



End of term project

**Outcome of the association between
Obsessive-Compulsive Symptomatology
and Anorexia Nervosa:**

A 2-year prospective cohort study

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My close friends and family were, are, and will always be the anchors of my life
and I thank them for that.

To my mother.

Index

ABSTRACT	4
ABBREVIATIONS	5
INTRODUCTION	6
ANOREXIA NERVOSA	6
<i>Definition</i>	6
<i>Epidemiology</i>	7
<i>Symptoms and comorbidity</i>	8
<i>Outcome</i>	8
OBSESSIVE-COMPULSIVE SYMPTOMATOLOGY	10
<i>Definition</i>	10
<i>Epidemiology</i>	11
<i>Symptoms and comorbidity</i>	11
<i>Outcome</i>	12
THE ASSOCIATION BETWEEN OCD AND AN.....	12
<i>Comorbidity, shared etiology or something else entirely?</i>	12
<i>Obsessive-Compulsive Disorder in Eating Disorders</i>	15
<i>The theory of starvation</i>	15
JUSTIFICATION	17
HYPOTHESIS	19
OBJECTIVES	19
METHODOLOGY	20
STUDY DESIGN	20
STUDY SUBJECTS.....	20
SAMPLE SELECTION	21
SAMPLE SIZE	21
STUDY VARIABLES	22
DATA COLLECTION.....	24
MEASURING INSTRUMENTS	24
STATISTICAL ANALYSIS	27
ETHICAL AND LEGAL CONSIDERATIONS	28
STUDY LIMITATIONS	29
WORK PLAN	31
CHRONOGRAM	35
IMPACT OF THE PROJECT ON THE NATIONAL HEALTH SYSTEM	36
BUDGET	38
REFERENCES	39
APPENDICES	43
APPENDIX 1: DSM-V DIAGNOSTIC CRITERIA FOR ANOREXIA NERVOSA (307.1)	43
APPENDIX 2: DSM-V DIAGNOSTIC CRITERIA FOR OBSESSIVE-COMPULSIVE DISORDER (300.3)	44
APPENDIX 3: YALE-BROWN OBSESSIVE COMPULSIVE SCALE (Y-BOCS).....	45
APPENDIX 4: MORGAN & RUSSELL OUTCOME ASSESSMENT SCHEDULE (MROAS)	46
APPENDIX 5: HOLMES AND RAHE STRESS SCALE	48
APPENDIX 6: MODULE H OF STRUCTURED CLINICAL INTERVIEW FOR DSM DISORDERS (SCID)	49
APPENDIX 7: INFORMATION FORM AND INFORMED CONSENT FORM	50
APPENDIX 8: CASE REPORT FORM.....	52
APPENDIX 9: CONSIDERATIONS ABOUT “PROGRAMA ESPECÍFIC DE TCA DE GIRONA”	53
APPENDIX 10: PROPORTION OF PATIENTS SERVED BY “PROGRAMA ESPECÍFIC DE TCA DE GIRONA”	54
APPENDIX 11: CONSIDERATIONS ABOUT “XARXA DE SALUT MENTAL”	54

Abstract

Title. Outcome of the association between Obsessive-Compulsive symptomatology and Anorexia Nervosa: a 2-year cohort prospective study

Background. Obsessive-compulsive manifestations have been recognized in anorexia, since the disorder's earliest descriptions. Persistent thoughts about thinness can be considered 'obsessions' and excessive exercise and calorie counting have similarities to 'compulsions'. It is estimated that up to 69% of anorexic patients manifest some degree of obsessive-compulsive symptoms. Although anorexia nervosa is one of the most severe chronic mental illnesses and it has been hypothesized that its relationship with obsessive-compulsive symptomatology has a negative effect on the anorexic individuals, there is little data about the outcome of this association, especially in Spain.

Aim. Determine whether the outcome of the association of anorexia nervosa and obsessive-compulsive symptomatology is worse than the outcome of anorexia nervosa without said comorbidity, using the Morgan & Russell Outcome Assessment Schedule to categorize the prognosis in "good" or "poor".

Methods. This study will be a longitudinal, prospective cohort study, which will include sixty-seven patients with anorexia nervosa, from those incorporated in "Programa Específic de Trastorns de Conducta Alimentària de Girona", using a consecutive sequential sampling. These patients will be followed for 2 years, after being assigned two separate groups, according to their scores in the Yale-Brown Obsessive Compulsive Scale (≥ 16 o < 16) (independent variable). Anorexia Nervosa's prognosis will be the dependent variable, measured with the Morgan and Russell Assessment Outcome Schedule, at the 6, 12, 18 and 24 months mark. Frequencies, percentages, Fisher's exact test and logistic regression analysis will be performed to analyze and describe the results of the study.

Keywords: anorexia nervosa, obsessive-compulsive symptoms, comorbidity, outcome, Yale-Brown Obsessive Compulsive Scale, Morgan and Russell Outcome Assessment Schedule

Abbreviations

AN Anorexia Nervosa

BMI Body Mass Index

CEIC Comité Ético de Investigación Clínica

CRF Case Report Form

CSMA Centre de Salut Mental de Adults

ED Eating Disorder

MOCI Maudsley Obsessive-Compulsive Inventory

MROAS Morgan and Russell Outcome Assessment Schedule

OC Obsessive-Compulsive

OCD Obsessive-Compulsive Disorder

SCID Structured Clinical Interview for DSM Disorders

WHO World Health Organization

XSM Xarxa de Salut Mental

Y-BOCS Yale-Brown Obsessive Compulsive Scale

Introduction

Anorexia Nervosa

Definition

Anorexia Nervosa (AN) is a psychiatric disorder, which consists on a restriction of energy intake by the patient, “leading to a significantly low body weight, in context of age, sex (...) and psychical health”. (1) Also defined as criteria of AN are the intense fear of gaining weight, that doesn’t decrease with weight loss, and acting in a way that interferes with weight gain. The fulfillment of this criterion might be difficult if we consider that a failure to recognize one’s symptoms is common in eating disorders (ED), particularly in younger individuals. Moreover, these patients view their bodies in a distorted way, feeling heavier than what they really are. (1) (Appendix 1)

It is important to understand that, for a patient with an ED, weight loss has a close relationship with the notion of ‘self-worth’. Losing a number of kilograms is considered an achievement; in the other hand, gaining weight feels like a failure, creating a mental scheme of “thinness equals higher self-esteem”. (1)

Considering that the concept of ‘normal’ weight varies within the broad spectrum of individuals, World Health Organization (WHO) has been employing the Body Mass Index (BMI) as a measure to assess body weight (weight in kilograms/height in meters²). According to this, the lower limit of normal body weight corresponds to a BMI of 18,5kg/m². DSM-V follows the WHO guidelines and specifies severity of an ED by using BMI: if higher than 17kg/m², it is considered mild AN but, if it lower than 15kg/m², it is categorized as an extreme anorexia. (1) (Appendix 1)

DSM-V Diagnostic Criteria for Anorexia Nervosa	
<p>A. <i>Restriction of energy intake relative to requirements, leading to a significantly low body weight in the context of age, sex, developmental trajectory, and physical health. Significantly low weight is defined as a weight that is less than minimally normal or, for children and adolescents, less than that minimally expected.</i></p>	<p><i>the seriousness of the current low body weight.</i></p> <p><i>Specify whether:</i></p> <p>Restricting type: During the last 3 months, the individual has not engaged in recurrent episodes of binge eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas). This subtype describes presentations in which weight loss is accomplished primarily through dieting, fasting, and/or excessive exercise.</p> <p>Binge-eating/purging type: During the last 3 months, the individual has engaged in recurrent episodes of binge eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas).</p>
<p>B. <i>Intense fear of gaining weight or of becoming fat, or persistent behavior that interferes with weight gain, even though at a significantly low weight.</i></p>	
<p>C. <i>Disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or persistent lack of recognition of</i></p>	

Table 1: Adapted from “Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition” (1) (Appendix 1)

It is not uncommon for a crossover between the subtypes to occur - that’s why the subtypes should only be used to describe the symptoms at the moment of diagnosis (as opposed to a long-term categorization of the disorder). (1)

Epidemiology

Anorexia nervosa commonly begins during adolescence or young adulthood, although cases of early or late onset have been described. (1-4) It is a relatively rare disorder, with a lifetime prevalence of 0,5-0,9%. (5) It should be noted, however, that this prevalence is increasing. (2-3) According to Hospital Santa Caterina’s “Protocol TCA de la Unitat d’Aguts de Psiquiatria i URPI”, the prevalence of ED in the general population is close to 5%, with 0,4% being anorexic patients. The same protocol estimates that, annually, there would be 175 cases of AN in Girona. (2) This data is confirmed by “Memòria del any 2013 del Programa Específic de TCA”, where it is mentioned that, in the year 2013, 16% of the patients enrolled in “Programa Específic de TCA de Girona” suffered from AN (140 patients). (6) (Appendix 10)

Although it is more common in women than men (2,4,6), the symptoms of ED are very similar in both sexes. (7)

Symptoms and comorbidity

DSM-V acknowledges a diverse list of symptoms present in people with anorexia:

- “Frequent weighing, obsessive measuring of body parts, (...) persistent use of mirrors to check for perceived areas of fat” (1)
- Concerns about eating in front of others (1)
- Desire to control its own environment (within its family, workplace or group of friends) (1)
- “Social isolation” (1)
- “Inflexible thinking” (1)
- Limited spontaneity and emotional expression. (1)
- Impulsivity (mainly in the purging subtype) (1)
- Physical symptoms and signs: “amenorrhea, constipation, abdominal pain, cold intolerance, lethargy”, emaciation, emergence of lanugo. (1)

Studies of comorbidity showed a relationship between ED and substance abuse (especially in patients with traits of impulsivity) (1), mood disorders (depression), anxiety disorders (obsessive-compulsive disorder), personality disorders (avoidant, obsessive-compulsive personality disorder) and Asperger’s Syndrome. (4,8)

Outcome

AN is one of the most serious chronic mental illnesses, ranking among the ten leading causes of disability, and it has the highest rate of mortality of all mental disorders. (2-3,9-11). According to DSM-V, the crude mortality rate of anorexia is around 5% per decade, with half of the deaths resulting from cardiac complications or suicide. (1,12) The different complications of AN are reflected in Table 2. (1,13-14)

<u>Complications of Anorexia Nervosa</u>	
Amenorrhea	
Osteoporosis/osteopenia	
Hypothermia	
Gastrointestinal complications	Delayed gastric emptying Dilation of the stomach and small intestine
Cardiac complications	Bradycardia Hypotension Reduced heart mass EKG abnormalities
Hematologic changes	Leukopenia Thrombocytopenia
Biochemical changes (due to dehydration)	Elevated Blood Urea Nitrogen levels Hypercholesterolemia Elevated hepatic enzymes Metabolic alkalosis, hypochloremia, hypokalemia (due to purging behaviors) Decreased T3 and T4 levels Decreased estrogen (in women) and testosterone (in men) levels
Neurologic complications	Metabolic encephalopathy
Higher suicide risk	Rates of 12 per 100.000 patients/year

Table 2: Adapted from “DSM-V” (1), “The pursuit of thinness: an outcome study of anorexia nervosa” (13) and “Indicators of nutritional status in restricting-type anorexia nervosa patients: a 1-year follow-up study” (14)

Although it is a debilitating disease, considerable heterogeneity exists in its long-term course and prognosis. Follow-up studies of ED describe disparate outcomes: some patients will recover completely, while others fluctuate between relapse and chronicity. (12) Some defend that recovery 4 years post disease onset is at 33% (10), while others refer recovery rates between 11 and 50% (at the ten year mark) and 16-73% (if more than ten years have passed since disease onset). (4,10) The possibility of chronicity, relapse or mortality is declared as being between 22 and 55%. (4,10,12) The highest risk of relapse presents itself between 4 and 9 months post-treatment (12). Several studies identified extreme exercise, purging behaviors and poor social relationships as risk factors for poor outcome. It was also proved that a shorter duration of the episode predicted better rates of recovery and a

decreased risk of relapse after 4 years. (4)

It is important to stress the lack of consensus, across the various studies, in defining recovery and relapse, which may be the cause of disparity between the outcome results. To avoid these discrepancies, in the last few years, the Morgan & Russell Outcome Assessment Schedule (MROAS) has been increasingly used. (4) (Appendix 4)

Obsessive-Compulsive Symptomatology

Definition

Obsessive-Compulsive (OC) symptomatology refers to the manifestations related to Obsessive-Compulsive Disorder (OCD). OCD consists on the mutual existence of, as the name indicates, obsessions and compulsions. Obsessions are “recurrent and persistent thoughts, urges, (...) that are experienced as intrusive and unwanted” and the definition of compulsions covers “repetitive behaviors or mental acts that an individual feels driven to perform in response to an obsession (...)”. The symptoms on the obsessive-compulsive usually persist beyond appropriate periods and the individuals leading with them can manifest a lack of insight (ranging from “fair insight” to the occurrence of “delusional beliefs”). (15-16) (Appendix 2)

The obsessions are not viewed as enjoyable or even voluntary (ego-dystonic), causing a great deal of anxiety in most patients, and the compulsions are performed, usually, as the answer to an obsession, in order to decrease the aforementioned levels of anxiety. (4) It is important to note that these compulsions are not realistic and are often excessive (e.g.: turning a switch on-and-off to avoid dying), even if its frequency, severity and content vary across the affect population. There are some themes, however, than are common in the presentation of the disease, presented here in pairs of obsession/compulsion: thoughts of contamination/cleaning, of symmetry/ordering and of harm/checking. Forbidden thoughts, either of aggressive, sexual or religious nature, and a tendency to hoarder also appear in

OCD.(15,17)

Epidemiology

Between females and males, the latter are more likely to show an earlier age of onset (4), comorbid tic disorders and symmetry-related symptoms. Women, on the other hand, show obsessions related to cleaning. (15)

The symptoms of OCD normally appear in childhood but the common presentation of the disorder is usually in adolescents or young adults. (4)

In relation to prevalence, studies cite a lifetime prevalence of 1.6-2,5% in adults. However, since there are methodological problems surrounding the assessment tools, the prevalence rates may not be entirely accurate. (4-5,16)

Symptoms and comorbidity

Insight may vary within the same patient over the course of the disease, as do the beliefs. These beliefs present themselves in varied ways:

- Great sense of responsibility (15)
- “Tendency to overestimate threat” (15)
- “Perfectionism and intolerance of uncertainty” (15)
- “Over-importance of thoughts (believing that having a forbidden thought is as bad as acting on it)” and an irresistible urge to control said ideas (15)
- Disgust or anxiety towards one’s own thoughts and actions (15)

The symptom dimensions are usually identified by using the Yale-Brown Obsessive-Compulsive Scale checklist (Y-BOCS) (17), and include, as mentioned, obsessions and compulsions ranging from aggression to contamination to even a need for symmetry and exactness. (Appendix 3)

These symptoms appear, not only in OCD, but also in a broad spectrum of disorders, such as: anxiety disorder (76%), mood disorders (63%, of which 41% are attributed to major depressive disorder), obsessive-compulsive personality disorder (23-32%) and tic-disorder (30%). Comorbidity with OCD and its symptoms is also present in schizoaffective disorders,

Tourette's syndrome and eating disorders. (15)

Outcome

WHO classifies OCD, as it did with AN, as being one of the top ten most disabling mental disorders, since the symptoms can cause functional deterioration. (16) It is associated with high rates of comorbidity and treatment resistance. (18) The course of the illness is fluctuating, with oscillations between partial remission and relapse, especially because the symptoms can interfere with the treatment. (15) Also, if left untreated, the course of OCD is chronic, with “waxing and waning” symptoms. (15,18) Despite this knowledge, or maybe because of it, there are doubts about the short and long-term course of OC symptoms. (18) The lack of information is such that studies differ in the rates of remission, from 20 to 65% (with some affirming that 40% of patients with childhood onset may experience full remission by the time they're adults). (15-18)

Poorer insight, internalized symptoms, behavioral inhibition, as well as abuse in childhood and traumatic events showed links to worse long-term outcome. Half of the individuals suffering from OCD exhibit suicide ideation (15) and 10-27% attempt it at least once. (16)

A bigger problem pertaining to this kind of manifestations, and that further complicates its study, is the excessive use of the terms “obsessive” and “compulsive”, often used to describe symptoms not related to the OC spectrum. (7)

The association between OCD and AN

Comorbidity, shared etiology or something else entirely?

Comorbidity is “the simultaneous occurrence of two separate disorders within the same person at a given point in time or all of the diagnoses for which an individual has ever met diagnostic criteria over a given period of time”. (4) It can involve two independent disorders, with the same underlying etiology, happening at the same time or two disorders

having a casual relationship. These definitions are important as there is still much confusion on whether AN and OCD share the same etiology or are just comorbid illnesses. (4)

Obsessive-compulsive symptoms have been recognized as present in AN, since the earliest descriptions of the disorder. (8,19) If it is considered that one of the characteristics of AN is “overvalued ideas about thinness” (1), then it could be contemplated that these ideas bear some kind of relationship with “obsessions”, such as those about weight. The persistent thoughts about thinness, followed by ‘compulsive-like’ behaviors (like excessive exercise or calorie counting) and ritual-like behaviors around food, suggest an overlap between AN and OCD. (1,8,11,20) Non-food related obsessions might be also present in anorexic patients, like ideas of symmetry. (11) One could consider that one of the most common compulsions in AN is the excessive exercising (lifetime occurrence in 80% of patients), which, as one of the first symptoms to manifest itself, leads to poorer recovery rates, more relapse and longer hospitalizations. (20)

While it is important to stress that the pattern of obsessions and compulsions in both disorders are different, as well as its character of invasiveness (OCD is ego-dystonic, eating disorders are ego-syntonic), recent studies describe AN patients with obsessions and/or compulsions (albeit more closely related with food, weight and shape, contrary to those in OCD). (4,15) One theory even proposes that ED and OCD are part of an obsessive-compulsive spectrum, with symptoms alternating between compulsivity (actions to avoid anxiety) and impulsivity (actions to seek pleasure). (21)

Altman & Shankman explained this connection in their study “What is the association between obsessive-compulsive disorder and eating disorders?”. (5)

<u>Comparison between Eating Disorders and Obsessive-Compulsive Disorder</u>		
	<u>Eating Disorder</u>	<u>OCD</u>
Repetitive thoughts and preoccupations about a feared stimulus	Food Body Image Weight	Symmetry Contamination Harm
Negative affect	Anxiety Fear	
Compensatory behaviors	Restriction Binge, purge Compulsive exercise	Hand washing Checking

Table 3: Adapted from “What is the association between obsessive-compulsive disorder and eating disorders?” (5)

The overlap between AN and OCD is explained by common characteristics, which can suggest a shared etiology (4):

Personality traits. High levels of obsessionality (worries about cleaning, symmetry, counting and order; strict eating and exercise routines) (9,22), rigidity, persistency (21-22), impulsivity and perfectionism (5) have been found in both disorders, some even as core personality characteristics.

Neurochemistry. The serotonergic function appears modified (7,9,19), with increased levels of 5-HIAA (5-Hydroxyindoleacetic acid), a major metabolite of serotonin, being found in both OCD with avoidant behavior and ED with food avoidance (such as restrictive AN). (8,11) Another factor that supports this idea is the fact that serotonin reuptake inhibitors have been used, with success, to attenuate symptoms of both OCD and ED (21).

Molecular genetics. Results are still inconclusive. (22)

Imaging. There are abnormalities reported, using functional imaging, in limbic and paralimbic structures, in both illnesses. (8) Also observed was an “hyperactivation of the prefrontal areas and basal ganglia structures” and an “excessive awareness of stimuli signaling punishment or non-reward”, which can contribute to the OC symptoms. (19-20)

Family studies. There is an increased risk for OCD in first-degree relatives of patients with an ED. (7,21)

Measuring tools. In observational studies, ED and OCD groups had similar values on measures of general anxiety, eating pathology and OCD symptoms. (7)

The studies conducted reported limitations and mentioned the need for future research, so that the specific nature of the shared etiology could be determined. However, it is clear that an overlap between both diseases exists, at least in some form. (5)

Obsessive-Compulsive Disorder in Eating Disorders

Many studies dwelled in the matter of the association of AN and OCD and its prevalence, with the latter being the fourth most common comorbid lifetime disorder in individuals with ED. Some reported that OCD is up to 15 times more common in anorexic patients than in the general population (for comparison, the same studies found that depression is 7 times more common). (8,23)

The lifetime prevalence of the comorbidity of OCD and AN (or ED) is reflected in the table below.

<u>Lifetime prevalence of OCD in patients with a primary diagnosis of AN or ED</u>			
	<u>OCD in ED</u>	<u>OCD in AN</u>	<u>Anxiety Disorder in AN or ED</u>
Speranza et al, 2001(9)	19,1%	22,4%	35-77%
Jimenez-Murcia et al, 2007 (22)	11-41%		
Olatunji et al, 2009(11)		10-60%	
Altman et al, 2009 (5)		0-69%	
Ha Kim et al, 2011(21)	9,4-41%		
Zerwas et al, 2013 (8)		53,3%	
Mas et al, 2013 (19)			7,8%

Table 4. Adapted from “Obsessive compulsive disorders in eating disorders” (9), “Obsessive-compulsive and eating disorders: Comparison of clinical and personality features” (22), “Mediation of symptom changes during inpatient treatment for eating disorders: The role of obsessive e compulsive features” (11), “What is the association between obsessive-compulsive disorder and eating disorders?” (5), “Depression mediates the relationship between obsessive – compulsive symptoms and eating disorder symptoms in an inpatient sample” (21), “Factors associated with recovery from anorexia nervosa” (8), “Common genetic background in anorexia nervosa and obsessive compulsive disorder: preliminary results from an association study” (19)

The theory of starvation

As it can be observed, there is a clear relationship between AN and OC symptoms. However, it has been hypothesized that the effects of starvation and weight loss are the cause

of this symptomatology, with some OC manifestations worsening after a prolonged illness with a BMI < 17 kg/m². (8) This generates a question: is obsessiveness a core feature of AN or is it due to the mechanism of malnutrition? (1,19-20)

As mentioned before, there is a proven association between AN and OC symptoms. In the great majority of studies concerned with this, OCD diagnosis preceded ED diagnosis. In these cases, the possibility that OCD may be a risk factor for developing an eating disorder was suggested. (1,4,15,19-20,23) Some cases report OC symptoms emergence even before the development of AN and the persistence of said symptoms even after weight restoration. (5,8) Likewise, the presence of obsessive traits as a child can predict disordered eating in adulthood. (21) Finally, Espíndola et al detected that “OCD current prevalence and Y-BOCS scores of underweight patients were not significantly higher than in normal weight patients, suggesting that there are only limited links between malnutrition and obsessiveness”. (23)

If these last observations are taken into account, the hypothesis of a direct cause-effect relationship between starvation and OC symptoms is less likely. (23) Even if, by gaining weight, the symptoms decrease, they still persist at significantly higher levels than in the population without AN (especially after a long period of weight stabilization). Hence, starvation, by itself, cannot completely explain the debut of obsessive-compulsive symptoms. (23)

Justification

Obsessive-compulsive disorder and obsessive-compulsive symptomatology are closely linked. However, they do not specifically depend on each other – there are other afflictions that exhibit these symptoms. (15)

As it has been explained so far, anorexia nervosa and obsessive-compulsive symptoms are closely connected, taking into consideration the possibility of a common etiology between AN and OCD.

In the works available, the OC symptomatology was often measured with different scales, such as the Maudsley Obsessive-Compulsive Inventory (MOCI) or the Y-BOCS. (23) The Y-BOCS was particularly useful in a study conducted in 1996 by Bastian et al, where patients with a main diagnosis of AN or OCD had their scores contrasted. It was reported that the scores were often comparable and 20-30% of patients with AN displayed obsessional and/or compulsive features at presentation. (8) Later, in 2012, another study also used this scale and found that, in AN, “the longer the illness, the more intense were the [OC] symptoms”. (24)

We know that the association between AN and OC symptoms affects treatment outcome and relapse (5). However, the studies developed so far didn't provide enough data. It has been hypothesized that the co-existence of OCD and AN worsens the prognosis of the latter (8-9) but most works only take into account either the reduction of the quality of life, the BMI or the sustainment of excessive exercise, neglecting to employ a valid prognostic scale. One particular research (23) observed a worse BMI in patients with a comorbidity of ED and OCD but didn't specify the types of eating disorders, combining the known ones (anorexia nervosa, bulimia nervosa, avoidant food intake disorder and unspecified eating disorder) (1) as one big group.

While these studies accomplished to compare scores of Y-BOCS in AN and OCD, they didn't apply it to prognosis. Furthermore, such works suffer from both a failure to

separate between AN, bulimia nervosa and other eating disorders; and the absence of a cohesive and thoroughly validated outcome scale.

Currently, no studies that examine this particular association are present in the assorted databases (Pubmed, Cochrane, Medscape).

Given the fact that anorexia nervosa is one of the most severe chronic mental illnesses, with high rates of disability and mortality, and the relationship with OC symptoms has a negative effect on the anorexic individuals, it is imperative to investigate the outcome of this association (using, for that, the most commonly used measures: Y-BOCS and MROAS).

Hypothesis

Main hypothesis

The outcome of the association between anorexia nervosa and obsessive-compulsive symptomatology is worse than the outcome of anorexia nervosa without said association.

Objectives

Main objective

To determine whether the outcome of the association of anorexia nervosa and obsessive-compulsive symptomatology is worse than the outcome of anorexia nervosa without said association, using the Morgan & Russell Outcome Assessment Schedule to categorize the prognosis in “good” or “poor”.

Methodology

Study design

Cohort study. Longitudinal, observational, analytic and prospective.

Study subjects

The study subjects will be all the patients that are included in the “Programa Específico de TCA de Girona”, with the diagnosis of AN, between 2015 and 2017.

Inclusion Criteria

- Women.
- Ages between 18 and 40 years old.
- Diagnosis of anorexia nervosa according to DSM-V axis I criteria, not subject to serious medical complications resulting from said disorder. The diagnosis of anorexia nervosa must have been met at least 3 years before study entry. The last criterion ensures that the participants are unlikely to develop binge eating in the future (because binge eating typically develops within the first 3 years of AN onset).

Exclusion criteria

- Diagnosis of any of the remainder eating disorders: bulimia nervosa, avoidant food intake and unspecified feeding or eating disorder.
- Any diagnosis regarding other psychiatric, severe somatic or neurological organic disorders.
- Treatment for any other pathology, either somatic or psychiatric.
- Past or present history of substance abuse.
- Impossibility of follow up (either by geographical reason or failure to continue the participation).
- Impossibility of answering the questions regarding the items in Y-BOCS or MROAS.

Sample selection

The sampling method will be a consecutive sequential sampling. The subjects admitted to the “Programa Específic de TCA de Girona” that fulfill the above-mentioned criteria will be recruited, as they come to the program’s appointments, for a period of 2 years. The “Programa Específic de TCA de Girona” has its foundation on a large net of integrating services, all belonging to Xarxa de Salut Mental (XSM), and covers, for adults, several levels of patient care: primary attention care (“Equipos de Atención Primaria”) (level 0), adult mental health centers (“Centres de Salut Mental de Adults” – CSMA) (level 1), day hospital at Parc Sanitari Martí i Julià (“Hospital de Dia”) (level 2) and hospitalization, also at Parc Sanitari Martí i Julià (“Hospitalización”) (level 3). (Appendix 9) This study will include the patients from the Gironès, Baix Empordà, La Selva Interior, La Selva Marítima, Alt Empordà, Garrotxa and Ripollès sectors. In 2013, 795 patients were a part of this program. (Appendix 10)

All the potential participants will be given an information sheet and an informed consent and will only be a part of the study after reading and signing said documents. (Appendix 7)

Sample size

The sample size and power calculator GRANMO was used to achieve our sample size. Using the POISSON approximation and accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test, **27** exposed and **40** non-exposed subjects are necessary to recognize as statistically significant a relative risk greater than or equal to 2 and if the proportion in the non-exposed group has been estimated to be of 0.4. It has been anticipated a dropout rate of 15%.

It is supposed that approximately 140 patients diagnosed with anorexia nervosa are a part of the “Programa Específic de TCA de Girona”, each year. This data makes it possible for the sample selection to be carried out to term in 2 years (≈ 280 patients). However, taking into

account that it is a consecutive sequential sampling, the patient's selection will end in the moment that the two groups are completed.

Study Variables

Independent Variable

- **Score in the Yale-Brown Obsessive-Compulsive Scale:** through the application of this variable, we will achieve the creation of two groups, one with patients diagnosed with anorexia nervosa and exactly or more than 16 (≥ 16) points in the Y-BOCS, and other also with patients diagnosed with anorexia nervosa but with less than 16 points (< 16) in said score. (Appendix 3)

This is a dichotomous nominal qualitative variable.

Dependent Variable

- **Outcome according to the Morgan & Russell Outcome Assessment Schedule:** after 2 years of follow-up (with consultations at the 6, 12, 18 and 24 months mark) and by applying the Morgan & Russell Outcome Assessment Schedule, we will classify the participants according to the measures of outcome “poor” (mean score of 0 to < 6) and “good outcome” (mean score from ≥ 6 to 12). The MROAS and its criteria are further explained in the “measuring instruments” paragraph. (Appendix 4)

This is a dichotomous nominal qualitative variable.

Co-Variables

- **Subtypes of anorexia nervosa:** “restrictive” and “purgative”. This is a dichotomous nominal qualitative variable and will be determined by DSM-V Anorexia Nervosa Criteria, using the module H of SCID (Structured Clinical Interview for DSM Disorders) (Appendix 6), if not specified in the patient's clinical history.
- **BMI (Body Mass Index):** “very severely underweight (< 15)”, “severely underweight (15-15.9)”, “underweight (16-18,4)”, “normal weight (18,5-24,9)” and “overweight (> 25)”. This is a nominal qualitative variable and will be determined in the clinical

interview and using the module H of SCID (Structured Clinical Interview for DSM Disorders), if not specified in the patient's clinical history.

- **Age of onset of anorexia nervosa and illness duration:** measured in months. This is a continuous quantitative variable and it will be determined using the module H of SCID (Structured Clinical Interview for DSM Disorders), if not specified in the patient's clinical history.
- **Treatment of the eating disorder:** “pharmacological and psychiatric”, “nutritional and psychiatric” or “combination of pharmacological, nutritional and psychiatric”. Although the type of treatment is considered a co-variable, it is important to stress that all the study's participants will already be under the “Programa Específico de TCA de Girona”, which allows for a close and, more importantly, unified actuation protocol. This is a nominal qualitative variable and it will be determined by accessing the patient's clinical history.
- **Sociodemographic variables.** These co-variables will be determined in the clinical interview.
 - Education: “less than high school”, “high school degree”, “college degree” and “graduate degree”. This is a nominal qualitative variable.
 - Marital status: “married”, “in a partnership”, “single”, “separated”, “divorced” and “widowed”. This is a nominal qualitative variable.
 - Employment situation: “employed”, “unemployed”, “student” and “retired”. This is a nominal qualitative variable.
 - Ethnic group: “Caucasian”, “Black”, “Latino”, “Asian” and “others”. This is a nominal qualitative variable.
- **A traumatic event in the last year:** “at risk of illness” (score >300), “moderate risk of illness” (score between 150 and 299) and “slight risk of illness” (score <150), according to the Holmes and Rahe Stress Scale. A distressing occurrence can be a trigger for the appearance of obsessive-compulsive symptomatology, thus, creating a confounding factor

in our study. This is a nominal qualitative variable and it will be determined by using the aforementioned scale. (Appendix 5)

Data collection

All the data will be collected in 5 meetings, with 6 months between them, in face-to-face interviews, after the patients' agreement to participate in the study. In the first appointment (appointment n° 1), the trained psychiatrist and psychologist working in this research will be given a Case Report Form (CRF), specially designed for this cohort, in which the measures of the independent and dependent variables as well as those of the co-variables will be stated. (Appendix 8) This information will then be reflected in a database (a password-protected Microsoft Access© file). The process of filling in the forms will be repeated in follow-up visits at 6, 12, 18 and 24 months of the first consultation (appointments n° 2, 3, 4 and 5, respectively) along with the entering of the data on said directory. Homogeneity in data collection must be ensured and that's why the only ones who can collect and insert the data are the above mentioned psychiatrist and psychologist working in this project.

Measuring instruments

Y-BOCS. The Yale-Brown Obsessive-Compulsive Scale is a semi structured, clinician-rated interview, designed to assess the presence and severity of obsessive and compulsive symptoms. It includes a symptom checklist (to identify the patient's obsessive and compulsive nature, both past and present), followed by a 10-item list that measures five parameters of obsessions (items 1-5) and compulsive rituals (items 6-10): time occupied, frequency, interference, distress, resistance and perceived control over symptoms. Each item is rated on a five point Likert type scale from 0 (no symptoms) to 4 (severe symptoms) that will be added to produce a total score from 0 to 40. A score of 16 on the Y-BOCS scale is considered as the necessary threshold for the inclusion of the subjects in pharmacological studies and is the threshold for the classification in 'moderate severity'. A patient was considered to be in remission (partial or full) if he or she scored less than 15 on the Y-BOCS.

It is the gold standard measure of OC symptoms because, in contrast to, for example, the self-questionnaire MOCI, it is hetero-administrated and relies on the observations of a professional. This scale has presented good convergent validity and satisfactory psychometric properties, when compared with other measures of OC symptomatology.

The Spanish version of the instrument will be used to select the study and control groups and to assess the severity of the obsessive-compulsive symptoms (independent variable). (Appendix 3)

MROAS. The Morgan & Russell Outcome Assessment Schedule is a semi structured, clinician-guided interview, designed to measure the outcome of anorexia nervosa. The assessment produces 5 scales A (food intake), B (menstrual state), C (mental state), D (psychosexual state) and E (socioeconomic state), which, in turn, have subscales (A1-A3, B, C, D1-D4, E1-E5). The score of each main scale will be achieved by averaging subscale scores, as exemplified below:

$$A = \frac{A1 + A2 + A3}{3}$$

Each item is rated in 0, 3, 4, 6, 8, 9 or 12 points, with the corresponding variables depending on the subscale. The final score should be the average of each one of the main scales, as shown below:

$$Final\ score = \frac{A + B + C + D + E}{5}$$

In this study, an adapted version of scoring will be used, in which “poor outcome” refers to the mean score of 0 to ≤6 and “good outcome” to the mean score from 7 to 12.

Besides being useful for outcome, this schedule can also be used in routine clinical settings, to provide a measure of symptom severity, and can be reapplied to monitor treatment response.

This instrument and its criteria will be used to determine the outcome of the association between AN and OC symptomatology (dependent variable). (Appendix 4)

BMI. The Body Mass Index consists on an equation of weight (in kilograms) divided by the square of height (in meters) (kg/m^2). Although it has been criticized as an inaccurate measure of body fat, it is considered by DSM-V to be a rather inexpensive and simple tool to quickly assess weight loss. It can be expressed in eight different categories: very severely underweight ($<15\text{kg}/\text{m}^2$), severely underweight ($15-15.9 \text{ kg}/\text{m}^2$), underweight ($16-18,4\text{kg}/\text{m}^2$), normal weight ($18,5-24,9\text{kg}/\text{m}^2$), overweight ($25-29,9\text{kg}/\text{m}^2$), moderately obese ($30-34,9\text{kg}/\text{m}^2$), severely obese ($35-39,9\text{kg}/\text{m}^2$) and very severely overweight ($>40\text{kg}/\text{m}^2$).

Weight and height should be measured with patients in their underwear and without shoes, using a digital electronic weighing scale and a digital stadiometer. Weight should be reflected in kilograms and height in meters.

The instrument and its stratification will be used to study one of the co-variables.

Homes and Rahe Stress Scale. This scale is used to assess the occurrence of traumatic events and their contribution to a person's well-being and risk of disease. It has been proven as a valid predictor of illness and allows the classification between "at risk of illness", "moderate risk" or "low risk". This instrument will be used to study one of co-variables. (Appendix 5)

A **Case Report Form** will express the data collected. (Appendix 8)

Statistical Analysis

Univariate Analysis

Categorical variables, such as the dependent and the independent variables, will be described using frequencies and percentages. The frequencies will be represented in frequency tables and in bar charts.

Bivariate Analysis

Comparisons of results for major variables will be performed using Fisher's exact test.

Multivariate Analysis

Multivariate analysis will be performed using multivariate logistic regression analysis to assess the relationship between Y-BOCS Score and outcome of Anorexia Nervosa conditioned on the presence or absence of other features and their contribution.

A descriptive analysis of the variables will be performed using IBM SPSS Statistics version 22, 2014 (IBM, Armonk, NY, US). The data set will be thoroughly screened prior to commencing analyses, and double-checking all entries and screening for the presence of missing data will ensure the accuracy of the information.

A p value <0.05 will be considered statistically significant.

Ethical and Legal Considerations

Before carrying out the study, the research protocol will be presented to the ethics committee, CEIC (Comisión de Ética para la Investigación Médica) from “Institut d’Assistència Sanitària de Girona”, and, to be carried out, it should be accepted by the same committee.

Since it is a prospective study, we will not depart from a previously constructed database. Therefore, we will need the acquiescence of the participants. At the time of inclusion, all potential participants will be informed of the research’s purpose and structure by the psychiatrist and psychologist and will also be given an information sheet that details the information transmitted beforehand and an informed consent form. (Appendix 7) They will only be a part of the study once and if they sign said form.

This study guarantees the confidentiality of the patient’s data as the Case Report Form will only use the medical record number and not the participant’s name. Clinical history information, names and surnames will remain anonymous when collecting data from the database and publishing results.

The present project will be conducted according to national and international ethics guidelines and laws:

- Ley Orgánica 15/1999, del 13 de Diciembre, de Protección de Datos de Carácter Personal
- Ley Orgánica 41/2002, del 14 de Noviembre, de Autonomía del Paciente y de Derechos y Obligaciones en Matéria de Información y Documentación Clínica.
- WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects, June 1964. Last revision, October 2013.

The investigators of this project declare that there are no conflicts of interests.

Study Limitations

One of the main problems of the study is the small sample size and, to counter that, it was used a non-probabilistic consecutive sampling, which, in turn, has its own limitations. This type of sampling is useful for small sample sizes, it is not time consuming and allows for minor changes and adjustments in the initial phases of research. However, it is hardly representative of the entire population. Therefore, it may not enable us to draw definitive conclusions concerning the outcome of the association of AN and OC symptoms. These results should be considered as preliminary and will be helpful in the case the study is repeated using a randomized, probabilistic sampling.

Another problem is due to the fact that this study is a prospective cohort. While a cohort allows a faithful follow-up, in which the risk factor (in this case, OC symptomatology) predates the illness (anorexia nervosa) and it is one of the commonly used studies to assess prognosis, it is very time consuming and expensive. Furthermore, the large duration of the study may account to higher dropout rates, either by death, geographical reasons (change of address) or lack of attendance (withdrawals to follow-up biases). To avoid sample losses, we will call each patient 1 (one) week before each meeting as a reminder.

Each and every participant will be a part of the same intervention program (“Programa Específico de TCA de Girona”) and, while that assures that the general guidelines are the same, a certain degree of treatment heterogeneity and the experience of stress-like events cannot be avoided. However, these possible limitations were taken into account and that is why “type of treatment” and “traumatic events” are co-variables.

We also have to take into account the additional biases:

- Confounding bias: the relationship is difficult to control due to co-variables. This limitation will be minimized by the use of a multivariate analysis.
- Reporting (information) bias: denial commonly occurs in anorexic patients, which can lead to an under or overestimation of the symptomatology. It is to prevent this bias that this study will use one psychiatrist and one psychologist, with the objective

of contrasting the information and assessing the veracity of the patient's statements, being careful to control, at the same time, the inter-observer variability. Having clear and objective measuring instruments will minimize the inter-observer variability.

- Observer/interviewer bias: in some cases, the interviewer might stress or emphasize some questions, which could lead to an information bias. To avoid this, both the psychiatrist and the psychologist will be trained professionals, with no personal links to the participants.

Work Plan

The duration of the study will be **4 years and 11 months** and it will consist on 7 stages:

Stage 1. Protocol Design Stage – 4 months (November 2014-February 2015)

This stage consisted on literature review, the present protocol's elaboration and its presentation to a group of "Facultat de Medicina de la Universitat de Girona"'s teachers, as well as the study's proposal to CEIC and its acceptance.

Stage 2. Coordination Stage – 2 months (March-April 2015)

In this phase, organizational and informative meetings will be held between the main investigators and the rest of the research team. The work team will consist on two main investigators (one of them a psychiatrist), one psychologist and one qualified statistician. The objectives of the study will be shared, as well as its methods of data collection and the timeline.

This study will benefit from the interdependent nature of the "Programa Específic de TCA de Girona". The main investigators and the psychologist will meet once with the heads of program's each sector (Gironès-Pla d'Estany, Baix Empordà, Alt Empordà, La Garrotxa-Ripollès, La Selva Maritima and La Selva Interior), with the aim of explaining the study's outline and its inclusion criteria. They will, in turn, transmit that information to the other working members of the program, making sure every doctor can help in the selection of the patients.

Any doubts the personnel might have about the project should be cleared in this stage.

It is important to use this point to translate all the measuring instruments (Y-BOCS, MROAS, Holmes & Rahe Stress Scale), if not already available in Spanish.

The training of the psychiatrist and psychologist and the database's creation will also happen here.

Stage 3. Participants' Recruitment Stage – 24 months (May 2015-May 2017)

We will screen the patients included in “Programa Específico de TCA de Girona”. Taking into account that said program has its foundation in an unified plan, we can count with the collaboration of the doctors working on it. That being said, when a patient that fulfills the inclusion criteria, arrives to its usual consultation, her doctor will introduce the concept of the study, giving them verbal information, the Information Sheet and the Informed Consent. The same doctor will later contact the main investigators, who will confirm that the patient can be included in the study. The participants' incorporation in the research will be only carried out following the confirmation that they were properly informed about the characteristics of the study and signed the Informed Consent Form.

It is also in this stage that will happen the application of the independent variable, with the objective of creating two groups:

- a) Group A: patients with the diagnosis of Anorexia Nervosa and a Y-BOCS score ≥ 16
- b) Group B: patients with the diagnosis of Anorexia Nervosa and a Y-BOCS score < 16

Both groups will go through the same steps, attending the consultations and answering the questions without disparities between groups.

The patients' recruitment will be carried out to term until the sample size is completed or the end of the 24 months (where, according to the data available, we can predict we will have all the members' needed).

Stage 4. Data Collection Stage – 48 months (May 2015-May 2019)

This stage will start when the first participant is recruited and will end two years after the last patient is included. The data will be collected in the appointments between the participants and the psychiatrist and psychologist. The patient will see both at the same time and both health professionals, reaching a consensus, will fill out the Case Report Form. In the case that a consensus cannot be reached, it should be expressed on the ‘observations’ paragraph of the CRF and thoroughly evaluated by the second main investigator.

1. Appointment n° 1: it will occur shortly after the Informed Consent's signing and agreement to participate in the research. In this meeting, the patient will answer the questions reflected in the Case Report Form, completing the MROAS. The Holmes & Rahe Stress Scale will also be performed here. We will also take the patients height and weight, as so to calculate their BMI.
2. Appointment n° 2: will occur 6 months after the first appointment. All the mentioned data will be taken, with the exception of the Holmes & Rahe Stress Scale.
3. Appointment n° 3: will occur 12 months after the first appointment. All the mentioned data will be taken, including the Holmes & Rahe Stress Scale.
4. Appointment n° 4: will occur 18 months after the first appointment. All the mentioned data will be taken, with the exception of the Holmes & Rahe Stress Scale.
5. Appointment n° 5: final appointment. Will occur 24 months after the first appointment. All the mentioned data will be taken, including the Holmes & Rahe Stress Scale.

To avoid sample losses, one week before each appointment, the participant will receive a phone call and a text message that will act as a reminder.

After each appointment, the database will be filled and the investigators and the psychologist will have a reunion, either in person or by phone. Some of those reunions will also assess the progress of the study and the data's quality.

The Holmes & Rahe Stress scale will only be assessed in appointments n° 1, 3 and 5.

Stage 5. Data Analysis Stage – 1 month (June 2019)

The statistician will take all the collected data and proceed to analyze it according to the already mentioned methods and using the appropriate software. A univariate and bivariate analysis will be used, as well as a multivariate analysis, to examine the contribution of the confounding variables.

Stage 6. Results' Interpretation and Writing Stage – 3 months (July-September 2019)

In this moment, the investigators will receive the analyzed data from the statistician and will interpret the results. From these results, they will draft a conclusion and start writing the final article.

Stage 7. Publication and Dissemination Stage – From October 2019

The main investigators will present the study's results in a prestigious psychiatric publication.

The final article will be sent, with the intent of acceptance and publication, to “JAMA Psychiatry”, formerly known as “Archives of General Psychiatry”.

The results will be then presented in a national and international specialty congress: “XXIII Congreso Nacional de Psiquiatria”, in Spain, and “International Conference on Eating Disorders 2020”, in the USA.

Chronogram

	<u>2014</u>		<u>2015</u>					<u>2016</u>	<u>2017</u>		<u>2018</u>	<u>2019</u>					
	Nov	Dec	Jan	Feb	Mar	Apr	May-Dec	Jan-Dec	Jan-May	Jun-Dec	Jan-Dec	Jan-May	Jun	Jul	Aug	Sep	From Oct
Stage 1																	
Protocol design and presentation																	
Presentation to CEIC																	
Stage 2																	
Team meetings																	
Additional meetings																	
Personnel Training																	
Stage 3																	
Patients' recruitment																	
Stage 4																	
Appointments 1-5																	
Team meetings																	
Stage 5																	
Data analysis																	
Stage 6																	
Writing																	
Stage 7																	
Publication and dissemination																	

Impact of the project on the National Health System

Despite the fact that research on the comorbidity and outcome of anorexia nervosa has increased in the last twenty years, information on the prevalence of obsessive-compulsive disorder and its symptoms, with or without an association with anorexia, hasn't been properly explored. The same happens with data on the prevalence of the comorbidity between the two disorders, the etiology of said commodity, its manifestations or even its outcome.

As it has been exposed, there is a possibility that the outcome of anorexia worsens if associated with another illness, especially mood and anxiety disorders (mainly of the OCD spectrum). If that hypothesis were proven, it would bring great benefit for the affected subjects, allowing the opening of new paths of research.

Currently, and according to “Estrategia en Salud Mental del Sistema Nacional de Salud”, the economic repercussions of mental health in Spain are estimated to be around 3005 millions of euros, with the social cost of mental health disorders bordering near 3375 euros per disorder¹. Psychiatric ailments are the cause of 10,5% of loss of workdays, in temporary disability, and 6,8% years of working life, in permanent disability. (25) The knowledge of how the comorbidity influences the prognosis would allow for the patients to benefit, in the long run, from new and/or enhanced treatment alternatives and a generally increased quality of life. By improving these factors, the rates of chronicity, relapse and death would decrease, which would lead a saving of money and resources by the National Health System.

At the time of the present protocol, and although there are many follow-up studies on the prognosis of anorexia nervosa, there haven't been published any other works about the outcome of the OC symptomatology and AN's association. It would also be the first study of sorts in Girona.

¹ Direct costs: 20,6% on hospitalization, 10,4% on consultations and 7,6% on medication.
Indirect costs: 21,8% on permanent disability, 21,6% on premature mortality, 9% on lack of productivity and 8,7% on temporary disability.

On the account of methodology, this study should be seen as a basis for future research: further studies should focus in applying the research to multicentric projects, which will allow the extrapolation of the results for the general population.

Budget

		<u>Maximum cost</u>
<u>Personnel and personnel costs</u>		
Psychologist	30€/hour x 67 patients x 2hours/patient + reunion hours	4200€
Statistician	35€/hour x 30hours	1050€
Psychiatrist and psychologist's Training		150€
Travelling	2 people x 5 appointments x 67 patients	650€
Team meetings		500€
		Subtotal 6550€
<u>Material and Services</u>		
Paper Stacks and Printing		150€
Translation of the scales		200€
		Subtotal 350€
<u>Publication and Dissemination</u>		
Publication		1000€
Conferences		
• National		
<i>Inscription fee</i>	780€ x 2 investigators	1560€
<i>Accommodation</i>	140€ x 2	280€
<i>Travel</i>	70€ x 2	140€
• International		
<i>Inscription fee</i>	600€ x 2	1200€
<i>Accommodation</i>	230€ x 2	460€
<i>Travel</i>	600€ x 2	1200€
		Subtotal 5840€
<u>TOTAL</u>		<u>12.740€</u>

Before starting the study it is necessary to ensure its financing.

Since the majority of the program's patients come from Gironès and La Selva Marítima and a big number visits the "Hospital de Dia", we can extrapolate that the displacement costs won't be that high. The patients from the Gironès sector will be seen at Parc Hospitalari Martí I Julià, in Salt, which doesn't entail these kinds of costs. For the remaining sectors, there will be efforts of coordination, to minimize the visits to each CSMA (Alt and Baix Empordà, La Selva Interior and Marítima, Garrotxa-Ripollès), and allow that all the participants from the region can be visited within the same displacement.

The investigators and the doctors working for the program will not receive a compensation for their work in this study. The budget does not include material as computers, scales and stadiometers, for they are already available in any of the CSMA.

Software such as SPSS and Microsoft Access© are not included because they are either available to the statistician or free of charge.

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Appendices

Appendix 1: DSM-V Diagnostic Criteria for Anorexia Nervosa (307.1)

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| <p>A. <u>Restriction of energy intake relative to requirements</u>, leading to a significantly low body weight in the context of age, sex, developmental trajectory, and physical health. Significantly low weight is defined as a weight that is less than minimally normal or, for children and adolescents, less than that minimally expected.</p> <p>B. <u>Intense fear of gaining weight or of becoming fat</u>, or persistent behavior that interferes with weight gain, even though at a significantly low weight.</p> <p>C. <u>Disturbance in the way in which one's body weight or shape is experienced</u>, undue influence of body weight or shape on self-evaluation, or persistent lack of recognition of the seriousness of the current low body weight.</p> |
|--|

Specify whether:

- | | |
|--|---|
| <ul style="list-style-type: none"> • <u>(F50.01) Restricting type</u>: During the last 3 months, the individual has not engaged in recurrent episodes of binge eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas). This subtype describes presentations in which weight loss is accomplished primarily through dieting, fasting, and/or excessive exercise. • <u>(F50.02) Binge-eating/purging type</u>: During the last 3 months, the individual has engaged in recurrent episodes of binge eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas). | <p>AND:</p> <ul style="list-style-type: none"> • <u>In partial remission</u>: After full criteria for anorexia nervosa were previously met. Criterion A (low body weight) has not been met for a sustained period, but either Criterion B (intense fear of gaining weight or becoming fat or behavior that interferes with weight gain) or Criterion C (disturbances in self-perception of weight and shape) is still met. • <u>In full remission</u>: After full criteria for anorexia nervosa were previously met, none of the criteria have been met for a sustained period of time. |
|--|---|

Specify current severity:

The minimum level of severity is based, for adults, on current body mass index (BMI) or, for children and adolescents, on BMI percentile. The ranges below are derived from WHO categories for thinness in adults; for children and adolescents, corresponding BMI percentiles should be used. The level of severity may be increased to reflect clinical symptoms, the degree of functional disability, and the need for supervision.

Mild: BMI > 17 kg/m²

Moderate: BMI 16-16.99 kg/m²

Severe: BMI 15-15.99 kg/m²

Extreme: BMI < 15 kg/m²

Appendix 2: DSM-V Diagnostic Criteria for Obsessive-Compulsive Disorder (300.3)

A. Presence of obsessions, compulsions, or both:	
<ul style="list-style-type: none"> • Obsessions are defined by (1) and (2): <ol style="list-style-type: none"> 1. Recurrent and persistent thoughts, urges, or images that are experienced, at some time during the disturbance, as intrusive and unwanted, and that in most individuals cause marked anxiety or distress. 2. The individual attempts to ignore or suppress such thoughts, urges, or images, or to neutralize them with some other thought or action (i.e., by performing a compulsion). 	<ul style="list-style-type: none"> • Compulsions are defined by (1) and (2): <ol style="list-style-type: none"> 1. Repetitive behaviors (e.g., hand washing, ordering, checking) or mental acts (e.g., praying, counting, repeating words silently) that the individual feels driven to perform in response to an obsession or according to rules that must be applied rigidly. 2. The behaviors or mental acts are aimed at preventing or reducing anxiety or distress, or preventing some dreaded event or situation; however, these behaviors or mental acts are not connected in a realistic way with what they are designed to neutralize or prevent, or are clearly excessive. Note: Young children may not be able to articulate the aims of these behaviors or mental acts.
<p>B. The obsessions or compulsions are time-consuming (e.g., take more than 1 hour per day) or cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.</p> <p>C. The obsessive-compulsive symptoms are not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.</p> <p>D. The disturbance is not better explained by the symptoms of another mental disorder (e.g., excessive worries, as in generalized anxiety disorder; preoccupation with appearance, as in body dysmorphic disorder; difficulty discarding or parting with possessions, as in hoarding disorder; hair pulling, as in trichotillomania [hair-pulling disorder]; skin picking, as in excoriation [skin-picking] disorder; stereotypies, as in stereotypic movement disorder; ritualized eating behavior, as in eating disorders; preoccupation with substances or gambling, as in substance-related and addictive disorders; preoccupation with having an illness, as in illness anxiety disorder; sexual urges or fantasies, as in paraphilia disorders; impulses, as in disruptive, impulse-control, and conduct disorders; guilty ruminations, as in major depressive disorder; thought insertion or delusional preoccupations, as in schizophrenia spectrum and other psychotic disorders; or repetitive patterns of behavior, as in autism spectrum disorder).</p> <p>Specify if:</p> <ul style="list-style-type: none"> • <u>With good or fair insight</u>: The individual recognizes that obsessive-compulsive disorder beliefs are definitely or probably not true or that they may or may not be true. • <u>With poor insight</u>: The individual thinks obsessive-compulsive disorder beliefs are probably true. • <u>With absent insight/delusional beliefs</u>: The individual is completely convinced that obsessive-compulsive disorder beliefs are true. <p>Specify if:</p> <p><u>Tic-related</u>: The individual has a current or past history of a tic disorder.</p>	

Appendix 3: Yale-Brown Obsessive Compulsive Scale (Y-BOCS)

Symptom checklist

Check all that apply, but clearly mark the principal symptoms with a "P", (Rater must ascertain whether reported behaviors are bona fide symptoms of OCD, and not symptoms of another disorder such as Simple Phobia or Hypochondriasis. Items marked "*" may or may not be OCD phenomena.)

AGGRESSIVE OBSESSIONS: 1. Fear might harm self; 2. Fear might harm others; 3. Violent or horrific images; 4. Fear of blurting out obscenities or insults; 5. Fear of doing something else embarrassing*; 6. Fear will act on unwanted impulses; 7. Fear will steal things; 8. Fear will harm others because not careful enough; 9. Fear will be responsible for something else terrible happening; 10. Other

CONTAMINATION OBSESSIONS: 11. Concerns or disgust with bodily waste or secretions; 12. Concern with dirt or germs. 13. Excessive concern with environmental contaminants; 14. Excessive concern with household items; 15. Excessive concern with animals; 16. Bothered by sticky substances or residues; 17. Concerned I will get ill because of contaminant; 18. Concerned I will get others ill by spreading contaminant; 19. Other

SEXUAL OBSESSIONS: 20. I have forbidden or perverse sexual thoughts, images, or impulses; 21. Content involves children or incest; 22. Content involves homosexuality*; 23. Aggressive sexual behavior toward others.*; 24. Other

HOARDING / SAVING OBSESSIONS: Distinguish from hobbies and concern with objects of monetary or sentimental value. 25. I have obsessions about hoarding or saving things.

RELIGIOUS OBSESSIONS: 26. Concerned with sacrilege and blasphemy; 27. Excess concern with right/wrong, morality.; 28. Other

OBSESSION WITH NEED FOR SYMMETRY OR EXACTNESS: 29. (Accompanied by magical thinking) Obsessions about symmetry or exactness; 30. Not accompanied by magical thinking

MISCELLANEOUS OBSESSIONS: 31. Need to know or remember_certain things;_32. Fear of saying certain things ; 33. Fear of not saying just the right thing; 34. Fear of losing things; 35. Intrusive (non-violent) images; 36. Intrusive nonsense sounds, words, or music.; 37. Bothered by certain sounds/noises*; 38. Lucky/unlucky numbers; 39. Colors with special significance; 40. Superstitious fears

Obsession Rating Scale (circle appropriate score)

Item	Range of Severity				
1. Time Spent on Obsessions Score:	0 hr/day 0	0-1 hr/day 1	1-3 hr/day 2	3-8 hr/day 3	> 8 hr/day 4
2. Interference From Obsessions Score:	None 0	Mild 1	Definite but manageable 2	Substantial impairment 3	Incapacitating 4
3. Distress From Obsessions Score:	None 0	Little 1	Moderate but manageable 2	Severe 3	Near constant, disabling 4
4. Resistance to Obsessions Score:	Always resists 0	Much resistance 1	Some resistance 2	Often yields 3	Completely yields 4
5. Control Over Obsessions Score:	Complete control 0	Much control 1	Some control 2	Little control 3	No control 4

Obsession subtotal (add items 1-5) _____

Compulsion Rating Scale (circle appropriate score)

Item	Range of Severity				
6. Time Spent on Compulsions Score:	0 hr/day 0	0-1 hr/day 1	1-3 hr/day 2	3-8 hr/day 3	> 8 hr/day 4
7. Interference From Compulsions Score:	None 0	Mild 1	Definite but manageable 2	Substantial impairment 3	Incapacitating 4
8. Distress From Compulsions Score:	None 0	Mild 1	Moderate but manageable 2	Severe 3	Near constant, disabling 4
9. Resistance to Compulsions Score:	Always resists 0	Much resistance 1	Some resistance 2	Often yields 3	Completely yields 4
10. Control Over Compulsions Score:	Complete control 0	Much control 1	Some control 2	Little control 3	No control 4

Compulsion subtotal (add items 6-10) _____

Y-BOCS total (add items 1-10)

Total Y-BOCS score: range of severity for patients who have both obsessions and compulsions:

0-7 Subclinical 8-15 Mild 16-23 Moderate 24-31 Severe 32-40 Extreme

Appendix 4: Morgan & Russell Outcome Assessment Schedule (MROAS)

	Scale	Subscale	Score	Score and outcomes
A	Food intake	A1: Dietary restriction “Are you restricting your diet, or have you done so, at any time in the last 6 months?”	0: At all times 3: More than half the time 6: About half the time 9: Less than half the time 12: Nil	<p style="text-align: center;"><i>Final score =</i></p> $\frac{A + B + C + D + E}{5} =$ $= \frac{\left(\frac{A1 + A2 + A3}{3}\right) + B + C}{5}$ $+ \frac{\left(\frac{D1 + D2 + D3 + D4}{4}\right) + \left(\frac{E1 + E2 + E3 + E4 + E5}{5}\right)}{5}$ <p style="text-align: center;">Outcome: “Poor”: final score from 0 to ≤4 “Intermediate”: final score from 5 to ≤8 “Good”: final score from 9 to 12</p> <p style="text-align: center;">Adapted score to be used in this study: “Poor outcome”: final score of 0 to ≤6 “Good outcome”: final score of 7 to 12.</p>
		A2: Worry about body weight or appearance “Have you been worried about your weight or your appearance in any other way, at any time in the last six months?”	0: At all times 3: More than half the time 6: About half the time 9: Less than half the time 12: Nil	
		A3: Body weight	0: always much deviation, sufficient to cause concern 4: always deviated but only at times, sufficient to cause concern 8: usually near average (weighting +/- 15% average body weight but occasionally deviant, sufficient to cause concern) 12: near average at all times	
B	Menstrual state in the last 6 months	0: no menstrual loss at any time 4: transient occasional menstrual loss, which is never cyclical 8: irregular menstrual loss with some cyclical pattern 12: regular and cyclical throughout		
C	Mental state at interview and reported abnormalities at any time in the previous 6 months	0: grossly abnormal and psychotic 4: marked disturbance but not psychotic 8: mild disturbance 12: normal		
D	Psychosexual state	D1: Attitude towards sexual matters “What is your attitude toward sexual matters?”	0: active dislike 4: variable: dislike or disinterest 8: disinterest 12: pleasurable	
		D2: Professed aims in a sexual relationship	0: wants to remain single 4: would marry but fears to do so 8: would marry appropriate person but would not want to have children 12: definitely wants to marry and have children or has already done so	

		D3: Overt sexual behavior	0: avoid sexual contacts 6: occasional superficial affairs without pleasurable sexual relationship 12: love affairs with pleasurable sexual relationship (may include married with children)	
		D4: Attitude to menstruation if it has returned	0: active dislike 4: variable: dislike or disinterest 8: disinterest 12: pleased that it has returned	
		D5: Attitude to menstruation if it has not returned	0: pleased that it has not returned 4: variable: pleased or disinterested 8: disinterest 12: regrets that has not returned	<u>Coding instructions</u>
E	Socioeconomic state	E1: Relationship with nuclear family “How would you assess your relationship with your parents (and siblings)?”	0: Very unsatisfactory 4: Unsatisfactory 8: Indifferent 12: Satisfactory	A1: Ignore minor carbohydrate restriction to the extent of being careful about the amount of sugar or bread, because such attitude is common even in normal individuals. A3: The patient's opinion on this issue may of course be highly unreliable; occasionally over-anxious relatives also seemed to be highly biased on this issue. The rating was therefore made after reference to the reported weight fluctuations over the previous 6 months and the weight measured at interview.
		E2: Emancipation from family	0: many difficulties. Sees no prospect of becoming independent to a satisfactory degree 4: As for 0 but at times feels difficulties can be surmounted 8: some difficulties but they are surmountable 12: no difficulties	C: This scale is based on a mental-state assessment during interview, and information about the psychiatric status during the preceding 6 months. The distinction between 'marked' and 'mild' disturbance of one type was made on the basis of interference with general activities: thus, symptoms which prevented the patient working at any time in the 6-month period would be rated as 'marked'. If symptoms are judged present and significant (excluding marked ideas about food), yet they have not interfered with normal activities, these are rated as 'mild'.
		E3: Personal contacts, apart from family or partner	0: none 4: few and superficial 8: many but superficial 12: many close and superficial friends	
		E4: Social activities, appropriate to status	0: nil outside family 4: solitary outside family 8: variable: mainly solitary but some group activities outside family 12: adequate group activities: mixes well outside family	E1: In view of the fact that relationship may vary with different members of the family, the lower individual rating is taken, whether it is with parent or sibling. When another informant is seen beside the patient, the final rating is taken as the average of these two scores.
		E5: Employment record in previous 6 months	0: no paid employment 4: up to 50% of the period in paid employment or occasional unpaid employment 8: more than 50% of the period in paid employment but less than 100% 12: regular full time paid employment without absences	

Appendix 5: Holmes and Rahe Stress Scale

The Holmes-Rahe Life Stress Inventory The Social Readjustment Rating Scale

INSTRUCTIONS: Mark down the point value of each of these life events that has happened to you during the previous year. Total these associated points.

Life Event	Mean Value
1. Death of spouse	100
2. Divorce	73
3. Marital Separation from mate	65
4. Detention in jail or other institution	63
5. Death of a close family member	63
6. Major personal injury or illness	53
7. Marriage	50
8. Being fired at work	47
9. Marital reconciliation with mate	45
10. Retirement from work	45
11. Major change in the health or behavior of a family member	44
12. Pregnancy	40
13. Sexual Difficulties	39
14. Gaining a new family member (i.e.. birth, adoption, older adult moving in, etc)	39
15. Major business readjustment	39
16. Major change in financial state (i.e.. a lot worse or better off than usual)	38
17. Death of a close friend	37
18. Changing to a different line of work	36
19. Major change in the number of arguments w/spouse (i.e.. either a lot more or a lot less than usual regarding child rearing, personal habits, etc.)	35
20. Taking on a mortgage (for home, business, etc..)	31
21. Foreclosure on a mortgage or loan	30
22. Major change in responsibilities at work (i.e. promotion, demotion, etc.)	29
23. Son or daughter leaving home (marriage, attending college, joined mil.)	29
24. In-law troubles	29
25. Outstanding personal achievement	28
26. Spouse beginning or ceasing work outside the home	26
27. Beginning or ceasing formal schooling	26
28. Major change in living condition (new home, remodeling, deterioration of neighborhood or home etc.)	25
29. Revision of personal habits (dress manners, associations, quitting smoking)	24
30. Troubles with the boss	23
31. Major changes in working hours or conditions	20
32. Changes in residence	20
33. Changing to a new school	20
34. Major change in usual type and/or amount of recreation	19
35. Major change in church activity (i.e.. a lot more or less than usual)	19
36. Major change in social activities (clubs, movies,visiting, etc.)	18
37. Taking on a loan (car, tv,freezer,etc)	17
38. Major change in sleeping habits (a lot more or a lot less than usual)	16
39. Major change in number of family get-togethers ("")	15
40. Major change in eating habits (a lot more or less food intake, or very different meal hours or surroundings)	15
41. Vacation	13
42. Major holidays	12
43. Minor violations of the law (traffic tickets, jaywalking, disturbing the peace, etc)	11

Now, add up all the points you have to find your score.

150pts or less means a relatively low amount of life change and a low susceptibility to stress-induced health breakdown.

150 to 300 pts implies about a 50% chance of a major health breakdown in the next 2 years.

300pts or more raises the odds to about 80%, according to the Holmes-Rahe statistical prediction model.

Image 1: Holmes and Rahe Stress Scale (29)

Appendix 6: Module H of Structured Clinical Interview for DSM Disorders (SCID)

1. Have you ever had a time when you weighed much less than other people thought you ought to weigh? (Criteria A of DSM-V) Answer from 0 to 3. IF YES: Why was that? How much did you weigh? How old were you then? How tall were you? Interviewer: Note body frame: Small, Medium, Large

2. At that time, were you very afraid that you could become fat? (Criteria B of DSM-V). Answer from 0 to 3.

3. At your lowest weight, did you still feel too fat or that part of your body was too fat? (Criteria C of DSM-V) Answer from 0 to 3. IF NO: Did you need to be very thin in order to feel good about yourself? IF NOT AND LOW WEIGHT IS MEDICALLY SERIOUS: When you were that thin, did anybody tell you it could be dangerous to your health to be that thin? What did you think?

4. FOR FEMALES: Before this time, were you having menstrual periods? (Did they stop? For how long?) (Criteria D of DSM-IV) Answer from 0 to 3.

ANOREXIA NERVOSA CRITERIA A, B, C, AND D ARE CODED "3"

5. Did you have eating binges in which you would eat a lot of food in a short period of time and feel that your eating was out of control? (How often?) IF NO: What kinds of things have you done to keep weight off? Ever made yourself vomit or take laxatives, enemas, or water pills? How often?

CURRENT STATE: (select one) In Partial Remission, In Full Remission, Current, No Information

CHRONOLOGY: When did you last have any (SYMPTOMS OF ANOREXIA NERVOSA)? Number of months prior to interview when last had a symptom of Anorexia Nervosa. IF UNKNOWN: How old were you when you first started having (SYMPTOMS OF ANOREXIA NERVOSA)? Age at onset of Anorexia Nervosa (CODE 99 IF UNKNOWN).

Appendix 7: Information Form and Informed Consent Form

HOJA DE INFORMACIÓN PARA EL PACIENTE

Este documento es destinado a todos los pacientes integrados en el “Programa Específico de TCA de Girona”, a los cuales se invita a la participación en el estudio “Outcome of the association between Obsessive-Compulsive Symptomatology and Anorexia Nervosa: a 2 year cohort prospective study”. Se divide en:

- Información para el paciente
- Formulario de Consentimiento Informado

El estudio mencionado tiene como objetivo determinar el pronóstico de la asociación entre Anorexia Nervosa y sintomatología obsesiva-compulsiva.

Anorexia Nervosa es una enfermedad del foro psiquiátrico que consiste en pérdida de peso con disminución de la ingesta de comida y miedo en ganar peso. Los síntomas obsesivos-compulsivos se caracterizan por obsesiones (ideas recurrentes que ocurren contra la voluntad del paciente) y compulsiones (comportamientos repetitivos, en respuesta a las obsesiones). Se pueden manifestar en hasta un 41% de personas con Anorexia.

Estudios hechos hasta este momento han comprobado la asociación entre los dos pero no el efecto que la sintomatología obsesiva-compulsiva tiene sobre la anorexia. Este proyecto fue creado para estudiar ese efecto, en un período de 2 años.

En este estudio, los participantes tendrán que estar presentes en 5 consultas, de cerca de 1 hora cada, en su Centro de Salud Mental de referencia o Hospital de Día, con 6 meses de diferencia entre ellas (visita nº 1 será la inicial, visita nº 2 a los 6 meses, nº 3 a los 12, nº 4 a los 18 y nº 5 a los 24 meses). En cada una de las visitas, el paciente será seguido por un psicólogo y un psiquiatra, se medirá su altura y peso y se le harán preguntas relacionadas con su diagnóstico y síntomas. No se hará cualquier procedimiento invasivo y el único contacto que habrá con el paciente será en las visitas y en los recordatorios de las mismas, 1 semana antes.

La participación en el estudio será totalmente voluntaria y podrá abandonar el estudio en cualquier momento. El participante no tendrá que contribuir con un valor monetario y no recibirá cualquier compensación por su participación. Sus derechos, anonimato y confidencialidad de los datos estarán garantizados y al abrigo de las leyes Españolas de investigación clínica.

Le invitamos a hacer parte de nuestro estudio. Su participación puede determinar un beneficio directo o indirecto para expandir el conocimiento sobre el trastorno.

Para alguna duda contactar, xxxxxxxxxxxx o xxxxxxxxxxxxxxxx (investigadores principales).

FORMULARIO DE CONSENTIMIENTO INFORMADO

Yo, _____, confirmo que:

- He recibido y he leído la hoja de información para el paciente y todas mis cuestiones, dudas y pedidos de información fueron resueltos.
- Entendí que mi participación será voluntaria y que puedo abandonar el estudio si lo desee, sin que eso repercuta en mi atención sanitaria futura.
- Comprendí que mi participación será confidencial.
- Acepto participar en el estudio “Outcome of the association between Obsessive-Compulsive Symptomatology and Anorexia Nervosa: a 2 year cohort prospective study”.

(Nombre)

(Firma)

(Fecha)

(Firma del investigador)

Appendix 8: Case Report Form

Case Report Form

Número Historia Clínica:

Visita nº

Fecha / /

Puntuación Y-BOCS _____ (rellenar sólo en visita nº 1)

Talla _____ m **Peso** _____ kg **IMC** _____ kg/m²

Puntuación MROAS _____

Puntuación Holmes and Rahe _____ (rellenar sólo en visitas nº 1, 3 y 5)

Subtipo de Anorexia restrictivo purgativo (rellenar sólo en visita nº 1)

Edad de comienzo de anorexia _____ (rellenar sólo en visita nº 1)

Duración de enfermedad _____ meses

Tratamiento Farmacológico y Psiquiátrico
 Nutricional y Psiquiátrico
 Farmacológico + Nutricional + Psiquiátrico

Educación menos que escuela secundaria escuela secundaria
 licenciatura máster o doctorado

Estado civil casada pareja de hecho soltera
 separada divorciada viuda

Trabajo empleada desempleada estudiante jubilada

Etnia Caucasiana Raza Negra Latina
 Asiática otras (rellenar sólo en visita nº 1)

Observaciones

Firmado por

_____ y _____

Appendix 9: Considerations about “Programa Específic de TCA de Girona”

NIVELL 1 D’ACTUACIÓ: AMBULATORI ESPECIALITZADA CSM/CSMIJ:

Una vegada realitzada la derivació des dels EAPs s’efectuarà l’avaluació diagnòstica i el diagnòstic diferencial així com s’elegirà el nivell assistencial més adequat pel pacient en aquell moment.

NIVELL 2: HOSPITAL DE DIA (HD), HD/HD ADOLESCENTS

L’Hospital de Dia constitueix una alternativa terapèutica tant des del CSM com, des de les Unitats d’hospitalització total. Són el nucli del Tractament Específic d’aquestes patologies, on la seva àmplia oferta terapèutica assegura un abordatge intensiu, integral i molt específic, sense separar al pacient del seu entorn sociofamiliar.

Aquesta especificitat terapèutica vindrà determinada per l’existència d’un Programa concret adreçat a aquestes patologies, i que pot ofertar-se des del model ideal d’Hospital de Dia monogràfic, específic pels TCA, o bé des d’un model més integrador i heterogeni, compartint espais amb altres patologies dins del marc d’un Hospital de Dia polivalent.

En tot cas, cal assegurar els requeriments imprescindibles per tal de ser eficients: personal propi i expert, espais propis pels TCA i protocols terapèutics específics.

L’Hospital de Dia ofereix un ambient terapèutic estable, que proporciona tractaments continuats, més intensius i més estructurats que l’atenció ambulatoria, on s’apliquen especialment programes de control i normalització biològica, recuperació ponderal i monitorització de la dieta (Programa de monitorització d’àpats) i, a més a més, tots els abordatges psicoterapèutics individuals i grupals específics per aquestes patologies.

NIVELL 3: HOSPITALITZACIÓ TOTAL, (UAP/URPI)

La hospitalització és una fase més del tractament dels TCA i pot ser o no necessària, tant a l’inici com durant l’evolució del trastorn.

L’ingrés s’efectuarà en unitats de psiquiatria, sempre que sigui possible, i en el cas de menors de 18 anys en unitats psiquiàtriques infantils.

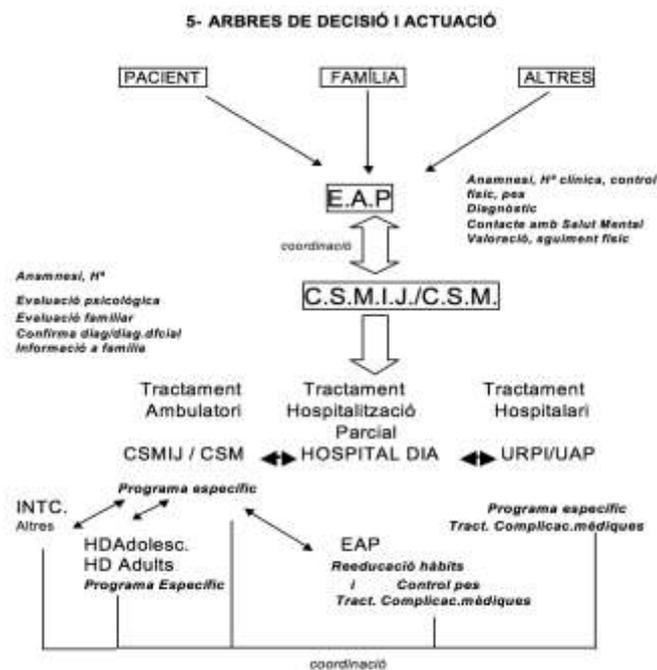


Image 2: Centers included in “Programa Específic de TCA de Girona” (27)

Appendix 10: Proportion of patients served by “Programa Específic de TCA de Girona”

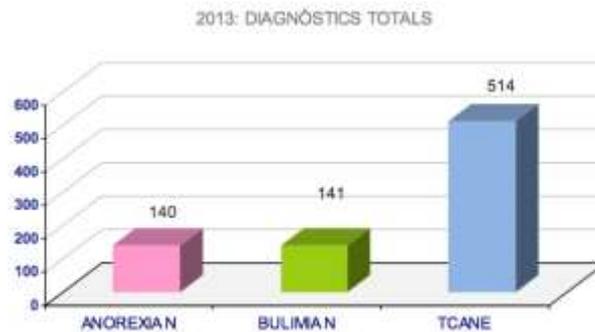


Image 3: Patients in “Programa Especific de TCA de Girona” (6)

Appendix 11: Considerations about “Xarxa de Salut Mental”

RECURSOS HOSPITALARIS (PARC MARTÍ I JULIÀ): Urgències (integrades a Urgències Generals del H. Sta Caterina, UHA (Unitat d’hospitalització d’Aguts, d’adults), Unitat de Subaguts (adults), Unitat de llarga estada (NO ingressos nous), URPI (Unitat d’Hospitalització Infanto –Juvenil), UPD (Unitat de Patologia Dual)

RECURSOS COMUNITARIS: CSMA (Centre de Salut Mental d’adults), CSMIJ (Centre de Salut Mental Infanto Juvenil), Centre de Dia (Centre de Rehabilitació Psicosocial), Hospital de Dia d’Adults (Tractament ambulatori intensiu), Hospital de Dia Infanto-Juvenil, EIP (Equip d’intervenció precoç en Psicosis), Equip de suport a primària, Interconsulta a Hospital Josep Trueta, Equip d’atenció a Trastorn de conducta Alimentària

RECURSOS ESPECÍFICS: Drogodependències, CAS (recurs comunitari), Patologia Dual (ingrés hospitalari), Comunitat Terpèutica (centres de deshabitució), Discapacitat Intel·lectual: SEMS-DI (recurs ambulatori), UHEDI (ingrés hospitalari)Til·lers (recurs hospitalari de mitja-llarga estada), UVAMID

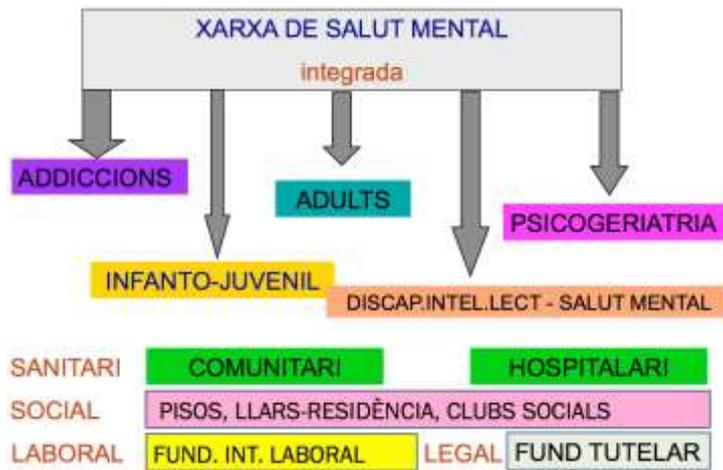


Image 4: Action areas of Xarxa de Salut Mental (27)



Image 5: Catalunya's Mental Health Map Services (27)