the eighth cause of hospitalization (13).

Psychosis is the third mental disorder with the highest costs, behind dementia and personality disorders. The costs associated to psychosis are higher than other diseases with more prevalence (for example epilepsy or anxiety), in particular indirect expenses (expenses that do not have a direct impact in health care system, as for example early mortality, unemployment and time spent by carers which is not remunerated) (14). In fact, schizophrenia's indirect expenses are similar to diabetic mellitus' indirect expenses (15).

All of these facts highlight the important impact that spectrum schizophrenic disorders have on our sociality, including decreased quality life and life expectancy (13).

3.1.3. CLINICAL STAGING

It is a novel strategy for diagnosis for diseases or disorders where delaying treatment can worsen quality of life and life expectancy (16,17).

In psychotic disorders, 3 stages can be found (17):

1. At-Risk Mental State for Psychosis (ARMS) or Ultra-High Risk of psychosis (UHR)
2. First Episode of Psychosis (FEP)
3. First five years after diagnosis

Clinical stages are defined by the degree of area, progression and biological impact of illness in the patient (Figure1). Clinically, these stages are useful because of their correlation with disorder or disease prognosis and, because they are a good tool to know when risk factors have caused a progression or susceptibility (17). For example, whereas some risk factor happens in a specific clinical stage (substance abuse or stress as FEP triggers), another may operate across several stage transitions(genes-environment interactions) (18–20). Aetiologically, clinical staging allows connecting biomarkers with the psychosis continuum (21,22).
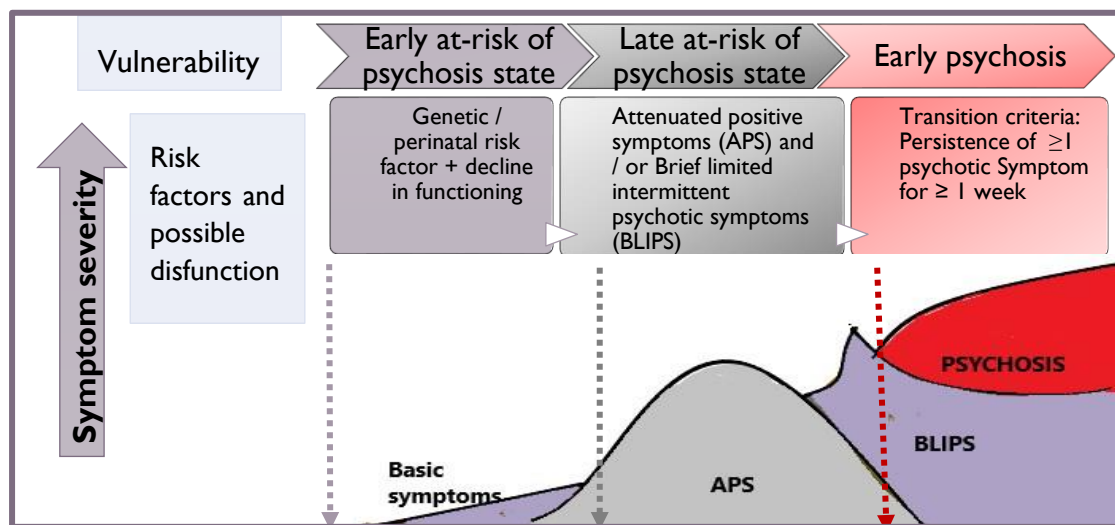

Figure1: Prediction of psychosis in at-risk mental state. Adapted from (23,24).

3.1.3.1. AT-RISK MENTAL STATE FOR PSYCHOSIS (ARMS)

This is a psychotic precursor stage, but it does not mean that psychosis is going to be developed (25). Although this group has a relative risk of 40% compared to the incident rate of psychotic disorders in the general population (26), there is 60-80% of false positive rate (13,27,28).

This stage includes 3 groups of individuals that have known risk factors:

1.-People who have a first-degree relative affected by a mental disorder, or schizotypal disorder with a significant persistent functional decline within the last year.

2. -People who have brief, intermittent and limited psychotic symptoms, or BLIPS (brief limited intermittent psychotic symptoms) that do not last more than a week and remit spontaneously.

3. -People with positive subthreshold symptoms that are neither severe nor persistent enough to meet criteria of first psychotic episode or brief psychotic disorder according to the DSM-5 or ICD-10. They are called attenuated psychotic symptoms (APS), and include reference ideas, magical ideation, strange perception and thinking and speech disorders (9,29–31).

It is important to note that in adolescents, psychotic characteristics are often unspecific, variable (32), transitory and discontinuous. For example, in adolescent females the most common symptoms are isolated hallucinations (most studies have shown that subthreshold hallucinations have limitations as a psychosis predictor. However, the German Cologne Early Recognition study reported that visual and acoustic hallucinations can predict later psychosis in a highly selective sample of patients). Other different psychotic symptoms in adolescents are unusual bodily perceptions, hypochondriac fears (characterised by somatic grudges with no medical cause) and cenestheric psychotic symptoms (the perception that something is happening inside our body, being the brain, heart or eyes the most affected organs.) In addition, depersonalization (a particular type of dissociation where self-perceptions have a disrupted integration) is the most common misdiagnoses of psychosis because DSM-5 includes it as a dissociative disorder. But depersonalization is typical in pre-psychotic states, being a good predictor of later schizophrenia.

In contrast, these symptoms are also reported in other non- psychotic disorders (for example in anxiety disorders or depression). So it has to be taken into account that these symptoms can appear in normal development, non-psychotic disorders, prodromal process of schizophrenia or other psychotic disorders (33).

- EVALUATION METHODS IN ARMS:

Different methods are used depending on clinical framework.

For individuals included in group one, who have a first-degree relative affected by mental disorder, the Global Assessment of Functioning Scale (GAF) is used to identify the significant persistent functional decline of adult patients showing a decrease of 30 points in the GAF scale during the last year. For patients younger than 18 years, the CGAS (Child Global Assessment of Functioning Scale) is used (9).

Despite groups 2 and 3 being included in the annex 3 of DSM- 5 as *"attenuated psychosis syndrome"*, recent findings have shown that the Comprehensive Assessment of At-Risk Mental State (CAARMS) is better than DSM-5 for monitoring underrated psychotic symptoms which can be developed in a psychotic disorder (27).

The CAARMS is an excellent concurrent and discriminant semi-structured interview schedule designed to be used repeatedly over time by trained mental health professionals who are able to evaluate the information of the patient. It is formed by various subscales of psychopathologic and functioning areas (positive symptoms, cognitive change, emotional alteration, negative symptoms, changes of behaviour, motor changes and general psychopathology) (34). It has predictive validity and excellent inter-rater reliability (27). Furthermore, it is a fast test that facilitates the screening because in the first medical visit, doctors only complete the section devoted to positive symptoms. It has been demonstrated as a good psychosis predictor (35). Later, doctors can complete a deeper study of the patient evaluating the sections devoted to basic symptoms (following Huber and Gross theory) and negative symptoms (9).

3.1.3.2. FIRST EPISODE OF PSYCHOSIS (FEP)

It is a term used in a psychotic episode which may be the first presentation of mental disorders within schizophrenic spectrum or schizoaffective disorders (6); happening after a prodromal phase characterized by sleep disorders, changes in mood (isolation, lack of hygiene), perception, thought and global functioning. Psychotic episodes can be diagnosed using PANNS scale and DSM-5 criteria as schizophrenia, delusional ideas disorder, acute psychotic disorder, schizoaffective disorder, schizophreniform disorder, non-organic psychotic disorder, maniac episode, bipolar disorder, severe depressive episode with psychotic symptoms or recurrent depressive disorder with psychotic symptoms (9).

In Spain, some FEP risk factors are: male sex, being a member of a racial or ethnic minority and age between 18 and 24 years old (13,36).

- EVALUATION METHODS: The Positive and Negative Syndrome Scale (PANNS)

This scale is a semi-structured interview tool developed by Kay in 1987 (37). Despite PANSS is used to evaluate psychosis treatment (7) and for the assessment of the gravity of schizophrenic symptoms, a number of studies (38,39) have used it as a psychosis diagnosis criteria.

PANNS evaluation includes 30 items: 7 positive symptoms items, 7 negative symptoms items and 16 items about general psychopathology. Each item is scored from 1 to 7 (37,40). Although the reliability of the general psychopathological items is low, its reliability and validity has been proved because positive and negative items have a good interrater reliability (41).

3.1.3.3. FIRST FIVE YEARS AFTER DIAGNOSIS

First 5 years post-diagnosis are key regarding long term recovery (42). This period is characterized by the highest risk of relapse and suicide, coinciding with maximum development challenges which consist in a stable identity, vocational training, intimate relationships and colleague network (17). These years have their significance because of the duration of untreated psychosis (DUP) too. The DUP is referred to the period from the onset of first psychotic symptoms to the beginning of an adequate treatment (43). Thus, and owing to believe that these untreated years carry important implication for long-term outcomes (44,45) because of the increment of positive psychotic symptoms and the decrement of quality of life (46); early diagnosis and intervention programmes are needed. Besides, short DUP (≤ 6 months) diminishes the rate of suicide attempts, the duration of the psychotic disorder and, increases the rate of full remission if it is compared with longer DUP (47) (Figure 2).

Because of all mentioned in this section, the promotion of early intervention programmes is needed, and more specific tools are required in order to detect high risk population. Therefore, DUP will be negligible and psychosis prognosis will be terrific.
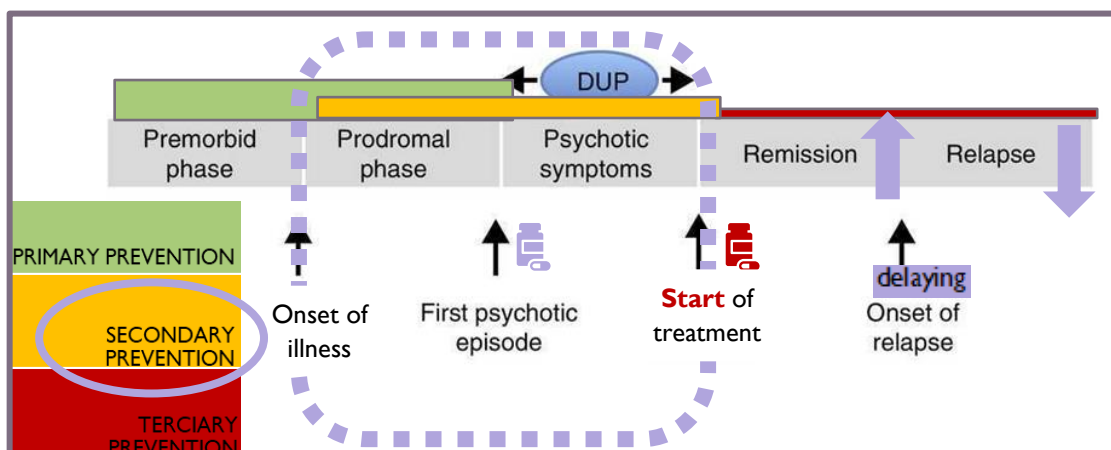

Figure 2: Phases of psychotic disroders and leveles of prevention. Adapted from (5,47).

3.2. PSYCHOPATHOLOGY OF PSYCHOSIS

The aetiology and pathogenesis of psychosis is not yet fully understood, although there is evidence that suggests a contribution of both genetic and environmental factors (48). Psychotic disorders typically emerge in adolescence and young adulthood although its pathogenesis should act since childhood (22). Psychosis can be understood as a neurodevelopmental disorder with onset during the period of brain cortex development (8).

3.2.1. PSYCHOSIS AS A "CONTINUUM"

Currently, studies show that the best way to understand psychosis is the dimensional perspective within a psychopathological continuum (49), having two paradigms of study: widespread psychosis phenotype (focusing on the psychotic-like experiences evaluation and schizotypia characteristic traits in non-clinical population) and attenuated psychosis model (focusing on the assessment of psychotic subthreshold symptoms, in order to predict and prevent future psychotic disorders). Regarding this, nowadays, Schizotypia model and Basic Symptoms Model of Huber are used to explain these two paradigms, respectively (50). Due to all of this, we can understand why the at-risk mental state of psychosis group is formed like that.

In summary, psychosis prodrome, which must be better considered as a "continuum" (because of the retrospective significance that prodrome meaning involves, as well as the prospective direction in "continuum" definition (24)), is the presence of symptoms and their temporal relation with the onset of psychosis (8). Despite 75-90% of psychotic symptoms being transitory and disappearing over time, there is evidence about the Proneness-Persistence-Impairment model which explains how the transitory expression of psychosis (psychosis proneness) may become persistent (persistence) and afterwards, it could come to an end as a clinically relevant disorder (impairment). This model considers that there are genetic background factors in psychotic symptoms that may be acting during development, and some of these genetic factors may interact with environmental exposures that predict persistence and impairment (49)(Figure 3).
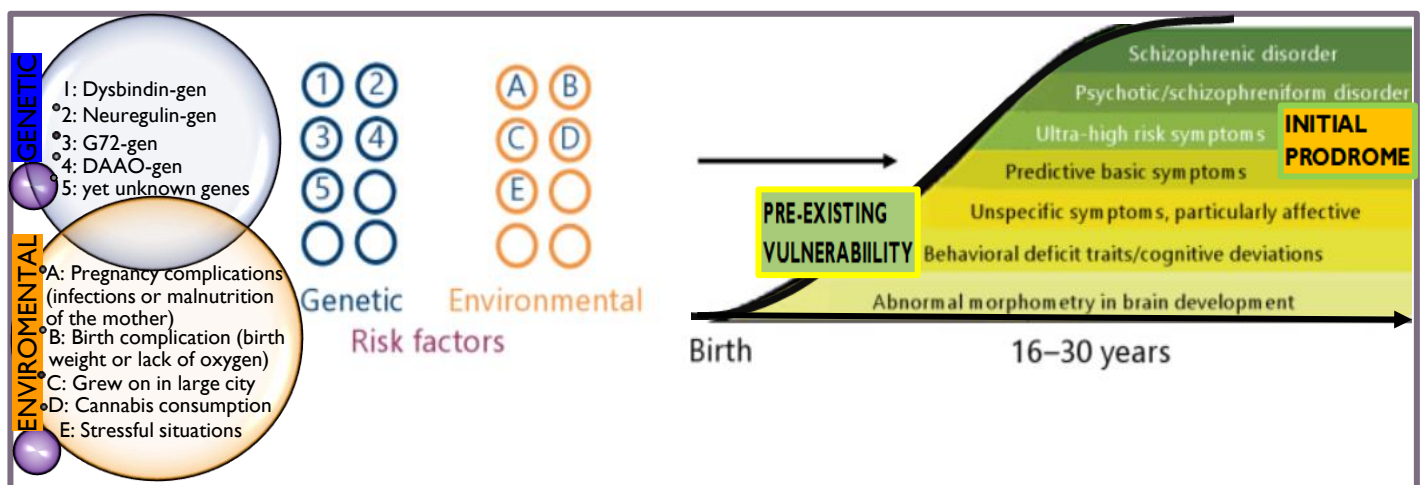

Figure 3: Indicators for increased of psychosis in relation with Basic Symptoms Model. Adapted from (23).

3.2.2. BIOMARKERS IN PSYCHOSIS

Biomarkers are traits that are objectively measured as indicators of normal or pathogenic biological processes, and are useful to asses pharmacological response to an intervention (51).

Also according to the Proneness-Persistence-Impairment and with the neurodevelopment theory of psychosis etiopathogenesis, there is evidence suggesting that psychotic disorders could be caused by perinatal, childhood or adolescent biological damage having as consequence an abnormal brain maturation in late adolescence and young adulthood (52), including abnormal differentiation and migration of neuronal precursors, axons or dendritic proliferation, apoptosis and synaptic pruning. These changes would interact with normal brain maturation especially in cortical areas involved in stress situations response (53).

Synaptic pruning is a natural process that consists in removing some extra synapsis in order to make only strong neuronal circuits (54). Mental function is characterized by a dynamic organization of neuronal networks. According to this, the constant and dynamic synaptic changes make possible adaptation to complex and unpredictable environments of life. To do this, brain is in a constant equilibrium between synaptic sprouting and pruning (55). Synaptic pruning is a critical etiological factor for both onset and psychosis course. It has been suggested that schizophrenia (studied because it is the most prevalent disorder in the psychotic field) occurs as a result of an extensive dendritic and synaptic destruction in the adolescent period entailing the development of an abnormal connections (56). BDNF, ApoE and IL-6, explained below, are involved in these processes (57).

These biomarkers are neurotrophines, which play an important role in our body. They are proteins needed for the peripheral and central nervous systems development (31). These brain lipoproteins protect the brain against oxidative damage, altered synaptic sprouting (58) and chronic latent neuroinflammation (which is involved in impaired neurodevelopment and neurogenesis) (30).

Because of all mentioned before, it is proposed that psychosis occurs as the result of an abnormality brain development. This abnormality make that mechanisms involve in brain maintenance are altered (Figure 4).

3.2.2.1. BRAIN-DERIVED NEUROTROPHIC FACTOR (BDNF)

BDNF is the major neurotrophin in the Central Nervous System, especially in prefrontal cortex and hippocampus, and interacts with different pathways implicated in psychotic disorders (amino-acid, monoamine, steroid and fatty acid mechanisms) (59). It has been demonstrated that BDNF can cross the blood-brain barrier, which allows us to understand what is happening in the CNS thanks to the BDNF levels in peripheric blood. BDNF regulates neurogenesis in the central nervous system,

neuronal survival and proliferation, dendritic growth, development of neuronal pathways, and synaptic plasticity regulation. All of these could be translated as synaptogenesis influence as they cause modelling of the morphological structure of dendrites and axons, increasing the number of synapses for neurodevelopment and regularising synapsis maturation. Besides, crucial changes in synaptic pruning are in the prefrontal brain during adolescence, coinciding with the psychosis onset (56).

Although BDNF has been profoundly studied in schizophrenia, bipolar disorder (60,61) and in first episodes of psychosis showing lower BDNF levels in cases than controls (38,39,56), there are not many studies about BDNF blood levels in ARMS. In addition, results in these studies are controversial (62); however, a systemic review (63) compiles that BDNF blood levels in UHR group were lower than in control group. In addition, a recent study (64) shows significant lower BDNF blood levels in ARMS compared to FEP and controls. This could be explained because of the important pathological process prior to the onset of psychosis (64).

3.2.2.2. APOLIPOPROTEIN E (APO E)

There is evidence of altered plasma apolipoproteins in schizophrenia and in first episodes of psychosis being the most replicable findings of blood biomarkers studies (65). Apo E is the mainly brain apolipoprotein and it is the primary transporter of cholesterol in the CNS. In this Final Degree Project other roles of the Apo E have to be emphasized: its function as myelin homeostatic; and also as oxidative stress and synaptic sprouting protector (58) involved in neuronal development.

In the last study mentioned (58), as the first study done in 12 years of age individuals with some psychotic manifestations, the findings showed an Apo E blood elevation (it is verified that Apo E can cross blood-brain barrier (66)) in persistent psychotic experiences at age of 18.

3.2.2.3. INTERLEUKIN 6 (IL-6)

IL-6 is a pleiotropic cytokine synthesized by Th2 lymphocytes and by activated monocytes. It induces acute-phase proteins and promotes differentiation of B cells into antibodies, producing plasmatic cells (67).

There is several evidence suggesting that psychotic disorders have a possible autoimmune component (2). This may be due to the pleiotropic cytokine roles, specially regulating early neurogenesis, maturation and neuroplasticity. Primarily, IL-6 levels increase because of alpha tumour necrosis factor (TNF-α) rising which reduce hippocampal neurogenesis. In addition, increased IL-6 levels in childhood were associated to schizophrenia in adult life (68). To date, only one study (67) has explored the increasing of IL-6 in patients who are at risk of psychosis, suggesting that IL-6 blood levels are elevated in ARMS. Despite of this rising, the study shows no statistical relation with posterior psychosis because of the small sample size (67).
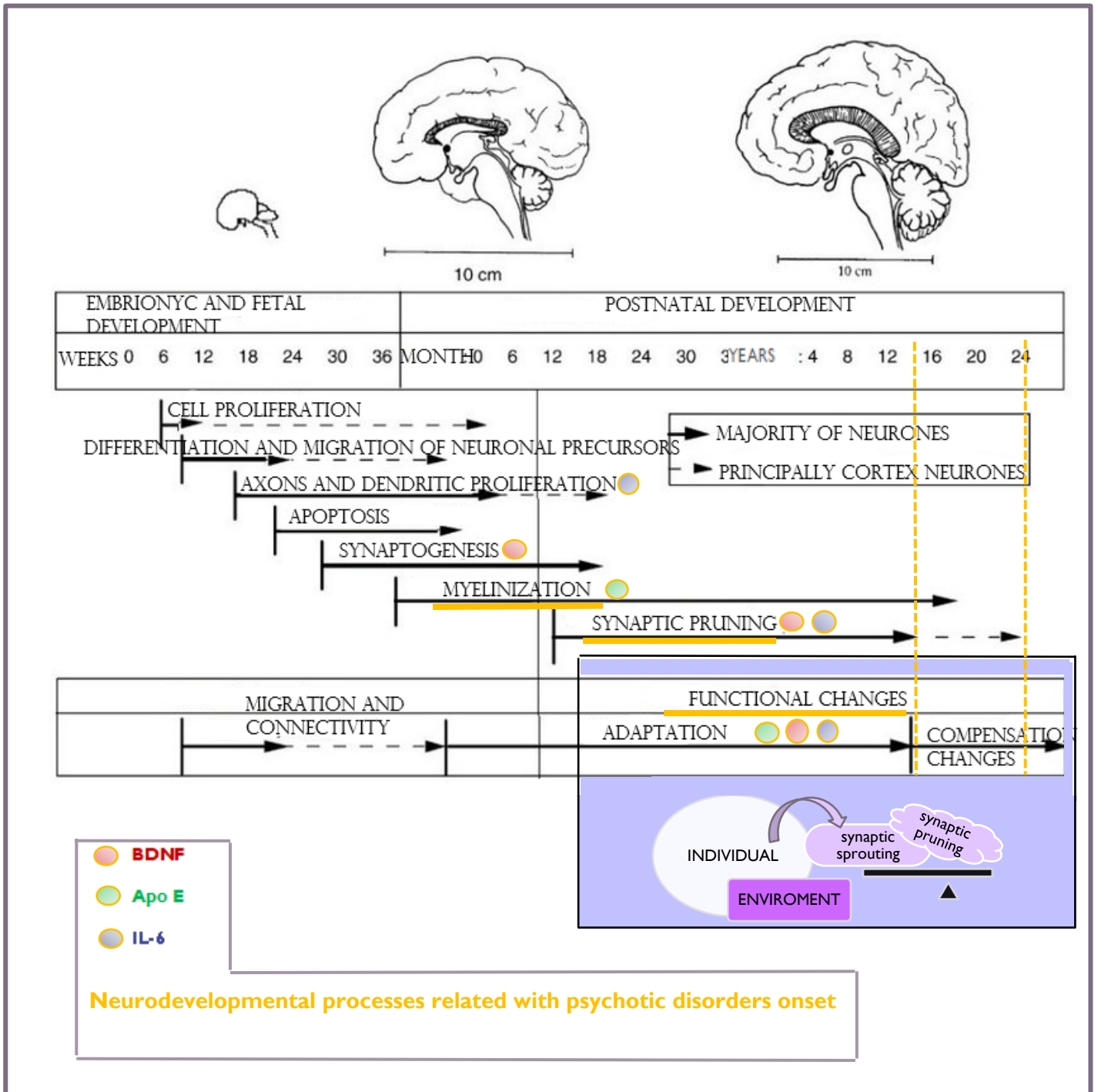
Figure 4: Neurodevelopment. Adapted from (54,55,57).

3.3. EARLY INTERVENTION IN PSYCHOSIS

Early intervention means adopting practical preventive strategies which are firmly established in mainstream health care, including better access and knowledge (17), improving psychotic disorder progression. Furthermore, it is considered that assistance resources and correct treatment are crucial in the first 5 years after a FEP; and actually, this moment is when there is less access to it (10,11).

Although prognosis is influenced by premorbid factors(69), early identification and appropriate treatment of the FEP lead to better long-term prognosis(5). This is because of a clear association between disorder evolution and duration of untreated psychosis (DUP), which increases complications (relationships loss, suicide risk, increasing attempted suicide rate, drug abuse and delinquent behaviour, or depression) (9,23). Also, early intervention programmes reduce number of relapses (70–72), suicide and employment rates, and school attendance (73). Improving treatment adhesion (74) and to be present at medical assistance (72,75).

Additionally, different studies bring to light the potential savings related to early intervention programmes of psychosis; because these programmes achieve to reduce DUP, psychosis development (76), the time (71) and number of hospitalizations, urgent visits (70), and therefore total costs (77). Although early intervention programmes of psychosis suppose an investment of money, studies estimate that as well as these programmes improve psychosis prognosis, it is demonstrated that early intervention programmes generate health care savings during the following years (78), obtaining the highest results in the first three years after early intervention. Nevertheless, economic savings in other public sectors should be more studied (14).

Besides, a recent metanalysis (31) shows that the transition to psychotic disorder in non-help-seeking general population with reported psychotic-like experiences is 0.56%, compared to 0.16% in those who did not report such symptoms. Using that baseline, ARMS criteria have good relative specificity for transition to psychosis, nevertheless most young individuals do not develop a full-threshold psychotic disorder, and 50% of them remit their psychotic symptoms within a year of seeking help. However, a substantial number of these young people continue to report clinically relevant symptoms (anxiety, depression, difficulties in social and occupational functioning, highlighting their need for ongoing care). Furthermore, long-term-follow-up studies have shown that transition to psychosis can occur up to 10 years following the initial diagnosis, clearly indicating that these young people remain vulnerable for long periods of time, and emphasizing again the need for careful monitoring and clinical care (31).

In spite of everything, the main problem of early interventions are the **true false positives** (referring to those who are identified as ARMS, but who never develop psychotic disorders (79)). It has been criticised that early treatment (78) and

prevention programmes can cause stigma in these individuals (80). However, there are differences in stigma experienced by individuals with ARMS, with respect to what is generally expected. In ARMS affected by stigma(considered as a stereotype awareness and self-stigmatization), early intervention provides an important benefit, by counteracting, preventing and fighting against stigma (81). On the other hand, in order to reduce the risk of developing psychotic disorder; treatment and educational early interventions, stress reduction or cessation of drug abuse may cause that individuals who could develop a psychotic disorder do not do it (**false false positives**) (56).

Finally, it should be pointed out that early intervention programmes should be aimed to people aged 14-25 years because this is the population with more withdrawal strengthening in a certain way the assistance continuation (13).

In Girona, following the "Pla de Salut de Catalunya 2016-2020" of Catalunya, these early intervention programmes are done by the "Equips d' Intervenciò Precoç de psicosi". However, the whole Primary and Mental Health Care centres of each region have to function as an integrated unit. ARMS detection and derivation to EIPPs, should be done through this integrated model, focus on Primary Health Care centres and schools (9) (Figure 5).
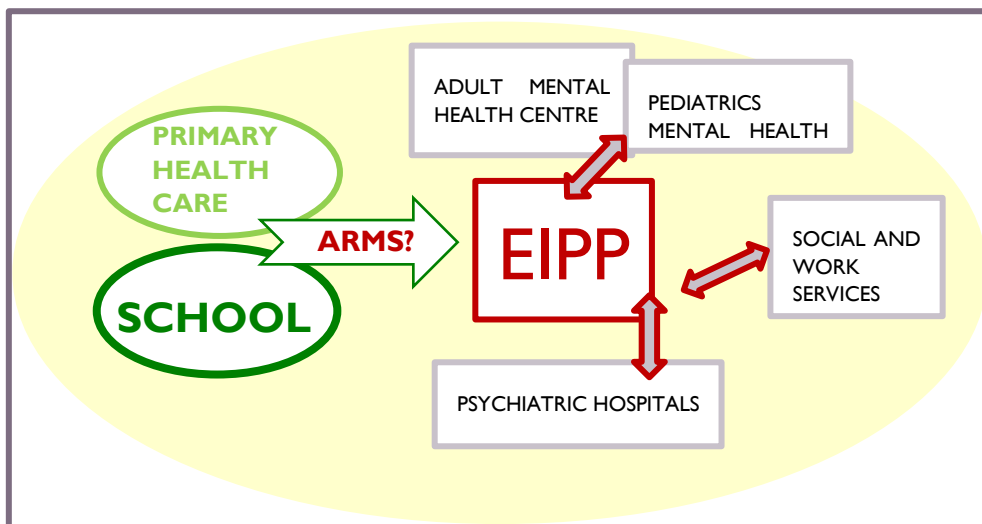

Figure 5: Integrated functional unit. Adapted from (9)

4. JUSTIFICATION

As previously referenced in the introduction of this project, psychosis is one of the main causes of disability in the world, decreasing the quality life and life expectancy. It has a prevalence of approximately 3% and although there are diseases more prevalent than psychosis, this disorder it responsible for one of the highest costs for the health care system. Besides, psychotic disorders are the most important health problem between 14 and 25 years of age, and they can become chronical.

Despite psychosis being a potentially progressive disease with a yet unknown complex pathophysiology (reflecting this complexity in the wide clinical courses that psychotic symptoms can take), there is evidence that suggests a contribution of both genetic and environmental factors within the dimensional perspective of the psychopathological continuum. However, the currently known genetic and environmental risk factors cannot be used for prediction and prevention.

The need to find predictors is one of the main reasons for the development of this study, since prediction and prevention are important for a better prognosis of psychosis, reducing the duration of psychotic episodes, the DUP, the number of hospitalization and urgent visits. Early intervention programmes of psychosis suppose an investment of money; however, these programmes not only improve psychosis prognosis, but also generate health care savings. However, nowadays the main problem of early interventions are the true false positives.

For all that was mentioned, a method to predict psychosis is necessary to improve the ARMS follow up, to diminish false positives, now that exists who will never develop a psychotic disorder and, to achieve an earlier detection of future development of psychosis in general population, in order to reduce the DUP and to increase the therapeutic follow up. Thus, to improve psychosis prognosis.

A general type of predictor used in medicine research are biomarkers, which are traits that are objectively measured showing normal or pathogenic biological processes. There is evidence proposing that psychotic disorders could be caused by perinatal, childhood or adolescent biological damage having as consequence an abnormal brain maturation in late adolescence and young adulthood. The biomarkers proposed in this study (BDNF, APOE and IL6) can be altered because of different mechanisms that result as an abnormal brain development and neurogenesis. Biomarkers will be measured in blood which is a mechanism with relative ease of accessibility and blood collection can be taken at any moment during a patient's life course (82).

Regarding the potential implications observed in some studies (56,63,64) for the field of early detection, the surprisingly low peripheral BDNF levels in ARMS patients might be a valuable marker to detect individuals at-risk for psychosis which might, in

combination with other markers (such as ApoE and IL-6 that are proposed), improve the accuracy of early detection.

It is important to do this study because there are some questions to answer. Among others, it is not clear that the validity of UHR could be generalized to primary care or general psychiatrics and, biomarkers are needed in order to stratify the high risk population according to the prediction of psychosis. To do that, experts recommend doing better validated longitudinal studies, comparing ARMS, healthy controls and their psychosis development (22). In addition, biomarkers are needed to increase the specificity of current ARMS criteria, since the majority of ARMS population do not develop psychosis (79) and, although early intervention is a good strategy to improve psychosis prognosis, all these prodromal interventions are blocked because of the problem of true false positives (79) and their implications for maybe unnecessarily preventive intervention (83–85).

In conclusion, biomarkers will be useful for decreasing ARMS false positives, to be used as a screening in general psychiatric health areas and, to improve prognosis, treatment and follow-up of patients.

5. HYPOTHESIS

Altered biomarkers (BDNF, IL-6 and ApoE) plasma levels will be an independent predictor of psychosis in ARMS population.

6. OBJECTIVES

6.1. MAIN OBJECTIVES:

- To analyse if lower BDNF blood levels in ARMS population are associated with later development of psychosis.
- To analyse if higher APO E blood levels in ARMS population are associated with later development of psychosis.
- To analyse if higher IL-6 blood levels in ARMS population are associated with later development of psychosis.

6.2. SECONDARY OBJECTIVES:

- To estimate biomarkers cut-offs which will be able to discriminate between FEP development or not in ARMS population.

7. METHODOLOGY

7.1. STUDY DESIGN

To analyse the objectives proposed, the study design that is more suitable is a prospective longitudinal and observational study. A pilot multicentric prospective cohort study will be performed with the participation of patients followed up by teams of early intervention of psychosis from Girona region.

At the beginning of the study, the BDNF, ApoE and IL-6 serum levels in peripheral blood will be determined. There will be a follow up period of 3 years, where biomarkers levels will be compared with the presence or absence of FEP development, using the PANNS every 6 months for symptom monitorization and assessment.

7.2. STUDY POPULATION

The population of the study will be patients diagnosed with ARMS, using GAF (Annex 1) and CAARMS scales (Annex 2), by teams of early intervention of psychosis (EIPP) from Girona region who are already involved in early intervention psychosis programme.

7.2.1. INCLUSION CRITERIA

- Patients with ARMS diagnoses done by the EIPP using, the GAF scale in patients with a first-degree relative affected by mental disorder, or the CAARMS.
- Patients aged 14-25 years both included.

7.2.2. EXCLUSION CRITERIA

In order to avoid false positives and bias related to the alteration of biomarkers levels, patients with the following characteristics, which are known to influence biomarkers levels, will be excluded (56,62,86–90).

- Patients with neurological disorders.
- Patients with other neurodevelopmental disorders (autism, attention-deficit/hyperactivity disorders).
- Patients in treatment with antipsychotics, antidepressants, oral contraceptives, cortisol therapy or vitamin use.
- Patients with comorbid diseases.
- Patients with PANNS positive or other psychiatric diagnoses.
- Patients with history of substance abuse in the last 6 months.
- Patients with a clinically active infection.
- Patients who deny informed consent.

7.3. SAMPLE SIZE AND SAMPLING METHOD

For this study, sample size cannot be calculated as there is a gap of knowledge in this subject, so it is not possible to establish reliable parameters. Therefore, this protocol has been proposed as a pilot study.

A non-probabilistic convenience sampling method has been selected because it will be faster, cost-effective and feasible in terms of sample availability. We will study a cohort of 100 volunteer patients who have been diagnosed with ARMS by 4 multidisciplinary teams of early intervention of psychosis, which are at Gironès-Pla de l'Estany, la Selva marítima, Alt Empordà and Baix Empordà. These teams depend on Adult Mental Health centre, but their organization and functioning depend on the territorial manager of incipient psychosis care program carried out in Girona region.

In a bilateral contrast with an alpha risk of 5% and supposing a high incidence (20% of ARMS patient will develop a FEP) for a sample size of 100 patients followed for 3 years, the statistical power is 85%. Computations were carried out with the Prof. Marc Saez' software based on the package pwr of the free statistical environment R (version 3.6.2).

7.4. VARIABLES

7.4.1. DEPENDENT VARIABLE

The development of a FEP will be considered as a nominal dichotomous variable (Yes/No) measured by PANNS (Annex 3).

The PANSS is a semi-structured interview with a duration of 30-40 minutes. It is done by a trained physician (91). PANNS is formed by 30 different symptoms that are distributed among three spheres: a positive scale (7 items), a negative scale (7 items) and a general psychopathology scale (16 items). In each of the items, a seven-point scale is used: 1 means absence of the symptom, and 7 is used when the symptom is extremely severe). Evaluating symptoms occurring during the last week. Therefore, the score for positive and negative scales fluctuate between 7 and 49 points, and the general psychopathology scale varies between 16 and112 points (minimum score, 7 and 16 respectively, means that none of the items are present (37). Still, PANNS is measured by percentiles through conversion tables (91).

In FEP, the most notable items are P1 (delusions), P3 (hallucinations), P5 (grandiosity), P6 (suspiciousness), G9 (unusual thought content), and G12 (lack of insight) if they are scored as a moderate range (≥4) in any of them (92,93).

In this project, the PANNS that will be used is taken from "Detección e intervención temprana en la psicosis" of Servicio Andaluz de Salud. It is adapted from different

studies (41,94,95) and it is the version used in EIPPs from Girona. We will use it to monitor psychotic symptoms.

Thus, PANSS will be applied by an expert and trained clinician, who will interpret (91) if PANNS is considered as altered or not.

7.4.2. INDEPENDENT VARIABLES

In this project BDNF, ApoE and IL6 blood levels will be expressed as continuous quantitative variables to assess whether there may be a relation between FEP development (dependent variable) and these biomarkers levels since the beginning of the follow-up. These variables have been chosen, based in evidence (section 3.2.2.) as possible psychosis predictors. They will be expressed using concentration measurements (pg/ml or µg/ml depending on each one).

To obtain these biomarkers, a fasting morning blood sample will be collected by antecubital needle venepuncture to obtain the blood levels of three different proteins.

After that, blood samples will be processed following the protocols of the laboratory in charge. BDNF, ApoE and IL6 blood levels will be obtained by immunoassay technique through different commercial ELISA sandwich kits. These kits will be chosen depending on cost-benefit relation. Some commercial kits, based on references, are proposed hereunder:

-BDNF plasma levels

Blood samples will be left at room temperature for 15 minutes to facilitate clotting. Then, they will be centrifuged at 5000 rpm for 6 minutes. The serum will be transferred to 1.5 mL polypropylene tubes and it will be stored at −80°C for later analysis. Serum levels of BDNF will be determined with an enzyme-linked immunosorbent assay (ELISA) (Millipore) (62):

 Briefly, samples will be added to monoclonal antibody enzyme well, which is precoated with BDNF monoclonal antibody, incubated. Then, BDNF antibodies labelled with biotin will be added and combined with streptavidin horseradish peroxidase to form immune complex; then, incubation and washing will be carried out again to remove the unlinked enzyme. With addition of chromogen solutions for 15 minutes, stopping the reaction. The absorbance will be measured at 450 nm.

-ApoE plasma levels

Once it is collected, samples will be stored in ice for a maximum of 90 minutes until processed. After centrifugation, the plasma will be stored at −80 °C down to quantitative detection of human apo E in plasma samples of patients. To do this, we will use Apolipoprotein E Human ELISA Kit (ready-to-use sandwich ELISA) with a

sensitivity of 1.5 ng/ml and a detection range of 1.64 ng/ml–400 ng/ml (TermoFisher Scientific). Plasma samples will be diluted 1 in 1000 before analysis (58).

-IL-6 plasma levels

Blood samples will be left at room temperature for 4 hours to facilitate clotting. Then, they will be centrifuged. After centrifugation, IL-6 levels will be measured after storing and freezing aliquots of serum at -80 °C. The determination of IL-6 will be performed using a standard high-sensitivity enzyme-linked immune-sorbent assay (ELISA) (IBL International GmbH, Hamburg, Germany), sensitivity of the assay is 0.03 pg/ml and a detection range of 4,69 pg/ml to 300pg/ml; the calculated overall intra- and inter-assay coefficients of variation are 4.9% and 6.0%, respectively (67,96).

7.4.3. COVARIATES

In order to reduce confusion bias, we will include in the statistical models the following covariates that are known to interact with biomarkers levels (6,7,56,62,86–90):

- Sex, it will be considered as a nominal dichotomous variable (Male/Female). It will be collected from the patient's ID or other valid document.
- Age, it will be expressed as a discrete quantitative variable measured in years. Collected from the patient's ID or another valid document.
- Obesity, it will be expressed as a nominal dichotomous variable defined by World Health Organization as a body mass index (BMI)(kg/m²) ≥ 30.
- Smoking, it will be presented as a nominal dichotomous variable (Yes/No). It will be evaluated by interviewing the patient.
- Socio-economic variables, approximated by educational level and occupation (97,98).

All variables are summarized in table 1.

VARIABLE	TYPE	VALUE	MEASURE INSTRUMENT
Development of a first episode of psychosis (FEP)	Nominal dichotomous qualitative	Yes / No	PANNS
BDNF blood levels	Continuous quantitative	pg/ml	ELISA in blood test
ApoE blood levels	Continuous quantitative	µg/ml	ELISA in blood test
IL-6 blood levels	Continuous quantitative	pg/ml	ELISA in blood test
Sex	Nominal dichotomous qualitative	Male/ Female	ID card or a valid document of participant
Age	Discrete quantitative	Number of years	ID or other valid document of participant
Obesity	Nominal dichotomous qualitative	Obese (≥ 30 BMI) / Not obese (<30)	BMI
Smoking	Nominal dichotomous qualitative	YES / NO	Interview of the participant
Socio-economic variables	Nominal qualitative	CSO-SEE12 categories	Interview of the participant

Table 1: Variables.

7.5. PROCEDURES

In this project, the coordination between the different staffs (EIPPs, laboratory, psychiatrics, psychologists and principal investigator) is very important. First of all, the cohort will be formed by participants with ARMS diagnoses done by specialists of EIPP.

Patients with ARMS diagnoses have obtained altered results in the GAF scale (using an adapted form (99) from the original version (100)) in patients with some first-degree relative affected by mental disorder, or CAARMS (using a modified version (34) of the original (27) in the rest of high risk of psychosis population), have been done by a trained physician of the EIPP. Annex 1 and 2 compile both of these scales which EIPP take from "Detección e intervención temprana en las psicosis. Documentos e instrumentos de evaluación" of the "Servicio Andaluz de salud".

ARMS diagnoses is done if the results obtained in these scales are considered altered by trained clinicians.

As it was previously mentioned, patients with ARMS diagnoses that come from Girona region EIPPs will be used as a cohort, provided that they were asked to sign voluntarily the informed consent (Annex 5) after a full explanation of the purpose and nature of all procedures used (Annex 4).

The first evaluation in these patients will be when they come to blood samples collection. To do this, a fasting morning blood sample will be collected between 8 to 10 am. To prevent potential conflicts with school or work attendance by our participants, as an exception, those patients who request it, will be able to get their blood samples taken on Saturdays. Participants will be presented with a breakfast and a rucksack as a token of appreciation. Every blood collection will be taken in their Health Care centres of reference. Thus, nurse team will have to be informed about the special care and delivery to the laboratory centre (IdiBGi Biobank).

In this first evaluation, demographic and clinical data will be obtained (sex, age, IBM, smoking, socio-economic variables and comorbid diseases); with a complete clinical history of the patient including neurological disorders, other neurodevelopmental disorders (autism, attention-deficit/hyperactivity disorders), history of substance abuse and current treatment, in order to ensure appropriate inclusion and exclusion criteria. Information will be always obtained, if possible, by asking both the patient and relatives, in order to increase the reliability of collected data. We will also ask for the mobile phone number of participants and their relatives to diminish the possible losses that could be caused by the study design.

Later on, one visit every 6 months (101) will be performed, taking as much advantage as possible from the visits that patients will have as routine follow-up of ARMS. We

will collect a fasting blood sample for biomarkers assessment (followed by a breakfast as token of appreciation) and a psychotic evaluation using PANNS will be performed. As an exception, patients that present psychotic symptoms before this period will go immediately to their EIPP.

Biomarkers and PANNS will be evaluated during 3 years, which is the duration of the study; despite knowing it is short as a cohort study we decide this follow-up because of the evidence that incidence FEP in ARMS is elevated in the first 3 years (102), and also, keeping in mind that if the expected result is obtained we can apply for an extension of the study.

The goal of the study is to assess the evolution of ARMS to FEP using PANNS and compare these results with the levels of biomarkers in plasma during the follow-up, to see if there is evidence of alteration of plasma levels related to FEP development (Figure 6 summarizes the different steps mentioned in this section).
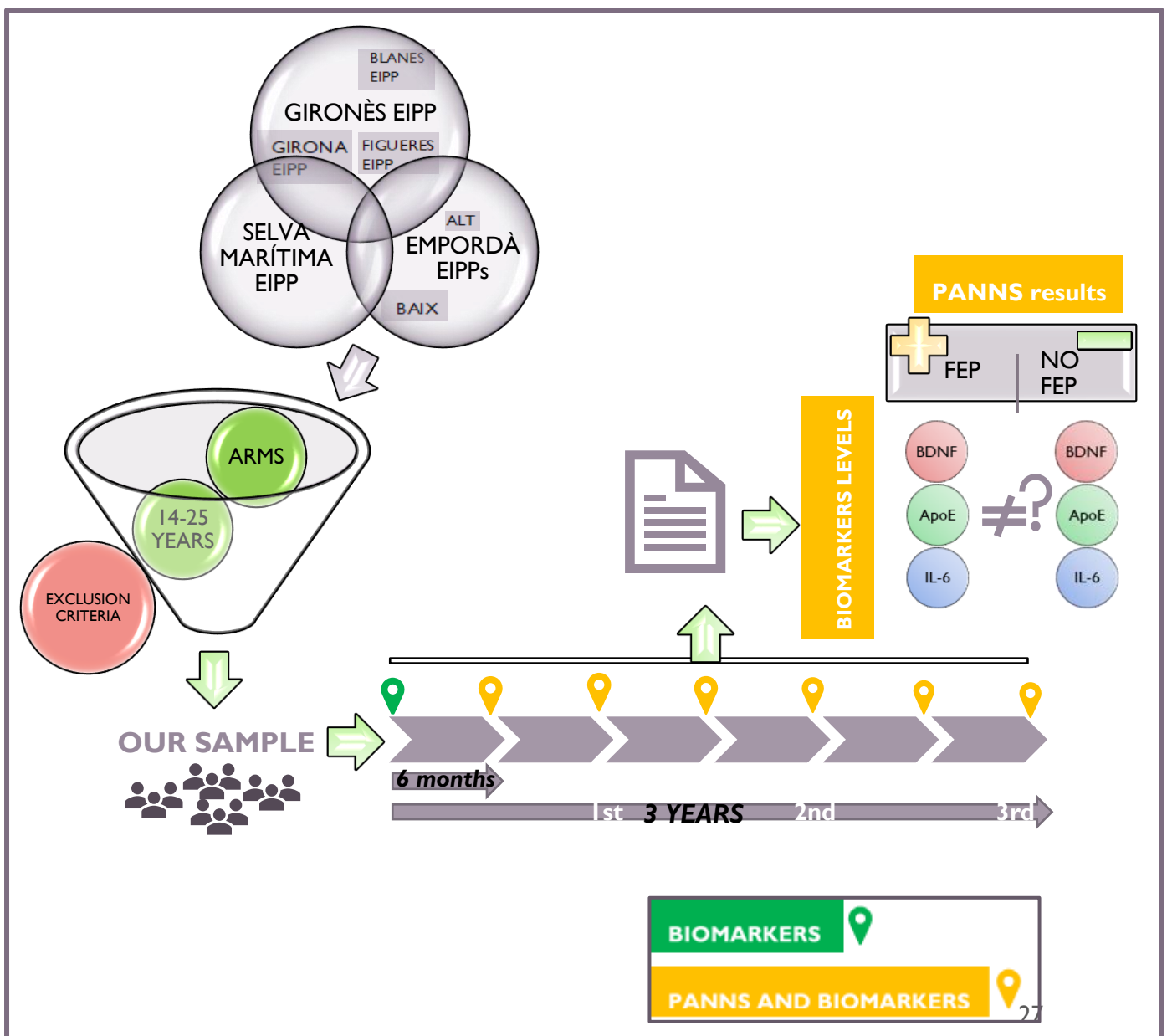

Figure 6: Schematized methodological steps.

8. STATISTICAL ANALYSIS

8.1. DESCRIPTIVE ANALYSIS

We will summarize the independent variables by the groups of the dependent variable (altered or not altered biomarkers in FEP developed), using mean, standard deviation, median and interquartile range (IQR).

This analysis will be stratified by covariates. Age variable will be categorized in quartiles.

Also, we will summarize the covariates by the groups of the dependent variable; using proportions, means/standard deviation and median/interquartile range depending if the covariate is qualitative, continuous or discrete, respectively.

8.2. BIVARIATE INFERENCE

Association between dependent and independent variables will be assessed using Student´s t (because the independent variables are continuous and the dependent variable dichotomous qualitative).

This analysis will be stratified by covariates. Age variable will be categorized in quartiles.

We will test the difference of proportions (qualitative variables), of means (continuous variables) and medians (discrete variables) of the covariates by the groups of the dependent variable using chi-squared (or exact Fisher´s test if the expected counts were lower than 5), Student´s t and Mann-Whitney´ U, respectively.

8.3. MULTIVARIATE ANALYSIS

Association between dependent and independent variables will be adjusted in a logistic regression, controlling by covariates. A logistic regression will be used because the main objective of this study is to know if a FEP is or not developed, and the model used depend on the dependent variable not on the study design.

On the other hand, logistical results will be used to obtain the biomarkers cut-offs, which could be able to discriminate if a person will develop psychosis or not. To do so, a ROC curve will be used.

9. ETHICAL CONSIDERATIONS

The research protocol will be presented and submitted for consideration and approval by the Clinical Research Ethical Committee (CEIC, "Comitè Ètic d'Investigació Clínica") of the Institut d'Assistència Sanitària de Girona (IAS)– "Hospital Universitari Dr Josep Trueta" before the study begins.

This protocol will be performed in accordance with the ethical principles established by the World Medical Association in the Declaration of Helsinki of Ethical Principles for Medical Research Involving Human Subjects (last updated in the 64th WMA General Assembly, Brazil in October 2013).

Due to the fact that in this study biological samples are used; the "Ley Orgánica 14/2007, de 3 de julio, de Investigación Biomédica" will be respected. Also, the "Real Decreto 1716/2011" must be respected, which establishes the basic requisites for the authorization and functioning of the biobanks for biomedical research purposes and the management of biological samples of human origin and regulate the functioning and organization of the "Registro Nacional de Biobancos para Investigación Biomédica".

The project will follow the "Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales" (BOE núm. 294, de 6 de diciembre de 2018), this law addresses that all patient data obtained during the study will be confidential and only used with the purpose of the research and the anonymity of the patients will be guaranteed.

To respect and guarantee the confidentiality of the patients, the investigators do not have access to individual confidential data, the patients will be codified on the database to maintain their anonymity and the data will be analysed anonymously. Patients will always be allowed to modify or destroy any of their collected data.

Furthermore, it will follow the "Ley 41/2002 Básica Reguladora de la Autonomía del Paciente y de Derechos y Obligaciones en materia de información y documentación clínica" in which it is collected that all patients interested on being part of the study and who meet the criteria to participate in it, will be asked to sign voluntarily the informed consent after a full explanation of the purpose and nature of all procedures used through a personal conversation with the research staff and the use of the information sheet.

We report no conflicts of interest in this study.

10. FEASIBILITY

10.1. RESEARCH TEAM

The research team will be formed by:

-The principal investigator (PI), who coordinates the integral project; participating at the beginning of the study transmitting and describing the importance of the project to the whole team, at baseline and in the follow-up of participants. PI will make an interpretation of the statistical analysis according to the EIPP specialist criteria, also PI will write the final paper and present its results.

-In each EIPP, clinicians will participate at baseline and in the follow-ups.

-All the personnel who work in mental health area in Girona region should know the project for the purpose of being able to offer to everyone interested the possibility to contact with EIPP for additional information about the project.

- A well-trained laboratory staff (including the nurse teams of the different health care centres) who will make the blood collection and the biomarkers concentration levels in blood.

- A qualified statistician, who will make the statistical analysis of the results of the project.

- Participants will be informed and motivated by the team, in order to express our gratitude for being involved in it. Asking for their opinion and showing that they are part of the project will improve their adherence.

10.2. WORK PLAN

10.2.1. STAGE I: Protocol design

After a deep literature review, the protocol development has been elaborated during approximately 2 months. Then, the study has to be presented to the CEIC for its approval, this will last between 30-90 days, depending on the CEIC.

10.2.2. STAGE II: Formation and initial coordination of staff

In this stage, the members of the research team will explain the protocol and the role of everyone to each EIPP from Girona, after the abstract and the chronogram have already been sent by email to each team. The team will go to each area to facilitate attendance. All doubts that staff might have will be resolved at this time and once all the meetings have been done in the different regions, an email responding to the questions that may have arisen will be sent.

An extra meeting will be programmed during the study to evaluate potential problems and propose potential improvements. Nurse teams of every health care centre which work with EIPPs will be informed about the project, specially about care and delivery conditions of the blood collections to the biobank. In addition, every Primary Health Care centre or Mental Health Care centre will be informed. Doing that may increase clinical ARMS suspicion, helping the sample collection.

All the team will keep in touch via e-mail and a WhatsApp group for the most urgent issues.

This stage will last approximately 2 months.

10.2.3. STAGE III: Data collection

It is estimated that this stage will last 3 years.

10.2.3.1. Sample collection

The principal investigator and the section boss of each EIPP will select patients who meet the inclusion and exclusion criteria using SAP information of their patients. We will contact to them by phone in order to set an appointment where they will be invited to participate in the study and be explained the purpose of the study and its procedure. In this time, the information sheet must be understood, and the informed consent must be signed if participants agree.

The sample collection will be done for 2 months, although it may be possible to conclude before 2 months if a sufficient number of patients is recruited.

10.2.3.2. Baseline visit and follow-ups

A visit every 6 months will be performed following for 3 years, if possible, using the usual schedule followed by ARMS patients.

At the baseline visit (participants will be contacted via phone, to remind participants about the appointment, approximately a week before, to minimize the loss of participants, as it was mentioned in 5.7. section (procedures) in this protocol), demographic and clinical data will be compiled in order to guarantee inclusion and exclusion criteria are respected. At the same time blood collection will be done to obtain BDNF, ApoE and IL6 serum levels by laboratory experts.

Later, patients will be cited every 6 months. In each visit, a blood collection and a PANNS will be done by expert clinicians of the EIPP well trained and qualified (following the methods were mentioned in sections 7.4. and 7.5. of this protocol). The principal investigator will compile every result in the same sheet using at the baseline too (Annex 6).

Once the 3 years are over, all results will be gathered and delivered to the expert statistician to analyse them.

10.2.4. STAGE IV: Data analysis and article elaboration

When the data collection is complete, the statistician will analyse the data and show the results obtained to the rest of the research team in order to have a general discussion of the results and their interpretation. According to this conclusion, the main investigator will develop the final article.

This stage will take approximately 3 months.

10.2.5. STAGE V: Publication and dissemination

The final article will be published in a psychiatric journal in order to properly disseminate the results of the study. Additionally, the results will be exhibited in the "Congreso Nacional de Psiquiatría" and international congresses of specialists.

This last stage will last 3 months.

All these stages can be seen in the chronogram.

11. CHRONOGRAM

ACTIVITIES	PERSONNEL	2019 Nov-Dec	2020 Jan	Feb-March	April-May	June-July	August-Dec	2021 Jan-June	July-Dec	2022 Jan-June	July-Dec	2023 Jan-June	July-August	Sep	Oct-Dec
STAGE I															
Bibliographic review	PI	▓	▓												
Protocol design	PI	▓	▓												
CEIC approvement	CEIC			▓											
STAGE II															
Meeting and coordination with the team	PI and TEAM				▓										
STAGE III															
Sample selection and processing	LAB, TEAM					▓									
Follow up	LAB, TEAM						▓	▓	▓	▓	▓	▓			
STAGE IV															
Statistical analysis	Statistician												▓		
Article elaboration	PI													▓	
STAGE V															
Results publication and dissemination	PI														▓

12. BUDGET

	Amount	Price/ Unit	TOTAL
PERSONNEL			
Statistician	50 h	50€/ hour	2.500€
Coordination, gifts, shift and meetings			500€
Laboratory staff	600h	30€/ hour	18.000€
Psichiatrist and psychologist trained staff	300h	60€/ hour	18.000€
MATERIALS			
Scales, informed consent, information sheets printing	8 units/participant	0,30€/unit	240€
Sample processing:			
IL6 in serum	7 samples/participant	35,22€/unit	24.654€
BDNF in serum	7 kits	444,36€/unit	3.110,52€
ApoE in serum	7 samples/participant	14,61€/unit	10.227€
PUBLICATION			
Article scientific revision and publication			1.500€
National and international congress			2.000€

TOTAL COST   **80.821,52€**

13. STUDY LIMITATIONS

In this study, there are some potential limitations which should be consider in order to minimize them:

- This is a pilot study; thus, a sample from a specific area (Girona) will be used, which may be not representative of the population of ARMS or the general population. To avoid selection bias caused by the sampling method, exclusion and inclusion criteria will be defined and individuals who participate in this study must fulfil the inclusion criteria.

- Considering the limited burden of ARMS in Girona EIIP, to get a sample with a good statistical power and in an acceptable period of time, it has been necessary to do a multi-centric study with every EIPP of Girona province (Gironès-Pla de l'Estany, la Selva marítima, Alt Empordà and Baix Empordà).

- In addition, related with the sample, participants are followed by teams that specialize in early intervention programmes. Therefore, although they will not do any drug treatment, they could have less incidence rates of FEP development because of this follow-up. If this will happen, an extension can be requested, increasing in this way the duration of the project and, thus, the incidence of FEP development (31).

- According to the study design, a cohort study will be long. This long duration can cause loss of participants. To avoid the withdrawal of participants some arrangements have been made: A phone call to each patient will be made a week before the appointment; when signing up for the project, the phone numbers of some relatives from the participant will be written down; the study duration has been reduced to 3 years (taking into account, that if the results from the pilot study are promising, there could be an extension of the project); participants will be stimulated and encouraged by caring about their suggestions.

- The project proposed might seem expensive; but as it was mentioned in section 3.1.2., nowadays psychosis causes expenses of 19.000 euros by patient/year (103), quantity which can be diminished investing in early intervention programmes and supporting tools to identify good candidates (references are mentioned in section 3.1.2.). Keeping this in mind, and also that it will be a long study; 80.800€ are approximately 270€ euros by patient/ year, a reasonable amount of money.

14. CLINICAL AND HEALTH SYSTEM IMPACT

Psychotic disorders are one of the main causes of disability in the world.

We propose that psychosis is the result of an abnormal brain maturation. This abnormal maturation might occur because of an interaction between the environment and our genes during brain development. As the result of this, some pathways involved in brain control are altered. Here, is where BDNF, ApoE and IL-6 get into the play.

If the hypothesis is confirmed; BDNF, ApoE and/or IL-6 will become potential biomarkers for the prediction of psychosis in population with high risk of developing psychosis. Meaning that the results obtained from this project will provide a really innovative tool in medicine:

There will be some biomarkers which predict the future development of psychosis.

Blood biomarkers could be useful for improving the future diagnosis and effective treatment of different psychotic disorders. Even saving money to the National Health System for years, after a first investment in order to promote early intervention tools and to continue with these lines of research. Research which will make it possible to improve psychotic disorder prognosis, early intervention programmes; and to reduce the huge number of false positive ARMS.

Besides, the several dimensions of the psychosis would benefit from this project if hypothesis were positive. First; patients would have better quality of life, due to the DUP reduction and improved early intervention programmes, thanks to an objective, easy and specific tool which would be able to identify population in true high risk for psychosis development. All of these would decrease comorbidities of psychotic disorders. Second, the national health system would be able to save resources and money because of the improvement in true ARMS detection and the decrease in expenses related to current psychotic comorbidities (hospitalizations, pensions for patients with inability to work, urgent visits…).

Thus, as it can be seen, if there is a tool that allows physicians to predict if a person will develop or not a psychotic disorder, we may have a better follow-up and we may put ahead unperceived psychotic symptoms. Having a better control of the disorder, starting treatment as soon it is necessary and reducing the burden of the psychosis and disability.

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ANNEXES

ANNEX 1: GAF

Hay que considerar la actividad psicológica, social y laboral a lo largo de un hipotético continuo (1-100) de salud-enfermedad. No hay que incluir alteraciones de la actividad debidas a limitaciones físicas (o ambientales). La evaluación es del funcionamiento de la persona durante los últimos 12 meses.

100 91	Actividad satisfactoria en una amplia gama de actividades, la persona evaluada nunca parece superada por los problemas de su vida, es valorada por los demás a causa de sus abundantes cualidades positivas. Sin síntomas.
90 81	Síntomas ausentes o mínimos (p. ej. ligera ansiedad antes de un examen), buena actividad en todas las áreas, el sujeto evaluado se muestra 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 71	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 61	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 51	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/as, conflictos con compañeros/as de trabajo o de escuela).
50 41	Síntomas graves (p. ej. ideación suicida, rituales obsesivos graves, robos en tiendas) o cualquier alteración grave de la actividad social, laboral o escolar (p. ej. sin amigos/as, incapaz de mantenerse en un empleo).
40 31	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. una persona adulta depresiva evita a sus amistades, abandona la familia y es incapaz de trabajar; un/a niño/a golpea frecuentemente a niños/as más pequeños/as, es desafiante en casa y deja de acudir a la escuela).
30 21	La conducta está considerablemente influida por ideas delirantes o alucinaciones 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/as).
20 11	Algún peligro de causar lesiones a otras personas o a sí mismo/a (p. ej. intentos de suicidio sin una expectativa manifiesta de muerte; frecuentemente violento/a; 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 1	Peligro persistente de lesionar gravemente a otras personas o a sí mismo/a (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.

Código. Nota: Utilizar los códigos intermedios cuando resulte apropiado. p. ej., 45, 68, 72.)

ANNEX 2: CAARMS

1. SÍNTOMAS POSITIVOS

1.1. CONTENIDO INUSUAL DEL PENSAMIENTO

Humor Delirante y Perplejidad ("Ideas no Cristalizadas")

- ¿Ha tenido la sensación de que está sucediendo algo extraño que no logra explicarse? ¿Cómo es?
- ¿Se siente confundido/a? ¿Nota extraños los entornos familiares?
- ¿Siente que ha cambiado de alguna manera?
- ¿Siente que las demás personas, o el mundo, han cambiado de algún modo?

Ideas de Referencia

- ¿Ha sentido que las cosas que han estado ocurriendo a su alrededor tienen un significado especial, o que la gente ha estado intentando hacerle llegar mensajes? ¿A qué se parece?
- ¿Cómo empezó?

Ideas Bizarras ('Ideas Cristalizadas")

- Haber tenido pensamientos, sentimientos, impulsos: ¿Ha sentido que alguien, o algo, fuera de usted, ha estado controlando sus pensamientos, sentimientos, acciones o impulsos?
- Pasividad Somática: ¿Tiene sensaciones corporales extrañas? ¿Sabe qué las causa? ¿Podrían deberse a otras personas o a fuerzas externas?
- Inserción del pensamiento: ¿Ha sentido que ideas o pensamientos, que no son suyos, han sido introducidos en su cabeza? ¿Cómo sabe que no son suyos? ¿De dónde provienen?
- Robo del pensamiento: ¿Ha sentido alguna vez que sus ideas o pensamientos han sido extraídos de su cabeza? ¿Cómo ocurre?
- Difusión del pensamiento: ¿Se difunden sus pensamientos de manera que otras personas sepan lo que piensa?
- Lectura del pensamiento: ¿Puede la gente leer su mente?

CONTENIDO INUSUAL DEL PENSAMIENTO: ESCALA DE EVALUACIÓN GLOBAL

0 Nunca, ausente	I Dudoso	2 Leve	3 Moderado	4 Moderadamente grave	5 Grave	6 Psicótico y Grave
No muestra contenido inusual del pensamiento.	Elaboración leve de creencias convencionales como podría hacerlo una parte de la población.	Vaga sensación de que algo es diferente, o de que algo no va del todo bien en ele mundo, la sensación de que las cosas han cambiado pero sin concretarlo bien. La persona no se siente concernida/preocupada por esta experiencia.	Sentimiento de perplejidad. Mayor sensación de incertidumbre en relación con dichos pensamientos que en 2.	Ideas referenciales de que ciertos acontecimientos, objetos o personas tienen un significado particular e inusual. La persona siente que sus experiencias pueden provenir de algo externo a ella. Creencia no sostenida con convicción, es capaz de cuestionarla. No determina un cambio en la conducta.	Pensamientos inusuales con contenido totalmente original y altamente improbable. La persona puede dudar (no los sostiene con convicción delirante), o no los mantiene todo el tiempo. Puede afectar levemente a la conducta.	Pensamientos inusuales con contenido original y altamente improbable sostenido con convicción delirante (sin dudas). Puede tener un marcado impacto en la conducta.

Fecha de inicio: _____ Fecha de finalización: _____

Frecuencia y duración. Patrón de Síntomas.

0	I	2	3	4	5	6
Ausente	Menos de una vez al mes	De una vez al mes hasta dos veces por semana- menos de una hora por episodio	De una vez al mes hasta dos veces por semana- más de una hora por episodio O De 3 a 6 veces por semana- menos de una hora por episodio	De 3 a 6 veces por semana- más de una hora por episodio O Diariamente- menos de una hora por episodio	Diariamente- más de una hora por episodio O Varias veces al día	Continuamente

0	I	2
No se aprecia relación con el uso de sustancias	Ocurre en relación con el uso de sustancias así como en otras circunstancias	Se aprecia únicamente en relación con el uso de sustancias

Nivel de malestar(en relación a los síntomas)

0 Ningún malestar									100 Malestar extremo

1.2 IDEAS NO BIZARRAS

Ideas No Bizarras ("Ideas Cristalizadas")

- Suspicacia. Ideas de Persecución: ¿Hay alguien que esté molestándole o tratando de hacerle daño? ¿Siente como si la gente hubiera estado hablando de usted, riéndose, u observándole? ¿Cómo es? ¿Cómo ha llegado a saberlo?

- Ideas de Grandeza: ¿Ha estado sintiendo como si fuera especialmente importante o que posee poderes que otras personas no tienen?

- Ideas Somáticas: ¿Ha tenido la sensación de que algo extraño sucede en su cuerpo que no puede explicarse? ¿Cómo es? ¿Siente que su cuerpo ha cambiado de alguna manera, o que hay algún problema con su forma?

- Ideas de Culpa: ¿Siente que merece castigo por algo que ha hecho mal?

- Ideas Nihilistas: ¿Ha sentido alguna vez que usted o una parte de usted no existiera o hubiera muerto? ¿Ha sentido alguna vez que el mundo no existiera?

- Ideas de Celos: ¿Es usted una persona celosa? ¿Le preocupan las relaciones que su pareja mantiene con otras personas?

- Ideas Religiosas: ¿Es usted muy religioso/a? ¿Ha tenido experiencias religiosas?

- Ideas Erotomaníacas: ¿Hay alguna persona enamorada de usted? ¿Quién? ¿Cómo lo ha sabido? ¿Le corresponde usted?

IDEAS NO BIZARRAS- ESCALA DE EVALUACIÓN GLOBAL

0 Nunca, ausente	1 Dudoso	2 Leve	3 Moderado	4 Moderadamente grave	5 Grave	6 Psicótico y Grave
Ausencia de ideas no bizarras.	Cambios sutiles que podrían basarse en la realidad. Ej. Marcada conciencia de sí mismo	Incrementada conciencia de sí mismo. Ej. La persona tiene la sensación de que le miran o hablan de ella, o sensación de incremento de su importancia. La persona es capaz de cuestionarlo.	Pensamientos extraños o inusuales, pero cuyo contenido es del todo inverosímil, pudiendo haber una evidencia lógica. Mayor evidencia que en el grado 4. El contenido del pensamiento no es original. Ej. Celos, leve paranoia.	Creencias claramente idiosincráticas que, aunque posibles, sean desarrolladas sin evidencia lógica. Menor evidencia que en el grado 3. Ej. Pensamientos de que otras personas desean hacerle daño, que pueden ser fácilmente descartados. Pensamientos de poseer poderes especiales, que pueden ser fácilmente descartados.	Pensamientos inusuales (no sostenidos con convicción delirante), o que la persona no los mantiene todo el tiempo. Puede producir algún cambio menor de conducta.	Pensamientos inusuales cuyo contenido es original y altamente improbable, sostenido con convicción delirante (sin dudas). Pueden tener un marcado impacto sobre la conducta.

Fecha de inicio: _____ Fecha de finalización: _____

Frecuencia y duración. Patrón de Síntomas

0	1	2	3	4	5	6
Ausente	Menos de una vez al mes	De una vez al mes hasta dos veces por semana- menos de una hora por episodio	De una vez al mes hasta dos veces por semana- más de una hora por episodio O De 3 a 6 veces por semana- menos de una hora por episodio	De 3 a 6 veces por semana- más de una hora por episodio O Diariamente- menos de una hora por episodio	Diariamente- más de una hora por episodio O Varias veces al día	Continuamente

0	1	2
No se aprecia relación con el uso de sustancias	Ocurre en relación con el uso de sustancias así como en otras circunstancias	Se aprecia únicamente en relación con el uso de sustancias

Nivel de Malestar (En relación a los síntomas)

0 Ningún malestar						100 Malestar extremo

1.3 ANOMALÍAS PERCEPTIVAS

Cambios Visuales

- Distorsiones, ilusiones: ¿Ha cambiado la forma en que ve las cosas? ¿Le parecen las cosas, de alguna manera, diferentes o anormales? ¿Han aparecido alteraciones en el color, o en el brillo de los objetos (las cosas aparecen más brillantes o más mates)? ¿Aparecen alteraciones en el tamaño y en la forma de los objetos? ¿Parece que los objetos estén en movimiento?

- Alucinaciones: ¿Tiene visiones, o ve cosas que puede que no estén realmente aquí? ¿Ve cosas que otros no pueden o no parecen ver? ¿Qué ve? Cuando ve estas cosas, ¿como de reales le parecen? ¿Se da cuenta en ese momento de que no son reales o sólo después?

Cambios Auditivos

- Distorsiones, ilusiones: ¿Hay algún cambio en la manera en como suenan las cosas? ¿Los sonidos son de alguna manera diferentes, o anormales? ¿Le parece que la audición es más aguda, o que ha aumentado su sensibilidad? ¿Le parece que su capacidad auditiva ha disminuido, o ha perdido agudeza?

- Alucinaciones: ¿Ha oído cosas que puede que no estén realmente aquí? ¿Oye cosas que otras personas no parecen oír (como sonidos o voces)? ¿Qué oye? Cuando oye estas cosas, ¿cómo de reales le parecen? ¿Se da cuenta en ese momento de que no son reales o sólo después?

Cambios Olfativos

- Distorsiones, ilusiones: ¿Le parece que su sentido del olfato es diferente, más o menos intenso de lo habitual?

- Alucinaciones: ¿Huele cosas que los demás no perciben? Cuando esto sucede, ¿le parecen reales esos olores? ¿Se da cuenta en ese momento de que no son reales o sólo después?

Cambios Gustativos

- Distorsiones, ilusiones: ¿Le parece que su sentido del gusto es diferente, como más o como menos intenso de lo habitual?

- Alucinaciones: ¿Ha experimentado algún sabor extraño en su boca? Cuando esto sucede, ¿cómo de real le parece? ¿Se da cuenta en ese momento de que no son reales o sólo después?

Cambios Táctiles

- Distorsiones, ilusiones, alucinaciones: ¿Ha experimentado alguna vez sensaciones extrañas sobre o bajo su piel? Cuando esto sucede, ¿cómo de reales le parecen? ¿Se da cuenta en ese momento de que no son reales o sólo después?

Cambios Somáticos

- Distorsiones, ilusiones: ¿Ha experimentado sensaciones extrañas en su cuerpo? (ej. sentir que partes de su cuerpo han cambiado de alguna manera, o que funcionan de modo distinto).

- ¿Siente/piensa que hay algún problema en alguna parte o en la totalidad de su cuerpo, por ejemplo que se ve distinto/a a otras personas, o que es de alguna manera diferente? ¿Cómo de real le parece esto? Alucinaciones: ¿Ha notado algún cambio en sus sensaciones corporales, como incremento o disminución de intensidad? ¿O sensaciones corporales inusuales como presiones, dolores, ardores, entumecimientos, vibraciones?

ANOMALÍAS PERCEPTIVAS- ESCALA DE EVALUACIÓN GLOBAL

0 Nunca, ausente	1 Dudoso	2 Leve	3 Moderado	4 Moderadamente grave	5 Grave	6 Psicótico y Grave
No experimenta anomalías perceptivas.		Percepciones agudizadas o empobrecidas, distorsiones, ilusiones (por ej. Luces/ sombras). No especialmente molesto. Experiencias hipnagógicas/ hipnopómpicas	Más experiencias desconcertantes: Distorsiones/ ilusiones más intensas y vivida, murmullos confesos, etc. La persona está insegura de la naturaleza de dichas experiencias. Capaz de desestimarlas No inquietantes. Desrealización / despersonalización	Experiencias más claras que en 3, tales como ser llamada por su nombre, oír sonar el teléfono, etc., pero fugaces/ transitorias. Es capaz de dar una explicación plausible de estas experiencias. Pueden asociarse con leve malestar.	Verdaderas alucinaciones, por ej. Oír voces o conversaciones, sentir que algo toca su cuerpo. La persona es capaz de cuestionar sus experiencias con esfuerzo. Pueden producir temor o asociarse con algún malestar.	Verdaderas alucinaciones que la persona considera reales en el momento de experimentarlas y también después. Pueden causar intenso malestar.

Fecha de inicio: _____ Fecha de finalización: _____

Frecuencia y duración

0	1	2	3	4	5	6
Ausente	Menos de una vez al mes	De una vez al mes hasta dos veces por semana- menos de una hora por episodio	De una vez al mes hasta dos veces por semana- más de una hora por episodio O De 3 a 6 veces por semana- menos de una hora por episodio	De 3 a 6 veces por semana- más de una hora por episodio O Diariamente- menos de una hora por episodio	Diariamente- más de una hora por episodio O Varias veces al día	Continuamente

Patrón de Síntomas

0	1	2
No se aprecia relación con el uso de sustancias	Ocurre en relación con el uso de sustancias así como en otras circunstancias	Se aprecia únicamente en relación con el uso de sustancias

Nivel de Malestar (En relación a los síntomas)

0 Ningún malestar							100 Malestar extremo

1.4 LENGUAJE DESORGANIZADO

Cambio subjetivo

- ¿Ha tenido dificultades al hablar, o problemas de habilidad para comunicarse con la gente?
- ¿Ha tenido problemas para encontrar la palabra adecuada en el momento apropiado?
- ¿Utiliza palabras que no vienen al caso, o que son totalmente irrelevantes?
- ¿Se ha encontrado yéndose por la tangente al hablar sin llegar nunca al asunto? ¿Es un cambio reciente?
- ¿Se da cuenta de estar hablando de cuestiones irrelevantes, o saliéndose del tema?
- ¿Tienen a veces otras personas dificultad para entender lo que está intentando decir, o para transmitir su mensaje?
- ¿Se encuentra a veces repitiendo las palabras de los demás?
- ¿Ha tenido que utilizar gestos o mímica para comunicarse debido a problemas para transmitir su mensaje? ¿Cómo de desagradable ha sido?
- ¿Le ha causado esto deseos de permanecer en silencio y no decir nada?

Evaluación Objetiva del Lenguaje Desorganizado

- ¿Resulta difícil seguir lo que la persona dice debido al uso de palabras incorrectas, a su circunstancialidad y tangencialidad?
- La persona es vaga, demasiado abstracta o concreta? ¿Se pueden sintetizar sus respuestas?
- ¿Suele salirse del tema y perderse al hablar? ¿Parece tener dificultad para encontrar las palabras adecuadas?
- ¿Repite palabras que usted ha utilizado o adopta palabras extrañas (o no palabras) en el curso de una conversación normal?

LENGUAJE DESORGANIZADO - ESCALA DE EVALUACIÓN GLOBAL

0 Nunca, ausente	1 Dudoso	2 Leve	3 Moderado	4 Moderadamente grave	5 Grave	6 Psicótico
Discurso lógico, normal, no desorganización, no problemas de comunicación o de comprensión.		Dificultades subjetivas leves, por ej. Problemas para hacerse entender. No perceptible por otros.	Algo vago, alguna evidencia de circunstancialidad, o irrelevancia en el discurso. Sensación de no ser entendido.	Clara evidencia de habla y pensamiento levemente desconectados. Asociación de ideas más bien tangencial. Mayor sensación de frustración en la conversación.	Marcada circunstacialidad o tangencialidad en el habla pero responde estructurándose en la entrevista. Puede tener que recurrir a gestos o a mímica para comunicarse.	Ausencia de coherencia, habla ininteligible, dificultad significativa para seguir el curso del pensamiento. Pérdida de asociaciones en el habla.

Fecha de inicio: _____ Fecha de finalización: _____

Frecuencia y duración

0	1	2	3	4	5	6
Ausente	Menos de una vez al mes	De una vez al mes hasta dos veces por semana- menos de una hora por episodio	De una vez al mes hasta dos veces por semana- más de una hora por episodio O De 3 a 6 veces por semana- menos de una hora por episodio	De 3 a 6 veces por semana- más de una hora por episodio O Diariamente- menos de una hora por episodio	Diariamente- más de una hora por episodio O Varias veces al día	Continuamente

Patrón de Síntomas

0	1	2
No se aprecia relación con el uso de sustancias	Ocurre en relación con el uso de sustancias así como en otras circunstancias	Se aprecia únicamente en relación con el uso de sustancias

Nivel de Malestar (En relación a los síntomas)

0 Ningún malestar							100 Malestar extremo

PANSS: SÍNTOMAS EN POSITIVO, EN NEGATIVO Y DE PSICOPATOLOGÍA GENERAL
INSTRUCCIONES
HOJA DE RESPUESTAS

		1: AUSENTE	2: MÍNIMO	3: LIGERO	4: MODERADO	5: MODERADO SEVERO	6: SEVERO	7: EXTREMO	TOTAL (1)
POSITIVA	P1: DELIRIOS								
	P2: DESORGANIZACIÓN CONCEPTUAL								
	P3: CONDUCTA ALUCINATORIA								
	P4: EXITACIÓN								
	P5: GRANDIOSIDAD								
	P6: SUSPICACIA/PERJUICIO								
	P7: HOSTILIDAD								
NEGATIVA	N1: EMBOTAMIENTO AFECTIVO								
	N2: RETRACCIÓN EMOCIONAL								
	N3: POBRE RELACIÓN								
	N4: RETRACCIÓN SOCIAL								
	N5: PENSAMIENTO ABSTRACTO								
	N6: FLUIDEZ EN LA CONVERSACIÓN								
	N7: PENSAMIENTO ESTEREOTIPADO								
ESCALA DE PSICOPATOLOGIA GENERAL	PG1: PREOCUPACIONES SOMATICAS								
	PG2: ANSIEDAD								
	PG3: SENTIMIENTOS DE CULPA								
	PG4: TENSIÓN MOTORA								
	PG5: MANIERISMOS Y POSTURAS								
	PG6: DEPRESIÓN								
	PG7: RETARDO MOTOR								
	PG8: FALTA DE COLABORACIÓN								
	PG9: INUSUALES CONTENIDOS DEL PENSAMIENTO								
	PG10: DESORIENTACIÓN								
	PG11: ATENCIÓN DEFICIENTE								
	PG12: AUSENCIA DE JUICIO E INTROSPECCIÓN								
	PG13: TRANSTORNOS DE LA VOLICIÓN								
	PG14: CONTROL DEFICIENTE DE IMPULSOS								
	PG15: PREOCUPACIÓN								
	PG16: EVITACIÓN SOCIAL ACTIVA								

(1) TOTAL: ES EL NÚMERO DE ÍTEMS DE ESTA SECCIÓN QUE PUNTÚAN IGUAL O MÁS DE 4.

ANNEX 4: SHEET INFORMATION FOR THE PARTICIPANT

¿QUIERES PARTICIPAR EN ESTE ESTUDIO?

SUS DERECHOS, OBLIGACIONES, PROCEDIMIENTOS, BENEFICIOS Y RIESGOS serán explicados en este documento.

Lea con atención este documento para tomar esta decisión y consulte con las personas que considere oportuno …
Para cualquier duda, contacte con nosotros:

INVESTIGADORA: **SARA PALLARES BARROS**

@ predictores.psicosis@gmail.com

☐ 698765432 / 972123456

◎

Su hospital o centro de Salud Mental de referencia

El estudio ha sido aprobado por el Comité Ético de Investigación Clínica realizándose de acuerdo a los requerimientos expresados en la Declaración de Helsinki.

Se dispondrán de versiones en otros idiomas

HOJA DE INFORMACIÓN PARA EL PARTICIPANTE

TÍTULO DEL ESTUDIO:

BIOMARCADORES COMO PREDICTORES DE PSICOSIS EN PACIENTES DE ESTADO MENTAL DE ALTO RIESGO

ESTIMADO PARTICIPANTE,

Nos dirigimos a usted para invitarle a participar en un proyecto de investigación que se llevará a cabo en el Área de Salud Mental de la provincia de Girona.

Debe saber que:

- Su participación será totalmente voluntaria y sin ánimo de lucro. Es usted quién decide, ni sus médicos ni nadie juzgará su decisión. Usted puede negarse a participar antes o una vez ya iniciado el estudio sin que su seguimiento se vea perjudicado. Así mismo, podrá ser retirado del estudio si el investigador principal o su médico lo decide, siempre y cuando recibiendo una explicación del motivo que ocasiona su retirada.

- El estudio ha sido diseñado para evaluar si es posible la predicción de psicosis en personas con un estado mental de alto riesgo mediante 3 proteínas medidas en la sangre. Cada 6 meses y durante 3 años, se realizará un análisis de sangre (que podría ocasionar el riesgo de mínimos y pequeños hematomas que desaparecerán en 1 o 2 días) junto con la monitorización de posible sintomatología psicótica mediante una entrevista.

- Toda la información obtenida será confidencial y ni usted ni sus datos, en ningún caso, estarán identificados en cualquier informe emitido por este proyecto. Si acepta participar, estos datos serán accesibles a las Autoridades Sanitarias, Comités Éticos de Investigación Clínica, auditores y al Promotor en el contexto de verificar los procedimientos y datos obtenidos durante el estudio, sin violar la confidencialidad de sus datos. Los datos resultantes podrán ser publicados en el ámbito científico pero su identidad permanecerá confidencial.

¿POR QUÉ ES IMPORTANTE?

Actualmente se sabe que el pronóstico de los trastornos psicóticos está firmemente ligado al tiempo de retraso del diagnóstico y, por tanto, de su tratamiento. Por esto, existen programas de intervención precoz cuya intención es adelantarse a la psicosis en aquellas personas que conocemos algún factor de riesgo. Como ustedes sabrán mejor que nadie, la mayoría de las personas incluidas en estos programas jamás llegan a desarrollar ningún tipo de trastorno psiquiátrico. Para evitar esta incertidumbre, mejorar los criterios de inclusión en estos programas y poder hacer un seguimiento más dirigido y agresivo en las personas que sí desarrollaran un trastorno en un futuro, queremos hacer este proyecto. Creemos que unas proteínas de la sangre podrían estar alteradas en aquellas personas que, en un futuro, acabarán desarrollando un trastorno psicótico. Y es por está razón que necesitamos su ayuda y colaboración, para hacer desaparecer la incertidumbre en personas actualmente incluidas en programas de intervención precoz, adelantarnos con pies de plomo a la psicosis y poder encontrar, al fin, una herramienta objetiva y diagnóstica de la psicosis.

Muchas gracias por su tiempo,
Atentamente, El equipo investigador.

CatSalut

Servei Català
de la Salut

DOCUMENTO DE CONSENTIMIENTO INFORMADO PARA INVESTIGACIÓN CLÍNICA QUE IMPLIQUE MUESTRAS BIOLÓGICAS

INVESTIGADOR RESPONSABLE: SARA PALLARES BARROS

TELÉFONO DE CONTACTO: 698765432   EMAIL: predictors.psicosis@gmail.com

NOMBRE DE LA LÍNEA DE TRABAJO: *Biomarcadores como predictores de psicosis en pacientes de estado mental de alto riesgo.*

I) Finalidad de la línea de trabajo propuesta:

1. Con esta investigación buscamos herramientas objetivas, sencillas y más precisas para la detección precoz de psicosis en pacientes considerados de alto riesgo. Pudiendo mejorar el seguimiento y tratamiento temprano de la psicosis en aquellas personas que realmente lo necesiten, ya que actualmente las pruebas de detección de estados de alto riesgo de psicosis son muy poco específicas.

2. Usted como participante voluntario deberá someterse a una extracción de sangre cada seis meses durante 3 años para poder determinar los niveles de BDNF, ApoE y IL6 en su serum plasmático, además de visitas periódicas cada 6 meses que haremos coincidir, en la medida possible, con las visitas usualmente programas debido a su seguimiento por el EIPP.

Los resultados de estos estudios ayudarán probablemente a diagnosticar de manera más precisa la futura aparición de clínica psicótica en personas, que como usted, se sienten en la incertidumbre de saber si en algún momento padecerán un trastorno de salud mental de este tipo.

II) Consideraciones a tener en cuenta sobre su participación:

Es importante que usted, como potencial donante de muestras, conozca estos aspectos:

A) La donación de muestras es totalmente voluntaria.

B) Puede plantear todas las dudas que considere sobre su participación en este studio durante todo el desarrollo del mismo poniéndose en contacto a través de dirección de correo eléctronico o número de teléfono móvil que le será facilitado.

C) Se solicita su autorización para la toma y uso en investigación biomédica de muestras de sangre. En dichas muestras se medirán las concentraciones en serum plasmático de 3 proteínas (BDNF, ApoE e IL-6) utilizando los métodos que el laboratorio considere necesarios.

D) Se le tomará un volumen relativamente pequeño (12 ml) de sangre venosa mediante una punción en el brazo cada seis meses durante 3 años. La donación de sangre apenas tiene efectos secundarios; lo más frecuente es la aparición de pequeños hematomas en la zona de punción que desaparecen transcurridos 1 o 2 días.

E) No percibirá ninguna compensación económica o de otro tipo por las muestras donadas y éstas no tendrán valor comercial. No obstante, la información generada a partir de los estudios realizados sobre su muestra podría ser fuente de beneficios comerciales. En tal caso, están previstos mecanismos para que estos beneficios reviertan en la salud de la población, aunque no de forma individual en el donante.

F) Las muestras y los productos obtenidos de las mismas serán almacenados y custodiados en IDIBGI Biobanc, lugar designado para este fin por el Investigador Principal del Estudio.

> **Dirección Biobanc**
>
> Avinguda de França s/n Hospital Universitary de Girona Dr Josep Trueta
>
> 17007 Girona
>
> Biobanc@IDIBGI.org Tlf: 972 940 282

G) Los datos personales serán tratados según lo dispuesto en la normativa que resulte de aplicación según el Reglamento (UE) 2016/679, de 27 de abril, General de Protección de datos, y su normativa de datos personales de desarrollo tanto a nivel nacional como europeo.

H) Los datos registrados serán tratados estadísticamente de forma codificada. En todo momento el donante tendrá derecho de acceso, modificación, oposición, rectificación o cancelación de los datos depositados en la base de datos siempre que expresamente lo solicite. Para ello deberá ponerse en contacto con el investigador principal. Los datos quedarán custodiados bajo la responsabilidad del Investigador Principal del Estudio. Así mismo, tiene derecho a dirigirse a la Agencia de Protección de Datos si no queda satisfecho.

I) Las muestras y/o la información clínica asociada a las mismas podrán ser utilizadas por el grupo del investigador principal en estudios futuros de investigación relacionados con la línea de trabajo arriba expuesta. Dichas muestras y/o la información clínica asociada a las mismas podrán ser cedidas a otros investigadores designados por el Investigador Principal para trabajos relacionados con esta línea, siempre al servicio de proyectos que tengan alta calidad científica y respeto por los principios éticos. En estos dos últimos casos, se solicitará antes autorización al CEIC.

J) La falta de consentimiento o la revocación de este consentimiento previamente otorgado no supondrá perjuicio alguno en la asistencia sanitaria que Vd. recibe/recibirá.

K) Sólo si Vd. lo desea, existe la posibilidad de que pueda ser contactado en el futuro para completar o actualizar la información asociada al estudio.

CONSENTIMIENTO INFORMADO DEL PACIENTE POR ESCRITO.

Yo,

_____

(nombre y apellidos del paciente ó representante legal)

He leído la información que me ha sido entregada.

He recibido la hoja de información que me ha sido entregada.

He podido hacer preguntas sobre el estudio.

He recibido suficiente información sobre el estudio.

He hablado del estudio con la investigadora principal.

Comprendo que mi **participación es voluntaria**.

Comprendo que **puedo retirarme del estudio**:

      1.- Cuando quiera.

      2.- Sin tener que dar explicaciones.

      3.- Sin que esto repercuta en mis cuidados médicos.

Por la presente, otorgo mi consentimiento informado y libre para:

- El fin para el que se utilizarán **mis muestras y datos personales** según lo recogido en la hoja de información al paciente que me ha sido entregada.

- Accedo a que los médicos del Equipo de Intervención Precoz de Psicosis de la region de Girona contacten conmigo en el futuro en caso de que se **necesite obtener nuevos datos**. …SI….. NO (marcar con una X lo que proceda)

- Accedo a que los médicos del Equipo de Intervención Precoz de Psicosis de la region de Griona contacten conmigo en caso de que los **estudios realizados sobre mis muestras / datos aporten información relevante** para mi salud o la de mis familiars

…..SI….. NO (marcar con una X lo que proceda)

Una vez firmada, me será entregada una copia del documento de consentimiento.

FIRMA DEL PACIENTE / REPRESENTANTE LEGAL   NOMBRE Y APELLIDOS

EN CALIDAD DE (Parentesco, tutor legar, etc.)

FECHA

Yo he explicado por completo los detalles relevantes de este estudio al paciente nombrado anteriormente y/o la persona autorizada a dar el consentimiento en nombre del paciente.

FIRMA DEL INVESTIGADOR   NOMBRE Y APELLIDOS
          FECHA

APARTADO PARA LA REVOCACIÓN DEL CONSENTIMIENTO (CONTACTAR CON EL INVESTIGADOR PRINCIPAL)

Yo _____ **revoco el consentimiento de participación en el estudio, arriba firmado con fecha** _____

Firma:

ANNEX 6: DATA COLLECTION SHEET

		Patient n°	Age(years)	Sex	BMI	smoking	Socio-economic cathegory
	Ist sample (JULY20)	6th month (DEC2O)	1 year (JUNE21)	1,5 year (DEC21)	2 year (JUNE22)	2,5 year (DEC22)	3 years (JUNE 23)
BDNF levels (pg/ml)							
ApoE levels (µg/ml)							
IL-6 levels (pg/ml)							
PANNS (altered/not)							

		Patient n°	Age(years)	Sex	BMI	smoking	Socio-economic cathegory
	Ist sample (JULY20)	6th month (DEC2O)	1 year (JUNE21)	1,5 year (DEC21)	2 year (JUNE22)	2,5 year (DEC22)	3 years (JUNE 23)
BDNF levels (pg/ml)							
ApoE levels (µg/ml)							
IL-6 levels (pg/ml)							
PANNS (altered/not)							

(x50 copies like this)

Girona, 28th January 2020.