UNIVERSITÀ DEGLI STUDI DI TORINO

Neuroscience Department “Rita Levi Montalcini”

Doctoral School of the University of Torino

Thesis

Duration of Untreated Illness in Eating Disorders

Tutor:

Prof. Giovanni Abbate Daga

Candidate:

Matteo Panero

34° Cycle

A.A. 2022-2023

Index

CHAPTER I

1. The duration of untreated disorder in mental disorders.

In medicine, the appropriate early treatment of a disease is generally recognized as a positive prognostic factor. Nevertheless, the importance of early intervention varies according to the specific pathology. In some cases, postponing the decision of an intervention does not necessarily imply negative consequences in terms of outcome (Montalescot et al., 2009); in other cases, such as the fields of application of orthopaedics, postponing the intervention and performing it with the appropriate preparation can represent the best strategy (Smith et al., 2010). In the psychiatric field, early pharmacological treatment and the duration of untreated disorder (DUI) are currently of great clinical interest as they can affect the course, comorbidity and mortality of several disorders. In the last two decades, DUI, described as the interval between the onset of a specific pathology and the first appropriate treatment, has been increasingly investigated as a prognostic and predictive factor in several psychiatric disorders Most of these studies focused on the role of DUI in schizophrenic spectrum disorders and psychotic disorders (DUPs). To a lesser extent, it has been analysed in affective disorders, anxiety disorders and other disorders. The greater importance that the research is assigning to the DUI derives not only from the fact that it represents a modifiable factor which, as such, can lead to important positive implications in the clinical course, but also in that it can lead to a better understanding of the aspects of neurobiological modification that occur during the progression of a psychiatric disease (Schneider et al., 2012). The greater importance that the research is assigning to DUI derives from the fact that it represents a modifiable factor which, as such, can lead not only to important positive implications in the clinical course, but also to a better understanding of the aspects of neurobiological modification that occur during the progression of a psychiatric pathology (Schneider et al., 2012).

Some considerations need to be made when discussing psychiatric treatment latency. Still nowadays, the social stigma connected to mental disorders tends

to greatly delay the request for help (Clement et al., 2015). The poor insight characteristic of certain psychopathological conditions is another important obstacle to access to services (Saravanan et al., 2007). Furthermore, the complexity of this subject, due to the lack of specificity of the symptoms with syndromes characterized by alterations in several dimensions of mental functioning, complicates the diagnostic classification into defined categories and, consequently, the planning of a treatment suitable for the clinical peculiarities of the case. Further factors, such as poor premorbid functioning and a subtle onset of symptoms, can negatively impact DUI (Poyraz et al., 2014).

1.1 DUI in mood disorders

With regard to unipolar depression and anxiety disorders, it is more difficult to obtain reliable evaluations of the mean DUI due to the high heterogeneity of expression and the frequent overlap between multiple psychopathological dimensions. In unipolar depression, the duration of untreated disorder is particularly complex to analyse also for the characteristic episodic expression with tendentially poor or absent residual symptomatology between episodes. For disorders with this type of clinical course, together with the concept of DUI, there is also the element of the duration of an untreated episode (DUE), that indicates latency in the appropriate treatment starting from the expression of the single depressive episode after the onset (Ghio et al., 2014). A 2010 observational naturalistic study analysed DUI in 181 subjects diagnosed with unipolar depression. The mean duration of untreated disorder was 39.1 months. It appears to be much shorter than the duration of untreated disorder in bipolar disorder, which, according to the same study, would be about 97.2 months for DB II and 81.11 months for DB I. The reasons for such high latency in DB II could be the common transversal presentation with DDM during episodes of depressive polarity, which can lead to an erroneous diagnostic evaluation with consequent inadequate therapeutic approach and the peculiar lack of awareness of disorder during hypomanic episodes that, together with a sense of well-being and a little marked impairment of work

and relational functioning, extends the time of arrival to clinical care (Altamura et al., 2010a). In BD I, due to the most evident symptomatology, the mean of DUI is lower.

In unipolar depression, a lower DUI seems to correlate with a better response to treatment, higher remission rates, and lower symptomatic persistence. As for the DUE, shortening this latency would not seem to have the same effect on health outcomes, probably due to the progression of the disorder (Ghio et al., 2014). The naturalistic study by Altamura and colleagues showed that a longer duration of untreated bipolar disorder correlates with a higher frequency of suicide attempts and with a longer duration of illness. Moreover, a longer DUI is also associated with a depressive onset of the disease. This study confirms the clinical relevance of a correct diagnostic framework and the early setting of adequate stabilizing therapy for a better outcome, especially in terms of suicide (Altamura et al., 2010b). Finally, another study by the same researchers also found significant correlations between a longer DUI and some factors such as female sex, longer total duration of disease, a greater number of recurrences of depressive episodes and greater comorbidities of axis I, concluding that a longer DUI could negatively affect the clinical course of the disease (Altamura et al., 2007). Such hypothesis is also supported by a recent study that has highlighted a considerable correlation between the duration of untreated disorder in affective disorders (unipolar and bipolar depression) and the seriousness of depressive and anxious symptomatology, the presence of medical comorbidities and a higher body mass index (BMI) (Menculini et al., 2022; Buoli et al., 2021).

1.2 **DUI in schizophrenic spectrum disorders**

In schizophrenia, despite consistent alterations such as hallucinations and delusions among the core symptoms, the period of the untreated disorder varies from months to years, depending on the study (Farooq et al., 2009). A 2012 meta-analysis collected data from 3339 participants from 16 different studies and calculated a mean DUP of 61.4 weeks, with a standard deviation of the individual cases of 132.7 weeks (Boonstra et al., 2012).

DUP has been divided into 3 components: 1) the period in which an individual experiences the symptoms but does not acknowledge having a problem; 2) the period in which the individual acknowledges having a problem but is not ready to ask for help; 3) the period in which the individual has asked for help and is waiting to receive adequate care (Birchwood et al., 2013). According to the aforementioned study, the greatest delays occur after the first contact with the services, while the component of a tendentially shorter duration is that between experiencing symptoms and acknowledging having a problem.

Gender does not seem to be a variable related to the DUP while in Western countries the times of DUP seem to be lower than in non-Western countries (Cascio et al., 2012). Other factors that seem to influence the latency of DUPs are school education, the severity of negative symptoms, and cannabis use (Souaiby et al., 2019).

According to a systematic review and meta-analysis from 2014, a longer duration of untreated psychosis would be significantly associated with worse overall symptomatic outcomes, more severe positive and negative symptoms, a lower likelihood of remission, and poor social functioning. A longer duration of untreated psychosis was not related to occupational status, quality of life or number of hospital admissions carried out (Penttilä et al., 2014). According to another study, DUP also seems to correlate with a worse response to treatment with a non-linear trend: in other terms, the initial period following psychotic onset seems to have a greater weight in terms of response to treatment, while as the DUP lengthens, the sensitivity to treatment and the potential clinical improvement are poorer (Drake et al., 2020; Brasso et al., 2021).

1.3 DUI in anxiety disorders

As regards generalized anxiety disorder, the duration of DUI is around 81.6 months (Dell 'Osso et al., 2013). Factors such as early onset, longer disease duration, and increased psychiatric comorbidity correlate positively with untreated disorder duration. The prognosis is better in terms of symptomatic outcomes (clinical global impressions-severity of disease scale) when an

adequate early pharmacological treatment is set up. In case of disorders of the anxiety spectrum, it is frequently witnessed, in the clinical context, an initial setting of anxiolytic therapy with benzodiazepine drugs instead of an adequate antidepressant therapy as guidelines prescribe: the use, albeit early, of benzodiazepine drugs would seem comparable, in terms of long-term symptomatic outcomes, to a long duration of untreated disorder (Altamura et al., 2008). In panic disorder, however, the duration of untreated disorder is shorter, with a mean of approximately 39.5 months, probably due to the paroxysmal anxiety symptomatology characteristic which results in a earlier request for help (Dell 'Osso et al., 2013).

1.4 DUI in Obsessive-compulsive Disorder

In obsessive-compulsive disorder, DUI evaluations are again very high, with a mean of 106.2 months and high standard deviation (118.1 months), with a latency from symptom onset to first professional contact of about 82 months (Albert et al., 2019). Among the different types of obsessions, those of symmetry seem to correlate with a greater DUI. Factors such as gender, school education and familiarity with psychiatric disorders do not seem to affect DUI (Perris et al., 2021). In this case, as in the previous ones, a greater DUI correlates significantly with a poor response to treatment and with a more severe clinical history (Y-BOCS scores) (Albert et al., 2019).

1.5 DUI in somatic symptom disorder

A 2018 study analysed the evaluations of DUI in somatic symptom disorder, estimating a mean of even 25.2 years, that is more than double than estimated means DUI of depressive disorders and anxiety disorders. According to the authors, one of the main reasons could be the difficult diagnostic evaluation made by general practitioners, the person who tend to tackle this disorder as a biomedical problem, not only because of the overlapping symptoms, but also because of the lack of information about treatment methods. Long waiting times for specialist care, possible poor motivation for a path of psychotherapy and lack of resources can contribute to treatment latency (Herzog et al., 2018).

1.6 DUI in personality disorders

Personality disorders represent a different case due to the complex and peculiar characteristics of this type of disorder. According to the psychodynamic theoretical evaluation, the consolidation of the defence mechanisms of a person, those that will form her/his personality, depends on the adaptive functionality of these characteristics during the early years of development (infancy), and on the temperamental constraints dictated by the inherited-constitutional heritage of that person. The context around which they are shaped, over the years and with the maturation of the subject, inexorably tends to change and can potentially make these mechanisms, when rigid and unbalanced, unsuitable for the functioning and well-being of the person. Thus, the harmony of the person with these personality characteristics is crucial in the process of identity development. A modification of these aspects is affected by the complex forces involved, among the persistence of mechanisms settled for years during the phases of greater plasticity of the personality and a current environmental context that makes these aspects poorly functional for the well-being of the person. Personality disorders are therefore considered to be generally stable over one's life; however, it is believed that some traits might dampen/soften over the years. Furthermore, the subject learns effective adaptive strategies to modulate their dysfunctional personality characteristics, making the trait less manifest and impacting on their life. Early onset and presence of premorbid symptoms during childhood are considered predictive factors of stability of a personality disorder. Borderline personality disorder and antisocial personality disorder seem to be more modifiable and more likely to go into remission over the years (Paris, 2003). Some studies evaluated the evolution of borderline personality disorder up to 27 years of follow-up and in most cases the criteria for the diagnosis of personality disorder were no longer met. These authors suggest that the remission of the disorder depends on several factors. Biological aging has a positive impact especially on impulsivity aspects. Impulsive self-harm, substance abuse, and food impulsiveness tend to diminish naturally over the years. A second factor concerns social learning: the subject learns over the

years to develop more stable and mature relationships; engaging in a stable close relationship with a partner seems to positively impact the relational skills of the subject. Further factors are related to the different aspects of personality that make the subject more or less prone to find a steady job and develop amicable relationships/make new friends. As regards gender, in the male sex, the traits of pathological personalities seem to attenuate more than the female one, allowing to the male subject a more frequent remission of the disorder (Paris, 2002).

It is in such context that the therapeutic approach to personality disorders comes into play/is involved. To date, psychotherapy is the gold standard; pharmacological treatment and therapeutic measures/steps of socio-rehabilitative nature can obviously be extremely useful tools to be evaluated for each case and according to the psychopathological characteristics of each disorder. Despite the complexity in standardizing the results in this area, many studies have proven the effectiveness of psychotherapy for personality disorders. An important meta-analysis by Perry et al. suggests that a course of psychotherapy can make the remission of symptoms up to 7 times faster than the natural history of the disorder (Perry et al., 1999). As for the efficacy of the duration of treatment in connection with the outcomes, the results seem to be conflicting (Paris, 2002), while there is currently no evidence in the literature regarding the precociousness of treatment or the duration of untreated disorder in personality disorders.

CHAPTER II

2. DUED and evidence-based treatment

2.1 The duration of untreated disorder in eating disorders

Feeding and Eating Disorders (FED) represent a very complex field. Anorexia nervosa is a peculiar disorder and, in some ways, the most serious among the eating disorders; bulimia nervosa and BED-binge eating disorder, under an epidemiological point of view, are more frequent and are less prone to attract the specialist services' attention. The DSM-5 classification of eating disorders also includes Unspecified Feeding or Eating Disorder, Unspecified Feeding or Eating Disorder — which group together all those cases that do not fully meet the diagnostic criteria for the main syndromes — pica, rumination disorder, and avoidant/restrictive eating disorder.

They share psychopathological characteristics with all the major psychiatric disorders (Bou Khalil, 2021). Strict, poorly criticisable beliefs about one's body and the polarisation of thought recall the contents of delirious thought typical of psychotic disorders (Steinglass et al., 2007). The body image disturbance experienced by patients with anorexia nervosa recalls the perceptive alteration of schizophrenic spectrum disorders (Engel and Keizer, 2017). The scarce or absent insight present in the most severe phases of AN also recalls the total lack of awareness present in the flourishing states of psychotic disorders (Konstantakopoulos et al., 2011). In eating disorders, these alterations in thought and perception are limited to the area of body image and of physical/eating control, while mental functioning is generally preserved for other mental functions. Mood disorders are often a key element in eating disorders. As shown by a recent network analysis, depressive symptomatology seems to be among the central elements, psycho-pathologically interconnected and with a mediating role among the propitious factors in the maintenance of the eating disorder (Solmi et al., 2018). Similarly, a further element that has been shown to be crucial is the anxious

symptomatology (Solmi et al., 2018). Intrusive thoughts, similar to those of obsessive-compulsive disorder, are present both in anorexia nervosa and in bulimia nervosa and binge eating disorder (Jarry and Vaccarino, 1996). In anorexia nervosa restricting, after a first stage characterized with obsessions it generally follows a stage of compulsive control (dietary, weight, exercise etc.), in AN binge-purging, in bulimia and in BED there is a loss of control with the failure to satisfy the impulse. There is a component of addiction similar to that observed in substance abuse disorders: in the AN, gratification is not linked to food intake but to the ability to control nutrition, physical fitness and performance, with activation of the dopaminergic areas involved in rewarding circuits (Davis and Claridge, 1998). The presence of somatic symptoms, especially of the gastrointestinal tract, with which sometimes the eating disorder occurs, together with the lack of awareness of the psychological components of the disorder, seem similar to the area of disorders caused by somatic symptoms (Cusack et al., 2022). Personality disorders are frequently related to eating disorders and often represent a comorbidity, especially with regard to clusters B and C (Lilenfeld et al., 2006). They share with anorexia nervosa the characteristic of ego-syntony, although nowadays defining it as an ego-syntonic disorder is perhaps reductive and incorrect, since ego-syntony is not a stable and unambiguous characteristic but a multifaceted and dynamic one, that constantly evolves during the course of the disorder (Gregertsen et al., 2017).

Over last two decades, also in light of the similarities with psychotic spectrum disorders, the attention to DUI in eating disorders has been increasing. Eating disorders tend to have an early onset, between adolescence and early adulthood (Smink et al., 2012), with a rare onset after 30 (Micali et al., 2013). A long duration of illness proved to be one of the major prognostic factors of poor clinical outcomes in FED (Steinhausen, 2002). Moreover, as for schizophrenic spectrum disorders and bipolar disorder, neurobiological alterations associated with the disorder were highlighted, in this case mainly located in the areas of the basal ganglion/nucleus striatus involved in the rewarding dopaminergic system, which seem to play an important role in the development and maintenance of the disorder (O'Hara et al., 2012; Steinglass and Walsh, 2016).

Like in other disorders, staging models were assumed also for FED, suggesting that the stage of the disease at diagnosis is a predictive and prognostic factor of subsequent outcomes (Maguire et al., 2017). Early-stage FED, defined as a disease duration of less than 3 years, seem to respond better to treatment and have a better prognosis (Fernandez-Aranda et al., 2021; Treasure et al., 2015). In this perspective, an early intervention model for services (The FREED Project-first episode and rapid early intervention in eating disorders) was developed (Brown et al., 2018) and tested in the UK. The results of applying such a model seem to be very encouraging in terms of symptomatic outcomes (Fukutomi et al., 2020) and the model is currently included in the good practice guidelines of the National Collaborating Centre for Mental Health (NCCMH) of the Royal College of Psychiatrist. The need for early intervention is also supported by the Guidelines of the National Institute for Health and Care Excellence (NICE).

Despite these evidences of effectiveness, there are some obstacles, including the traditional separation between adult psychiatric services and adolescent services, which complicate the application of these models.

Even though it is clear that a longer duration of disease is prognostically unfavourable, the duration of untreated Eating Disorder (DUED), the treatment pathways and the delays in accessing to specialist care during the first episode of the eating disorder have not yet been well clarified and further in-depth analysis are necessary.

A recent systematic literature review by Austin colleagues selected 14 studies estimating the duration of untreated disorder in eating disorders (Austin et al., 2019). 11 studies evaluated DUED in Anorexia Nervosa, with results ranging from 6.39 to 39.96 months. The simple mean of the results is 29.9 months while the weighted mean is 14.6 months (99% CI [5.1; 24.0]). The heterogeneity among studies' results is very high (I2 99%; 95% CI [98.6; 99.1]). 4 studies evaluated DUED for Bulimia Nervosa, with results ranging from 23.05 to 58.56 months. The simple mean is 53.0 months while the weighted mean is 34.3 months (95% CI [3.6, 65]). Again, the heterogeneity was very high with an I2 index of 98%. Only one study evaluated DUED in Binge Eating Disorder, with a result of 67.4 months (SD=39.7) (beat, 2017).

As regards Unspecified Feeding and Eating Disorder or Unspecified Feeding or Eating Disorder, 3 studies estimated a duration ranging from 19.9 months to 53.0 months, with a simple mean of 43.8 months and a weighted mean of 29.5 months (95% CI [7.5, 51.6]) The heterogeneity (I2) in this case was 95% (95% CI [89.2, 97.9]).

All the studies included in this meta-analysis consider the age at the onset of the eating disorder and evaluate the DUED by age groups. For children (<12 years), the weighted mean of the DUED was 9.8 months, while for adolescents/adults (>12 years), the weighted mean of the DUED was 34.7 months. Again, with reference to age, 2 studies that correlated sociodemographic variables with the duration of ED showed that a longer DUED correlates with a higher age (Beat, 2017; Weigel et al., 2014). As regards gender, only one study analysed this variable in relation to DUED, in a population of paediatric age. In this study, gender was not related to DUED (Shu et al., 2015).

Three studies identified and divided DUED into components. The study by Brown and colleagues, where DUED meant the period between the onset of the disorder and the beginning of evidence-based treatment according to the LG NICE (NICE, 2017), identified as the first component the period between the onset of the disorder and contact with a specialist service (Brown et al., 2018). The study by Gumz and colleagues identified as the first component the period of time between symptom onset and first contact with any health professional for eating symptomatology (Gumz et al. 2014). The study by Schlegl and colleagues divided DUED in two components according to when the diagnosis by the general practitioner was made (Schlegl et al., 2019). The 2017 Beat study further deconstructed DUED, splitting it into several components: 1. The period before the realization of having a disorder; 2. The period between realizing to have a disorder and seeking help; 3. The period preceding the visit of the general practitioner and referral to the specialist; 4. The period between referral to the specialist and clinical evaluation by the latter; 5. The period between clinical evaluation and the commencement of the specific treatment. In summary, DUED can be conceptualized with different components but all of them include a user-dependent delay (e.g., the

period before seeking help) and a service-dependent delay (e.g., the period between the request for help and the start of treatment).

Connection with clinical outcomes:

The study by Bühren and colleagues focused on the role of DUED in children and adolescents with AN. In this study, the authors found no association between the duration of untreated disorder and the BMI value when controlled to age (Bühren et al., 2013). Similarly, the study by Flynn and colleagues did not find an association between the duration of untreated AN and BMI at the time of evaluation in a clinical population of young adults (Flynn et al., 2021).

As for long-term clinical outcomes, the retrospective study of Andrés-Pepiñá and colleagues found, in a clinical population of young adults diagnosed with AN (range 17-29 years; mean 22 years), that subjects who still met the criteria for AN diagnosis at follow-up clinical controls were more likely to have had a higher DUED (mean 18 months; SD=10.8 months) than subjects in remission from the disorder (mean 8.4 months; SD=8.4 months), with an odds ratio of 3.33 (95% CI: 1.3-8.7; $p < 0.014$).

An interesting English quasi-experiment study carried out with pre-post design compared DUEDs following the introduction of the early intervention model (FREED project; first episode rapid early intervention for EDs) in a clinical population of young adults with a recent onset of eating disorder, with DUED in a similar clinical population (tallying with age, duration of disease and diagnosis) who had previously received treatment (TAU, treatment as usual) in the same service (Fukutomi et al., 2020). According to this analysis, patients who had access to the FREED project under optimal conditions achieved an average DUED of about 6 months lower compared to patients who had previously been offered treatment. Patients who were offered the FREED intervention also participated more consistently (100% VS 73%) in the treatments and tended to obtain better clinical results. At 12 months from the start of treatment, 59% of subjects diagnosed with AN in the group included in the FREED project recovered a BMI generally against 17% of subjects who had been offered TAU. Similar results were obtained from a

second study that evaluated the effectiveness of the FREED project offered to patients in optimal conditions for access to services (Flynn et al., 2021).

On the other hand, a pre-post design study carried out in Germany shown contrasting results; this study aimed at evaluating the effectiveness of a multi-faceted public health intervention, which included an awareness campaign, prevention activities implemented in schools and implementation of economic resources for treatment. According to this study, the DUED in patients of all ages, diagnosed with AN, did not change significantly after the introduction of such intervention (Pre-intervention mean =36.5 months; SD 68.2 months VS Post-intervention mean =40.1 months; SD 89.4 months) (Gumz et al., 2018). Similarly, this study found no statistically significant differences between before and after in terms of clinical outcomes evaluated with BMI and EDE-Q.

2.2 Evidence-based treatment of eating disorders

Although a great deal of research has been carried out in the last 3 decades to rigorously analyse, with randomized-controlled studies, the impact of medical and psychological treatments in eating disorders (Hay, 2013; Mitchell et al., 2013), a growing quantity of evidences tends to argue that individuals with DA often do not receive evidence-based treatment (Kazdin et al., 2017; Cooper et al., 2015; Kessler et al.). A very important study on 24124 cases from 14 countries showed that only 47.4% of subjects suffering from BN and 38.3% of adults suffering from BED receive specific treatment for their disorder (Kessler et al., 2013). A further study on 5658 women aged 40-50 from the UK showed that only 27.4% of them, who were diagnosed with DA according to the DSM-5 criteria, received specific treatment throughout the course of their disorder (Micali et al., 2017). In addition to the reasons previously explored that complicate the identification and the process that brings subjects with DA to treatment, a "research-practice gap" has also been highlighted, that is, a discrepancy between the evidence-based treatments supported by the literature and the actual treatments proposed in

clinical practices. Some studies show that most therapists for eating disorders do not adhere to evidence-based treatment protocols but mostly pursue eclectic combinations of interventions (Kosmerly et al., 2015; Von Ranson et al., 2013; Waller, 2016).

2.2.1 Guidelines for Eating Disorders management

In order to spread and implement evidence-based treatments in clinical practices, several countries have developed some guidelines. Their goal is to inform and assist the mental health professional in the clinical decision-making process regarding effective treatment and intervention strategies. There are 9 guidelines available from 8 countries for the treatment of eating disorders altogether (Hilbert et al., 2017). In particular, 7 guidelines contain recommendations for the AN, BN and BED: Guidelines of Australia and New Zealand of the Royal Australian and New Zealand College of Psychiatrists (Hay et al., 2014); German guidelines (Association of the Scientific Medical Societies in Germany, 2010), with a revised version in 2019 (Herpertz et al., 2019); Dutch guidelines (Dutch Foundation for Quality Development in Mental Healthcare, 2017); Spanish guidelines (Working Group of the Clinical Practice Guideline for Eating Disorders, 2009); United Kingdom's guidelines (National Institute for Health and Care Excellence, 2017); USA's guidelines of the APA (Yager et al., 2012); guidelines of the World Federation of Societies of Biological Psychiatry (WFSBP) (Aigner et al., 2011). The Danish guidelines (Danish Health Authority, 2016), contain recommendations for the treatment of AN and BN. The French ones (Haute Autorité de Santé, 2010) contain indications only for the AN. The WFSBP guidelines contain recommendations only for the medical treatment of eating disorders, while the other guidelines contain indications concerning different treatment approaches. Most guidelines were developed by multidisciplinary working groups (Australia and New Zealand; France; Germany; Netherlands; Spain; UK), while those from WFSBP and APA were developed by a group of psychiatrists.

2.2.2 Comparison among guidelines

2.2.2.1 Anorexia Nervosa

All guidelines that contain indications regarding the treatment setting indicate the outpatient regimen as the first indication. For a higher level of care intensity most guidelines provide criteria for partial and full-time hospitalization. The level of detail varies among guidelines but all of them emphasize the need to assess on an individual basis taking into account multiple factors, especially the failure of the outpatient treatment and the risk of medical complications. The risk of medical complications is mainly evaluated on the basis on the patient's weight and BMI, behavioural factors (e.g., extreme restriction of calorie intake or frequency of compensatory behaviors), vital signs (e.g., FC <40 BPM; PAO < 60/40), psychiatric comorbidities (e.g., suicidal risk) and other aspects related to the context (e.g. family support). For severely malnourished patients who do not give their consent to treatment, most guidelines contain indications for coercive treatment. The criteria for discharge from hospital are also specified by most guidelines. 6 out of 9 guidelines specify the importance of patients suffering from DA to be followed by professionals specialised in the treatment of DAs or by professionals with experience in this field. As for specific treatment modalities, most guidelines include recommendations for nutritional management, from artificial nutrition to nutritional counselling. Guidelines tend to favour oral nutrition over the artificial one, considered of secondary importance; some guidelines also give indications regarding duration, use criteria and the risk of refeeding with respect to enteral nutrition. Only the guidelines from Germany and the UK explain that nutritional counselling must be part of a multidisciplinary approach and not be the only approach used. As for the goals of weight recovery among the various treatment regimens, there is a substantial agreement between the guidelines, with ranges from 0.2 kg and 0.5 kg for the outpatient regimen to 0.5 and 1.5 kg for the hospital regimen. Germany and USA's guidelines recommend a daily intake between 30-40 kcal/kg, while it is higher for Dutch guidelines and lower for Spain and UK's guidelines, especially for severely malnourished patients at high risk of refeeding syndrome. Among the 7 guidelines that take into account the use of nutritional supplements, there is a wide variability between the recommendations about the type of and the indication for nutritional

supplements. The most frequent specifically recommended are phosphate supplements (6 guidelines), thiamine (3 guidelines), zinc (2 guidelines), potassium (2 guidelines), while 3 guidelines recommend a general supplement of vitamins and minerals. Although psychotherapy is considered a central element by all guidelines, only 7 of them recommend specific psychotherapy interventions. All 7 recommend family-based approaches, especially for younger users (Blessit et al., 2015). As regards individual psychotherapy, 6 guidelines recommend cognitive-behavioral psychotherapy (CBT), which intervenes on symptoms and is focused on changes in dysfunctional behaviors and cognitive patterns that maintain the disorder (Fairburn, 2008). This approach is recommended as the first line by the guidelines from Netherlands and the UK. A lower degree of agreement between the guidelines is reached with regard to psychodynamic and interpersonal psychotherapies, which are specifically indicated as an alternative by 4 and 2 guidelines respectively. While psychodynamic-oriented psychotherapy includes treatments that operate on an interpretive-supportive continuum (Leichsenring et al., 2015), interpersonal psychotherapy is focused on the goal of the treatment that consists in treating the eating disorder through the resolution of interpersonal problems in the context in which the disorder has developed (McIntosh et al., 2000). In addition, the Maudsley approach to cognitive-interpersonal psychotherapy for the treatment of AN in adults (Schmidt et al., 2014) and specialist supportive clinical management (McIntosh et al., 2006) are recommended as first lines of therapy by the guidelines from Netherlands and the UK. The German guidelines, on the other hand, proposes a general recommendation for psychological interventions which consists of involving the patient's family members for patients that are children or adolescents. Some guidelines report that psychological interventions are more effective in patients who are internally stable and cognitively intact, or in combination with nutritional interventions. As regards pharmacological treatment, 5 out of 9 guidelines provide specific recommendations with some considerable variations. The Spanish and UK's guidelines make a general recommendation that psychopharmacological treatment should not be the only or main treatment while the French guidelines note that there is no specific pharmacological treatment for AN.

Antidepressant drugs are generally recommended in 4 guidelines in case of concomitant depressive symptomatology. The German guidelines also warns about the use of antidepressants in order to gain weight. As for selective serotonin inhibitors (SSRIs), the American guidelines recommend their use for the treatment of depressive symptoms, in conjunction with psychotherapy, or after weight re-establishment, while the Australian and New Zealand and Dutch guidelines recommend not to use them, particularly in children and adolescents. With regard to the use of tricyclic antidepressants (TCAs), the American guidelines do not recommend their use, while the French ones seem cautiously favourable. Monoamine oxidase inhibitors (MAOIs) and Bupropion are mentioned only by the American guidelines who do not recommend their use. 4 guidelines are in favour of the use of antipsychotics, in particular olanzapine, for the treatment of obsessive thinking; however, they recommend a prudent use of it as there is no evidence of long-term efficacy. As regards the use of antipsychotic drugs for weight gain, there are conflicting recommendations between the American guidelines, which are in favour of their use, and the German guidelines, which reiterate their misuse and ineffectiveness. Prokinetic agents and anxiolytic drugs are only recommended by the American guidelines for the treatment of gastrointestinal disorders and to reduce the anticipatory anxiety associated with the meal respectively. The use of appetite stimulating drugs and of lithium are not recommended by the German guidelines. 4 guidelines also do not recommend the routine use of oestrogens to regularize the menstrual cycle. Other recommendations are offered by the Danish guidelines on meal support, food training and physical activity supervision. Physical therapies such as electroconvulsive therapy and transcranial magnetic stimulation are not recommended by the guidelines from the UK and USA. 4 guidelines contain indications on the internal management of the AN and 3 guidelines also report indications in case of pregnancy. 2 guidelines report indications on the treatment of medical and psychiatric comorbidities as well as artificial nutrition and the management of refeeding syndrome.

2.2.2.2 Bulimia Nervosa

Among the guidelines that report the main treatment setting for BN, all recommend outpatient management as the first line. Respectively, 4 and 5 guidelines provide the criteria for the Day Hospital regime and for the hospitalisation regime. As for the specific treatment modalities, nutritional counselling is generally recommended by the Danish guidelines, while the Spanish and American guidelines report that nutritional counselling should not be offered as the only type of treatment. All guidelines, except WFSBP, recommend specific psychological interventions. Cognitive-behavioural therapy is indicated as the first line in 5 guidelines, while among the remaining 2, the English ones indicate self-help guides as the first step of treatment while the Spanish ones do not have an explicit hierarchy of treatment. Self-help approaches are recommended by 6 guidelines, of which 4 specify the use of guides, based on cognitive-behavioural interventions, which consist in the use of manuals alongside short support sessions (Wilson et al., 2012). Interpersonal psychotherapy is recommended as an alternative to CBT by most guidelines, while psychodynamic psychotherapy is only recommended by German and American guidelines. Family-based psychotherapy is recommended especially for younger patients while for adults it is explicitly recommended only by the American guidelines. The German ones propose the CBT approach even in childhood and adolescence, however, they recommend the inclusion of family members in the treatment. Further psychological interventions indicated are for example the combination of psychodynamic psychotherapy and CBT, couple therapy or support groups. Among the recommendations for psychopharmacological treatments 7 out of 8 guidelines recommend the use of antidepressants, especially SSRI fluoxetine, although with some restrictions, such as combining them with a psychotherapeutic pathway. Contrasting recommendations concern the use of TCA drugs, such as imipramine and desipramine, which are recommended by the WFSBP guidelines, while they are explicitly not recommended for initial pharmacological treatment by the American ones. MAOIs are only mentioned by American and WFSBP guidelines which discourage their use. The use of anticonvulsant drugs, specifically topiramate, is recommended by 2 guidelines (New Zealand and Australia and USA), while it is not reported by the remaining ones. The only

guidelines that refer to the use of lithium are the American ones, which do not recommend its use. In case of concomitant obesity, the Australia and New Zealand's guidelines recommend the antiobesity drug Orlistat. Finally, 4 guidelines provide specific indications for the treatment of comorbidities and 3 guidelines contain recommendations on the management of the internistic aspects of BN.

2.2.2.3 Binge Eating Disorder

Only 3 out of the 7 available guidelines include explicit recommendations on the treatment setting, indicating outpatient management as the first line (Germany, UK and the Netherlands). The criteria for hospitalisation are provided by 4 guidelines (Australia and New Zealand, Germany, Netherlands and UK). As regards nutritional counselling, only the American guidelines recommend it specifically, within a behavioural program for weight loss. The Spanish guidelines recommends general nutritional counselling for eating disorders, within a context of psychiatric care. All guidelines except WFSBP contain recommendations for specific psychological interventions. Cognitive-behavioural therapy is recommended by all 6 guidelines, followed by guided or unguided cognitive-behavioural self-help therapy and interpersonal psychotherapy. A specific recommendation for psychodynamic psychotherapy is made exclusively by German guidelines. With regard to the psychotherapy format, the guidelines vary substantially, with the guidelines from Australia and New Zealand favouring the individual approach while the guidelines from the United Kingdom prioritise group sessions. Family-based therapy is recommended for children and adolescents with BED only by the Dutch guidelines. The use of antidepressant drugs is generally recommended by 3 guidelines (Australia and New Zealand, Spain and the United States), while 3 guidelines (Germany, Holland and WFSBP) specifically recommend SSRIs in order to reduce binge-eating episodes, at least in the short term. With regard to TCAs, only WFSBP guidelines recommend their use, in particular of imipramine. For anticonvulsants, 3 guidelines (Australia and New Zealand, USA and WFSBP) recommend the use of topiramate, while the remaining guidelines do not provide guidance. For patients with obesity 2 guidelines

recommend the use of anti-obesity drugs, especially orlistat. American guidelines also recommend the drug sibutramine to reduce binge eating and weight loss. 2 guidelines explicitly recommend the association between pharmacological therapy and psychotherapy (Australia and New Zealand and USA). Finally, 3 guidelines report the treatment of comorbidities while 2 guidelines provide indications for the internal management of patients with BED.

2.2.4 *Evidence on treatment recommendations*

From this systematic review of evidence-based guidelines on eating disorders, consistent recommendations emerge but also significant discrepancies. As to the treatment of AN, the guidelines show considerable agreement on the weight gain goals while the recommended caloric intake varies considerably, as well as the need for nutritional supplements, which reflect a lack of solid evidence in such topic. There is good consistency on the use of family-based psychotherapy approaches for younger subjects, as there is good supporting evidence-based literature (Blessit et al. 2015; Forsberg and Lock, 2015; Lock, 2015). Cognitive-behavioral psychotherapy approaches are also recommended with good consistency (Kass et al., 2013). A lower degree of agreement is obtained on the psychodynamic psychotherapy and interpersonal therapy as alternative treatments, mainly due to lack of adequate evidence on the efficacy of their use (Carter et al., 2011; McIntosh et al., 2005; Zipfel et al., 2014). There is a need for more evidence on psychotherapeutic approaches for AN (Herpertz-Dahlmann et al., 2015; Hay et al., 2015). As to psychopharmacotherapy for AN, the recommendations vary widely and 4 guidelines, including those from WFSBP which offer a more biomedical approach, do not provide any specific recommendation for drugs nor discourage their primary or sole use. The greatest agreement is found on the cautious use of antipsychotic drugs for the treatment of obsessive thinking, but there is no consistency on their use for weight gain. Antidepressants are generally recommended primarily by 3 guidelines but there is no consistency on which are to be preferred specifically. On the other

hand, there is consistency in the use of oestrogens only if certain osteoporosis conditions occur (Robinson et al., 2017). Also, as regards pharmacotherapy, the lack of agreement among the guidelines reflects a substantial lack of strong and unequivocal evidence on the efficacy of drug treatment (McElroy et al., 2015; Herpertz-Dahlmann et al., 2015; Miniati et al., 2016). As for the treatment of BN, there is good consistency on the use of CBT in the first line, with respect to moderate evidence on this specific topic (Hay, 2013; Kass et al., 2013), while the UK's guidelines recommend in the first line the suggestion of a self-help cognitive-behavioural program, probably emphasizing the evidence of cost-benefit that are emerging (Lynch et al., 2010). Among others, interpersonal psychotherapy is recommended, which seems to be less effective in the short term but equally effective in the long one (Kass et al., 2013) and psychodynamic psychotherapy, indicated by German guidelines despite the poor evidence in this topic (Abbate Daga et al., 2016; Poulsen et al., 2014). Also in this case, family-based therapy is recommended especially for children and adolescents, recommendation supported by recent evidence (Le Grange et al., 2015). Many guidelines and especially the most recent ones indicate self-help guided programs as an alternative treatment, which have proven to be effective for BN (Beintner et al., 2014). As for the pharmacological therapy for BN, there is good agreement on the use of SSRIs, in particular fluoxetine, approved for the treatment of BN in adults in multiple states, although several guidelines warn that it should not be the only treatment but in should be combined with psychotherapy. Recommendations on other psychopharmaceuticals, such as TCA, topiramate, or against the use of Lithium and MAOI are unfounded and inconsistent among guidelines, due to the scarce scientific evidence supporting or against these classes of drugs (McElroy et al., 2015). For the treatment of BED, all guidelines analysed (with the exception of WFSBP, biologically oriented) recommend psychotherapy, in particular CBT is more frequently indicated in the first line against solid evidence on its effectiveness (Brownley et al., 2016). Secondly, the most indicated is cognitive-behavioural self-help therapy in the guided format, of which evidence of efficacy is available (Beintner et al., 2014). It is even referred to as the first line by the UK's guidelines, probably considering the cost-effectiveness

impact of such an approach, as in the case of the BN. As for regard to psychodynamic psychotherapy, it is recommended, as in the case of BN, only by German guidelines, despite the absence of evidence-based efficacy tests in its favor (Vocks et al., 2010). Only 2 guidelines indicate nutritional counselling as the literature on the topic shows a poor effectiveness of this approach (Grilo, 2017). As for drug therapy, for BED and for BN as well, most guidelines recommend SSRIs, in line with the current literature (Brownley et al., 2016), while only WFSBP guidelines, based on studies published before 1999, also recommend the use of tricyclic antidepressant drugs. 3 guidelines also recommend the use of the topiramate anticonvulsant drug, despite its side effects have been widely highlighted, especially from a cognitive point of view (McElroy et al., 2015). As for antiobesity drugs, 2 guidelines recommend the use of orlistat to lose weight in BED and in BN (Golay et al., 2005; Grilo et al., 2005) and of sibutramine to reduce binge eating, despite the latter was withdrawn from the market in many countries due to cardiovascular side effects (Shakeel Khan, 2021). The combination of psychological and pharmacological treatment is recommended by 2 guidelines, although there is no scientific evidence to support it (Grilo et al., 2016).

Ultimately, consistency between guidelines seem to be greater for psychological treatments and for recommendations on individual drugs for which there are more evidences in the literature, while for medical and pharmacological therapies less supported by scientific evidence the recommendations vary significantly and the consent of experts plays an important role in this topic. As for to the dissemination and implementation of evidence-based treatments in clinical practice, the guidelines approve the main empirically validated therapeutic approaches with considerable agreement, while the variability in the recommendations of the guidelines is greater when the validity of an approach is taken without strong empirical validation. A broader evidence base is critical to provide clinically reliable and consistent guidelines for eating disorders. Several important areas for future clinical research were. identified for all eating disorders even in different age groups and could fill the therapeutic gap and the research-

practice gap that have been highlighted in the clinical practice of eating disorders (Hilbert 1e al., 2017)

Chapter III

Data from the Turin ED Center

3.1.1 Introduction

The duration of untreated disorder in eating disorders (DUED) is an area still partially investigated and understood in its components especially with regard to those factors that might exert an influence on DUED duration and on pathways to care. A recent systematic literature review by Austin colleagues selected 14 studies estimating the duration of untreated disorder in eating disorders (Austin et al., 2019). 11 studies evaluated DUED in Anorexia Nervosa, with results ranging from 6.39 to 39.96 months. Only few studies attempted to divide DUED into components, which were not uniform between them (Brown et al., 2014; Gumz et al., 2018; Schlegl et al., 2019): it is still debated if DUED should start with first symptoms or with a full blown ED syndrome and if it should end with the occurrence of a diagnosis or with the prescription of a treatment. Studies in the literature are still not uniform in describing the definition and the measurement method (Austin et al., 2021). The path from the onset of eating symptoms to the setting of evidence-based specialist therapy is fundamental for the course of the disorder and could be a modifiable factor with positive prognostic implications. Furthermore, in anorexia nervosa motivation to treatment is a crucial aspect in treatment pathways, as studied in the State of Change Model (Prochascka., 1999), thus a better evaluation of the DUI could offer an option for a more accurate characterization of the motivation to treatment. Finally, the majority of the pathway studies are retrospective: they describe historical data from clinical databases. In our study we decided to evaluate subjects at the psychiatric intake moment, with the aim to describe actual symptomatology and the history of the illness.

The goal of our study is to investigate DUED in its components using a cross sectional and prospective model. In fact, we have subsequently recruited individuals who were admitted at the Eating Disorder Center (CER DCA) of the University Hospital "Città della Salute e della Scienza di Torino". With each new subject has been performed a semi structured interview. The interview was focused on the present symptomatology and on the past history. Our first aim was to evaluate and describe DUED and comparing our results to findings from previous researches. Then our second aim was to describe DUED and his characteristic including age of onset, which health professionals and which treatment pathways has been undertaken, at what age the ED has received a proper diagnosis. A third aim was to understand which variables could have an impact on such path. Finally, the fourth aim was to investigate whether a longer DUED could have influenced symptoms presentation at the intake.

3.1.2 Methods

Individuals who were subsequently admitted for the first time at the Eating Disorder Center (CER DCA) of the University Hospital "Città della Salute e della Scienza di Torino" were recruited. All individuals were diagnosed with a FED, assessed by an experienced psychiatrist using the Structured Clinical Interview for DSM-5 Axis-I Disorders (SCID-I). As we want to assess a sample of the population of individuals who sought treatment, we decided not to define any exclusion criteria for the recruitment. Therefore, the only inclusion criteria was to have a diagnosis of FED and being admitted for the first time at the ED Center.

All subjects underwent a structured interview that was created by a team composed of clinicians and researchers containing, the following specific questions aimed at investigating the pathway from onset of symptoms and the arrival at the Regional Expert Centre for Feeding and Eating Disorders of the Città della Salute e della Scienza di Torino):

- What was the age of onset of food symptoms
- Who was the first health professional you approached?
- Did the first therapeutic approach take place in a public or private context?
- On what date did the first therapeutic approach take place?
- How old were you at the time of the first treatment approach?
- What was the course of care proposed by the professional to whom you turned?
- Who requested the first therapeutic approach?
- What was the main symptom for which you have approached a healthcare professional?
- When was the diagnosis of eating disorder first made?
- Who was the healthcare professional who initially made this diagnosis?
- On what date was this diagnosis initially made?
- When did you first perform a psychiatric evaluation for your eating disorder?
- How old were you when you made that visit?
- When did the psychiatric treatment for the eating disorder actually take place?
- How old were you when this treatment took place?
- How many treatment proposals did you reject before initially accepting the proposed treatment pathway?
- How many treatment proposals did you decline later?
- What was the first treatment proposed?
- What was the first treatment actually accepted and carried out?

Finally, to assess the reliability of the answers provided, the interviewees were asked to indicate on a Visual Analogue Scale (VAS) how much, in their opinion, they were reliable in providing the answers to that interview (VAS 0-100), how much they felt it difficult to answer those questions (VAS 0-100) and how much they feel fatigued at the time of the evaluation (VAS 0-100).

The researchers who conducted the structured interview were psychiatrist with expertise in the ED field. Before the interview, they underwent specific training to collect information as consistently as possible. They were asked to

indicate, also according to their opinion, how the recruited subjects were reliable in answering the proposed questions (VAS 0-100) and how long the interview lasted. The interviews lasted 10.3 minutes, on average.

Participant were interviewed during the first month after the intake.

The Duration of Untreated Disorder in our study was defined as the time from the onset of the disorder to the first appropriate treatment. The onset of the disorder the moment in which the clinical criteria for diagnosis of the disorder were first met. In our study, due to the difficulty in identifying or reconstructing the onset that would lead to unreliable data, we identified the moment of appearance of eating disorders symptoms (e.g., beginning of weight loss, appearance of food binge eating or purging behaviours, appearance of avoidance or eating restrictions) as the moment of onset of the eating disorder. With first adequate treatment, we mean the first specific treatment according to appropriate evidence-based guidelines for the treatment of eating disorder (e.g., cognitive-behavioural psychological intervention or psychopharmacological therapy at right dosage). The first therapeutic approach refers to the first specialized professional figure to whom the patient (and family members) has turned to tackle the food symptomatology. Diagnosis refers to the assessment of a professional figure (e.g., psychiatrist, dietician) who evaluate the criteria to obtain a diagnosis of eating disorder.

Participants were also given self-report questionnaires: Eating Disorder Inventors 2 (EDI-2), Eating Disorder Examination Questionnaire (EDE-Q), Beck Depression Inventors (BDI) and the State-Trait Anxiety Inventors (STAI), to evaluate eating symptomatology and psychopathology, anxiety levels and presence of depressive symptomatology.

This study was approved by the Ethical Committee of the Azienda Ospedaliera Universitaria “Città della Salute e della Scienza” in Turin, Italy. Participants provided written informed consent. All procedures were conducted in accordance with the latest version of the Declaration of Helsinki.

3.1.3 Measures

3.1.3.1 Body Mass Index (BMI)

The Body Mass Index is the result obtained by dividing the weight in kilograms by the square of the height in meters. In DSM-5, a significantly low body weight in relation with age, sex, developmental trajectory and physical health is indicated as a weight criterion for the diagnosis of Anorexia Nervosa. Significantly low weight is defined as weight below the normal minimum or, for children and adolescents, less than the expected minimum. In the study, the patients' current BMI and the minimum BMI achieved in the history of disease were evaluated.

3.1.3.2 Eating Disorder Examination Questionnaire (EDE-Q)

The EDE-Q (Fairburn & Beglin, 1994) is a self-administered version of the EDE (Eating Disorder Examination) interview, aimed at investigating the severity of eating symptoms in patients with FED and subjects at risk of developing the disease. It consists of 41 items, with a score divided into four subscales (Restriction, Food Concern, Shape Concern, and Weight Concern) and a global score.

3.1.3.3 State-Trait Anxiety Inventory (STAI)

The STAI (Spielberger, 1994) is a self-conducted questionnaire composed of 40 items, divided into two groups: 20 items investigate State Anxiety (A-State) and 20 Trait Anxiety (A-Trait); each item can be assigned a score from 1 to 4. Its most widely used version is the STAI-FORMA Y. High scores on this test suggest high levels of anxiety.

3.1.3.4 Beck Depression Inventory (BDI)

The BDI (Beck et al., 1961) is a self-conducted questionnaire widely used for the evaluation of the degree of Depression. The test assesses the presence of depressive symptoms, from a motivational, cognitive, vegetative and psychomotor point of view. In its short version, that is the most employed in clinical practice, it consists of 13 items, each one having four statements that define it in order of increasing severity (e.g. regarding sadness: 0 = I do not feel sad, 1 = I feel sad or melancholy, 2 = I am melancholy or sad all the time and I do not know how to get out of it, 3 = I am so sad or unhappy that I cannot bear it). The maximum score is 39, corresponding to a severely depressed mood. The cut-offs usually considered range from 9-10 pt, for a high sensitivity screening and 13-14 pt for a high specificity clinical analysis for the depressive episode (Furlanetto et al., 2022).

3.1.4 Statistical analysis

The SPSS version 23.0 package was used for analysis. Statistical significance was set at $p < 0.05$. First, data were inspected, and descriptive statistics were calculated for all participants.

Mean DUED was compared with data from samples retrieved from previous research, collected with literature search in database (Pubmed and Psychinfo)

To analyse the correlation between DUED and psychometric and clinical variables Pearson correlations and linear regressions were conducted in the total sample and in the sample composed by AN individuals.

To analyse whether multiple qualitative variable (such as “who requires treatments” or “symptoms that were first treated”) influenced DUED ANOVA were conducted in the total sample and in the sample composed by AN individuals.

Furthermore, to ascertain the presence of differences among diagnosis (ANR; ANBP, etc) were conducted ANOVAs for continuous variable and X^2 for qualitative variables in the total sample and in the sample composed by AN individuals.

3.1 RESULTS

3.2.1 Sample characteristics

The sample of patients evaluated in this study was enrolled from October 2019 until February 2022 and consists of 136 subjects, of which 134 (98.5%) are female and 2 (1.5%) are male, at the ED Center at the Città della Salute e della Scienza di Torino Hospital. Subjects were retrieved in different clinical settings (Table 1): 71 subjects (52.2%) were evaluated during hospitalization, therefore during an acute phase of eating disorder; 41 subjects (30.1%) at the outpatient service of the ED Center were interviewed during the first month of the pathway; 24 subjects (17.6%) were interviewed during hospitalization in Day Hospital treatment, where the patients were facing a multistructured treatment pathway with multiple weekly accesses (with nutritional evaluation and both individual and group psychotherapy).

TABLE 1: recruitment setting

	Frequency	%
Outpatient Service	41	30,1
Day Hospital	24	17,6
Hospitalisation	71	52,2
Total	136	100,0

The diagnosis of eating disorder was made by an experienced psychiatrist following the criteria of DSM 5 (American Psychiatric Association, 2013) at the time of hospitalization or during the outpatient visit. All patients (136 subjects) with a diagnosis of ED (Table 2)

were enrolled. 81 (59.6%) were diagnosed with Anorexia Nervosa Restricting (ANR), 24 (17.6%) were diagnosed with Anorexia Nervosa Binge Purging (ANBP), 22 (16.2%) had a diagnosis of Bulimia Nervosa (BN), 5 (3.7%) had a diagnosis of Binge Eating Disorder (BED), 4 (2.9%) received a diagnosis of Other Feeding and Eating Disorders (OSFED).

TABLE 2: Diagnosis

	Frequency	%
Anorexia Nervosa Restricting	81	59,6
Anorexia Nervosa	24	17,6
Bulimia Nervosa	22	16,2
Binge eating disorder	5	3,7
Unspecified Feeding and Eating Disorders	4	2,9
Total	136	100,0

The mean age of the subjects (TABLE 3) enrolled in the study was 25.54 years, with a standard deviation of 9.48 years. The youngest subjects enrolled were 18 years old while the oldest one was 64 years old.

TABLE 3: Age

No.	Mean (years)	Standard deviation
136	25,037	9,479

The mean BMI (Table 4) was calculated according to diagnostic categories, and was 14.5 kg/m² (sd=2.15 kg/m²) for the subsample with a diagnosis of ANR, 15.9 kg/m² (sd=2.40 kg/m²) for the subsample with a diagnosis of ANBP, 22.4 kg/m² (sd=2.31 kg/m²) for the subsample with a diagnosis of BN, 44.0 kg/m² (sd=5.97 kg/m²) for the subsample with a diagnosis of BED and 23.3 kg/m² (sd=9.95 kg/m²) for the subsample with a diagnosis of Unspecified Feeding or Eating Disorder.

TABLE 4: BMI

Diagnosis	N.	Mean	Standard deviation
Anorexia Nervosa Restricting	81	14,50	2,148
Anorexia Nervosa Binge Purging	24	15,859	2,359
Bulimia Nervosa	22	22,360	2,312
Binge Eating Disorder	5	44,030	5,971
Unspecified Eating Disorder	4	23,307	8,284
Total	136	17,329	6,598

3.2.2 DUED and its components

3.2.2.1 Duration of untreated eating disorder

The total mean duration of untreated disease within the sample of subjects diagnosed with feeding and eating disorder was 60.9 months, with a standard deviation of 81.9 months. Stratifying by diagnosis, it was found that the mean DUI among patients diagnosed with Anorexia Nervosa Restricting Subtype (n=81) amounted to 60.7 months, with a standard deviation of 88.3 months. For the subsample diagnosed with Anorexia Nervosa Binge Purging (n=24), the mean was 64.0 months with a standard deviation of 79.6 months. For the group diagnosed with Bulimia Nervosa (n=22), the mean DUED was 48.4 months, with a standard deviation of 44.0 months. The sample diagnosed with Binge Eating Disorder (n=5) reported a mean DUED of 130.6 months with a standard deviation of 115.3 months. The 4 subjects diagnosed with Unspecified Feeding and Eating Disorder (OSFED) reported a DUED mean

of 19.5 months and a standard deviation of 9.2 months. Finally, the subject diagnosed with Purging disorder reported a DUED of 5 months.

3.2.2.2 Duration of eating disorder from its onset to diagnosis

The mean duration of the time elapsed between the onset of the eating symptomatology and the time when the diagnosis of eating disorder was first made is 9.3 months for the entire sample, with a standard deviation of 6.5 months. For the subsample of subjects who were diagnosed with Anorexia Nervosa Restricting (n=81) the mean duration was 9.2 months, with a standard deviation of 7; for the group with Anorexia Nervosa Binge Purging (n=24) the mean is also 9.2 months, with a standard deviation of 6.2; the group that was diagnosed with Bulimia Nervosa (n=22) had a mean duration of 9.01 months, with a standard deviation of 3.8 months; the group with a diagnosis of BED (n=5) presented a mean duration of 16 months, with a standard deviation of 9.8 months; finally, the OSFED group (n=4) presented a mean of 7.7 months with a standard deviation of 2.9 months.

3.2.2.3 Duration from onset to first therapeutic approach

The mean duration of the period between symptom onset and the first approach with a health professional for an eating disorder is, for the entire sample, 38.5 months, with a standard deviation of 72.1 months. For the sample with ANR (n=81) the mean duration is 42.3 months (sd=77.7 months). For the group with an AN-BP diagnosis (n=24) the average duration is 34.3 months (sd=72.5 months). The sample diagnosed with BN (n=22) had a mean duration of 26.8 months (sd=26.6 months). The group diagnosed with BED (n=5) had an average of 71 months (sd=132.8 months). Finally, the OSFED group (n=4) averaged 35.0 months (sd=30.8 months).

3.2.2.4 Duration from onset to admission at CER DCA

The mean duration of the entire sample from onset of eating symptomatology to arrival at the ED Center is 72.6 months, with a standard deviation of 82.3 months. The group with ANR diagnosis (n=81) took 72.2 months on average, with a standard deviation of 90.1 months; the group with AN BP diagnosis (n=24) had a mean duration of 71.5 months, with a standard deviation of 76.3 months; the sample with a BN diagnosis (n=22) had 61.4 months with a

standard deviation of 49.8 months; the group with a BED diagnosis (n=5) took 155.4 months before arriving at the ED center, with a standard deviation of 95.9 months; the subgroup with OSFED diagnosis (n=4) had a mean of 44.5 months with a standard deviation of 30.8 months.

Diagnosis		DUED from onset to diagnosis	DUED from onset to first approach	DUED from onset to treatment	DUED from onset to admission at CER DCA
Anorexia Nervosa Restricting N= 81	Mean	9,187	41,358	60,753	72,259
	Standard deviation	7,001	77,705	88,314	90 ,103
Anorexia Nervosa Binge Purging N= 24	Mean	9,208	34,292	63,958	71,500
	Standard deviation	6,122	72,474	79,643	76,305
Bulimia Nervosa N=22	Mean	9,091	26,773	48,454	61,454
	Standard deviation	3,816	26,558	44,029	49,805
Binge eating disorder N=5	Mean	16,000	71,000	130,600	155,400
	Standard deviation	9,798	132,819	115,266	95,887
Unspecified Feeding or Eating Disorder N=4		7,750	29,500	14,667	44,500
	Standard deviation	2,872	34,971	10,598	30,817
Total N=136	Mean	9,385	38,493	60,881	72,618
	Standard deviation	6,513	72,143	81,874	82,342

TABLE 6A: Comparison between DUI and DUED in literature

	Study	Mean DUI reported	Sample size
Schizophrenia (DUP)	Boonstra et al., 2012* (*Meta-analysis 16 studies included)	61,4 weeks (14,1 months)	3339
Unipolar depression	Altamura et al., 2010	39,1 months	181
Bipolar disorder I	Altamura et al., 2010	81,1 months	115
Bipolar Disorder II	Altamura et al., 2010	97,2 months	186
Generalised anxiety disorder	Dell'Osso et al., 2013	81,6 months	127
Panic disorder	Dell'Osso et al., 2013	39,5 months	138
Obsessive-compulsive Disorder	Albert et al., 2009	106,2 months	251
Somatization Disorder	Herzog et al., 2018	25,2 years (306 months)	139
Anorexia Nervosa	Austin et al., 2019 (Meta-analysis 11 studies included)	14,6 months	2920
Bulimia Nervosa	Austin et al., 2019 (Meta-analysis 4 studies included)	34,3 months	534
Binge Eating disorder	Beat, 2017	67,4 months	63

TABLE 6B: comparison between DUED in literature and DUED in our study

	Study	Mean DUI reported	Sample size	DUI analysed in our sample	Sample size of our study
Anorexia Nervosa	Austin et al., 2019 (Meta-analysis 11 studies included)	14,6 months	2920	61,5 months	105
Bulimia Nervosa	Austin et al., 2019 (Meta-analysis 4 studies included)	34,3 months	534	48,4 months	22

Binge Eating disorder	Beat, 2017	67,4 months	63	130,6 months	5

3.2.3 Factors that might have affected DUED

3.2.3.1 Age at assessment and DUED

From the linear regression analysis (TABLE 7), age at assessment appears to be a significantly correlated factor with the duration of untreated disorder. An older age correlates with a statistically higher DUED.

TABLE 7: Linear regression total sample mean age and DUED

Model	Sum of squares	df	Mean square	F	Sig.
Regression	341056,590	1	341056,590	81,409	<0,001
Residual	557195,514	133	4189,440		
Total	898252,104	134			

In the AN sample, mean age at assessment is also significantly correlated with the DUED.

TABLE 8: Linear regression AN sample (N=106) mean age and DUED

Model	Sum of squares	df	Mean square	F	Sig.
Regression	366026,571	1	366026,571	93,493	<0,001
Residual	407160,193	104	3915,002		
Total	773186,764	105			

3.2.3.2 Age of onset (Table 9)

The mean age of onset of eating disorder is 17.9 years, with a standard deviation of 5.6 years and a high mean trans-nosographic consistency, with the exception of subjects diagnosed with Binge Eating Disorder who, on the mean, have a later onset age (22.8 years).

TABLE 9: Age of onset

Diagnosis	No.	Mean age (years)	Standard deviation
Anorexia Nervosa Restricting	81	17,963	5,142
Anorexia Nervosa Binge-Purging	24	17,042	3,770
Bulimia Nervosa	22	17,500	3,502
Binge Eating Disorder	5	22,800	18,539
Unspecified Feeding or Eating Disorder	4	18,000	6,000
Total	136	17,904	5,636

3.2.3.2.1 Age of onset and DUED

The linear regression analysis between the age of onset of symptoms and DUED does not seem to show a statistically significant correlation between these 2 variables (TAB 10).

TABLE 10: age of onset in total sample and DUED

Model	Sum of squares	df	Mean square	F	Sig.
Regression	7216,631	1	7216,631	1,077	0,301[b]
Residual	891035,473	133	6699,515		
Total	898252,104	134			

In the AN sample the age of onset of symptoms and DUED does not show a significant correlation (Table 11).

TABLE 11: age of onset in total sample and DUED

Model	Sum of squares	df	Mean square	F	Sig.
Regression	5565,085	1	5565,085	0,754	0,387
Residual	767621,679	104	7380,978		
Total	773186,764	105			

3.2.3.3 Age at diagnosis (TABLE 12)

The mean age at diagnosis of our sample is 21.6 years, with a standard deviation of 8.3 years. Also in this case, there is a good trans-nosographic consistency with the exception of the subjects with a diagnosis of Binge Eating Disorder, whose mean age at diagnosis is 33.2 years, with a standard deviation of 19.0 years.

TABLE 12: Age at diagnosis

Diagnosis	N.	Mean age (years)	SD
Anorexia Nervosa Restricting	80	21,550	8,333
Anorexia Nervosa Binge-Purging	24	20,667	7,191
Bulimia Nervosa	22	20,500	3,726
Binge Eating Disorder	5	33,200	19,031
Unspecified Feeding or Eating Disorder	4	20,000	3,464
Total	135	21,593	8,277

3.2.3.3.1 Age at diagnosis and DUED (table 13)

The linear regression analysis between the age at diagnosis and length of DUI shows, in this case, a statistically significant correlation ($p<0.001$), in which a lower age at diagnosis correlates with a lower total DUED.

TABLE 13: Linear regression between age at diagnosis and DUED

Model	Sum of squares	df	Mean square	F	Sig.
Regression	405928,717	1	405928,717	109,349	<0,001
Residual	490013,642	132	3712,225		
Total	895942,358	133			

In the AN Sample age at diagnosis and length of DUI also shows, a statistically significant correlation ($p<0.001$): lower age at diagnosis correlates with a lower total DUED.

TABLE 14: Linear regression between age at diagnosis and DUED in the AN sample (n=105)

Model	Sum of squares	df	Mean square	F	Sig.
Regression	412070,768	1	412070,768	118,294	<0,001
Residual	358794,623	103	3483,443		
Total	770865,391	104			

3.2.3.3.2. Age at diagnosis and the person who asks for the first therapeutic approach (Table 15 and 16)

The statistical data show a significant correlation between the age at diagnosis and the person who asks for the first approach: the request of a first approach by the patient correlates with a higher age at diagnosis on average (23.3 years; ds=8.6 years), while the request of a first approach by the parents correlates with a lower age at diagnosis on average (18.6 years; σ=3.3 years).

TABLE 15: Age at diagnosis and the person who asks for the first approach

the person who asks for the first approach	No.	Mean age (years)	Standard deviation
Patient	43	23,270	8,617
Parents	78	18,590	3,3320
Teachers	2	16,000	2,828
General practicioners	2	28,500	9,192
Other	10	37,500	13,335
Total	135	21,593	8,277

TABLE 16: Analysis of the variance between age at diagnosis and the person who asks for the first approach

	Sum of squares	df	Mean square	F	Sig.
Among groups	3514,070	4	878,517	20,155	<0,001
Within groups	5666,523	130	43,589		
Total	9180,593	134			

3.2.3.3.3. First therapeutic professional to whom the subjects went for the first time and correlation with DUED (Table 17 and 18).

The first therapeutic professional to the person whom the subjects of our study turned in order to face eating symptoms were: psychiatrists in 24.3% of cases and psychologists/psychotherapists in 24.3% of cases; to a slightly lesser extent, patients turned to general practitioners (21.3% of cases); it follows medical nutritionist (13.2% of cases) and dieticians (8.8% of cases). Few subjects initially spoked gynaecologists (3.7% of cases), endocrinologists (2%) or other professionals (4%). From a statistical point of view, these data

were not significantly correlated with the duration of untreated disorder in eating disorders.

TABLE 17: First professional to whom the subjects asked a treatment for the first time

	Frequency	%
General practitioner	29	21,3
Psychiatrist	33	24,3
Gynaecologist	5	3,7
Medical nutritionist	18	13,2
Dietician	12	8,8
Psychologist/ Psychotherapist	33	24,3
Endocrinologist	2	1,5
Other	4	2,9
Total	136	100,0

TABLE 18: ANOVA First professional and DUED in the total sample

	Sum of squares	df	Mean square	F	Sig.
Among groups	46384,359	7	6626,337	0,988	0,443
Within groups	852867,745	127	6707,620		
Total	898252,104	134			

In the AN sample, these data were also not significantly correlated with the duration of untreated disorder in eating disorders.

TABLE 19: ANOVA First professional and DUED in the AN sample (n=105)

	Sum of squares	df	Mean square	F	Sig.
Among groups	8616,103	1	8616,103	1,172	0,281
Within groups	764570,661	104	7351,641		

Total	773186,764	105

3.2.3.4 The professional who diagnosed the eating disorder (Table 20-21)

Our analysis shows that the professional that most frequently diagnoses, formally or informally, the eating disorder for the first time is the psychiatrist or pediatric neuropsychiatrist (94 cases, equal to 70.4% of the sample); in 13 cases (9,6%) this is carried out by a psychologist or psychotherapist; in 12 cases (8.9%) it is a general practitioner the person who formulates a diagnosis, while in 10 cases (7.4%) it is a medical nutritionist or dietitian. Gynaecologist or other professional figures seldom diagnosed an eating disorder. The mean DUED, i.e. the time between the onset of symptoms and the first evidence based approach, of subjects diagnosed by a psychiatrist is approximately 57.3 months (sd=80.1 months), while those diagnosed by a dietician are 48.3 months (sd=63.5 months), those diagnosed by a general practitioner show a mean DUED of 73.5 months (sd=90.4 months), and those diagnosed by a psychologist or psychotherapist show a mean DUED of 69.5 months (sd=110.4 months). As shown by the analysis of variance (TABLE 17) this trend does not seem statistically significant (p=0,754).

TABLE 20: Professional who formulates first diagnosis and mean DUED

Professional who first formulates a diagnosis	No.	Mean DUED (months)	%	Standard deviation
Child Psychiatrist/Psychiatrist	94	57,266	70,4	80,130
Psychologist/Psychotherapist	13	69,538	9,6	110,419
General Practitioner	12	73,500	8,9	90,401
Mediacl nutritionist/dietician	10	48,300	7,4	63,559
Gynaecologists	3	110,667	2,2	61,044
Other	2	111,000	1,5	25,456
Total	134	61,239	100,0	82,076

TABLE 21: ANOVA Professional who formulates first diagnosis and DUED in the total sample

	Sum of squares	df	Mean square	F	Sig.
Among groups	18139,010	5	3627,802	0,529	0,754
Within groups	877803,348	128	6857,839		
Total	895942,358	133			

Also in the AN sample this analysis does not present significant findings.

TABLE 22: ANOVA Professional who formulates first diagnosis and DUED in the AN sample (n=105)

	Sum of squares	df	Mean square	F	Sig.
Among groups	938,114	1	938,114	0,125	0,724
Within groups	769927,277	103	7475,022		
Total	770865,391	104			

3.2.3.5 Symptoms for which the first therapeutic approach was requested

Among the main factors investigated there are the symptoms for which the first therapeutic approach was requested.

The symptoms for which was requested most frequently the help of a health professional, in our sample, was weight loss (n=56), eating restrictions (n=25) binge-purging behaviours (n=20), and depressive symptoms (n=19); the rarest were anxious symptoms (n=4), alterations in the menstrual cycle (n=3), gastrointestinal symptoms (n=2), ideas of death (n=2), lipothymia (n=1) and other unspecified symptoms (n=3). As regards the length of DUI for the main

symptoms, we noticed a duration of 61.1 months for weight loss, 66.1 months for binge-purging symptoms, 59.2 months for depressive symptoms and finally 45.7 months for eating restrictions.

TAB 23 Symptoms that require treatment in the total sample

Symptoms	No.	Mean DUED (months)	Standard deviation
Weight loss	56	61,071	82,655
Restrictive food intake	25	45,680	65,296
Binge-purging symptoms	20	66,100	76,726
Depressive symptoms	19	59,210	82,034
Anxiety symptoms	4	81,250	61,991
Ideas of death	2	25,000	1,414
Lipothymia	1	209,000	.
Alteration of menstrual cycle	3	33,000	11,532
Gastrointestinal symptoms	2	44,000	25,456
Other	3	146,333	242,261
Total	135	60,881	81,874

Regarding the analysis of variance (ANOVA), the symptoms reported as a factor that led to the request for the first therapeutic approach were found to correlate significantly with the subsequent duration of untreated disorder. Particularly, the symptoms that have shown correlation with a shorter duration are the ideas of death, alterations of the menstrual cycle and gastrointestinal symptoms; on the other hand, symptoms such as lipothymia, anxious symptoms and binge-purging symptoms are correlated with a longer duration of the disease.

TABLE 24: Anova confronting Symptoms and DUED

	Sum of squares	df	Mean square	F	Sig.
Among groups	204529,883	4	51132,471	9,582	<0,001
Within groups	693722,221	130	5336,325		
Total	898252,104	134			

TAB 25: Symptoms that require treatment in the AN sample

Symptoms	No.	Mean DUED (months)	Standard deviation
Weight loss	47	65,121	88,655
Restrictive food intake	23	45,910	67,376
Binge-purging symptoms	20	52,800	55,746
Depressive symptoms	19	53,285	88,771
Anxiety symptoms	4	105,500	72,991
Ideas of death	1	24,000	
Lipothymia	1	209,000	.
Alteration of menstrual cycle	3	33,000	11,532
Gastrointestinal symptoms	2	44,000	25,456
Other	3	146,333	242,261
Total	105	60,951	85,119

TABLE 26: Anova confronting Symptoms and DUED in the AN sample (n=105)

	Sum of squares	df	Mean square	F	Sig.
Among groups	57358,574857	4	6373,174	9,582	<0,001
Within groups	193001,030	100	5336,325		
Total	1398637,00	104			

The analysis of the main symptoms reported and of the person who asks for a treatment shows that in the case of restrictive food intake and ponderal loss, parents are more prone to seek the first therapeutic treatment, compared to when the reported symptoms are binge-purging symptoms, depressive symptoms, anxious symptoms, ideas of death, lipothymia, menstrual cycle disorders or gastrointestinal symptoms.

TABLE 27: symptoms and the person who asks for the first treatment

	The person who asks for the first help				
symptoms that required treatment	patient	parents	teachers	GP	Other
Restraint	8	14	1	0	2
binge-purging symptoms	9	9	0	1	2
depressive symptoms	8	9	0	0	2
Anxiety symptoms	3	1	0	0	0
Death ideation	1	1	0	0	0
Weight loss	8	43	1	1	3
Lypothymia	1	0	0	0	0
Menstrual cycle alterations	3	0	0	0	0
G.I. symptoms	1	1	0	0	0
Other	1	1	0	0	1
Total	43	79	2	2	10

However, as shown by chi-squared test (Table 19) this correlation between the reported symptoms and those who ask for the first therapeutic approach would not appear to be statistically significant.

TABLE 28: Chi-squared test between reported symptoms and those asking for treatment

	Value	df	p
Pearson's Chi-Squared	32,327	36	0,644
Likelihood ratio (test)	33,362	36	0,595
Linear-Linear Association	0,065	1	0,799
Number of valid cases	136		

A further analysis (tables 22 and 23) was carried out to understand whether, on the other hand, the type of diagnosis can correlate with the person who requires the first approach. Even in this case, despite the following table showing that when the diagnosis is Anorexia Nervosa Restricting the request for first treatment by the parents is relatively more frequent, this relationship was not statistically significant.

TABLE 29: diagnosis-Who require first approach

	Who require the first therapeutic approach					
Diagnosis	Patient	Parents	Teachers	GP	Other	Total
Anorexia Nervosa Restricting	22	50	0	1	8	81
Anorexia Nervosa Binge-Purging	9	13	1	0	1	24
Bulimia Nervosa	8	12	1	1	0	22
Binge Eating Disorder	2	2	0	0	1	5
Unspecified Feeding or Eating Disorder	2	2	0	0	0	4
Total	43	79	2	2	10	136

TABLE 30: X^2 between diagnosis and who requires treatment

	value	df	p
Pearson's Chi-Squared	13,605	20	0,850
Likelihood ratio (test)	15,615	20	0,740
Linear-Linear Association	1,001	1	0,317
Number of valid cases	136		

3.2.3.6 Context of the first therapeutic approach (Table 24)

In our study we also tried to understand whether the first contact of individuals with an eating disorder and a professional occurred in a public context, such as services offered by the national health system, or whether it occurred in a private context; moreover, we tried to understand whether the context of the first therapeutic approach could affect the duration of the untreated disorder. In our sample, 77 subjects (57.5%) were referred to a professional figure within the services offered by the national health system, while 57 subjects (42.5%) to a professional in the private context. Those who choose the public sector presented a DUED of 64.1 months, with a standard deviation of 94.0 months, while those who choose the private services awaited 55.8 months, with a standard deviation of 63.1 months.

TABLE 31: context of first approach and DUED

Context first approach	N.	%	DUED Mean	SD
Public	77	57,46	64,117	93,986
Private	57	42,54	55,807	63,109
Total	134		60,582	82,107

The analysis of variance (ANOVA, TAB. 24) did not show a statistically significant correlation between the context in which the first contact with a professional figure took place and the wait for a treatment.

TABLE 32: ANOVA context of first approach and DUED

	Sum of squares	df	Mean square	F	Sig.
Between groups	2261,772	1	2261,772	0,334	0,564
Within groups	894368,825	132	6775,521		
Total	896630,597	133			

3.2.4 DUED and its correlation with Body Mass Index (BMI).

After the analysis of the factors that might have influenced DUED, we focused on the clinical and psychometric outcomes that might correlate with DUED. Firstly, we try to understand whether the duration of untreated disorder might have affected the body mass index (BMI) at the time of evaluation. From our analysis (Table 26), DUED does not seem to correlate with BMI at the time of the structured interview.

TABLE 33: ANOVA BMI and DUED

Model	Sum of squares	df	Mean square	F	Sig.
Regression	4291,861	1	4291,861	0,639	0,426
Residual	893960,242	133	6721,506		
Total	898252,104	134			

When analyzing the correlation between DUED and BMI in the AN sample, there were no statistical significance as well (p=0,134).

TABLE 34: ANOVA BMI and DUED in the AN sample

Model	Sum of squares	df	Mean square	F	Sig.
Regression	16572,844	1	16572,844	2,278	0,134

Residual	756613,921	104	7275,134
Total	773186,764	105	

3.2.5 DUED and its correlation with psychometric tests

3.2.5.1 DUED and EDE-Q

From the correlation analysis, the duration of the untreated disorder does not seem to correlate with the values reported in the EDE-Q eating symptomatology and psychopathology test, neither regarding the total EDE-Q value, nor to the scale aimed at specifically investigating eating restriction, eating concerns, body shape and weight concerns.

TABLE 35: Pearson correlation EDE-Q and DUED

		Total sample (n=136)		AN sample (N=105)	
		p	Sig.	p	Sig.
EDE-Q	Restrictions	-0.20	0.073	-0.18	0.137
EDE-Q	Concerns about food	-0.06	0.590	-0.05	0.645
EDE-Q	Concerns about body shape	0.05	0.615	0.03	0.757
EDE-Q	Concerns about body weight	-0.01	0.940	-0.11	0.392
EDE-Q	Total	0.11	0.328	0.347	0.347

3.2.5.2 DUED and EDI-2

As for the EDI-2 psychometric test, the only dimension that from our analyses seems to correlate in a statistically significant way with the duration of untreated disorder is the dimension of Bulimia, which investigates the tendency to have binge purging episodes. As regards the other dimensions

investigated (drive for thinness, body dissatisfaction, inadequacy, perfectionism, interpersonal mistrust, interoceptive awareness, fear of maturity, asceticism, impulsiveness and interpersonal insecurity) they do not significantly correlate with DUED.

TABLE 36: EDI-2 and DUED Pearson correlation

		Total sample (n=136)		AN sample (N=105)	
		P	Sig.	P	Sig.
EDI-2	Drive for thinness	0,129	0.231	0.12	0.33
	Bulimia	0.256	**0.016**	0.11	0.389
	Body dissatisfaction	0.097	0.369	0.09	0.422
	Ineffectiveness	0.035	0.744	-0.04	0.69
	Perfectionism	0.063	0.560	-0.08	0.484
	Interpersonal mistrust	0.137	0.203	0.15	0.19
	Interoceptive awareness	0.06	0.581	-0.01	0.93
	Fear of maturity	0.026	0.812	-0.06	0.58
	Ascetism	0.08	0.466	0.01	0.93
	Impulsiveness	0.032	0.769	-0.08	0.48
	Social insecurity	0.189	0.082	0.06	0.62

3.2.5.3 DUED-BDI and anxious symptomatology

The correlation analysis did not show a statistically significant relationship between the duration of untreated disorder and the depressive (BDI) and anxious (STA), state and trait symptomatic dimensions in the total sample and the AN sample.

TABLE 37: Pearson correlation DUED-BDI and STAI

	Total sample (n=136)		AN sample (N=105)	
	p	Sig.	p	Sig.
BDI total	-0.036	0.783	-0.045	0.755
STAI state	-0.029	0.802	-0.019	0.886
STAI trait	0.050	0.663	0.063	0.620

3.3 DISCUSSION

The results obtained from our study on duration of untreated disorder in eating disorders (DUED) have shown a duration comparable to the previous data in the literature with regard to subjects diagnosed with Bulimia Nervosa: the mean resulting from our study is 48.4 months with a standard deviation of 44.0 months, while the meta-analysis of Austin and colleagues reports a weighted mean among the studies of 34.3 months, with results ranging from 23.0 to 58.6 months and a high heterogeneity among the studies. For Anorexia Nervosa, the data obtained from our study show a longer duration of untreated disorder (60.7 months for Anorexia Nervosa Restricting; 64.0 months for Anorexia Nervosa Binge-Purging; 61.5 months the weighted average between the two groups) compared to the data currently present in the literature, which attest to a duration of untreated eating disorder for those who suffer from Anorexia Nervosa ranging from 6.4 months (Lieberman et al., 2019) to 40.0 months (Schlegl et al., 2019) with a weighted mean among the 11 studies that in the literature report DUED in Anorexia Nervosa of 14.6 months (Austin et al., 2019). This result might be influenced by several elements. First, all studies in the literature have been performed on paediatric and adolescent populations (Lieberman et al., 2019; Andrés-Pepiñá et al., 2020; Bühren et al., 2013) or including subjects of paediatric or adolescent age (Gumz et al., 2014; Kwok et al., 2020; Neubauer et al., 2014; Weigel et al., 2014; Flynn et al., 2021; Ng et al., 2018; Schlegl et al., 2019; Beat, 2017),

with mean sample ages ranging from 11.3 years of age (Lieberman et al., 2019) to 24.3 years (Schlegl et al., 2019), while the mean sample age presented in our study is 25.0 years. As already highlighted by the studies of the Beat group in 2017 and by Weigel and colleagues in 2014 and confirmed by our analysis (Table 7) the age of the recruited subjects is a factor that correlates with the duration of the untreated disorder. The analyses carried out later, on the other hand, argue that the age of onset of eating disorder does not correlate with DUED (Table 9) but that a lower age at diagnosis correlates with a lower DUED (Table 13). A second aspect that could impact our results, as already highlighted by the meta-analysis of Austin and colleagues, is the heterogeneity in the definition of DUED, especially with regard to the onset of the disorder. Among the 14 studies in literature that investigate the duration of untreated disorder in eating disorders, 8 do not specify how they operationally define the onset of the disorder (Andrés-Pepiñá et al., 2020; Kwok et al., 2020; Weigel et al., 2014; Nicholls et al., 2011; Ng et al., 2018; Schlegl et al., 2019; Shu et al., 2015; Beat, 2017), 4 studies define the onset of the disorder with having all diagnostic criteria (Gumz et al., 2014; Neubauer et al., 2014; Brown et al., 2018; Flynn et al., 2021) and this would theoretically be the most correct way to understand DUED. However it is notoriously difficult to identify retrospectively a precise time when the criteria were met by carrying out a self-reported survey, while if the evaluation was made by a clinician it is likely that onset occurred much earlier; two studies consider DUED starting from the symptomatological onset (Bühren et al., 2013; Lieberman et al., 2019), in particular the study by Bühren and collegues defines it as starting when the subject start to lose weight. A further element that could contribute to the interpretation of our evidence is given by the regional characteristics of the organization of access to care in Piedmont, where most of the subjects of the study have undertaken the therapeutic pathway. Although in Piedmont there are centres of excellence for the evaluation and treatment of eating disorders such as the CER DCA of the Città Della Salute e Della Scienza of Turin or the Center for Child Neuropsychiatry of the same University Hospital, it is possible that, being Piedmont a large region and partially embedded in the Alpine chain, for some subjects to reach specialized centres can lead to a considerably long trip, such

as to discourage a path of treatment. For this reason, in collaboration with the Mental Health Centres operating in the area, general practitioners, hospitals, rehabilitation residences and provincial therapeutic communities, a regional assistance network for feeding and eating disorders has been developed, which is currently being consolidated and expanded. Another possible flaw in the organization could be the aforementioned separation between specialized care in childhood-adolescent age and adult care, with a possible delay in taking charge when the age of onset falls between the competences of the two services (epidemiologically one of the most frequent moments of onset of nutrition and eating disorders).

Our analysis seems to show that the age of onset of eating symptoms does not influence the subsequent DUED, while the age at diagnosis correlates proportionally. This evidence suggests some considerations: when the age of diagnosis is lower, it is likely that the autonomy and the possibility of self-determination of the subject is more limited and influenced by the parents, who are likely to encourage the subject or impose themselves on them in order to proceed with a therapeutic path.

An element highlighted by this study is the short mean time between the onset of eating symptoms and the first diagnosis of eating disorder (9.4 months; σ=6.5 months), compared to the mean time between the onset and the start of treatment (60.9 months; σ=81.9 months) (TABLE 5). Another study had investigated the time between onset and diagnosis (Schlegl et al., 2019) and instead found it as being longer when compared to the distance between diagnosis and treatment. In the study by Schlegl and colleagues, however, it is considered only the diagnosis made by the general practitioner/paediatrician, while in our study the professionals who for the first time make a diagnosis are different and the analysis shows that psychiatrists were more frequent and to a lesser extent general practitioners, dieticians, psychologists or psychotherapists (Table 21); moreover, there seems to be a trend, although not statistically significant, that would indicate a lower DUED when it comes to diagnosis by child psychiatrists and neuropsychiatrists, or dieticians and medical nutritionists compared to other professional figures. However, this data could be influenced by the context in

which the data collection took place, which is precisely an Eating Disorder Center, with a mainly psychiatric management, and, in particular in the setting of hospitalization for severe conditions (52.2% of the sample). Therefore, according to our analysis, there is a long relative time between the moment in which the diagnosis of ED is made and the actual start of treatment. Similar results were found in studies on the duration of untreated disorder in schizophrenic spectrum disorders, where the most conspicuous component of untreated disorder duration appears to be the one that follows the contact with services (Birchwood et al., 2013). This data is noteworthy because it highlights a possible lack in the treatment pathway. It seems that in our sample we have a relatively short time between onset and diagnosis, but a conspicuous time between diagnosis and first treatment. When studying schizophrenic disorders (Brasso et al 2021, Norman et al 2005) it is known that a longer duration of untreated psychosis shows a negative correlation with outcome; nonetheless in eating disorder DUED may entail a more complex approach. Data can be interpreted considering several elements. Surely, there is a time, necessary for the subject, to accept the diagnosis and convince himself/herself to undertake a treatment. This time could be a very important moment fostering motivation and self-consciousness. On the other hand data may be affected by delays in the health system due to waiting lists and system inefficiencies (Treasure et al., 2021). This last aspect appears to be modifiable with adequate health-care policy measures. As for the pathway taken, we investigated which was the first therapeutic figure to whom the subjects of the study turned to obtain treatment for the symptoms of eating disorders. In most cases the two figures, to whom the subjects initially ask for treatment, were psychiatrists (24.3%) and psychologists (24.3%); to a lesser extent were general practitioners (21.3%), nutritionists (13.2%) and dieticians (8.8%). These evaluations are slightly different from those reported from a recent multicentral study that enrolled 246 subjects diagnosed with eating disorder (Volpe et al., 2019). In this study it was found that the figure most frequently approached by subjects were general practitioners (23% of cases), then in order of frequency were the non-specialist mental health services (18%) and specialized services for eating disorders (17%). The nutritionist was chosen by the 17% of the sample while the psychologist only by the 8%.

From the analysis of our study (Table 15) it does not seem that the first therapeutic figure chosen by subjects had a statistically significant impact on the duration of untreated disorder. However considering that general practitioners and dieticians are those to whom subjects and families often turn as the first figures to frame the problem, it is plausible, as Volpe and colleagues argue, that by strengthening the network for the treatment of eating disorders, involving GP and dieticians, the treatment paths can be more integrated and there can be a shortening for specialist care. Furthermore, our data may be a description of a fragmentated network, in which the single nodes offer a specific treatment, and this is not an evidence-based approach to eating disorders. It would be of help a program of education for professional and general population.

As for the age of onset, there is good trans nosographic consistency, reaching around 18 years both for Anorexia Nervosa (17.0 years for Anorexia Nervosa Binge-Purging; 18.0 years for Anorexia Nervosa Restricting) and for Bulimia Nervosa (18.5 years) and a little later for Binge Eating Disorder (22.8 years) (Table 7.) This data are in line with the epidemiological investigations in literature (Volpe et al., 2016). This trans-nosographic consistency probably partly underlies the fact that some of the psychopathological processes, with biological or psychological matrix, are in common between different nosographic categories and reflects the high crossover between diagnosis (Milos et al., 2005). From this study it seems that only in one third of the cases the diagnosis of eating disorder persists throughout the disorder.

Regarding the reported symptoms (Table 23), there seems to be a statistically significant association (Table 24) between which symptoms were indicated by patients as more significant in leading to the request for health intervention and DUED: in particular, when the reported symptoms were eating restrictions, ideas of death, menstrual cycle disorders, gastrointestinal disorders, DUED was significantly lower than when the reported symptoms were weight loss, binge-purging behaviours, depressive and anxious symptoms and lipothymia. To understand if this relationship could be influenced by which person requires the first approach (Table 27), we have conducted a chi-square test and analysed the correlation between the

symptoms reported and which person have requested the first approach; this analysis was however not statistically significant (Table 28).

The therapeutic context (Table 31 and Table 32), whether was public or private, was not found to be a statistically significant influence on the duration of untreated disorder neither in the total or in the AN sample.

As regards clinical and psychometric assessments, we wanted to investigate whether the duration of untreated disorder can correlate with clinical outcomes (BMI), reported eating symptoms (EDE-Q), the psychopathological aspects of eating disorders (EDI-2) and depressive and anxious symptoms, central for the onset and maintenance of the disorder (Solmi et al., 2018).

As regards BMI, our analysis (Table 33), did not find a statistically significant association between body mass index and duration of untreated disorder. This data is consistent with the two previous studies that investigated this correlation (Bühren et al., 2013; Flynn et al., 2020) and in line with the literature and modern guidelines that recommend to not consider only or mainly BMI to assess the severity of the eating disorder, although, for DSM-5, it remains the only discriminant of severity when it comes to Anorexia Nervosa. A recent study proposed to consider drive for thinness as discriminant for the severity of the eating disorder, suitable not only in evaluating the severity in Anorexia Nervosa but also in Bulimia Nervosa and Binge Eating Disorder, along with frequency of episodes of binge eating and vomiting or just of binge eating (Krug et al., 2021).

As for the possible correlation between the duration of the untreated disorder and the scores of the psychopathological and symptomatic dimensions investigated through a set of tests administered to the participants, the analysis did not show any correlation, with the exception of the Bulimia subscale, aimed at investigating the tendency to have uncontrollable binge eating symptoms. It can be assumed that with greater sample power other correlations with dimensions of psychometric tests could have reached statistical significance, however this dimension would seem at the moment to be the most sensitive and influenced by the duration of untreated disorder.

To summarize, among the clinical and psychopathological severity outcomes investigated in our study, in correlation with the duration of untreated disorder, it does not seem that a longer duration of untreated disorder clearly affects clinical and psychopathological parameters except for the tendency to have binge eating symptoms. As for long-term clinical outcomes, only the study by Andrés-Pepiñá and colleagues in 2019 had shown that subjects who, at a mean distance of 22 years (range 17-29 years) from the initial assessment still met the criteria for a diagnosis of eating disorder, had a tendency to have a higher DUED. However, this data could be interpreted considering that those who have a longer history of disease, regardless of DUED, already have a more severe prognosis with a lower probability of remission, therefore, this correlation should be analysed according to the possible mediation of the duration of disease.

These preliminary results appear in contrast to the current evidences on the importance of untreated disorder in psychiatric disorders (Dell'Osso et al., 2013). The absence of evidences of significance might be due to the limitations of this study. Further analysis would be needed to confirm these preliminary data and, with suitable sample size, it would be desirable to renew analyses for the specific diagnostic categories of eating disorders. The only variable of clinical severity that correlates with DUED is, for example, the tendency to have uncontrolled binge eating episodes, a psychopathological aspect that is represented in a quantitatively different way depending on the diagnostic category and the phase of the diseases. These results, however, tend to be in line with data from literature and open to some reflections. Eating disorders, due to their peculiarities, such as egosyntonicity, which characterizes, at least in the early stages, Anorexia Nervosa, and for the psychopathological complexity, lend themselves to multiple models and interpretations that, due to the natural epistemological fragility of this area, are, to date, scarcely reducible and demonstrable in an exhaustive way (Mizachi et al., 2002; Lester et al., 2007; Hussain et al., 2022).

Finally, the importance of subjective experience in approaching these illnesses has already been highlighted (De Groot et al., 1998; Brogna e Caroppo, 2010). DUED does not represent a clear predictor of symptom

severity. Professionals must approach each individuals avoiding easy simplification. Consequently, is important planning "tailored" treatments on the individual characteristics of the subject (Flatt et al., 2021; Richardson and Paslakis, 2021). Furthermore, it is plausible that the timing of treatment is central for the motivation to treatment (Hoetzel et al., 2013; Sansfaçon et al., 2017; Denison-Day et al., 2018), and long duration of untreated illness may be a necessary time to develop enough motivation to undertake treatment.

To summarize, in this complex type of disorder, it is not obvious that undertaking a course of treatment as soon as possible, although evidence-based, is necessarily the best strategy, at least in terms of cost-effectiveness. On the contrary, understanding which aspects allow a greater motivation for change and a greater susceptibility to the therapeutic path could be one of the research challenges in the future.

3.4 STUDY LIMITATIONS

The major limitation of the study is the small sample size, with underrepresentation of some diagnostic categories, such as Bulimia Nervosa (n=22), Binge Eating Disorder (n=5) and Unspecified Feeding or Eating Disorder (n=4). This did not allow us to carry out the correlation analysis between the pre-treatment variables and the variables of clinical and psychopathological severity with the duration of untreated disorder for the various diagnostic populations. Some clinical and psychopathological characteristics are represented in a different way among the various clinical populations and a category-specific analysis could show correlations not highlighted by our study. An important limitation is given by the data collection tool, that is the structured interview, which does not allow an objective analysis of the path taken but is affected by the subjectivity of the reconstruction of the interviewee. Comparing the data collected from this interview with the data provided by the subject's parents or the subject's most relevant case manager or caregiver could highlight quantitatively different data (for example, the influence of the parents in requesting the first therapeutic approach or the symptoms most represented at the onset of the

eating disorder). Also due to the subjectivity of this interview, we considered some of the data collected to be unreliable, such as the quantification of the refusal of treatment at the beginning of and throughout the pathway, or the time required to accept the pharmacological treatment (if indicated), since there appeared to be amply underestimated and unreliable. Another limitation may be due to the context of the administration of the structured interview, which took place in a psychiatric centre for the evaluation and treatment of eating disorders, which may have influenced the responses of the subjects, perhaps overestimating the representation of psychiatrists at the beginning of the treatment path.

3.5 CONCLUSION

In the last two decades the duration of untreated disorder (DUI), defined as the time between the onset of a specific pathology and the setting of the first appropriate treatment, has been increasingly investigated because, being a modifiable element, it can not only lead to important positive prognostic implications in the clinical course of psychiatric pathology but also in that it could allow a greater understanding of the aspects of neurobiological modification that occur during the progression of the pathology. As regards schizophrenic spectrum disorders, mood disorders, anxiety disorders and obsessive-compulsive disorder, there are numerous studies that investigated the duration of untreated disorder, its components and prognostic implications, highlighting that a greater DUI correlates significantly with a poor response to treatment and with a more severe symptomatology (Altamura et al., 2010; Dell'Osso et al., 2013; Penttilä et al., 2014; Albert et al., 2019). The discourse is more complex and the evidence is scarce and conflicting as regards personality disorders (Paris, 2002).

Studies aimed at investigating the duration of untreated disorder in eating disorders, to date, have revealed high heterogeneity in terms of duration and analyses on the elements related to it are preliminary (Austin et al., 2019). In the literature there are also studies that evaluated two important public health

projects, the English FREED project designed to improve the speed and efficiency of the treatment pathway in the early stages of eating disorders and a German project for the prevention, awareness and implementation of resources in the treatment of eating disorders, which showed contrasting efficacy results in terms of clinical outcomes (Gumz et al., 2018; Flynn et al., 2021).

Therefore, our goal was to investigate the duration of untreated disorder in eating disorders by investigating the components and factors related to it, both in terms of variables that impact on the duration of this period and in terms of clinical and psychopathological outcomes related to it. The initial hypothesis, considering that feeding and eating disorders are characterized by a complex and multifactorial pathogenesis, a peculiar clinical presentation with a tendency to symptoms self-maintenance (Kaye et al., 2009) is that a longer duration of untreated disorder may not significantly correlate with a greater clinical and psychopathological severity.

The analysis of the data related to our study showed that:

- The duration of untreated disorder was on average 60.7 months (ds= 88.3 months) for Anorexia Nervosa Restricting and 64.0 months (ds=79.6 months) for Anorexia Nervosa Binge Purging. These evaluations are higher than those reported in the literature (from 6.4 months to 40 months), but consistent if considered the average age of the selected sample (25.0 years VS from 11.3 years to 24.3 years), the definition of DUED starting from the symptomatologic onset and the high heterogeneity between studies (I^2=99%) (Austin et al., 2019). The mean DUED in Bulimia Nervosa was 48.4 months (ds=44.0 months), consistent with the data in the literature (23.0-58.6 months; I^2=98%).

- The time between symptom onset and first diagnosis of eating disorder is relatively shorter (9.4 months) than the time between diagnosis and the beginning of specialist treatment (51.5 months). Factors such as the motivation to care and the latencies of the health system could explain these data.

- The professionial that most frequently diagnoses an eating disorder was the child psychiatrist or neuropsychiatrist and the parents of the patients are more frequently those who require the first treatment. However, these variables do not correlate statistically significantly with the duration of the untreated eating disorder. Age of onset does not seem to correlate significantly with DUED while age at diagnosis does. Symptoms that have most frequently been reported at the onset of eating disorder include weight loss, eating restrictions, binge-purging symptoms, and depressive symptoms. These symptoms were significantly associated with DUED. Being treated in public or private context was not found to be correlated with DUED.

- The duration of untreated disorder was not significantly correlated either with patients' BMI or with the results of psychometric tests aimed at investigating the severity of symptomatology and eating psychopathology (EDE-Q; EDI-2), and the severity of anxiety (STAI) and depressive symptomatology (BDI), except for the Bulimia subscale of EDI-2. This would indicate that a longer duration of untreated disease affects increasing the tendency to have binge eating symptoms. The poor correlation between the duration of untreated disorder and clinical and psychopathological outcomes, in line with the a priori hypothesis, could reflect the peculiarity of these disorders and require further study on the aspects of motivation to care and susceptibility to change.

Our data may suggest, in line with Johns, Taylor, John, & Tan, 2019 that three main themes have to be strengthen in the pathway of ED treatments: 1) a better use of primary care to engage patients, 2) the involvement of a range of services from primary care through to acute medical services; 3) mutual collaboration between professionals, patients and families.

With such preliminary evidence, we believe it is necessary to further investigate the role of untreated disorder duration in eating disorders, focusing on long-term clinical outcomes and motivational aspects of care that appear to be central for evidence-based treatment of eating disorders.

Bibliography

- Abbate Daga, G., Marzola, E., Amianto, F., & Fassino, S. (2016). A comprehensive review of psychodynamic treatments for eating disorders. *Eating and weight disorders: EWD*, *21*(4), 553–580. https://doi.org/10.1007/s40519-016-0265-9
- Aigner M, Treasure J, Kaye W, et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the pharmacological treatment of eating disorders. World J Biol Psychiatry 2011; 12:400–443
- Albert, U., Barbaro, F., Bramante, S., Rosso, G., De Ronchi, D., & Maina, G. (2019). Duration of untreated illness and response to SRI treatment in Obsessive-Compulsive Disorder. *European psychiatry: the journal of the Association of European Psychiatrists*, *58*, 19–26. https://doi.org/10.1016/j.eurpsy.2019.01.017
- Altamura, A. C., Dell'Osso, B., Mundo, E., & Dell'Osso, L. (2007). Duration of untreated illness in major depressive disorder: a naturalistic study. *International journal of clinical practice*, *61*(10), 1697–1700. https://doi.org/10.1111/j.1742-1241.2007.01450.x
- Altamura AC, Dell'Osso B, D'Urso N, Russo M, Fumagalli S, Mundo E. Duration of Untreated Illness as a Predictor of Treatment Response and Clinical Course in Generalized Anxiety Disorder. CNS Spectrums. Cambridge University Press; 2008;13(5):415–22.
- Altamura, A. C., Buoli, M., Albano, A., & Dell'Osso, B. (2010). Age at onset and latency to treatment (duration of untreated illness) in patients with mood and anxiety disorders: a naturalistic study. *International clinical psychopharmacology*, *25*(3), 172–179. https://doi.org/10.1097/YIC.0b013e3283384c74
- Altamura, A.C., Dell'Osso, B., Berlin, H.A. et al. Duration of untreated illness and suicide in bipolar disorder: a naturalistic study. *Eur Arch Psychiatry Clin Neurosci* 260, 385–391 (2010b). https://doi.org/10.1007/s00406-009-0085-2
- Andrés-Pepiñá, S., Plana, M. T., Flamarique, I., Romero, S., Borràs, R., Julià, L., Gárriz, M., & Castro-Fornieles, J. (2020). Long-term outcome and psychiatric comorbidity of adolescent-onset anorexia nervosa. *Clinical child psychology and psychiatry*, *25*(1), 33–44. https://doi.org/10.1177/1359104519827629

- Association of the Scientific Medical Societies in Germany [Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften, AWMF]. S3-guideline for the assessment and therapy of eating disorders [S3 Leitlinie Diagnostik und Therapie von Esssto¨rungen]. 2010; Available at: www.awmf.org/leitlinien/detail/ll/051-026.html.
- Austin, A., Flynn, M., Richards, K., Hodsoll, J., Duarte, T. A., Robinson, P., Kelly, J., & Schmidt, U. (2021). Duration of untreated eating disorder and relationship to outcomes: A systematic review of the literature. *European eating disorders review: the journal of the Eating Disorders Association*, *29*(3), 329–345. https://doi.org/10.1002/erv.2745
- Beat. (2017). Delaying for years, denied for months. Norwich, UK: B. Retrieved from https://www.beateatingdisorders.org.uk/uploa /documents/2017/11/delaying-for-years-denied-for-months.pdf
- Beintner, I., Jacobi, C., & Schmidt, U. H. (2014). Participation and outcome in manualized self-help for bulimia nervosa and binge eating disorder - a systematic review and metaregression analysis. *Clinical psychology review*, *34*(2), 158–176. https://doi.org/10.1016/j.cpr.2014.01.003
- Birchwood, M., Connor, C., Lester, H., Patterson, P., Freemantle, N., Marshall, M., Fowler, D., Lewis, S., Jones, P., Amos, T., Everard, L., & Singh, S. P. (2013). Reducing duration of untreated psychosis: care pathways to early intervention in psychosis services. *The British journal of psychiatry : the journal of mental science*, 203(1), 58–64. https://doi.org/10.1192/bjp.bp.112.125500
- Blessitt, E., Voulgari, S., & Eisler, I. (2015). Family therapy for adolescent anorexia nervosa. *Current opinion in psychiatry*, *28*(6), 455–460. https://doi.org/10.1097/YCO.0000000000000193
- Boonstra N, Klaassen R, Sytema S, et al. Duration of untreated psychosis and negative symptoms--a systematic review and meta-analysis of individual patient data. *Schizophr Res*. 2012;142(1-3):12-19. doi:10.1016/j.schres. 2012.08.017
- Bou Khalil R. (2021). Targeting all psychopathological dimensions in the treatment of anorexia nervosa. *L'Encephale*, *47*(1), 79–81. https://doi.org/10.1016/j.encep.2020.06.002
- Brasso C, Giordano B, Badino C, Bellino S, Bozzatello P, Montemagni C, Rocca P. Primary Psychosis: Risk and Protective Factors and Early Detection of the Onset. *Diagnostics* (Basel). 2021 Nov 19;11(11):2146. doi: 10.3390/diagnostics11112146. PMID: 34829493; PMCID: PMC8622963.
- Brogna, P., & Caroppo, E. (2010). The body as a simulacrum of identity: the subjective experience in the eating disorders. *Annali dell'Istituto superiore di sanita*, *46*(4), 427–435. https://doi.org/10.4415/ANN_10_04_11
- Brown, A., McClelland, J., Boysen, E., Mountford, V., Glennon, D., & Schmidt, U. (2018). The FREED Project (first episode and rapid early intervention in eating disorders): service model, feasibility and acceptability. *Early intervention in psychiatry*, *12*(2), 250–257. https://doi.org/10.1111/eip.12382
- Brownell, Kelly D., and B. Timothy Walsh. 2017. *Eating Disorders and Obesity: A Comprehensive Handbook*
- Brownley, K. A., Berkman, N. D., Peat, C. M., Lohr, K. N., Cullen, K. E., Bann, C. M., & Bulik, C. M. (2016). Binge-Eating Disorder in Adults: A Systematic Review and Meta-analysis. *Annals of internal medicine*, *165*(6), 409–420. https://doi.org/10.7326/M15-2455
- Buoli M, Cesana BM, Fagiolini A, Albert U, Maina G, de Bartolomeis A, Pompili M, Bondi E, Steardo L Jr, Amore M, Bellomo A, Bertolino A, Di Nicola M, Di Sciascio G, Fiorillo A, Rocca P, Sacchetti E, Sani G, Siracusano A, Di Lorenzo G, Tortorella A, Altamura AC, Dell'Osso B; ISBD Italian Chapter Epidemiologic Group. Which factors delay treatment in bipolar disorder? A

nationwide study focussed on duration of untreated illness. *Early Interv Psychiatry*. 2021 Oct;15(5):1136-1145. doi: 10.1111/eip.13051. Epub 2020 Oct 15. PMID: 33058435.

- Bühren, K., von Ribbeck, L., Schwarte, R., Egberts, K., Pfeiffer, E., Fleischhaker, C., Wewetzer, C., Kennes, L. N., Dempfle, A., & Herpertz-Dahlmann, B. (2013). Body mass index in adolescent anorexia nervosa patients in relation to age, time point and site of admission. *European child & adolescent psychiatry*, *22*(7), 395–400. https://doi.org/10.1007/s00787-013-0376-z
- Carter, F. A., Jordan, J., McIntosh, V. V., Luty, S. E., McKenzie, J. M., Frampton, C. M., Bulik, C. M., & Joyce, P. R. (2011). The long-term efficacy of three psychotherapies for anorexia nervosa: a randomized, controlled trial. *The International journal of eating disorders*, *44*(7), 647–654. https://doi.org/10.1002/eat.20879
- Cascio, M.T., Cella, M., Preti, A., Meneghelli, A. and Cocchi, A. (2012), Gender and duration of untreated psychosis: a systematic review and meta-analysis. *Early Intervention in Psychiatry*, 6: 115-127. https://doi.org/10.1111/j.1751-7893.2012.00351.x
- Clement S, Schauman O, Graham T, Maggioni F, Evans-Lacko S, Bezborodovs N, et al. What is the impact of mental health-related stigma on help-seeking? A systematic review of quantitative and qualitative studies. *Psychological Medicine. Cambridge University Press*; 2015;45(1):11–27.
- Cooper, M., & Kelland, H. (2015). Medication and psychotherapy in eating disorders: is there a gap between research and practice?. *Journal of eating disorders*, *3*, 45. https://doi.org/10.1186/s40337-015-0080-0
- Cusack, Claire & Ralph-Nearman, Christina & Nicholas, Julia & Levinson, Cheri. (2022). New directions in research on somatic concerns in individuals with eating disorders. New Ideas in Psychology. 66. 100937. 10.1016/j.newideapsych.2022.100937.
- Danish Health Authority. National clinical guideline for the treatment of anorexia nervosa. Quick guide. 2016; Available at: www.sst.dk/da/udgivelser/2016/———————————————————/media/36D31B378C164922BCD96573749AA206.ashx.
- Danish Health Authority. National clinical guideline for the treatment of moderate and severe bulimia. Quick guide. 2016; Available at: www.sst.dk/ en/publications/2015/national-clinical-guideline-for-the-treatment-of-moderateand-severe-bulimia.
- Davis, C., & Claridge, G. (1998). The eating disorders as addiction: a psychobiological perspective. *Addictive behaviors*, *23*(4), 463–475. https://doi.org/10.1016/s0306-4603(98)00009-4
- De Groot J, Rodin G. Coming Alive: The Psychotherapeutic Treatment of Patients with Eating Disorders. *The Canadian Journal of Psychiatry*. 1998;43(4):359-366. doi:10.1177/070674379804300403
- Dell'Osso, B., Camuri, G., Benatti, B., Buoli, M., & Altamura, A. C. (2013). Differences in latency to first pharmacological treatment (duration of untreated illness) in anxiety disorders: a study on patients with panic disorder, generalized anxiety disorder and obsessive-compulsive disorder. *Early intervention in psychiatry*, *7*(4), 374–380. https://doi.org/10.1111/eip.12016
- Dell'Osso, B., Glick, I. D., Baldwin, D. S., & Altamura, A. C. (2013). Can long-term outcomes be improved by shortening the duration of untreated illness in psychiatric disorders? A conceptual framework. *Psychopathology*, *46*(1), 14–21. https://doi.org/10.1159/000338608
- Denison-Day, J., Appleton, K. M., Newell, C., & Muir, S. (2018). Improving motivation to change amongst individuals with eating disorders: A systematic review. *The International journal of eating disorders*, *51*(9), 1033–1050. https://doi.org/10.1002/eat.22945
- Drake, R. J., Husain, N., Marshall, M., Lewis, S. W., Tomenson, B., Chaudhry, I. B., Everard, L., Singh, S., Freemantle, N., Fowler, D., Jones, P. B., Amos, T., Sharma, V., Green, C. D., Fisher, H., Murray, R. M., Wykes, T., Buchan, I., & Birchwood, M. (2020). Effect of delaying treatment of

first-episode psychosis on symptoms and social outcomes: a longitudinal analysis and modelling study. *The lancet. Psychiatry*, *7*(7), 602–610. https://doi.org/10.1016/S2215-0366(20)30147-4

- Dutch Foundation for Quality Development in Mental Healthcare. Practice guideline for the treatment of eating disorders [Zorgstandaard Eetstoornissen]. Utrecht: Netwerk Kwaliteitsontwikkeling GGz; 2017
- Engel, M. M., & Keizer, A. (2017). Body representation disturbances in visual perception and affordance perception persist in eating disorder patients after completing treatment. *Scientific reports*, *7*(1), 16184. https://doi.org/10.1038/s41598-017-16362-w
- Fairburn, C. G. (2008). *Cognitive behavior therapy and eating disorders.* Guilford Press.
- Farooq S, Large M, Nielssen O, Waheed W. The relationship between the duration of untreated psychosis and outcome in low-and-middle income countries: a systematic review and meta analysis. *Schizophr Res*. 2009;109(1-3):15-23. doi:10.1016/j.schres.2009.01.008
- Fernández-Aranda, F., Treasure, J., Paslakis, G., Agüera, Z., Giménez, M., Granero, R., Sánchez, I., Serrano-Troncoso, E., Gorwood, P., Herpertz-Dahlmann, B., Bonin, E. M., Monteleone, P., & Jiménez-Murcia, S. (2021). The impact of duration of illness on treatment nonresponse and drop-out: Exploring the relevance of enduring eating disorder concept. *European eating disorders review : the journal of the Eating Disorders Association*, *29*(3), 499–513. https://doi.org/10.1002/erv.2822
- Flatt, RE, Thornton, LM, Fitzsimmons-Craft, EE, et al. Comparing eating disorder characteristics and treatment in self-identified competitive athletes and non-athletes from the National Eating Disorders Association online screening tool. *Int J Eat Disord*. 2021; 54: 365– 375. https://doi.org/10.1002/eat.23415
- Flynn, M., Austin, A., Lang, K., Allen, K., Bassi, R., Brady, G., Brown, A., Connan, F., Franklin-Smith, M., Glennon, D., Grant, N., Jones, W.R., Kali, K., Koskina, A., Mahony, K., Mountford, V., Nunes, N., Schelhase, M., Serpell, L. and Schmidt, U. (2021), Assessing the impact of First Episode Rapid Early Intervention for Eating Disorders on duration of untreated eating disorder: A multi-centre quasi-experimental study. Eur Eat Disorders Rev, 29: 458-471. https://doi.org/10.1002/erv.2797
- Forman, M., & Davis, W. N. (2005). Characteristics of middle-aged women in inpatient treatment for eating disorders. *Eating disorders*, *13*(3), 231–243. https://doi.org/10.1080/10640260590932841
- Forsberg S, Lock J. Family-based treatment of child and adolescent eating disorders. Child Adolesc Psychiatr Clin N Am 2015; 24:617–629.
- Fukutomi, A., Austin, A., McClelland, J., Brown, A., Glennon, D., Mountford, V., Grant, N., Allen, K., & Schmidt, U. (2020). First episode rapid early intervention for eating disorders: A two-year follow-up. *Early intervention in psychiatry*, *14*(1), 137–141. https://doi.org/10.1111/eip.12881
- Furlanetto, L. M., Mendlowicz, M. V., & Romildo Bueno, J. (2005). The validity of the Beck Depression Inventory-Short Form as a screening and diagnostic instrument for moderate and severe depression in medical inpatients. *Journal of affective disorders*, *86*(1), 87–91. https://doi.org/10.1016/j.jad.2004.12.011
- Ghio L, Gotelli S, Marcenaro M, Amore M, Natta W. Duration of untreated illness and outcomes in unipolar depression: a systematic review and meta-analysis. *J Affect Disord.* 2014;152-154:45-51. doi:10.1016/j.jad.2013.10.002
- Golay, A., Laurent-Jaccard, A., Habicht, F., Gachoud, J. P., Chabloz, M., Kammer, A., & Schutz, Y. (2005). Effect of orlistat in obese patients with binge eating disorder. *Obesity research*, *13*(10), 1701–1708. https://doi.org/10.1038/oby.2005.208

- Gregertsen, E. C., Mandy, W., & Serpell, L. (2017). The Egosyntonic Nature of Anorexia: An Impediment to Recovery in Anorexia Nervosa Treatment. *Frontiers in psychology*, *8*, 2273. https://doi.org/10.3389/fpsyg.2017.02273
- Grilo, C. M., Masheb, R. M., & Salant, S. L. (2005). Cognitive behavioral therapy guided self-help and orlistat for the treatment of binge eating disorder: a randomized, double-blind, placebo-controlled trial. *Biological psychiatry*, *57*(10), 1193–1201. https://doi.org/10.1016/j.biopsych.2005.03.001
- Grilo, C. M., Reas, D. L., & Mitchell, J. E. (2016). Combining Pharmacological and Psychological Treatments for Binge Eating Disorder: Current Status, Limitations, and Future Directions. *Current psychiatry reports*, *18*(6), 55. https://doi.org/10.1007/s11920-016-0696-z
- Grilo C. M. (2017). Psychological and Behavioral Treatments for Binge-Eating Disorder. *The Journal of clinical psychiatry*, *78 Suppl 1*, 20–24. https://doi.org/10.4088/JCP.sh16003su1c.04
- Gumz, A., Uhlenbusch, N., Weigel, A. *et al.* Decreasing the duration of untreated illness for individuals with anorexia nervosa: study protocol of the evaluation of a systemic public health intervention at community level. *BMC Psychiatry* **14,** 300 (2014). https://doi.org/10.1186/s12888-014-0300-1
- Gumz, A., Weigel, A., Wegscheider, K., Romer, G., & Löwe, B. (2018). The psychenet public health intervention for anorexia nervosa: a pre-post-evaluation study in a female patient sample. *Primary health care research & development*, *19*(1), 42–52. https://doi.org/10.1017/S1463423617000524
- Haute Autorite´ de Sante´. Clinical practice guidelines: anorexia nervosa: management. 2010; Available at: https://www.has-sante.fr/portail/upload/ docs/application/pdf/2013-05/anorexia_nervosa_guidelines_2013-05-15_ 16-34-42_589.pdf.
- Hay P. (2013). A systematic review of evidence for psychological treatments in eating disorders: 2005-2012. *The International journal of eating disorders*, *46*(5), 462–469. https://doi.org/10.1002/eat.22103
- Hay, P., Chinn, D., Forbes, D., Madden, S., Newton, R., Sugenor, L., Touyz, S., Ward, W., & Royal Australian and New Zealand College of Psychiatrists (2014). Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the treatment of eating disorders. *The Australian and New Zealand journal of psychiatry*, *48*(11), 977–1008. https://doi.org/10.1177/0004867414555814
- Hay, P. J., Claudino, A. M., Touyz, S., & Abd Elbaky, G. (2015). Individual psychological therapy in the outpatient treatment of adults with anorexia nervosa. *The Cochrane database of systematic reviews*, *2015*(7), CD003909. https://doi.org/10.1002/14651858.CD003909.pub2
- Herpertz-Dahlmann, B., van Elburg, A., Castro-Fornieles, J., & Schmidt, U. (2015). ESCAP Expert Paper: New developments in the diagnosis and treatment of adolescent anorexia nervosa--a European perspective. *European child & adolescent psychiatry*, *24*(10), 1153–1167. https://doi.org/10.1007/s00787-015-0748-7
- Herpertz S., Herpertz-Dahlmann B., Fichter M., Tuschen-Caffier B., Zeek A. S3-Leitlinie Diagnostik und Behandlung der Essstörungen (Online); Available online: https://www.awmf.org/leitlinien/detail/ll/051-026.html
- Herzog A, Shedden-Mora MC, Jordan P, Löwe B. Duration of untreated illness in patients with somatoform disorders. *J Psychosom Res*. 2018;107:1-6. doi:10.1016/j.jpsychores.2018.01.011
- Hilbert, A., Hoek, H. W., & Schmidt, R. (2017). Evidence-based clinical guidelines for eating disorders: international comparison. *Current opinion in psychiatry*, *30*(6), 423–437. https://doi.org/10.1097/YCO.0000000000000360

- Hoetzel, K., von Brachel, R., Schlossmacher, L., & Vocks, S. (2013). Assessing motivation to change in eating disorders: a systematic review. *Journal of eating disorders*, *1*, 38. https://doi.org/10.1186/2050-2974-1-38
- Jarry, J. L., & Vaccarino, F. J. (1996). Eating disorder and obsessive-compulsive disorder: neurochemical and phenomenological commonalities. *Journal of psychiatry & neuroscience : JPN*, *21*(1), 36–48.
- Kass, A. E., Kolko, R. P., & Wilfley, D. E. (2013). Psychological treatments for eating disorders. *Current opinion in psychiatry*, *26*(6), 549–555. https://doi.org/10.1097/YCO.0b013e328365a30e
- Kaye, W. H., Fudge, J. L., & Paulus, M. (2009). New insights into symptoms and neurocircuit function of anorexia nervosa. *Nature reviews. Neuroscience*, *10*(8), 573–584. https://doi.org/10.1038/nrn2682
- Kazdin, A. E., Fitzsimmons-Craft, E. E., & Wilfley, D. E. (2017). Addressing critical gaps in the treatment of eating disorders. *The International journal of eating disorders*, *50*(3), 170–189. https://doi.org/10.1002/eat.22670
- Kessler, R. C., Berglund, P. A., Chiu, W. T., Deitz, A. C., Hudson, J. I., Shahly, V., Aguilar-Gaxiola, S., Alonso, J., Angermeyer, M. C., Benjet, C., Bruffaerts, R., de Girolamo, G., de Graaf, R., Maria Haro, J., Kovess-Masfety, V., O'Neill, S., Posada-Villa, J., Sasu, C., Scott, K., Viana, M. C., … Xavier, M. (2013). The prevalence and correlates of binge eating disorder in the World Health Organization World Mental Health Surveys. *Biological psychiatry*, *73*(9), 904–914. https://doi.org/10.1016/j.biopsych.2012.11.020
- Konstantakopoulos, G., Tchanturia, K., Surguladze, S. A., & David, A. S. (2011). Insight in eating disorders: clinical and cognitive correlates. *Psychological medicine*, *41*(9), 1951–1961. https://doi.org/10.1017/S0033291710002539
- Kosmerly, S., Waller, G., & Lafrance Robinson, A. (2015). Clinician adherence to guidelines in the delivery of family-based therapy for eating disorders. *The International journal of eating disorders*, *48*(2), 223–229. https://doi.org/10.1002/eat.22276
- Krug, I., Binh Dang, A., Granero, R., Agüera, Z., Sánchez, I., Riesco, N., Jimenez-Murcia, S., Menchón, J. M., & Fernandez-Aranda, F. (2021). Drive for thinness provides an alternative, more meaningful, severity indicator than the DSM-5 severity indices for eating disorders. *European eating disorders review: the journal of the Eating Disorders Association*, *29*(3), 482–498. https://doi.org/10.1002/erv.2776
- Kwok, C., Kwok, V., Lee, H. Y., & Tan, S. M. (2020). Clinical and socio-demographic features in childhood vs adolescent-onset anorexia nervosa in an Asian population. *Eating and weight disorders: EWD*, *25*(3), 821–826. https://doi.org/10.1007/s40519-019-00694-9
- Le Grange, D., Lock, J., Agras, W. S., Bryson, S. W., & Jo, B. (2015). Randomized Clinical Trial of Family-Based Treatment and Cognitive-Behavioral Therapy for Adolescent Bulimia Nervosa. *Journal of the American Academy of Child and Adolescent Psychiatry*, *54*(11), 886–94.e2. https://doi.org/10.1016/j.jaac.2015.08.008
- Leichsenring, F., Luyten, P., Hilsenroth, M. J., Abbass, A., Barber, J. P., Keefe, J. R., Leweke, F., Rabung, S., & Steinert, C. (2015). Psychodynamic therapy meets evidence-based medicine: a systematic review using updated criteria. *The lancet. Psychiatry*, *2*(7), 648–660. https://doi.org/10.1016/S2215-0366(15)00155-8
- Lester, R.J. (2007), Critical Therapeutics: Cultural Politics and Clinical Reality in Two Eating Disorder Treatment Centers. Medical Anthropology Quarterly, 21: 369-387. https://doi.org/10.1525/maq.2007.21.4.369

- Lieberman, M., Houser, M. E., Voyer, A. P., Grady, S., & Katzman, D. K. (2019). Children with avoidant/restrictive food intake disorder and anorexia nervosa in a tertiary care pediatric eating disorder program: A comparative study. *The International journal of eating disorders*, *52*(3), 239–245. https://doi.org/10.1002/eat.23027
- Lilenfeld, L. R., Wonderlich, S., Riso, L. P., Crosby, R., & Mitchell, J. (2006). Eating disorders and personality: a methodological and empirical review. *Clinical psychology review*, *26*(3), 299–320. https://doi.org/10.1016/j.cpr.2005.10.003
- Lock J. (2015). An Update on Evidence-Based Psychosocial Treatments for Eating Disorders in Children and Adolescents. *Journal of clinical child and adolescent psychology : the official journal for the Society of Clinical Child and Adolescent Psychology, American Psychological Association, Division 53*, *44*(5), 707–721. https://doi.org/10.1080/15374416.2014.971458
- Lynch, F. L., Striegel-Moore, R. H., Dickerson, J. F., Perrin, N., Debar, L., Wilson, G. T., & Kraemer, H. C. (2010). Cost-effectiveness of guided self-help treatment for recurrent binge eating. *Journal of consulting and clinical psychology*, *78*(3), 322–333. https://doi.org/10.1037/a0018982
- Maguire, S., Surgenor, L. J., Le Grange, D., Lacey, H., Crosby, R. D., Engel, S. G., Fromholtz, K. M., Bamford, B., & Touyz, S. (2017). Examining a staging model for anorexia nervosa: empirical exploration of a four-stage model of severity. *Journal of eating disorders*, *5*, 41. https://doi.org/10.1186/s40337-017-0155-1
- McElroy, S. L., Guerdjikova, A. I., Mori, N., & Keck, P. E., Jr (2015). Psychopharmacologic treatment of eating disorders: emerging findings. *Current psychiatry reports*, *17*(5), 35. https://doi.org/10.1007/s11920-015-0573-1
- McElroy, S. L., Guerdjikova, A. I., Mori, N., Munoz, M. R., & Keck, P. E. (2015). Overview of the treatment of binge eating disorder. *CNS spectrums*, *20*(6), 546–556. https://doi.org/10.1017/S1092852915000759
- McIntosh, V. V., Bulik, C. M., McKenzie, J. M., Luty, S. E., & Jordan, J. (2000). Interpersonal psychotherapy for anorexia nervosa. *The International journal of eating disorders*, *27*(2), 125–139. https://doi.org/10.1002/(sici)1098-108x(200003)27:2<125::help-eat1>3.0.co;2-4
- McIntosh VV, Jordan J, Carter FA, et al. Three psychotherapies for anorexia nervosa: a randomized, controlled trial. Am J Psychiatry 2005; 162:741–747
- McIntosh, V. V., Jordan, J., Luty, S. E., Carter, F. A., McKenzie, J. M., Bulik, C. M., & Joyce, P. R. (2006). Specialist supportive clinical management for anorexia nervosa. *The International journal of eating disorders*, *39*(8), 625–632. https://doi.org/10.1002/eat.20297
- Menculini, G., Verdolini, N., Gobbicchi, C., Del Bello, V., Serra, R., Brustenghi, F., Armanni, M., Spollon, G., Cirimbilli, F., Brufani, F., Pierotti, V., Di Buò, A., De Giorgi, F., Sciarma, T., Moretti, P., Vieta, E., & Tortorella, A. (2022). Clinical and psychopathological correlates of duration of untreated illness (DUI) in affective spectrum disorders. *European neuropsychopharmacology: the journal of the European College of Neuropsychopharmacology*, *61*, 60–70. https://doi.org/10.1016/j.euroneuro.2022.06.00
- Micali, N., Hagberg, K. W., Petersen, I., & Treasure, J. L. (2013). The incidence of eating disorders in the UK in 2000-2009: findings from the General Practice Research Database. *BMJ open*, *3*(5), e002646. https://doi.org/10.1136/bmjopen-2013-002646
- Micali, N., Martini, M. G., Thomas, J. J., Eddy, K. T., Kothari, R., Russell, E., Bulik, C. M., & Treasure, J. (2017). Lifetime and 12-month prevalence of eating disorders amongst women in mid-life: a population-based study of diagnoses and risk factors. *BMC medicine*, *15*(1), 12. https://doi.org/10.1186/s12916-016-0766-4

- Milos, G., Spindler, A., Schnyder, U., & Fairburn, C. G. (2005). Instability of eating disorder diagnoses: prospective study. *The British journal of psychiatry : the journal of mental science*, *187*, 573–578. https://doi.org/10.1192/bjp.187.6.573
- Miniati, M., Mauri, M., Ciberti, A., Mariani, M. G., Marazziti, D., & Dell'Osso, L. (2016). Psychopharmacological options for adult patients with anorexia nervosa. *CNS spectrums*, *21*(2), 134–142. https://doi.org/10.1017/S1092852914000790
- Mitchell, J. E., Roerig, J., & Steffen, K. (2013). Biological therapies for eating disorders. *The International journal of eating disorders*, *46*(5), 470–477. https://doi.org/10.1002/eat.22104
- Mizrachi, N. (2002), Epistemology and legitimacy in the production of anorexia nervosa in the journal *Psychosomatic Medicine* 1939–1979. Sociology of Health & Illness, 24: 462-490. https://doi.org/10.1111/1467-9566.00304
- Montalescot G, Cayla G, Collet J, et al. Immediate vs Delayed Intervention for Acute Coronary Syndromes: A Randomized Clinical Trial. *JAMA*. 2009;302(9):947–954. doi:10.1001/jama.2009.1267
- National Institute for Health and Care Excellence (2017). Eating disorders: Recognition and treatment. NICE Guideline NG 69. Retrieved from https://www.nice.org.uk/guidance/ng69
- Neubauer, K., Weigel, A., Daubmann, A., Wendt, H., Rossi, M., Löwe, B., & Gumz, A. (2014). Paths to first treatment and duration of untreated illness in anorexia nervosa: are there differences according to age of onset?. *European eating disorders review : the journal of the Eating Disorders Association*, *22*(4), 292–298. https://doi.org/10.1002/erv.2300
- Ng, K. W., Kuek, A., & Lee, H. Y. (2018). Eating psychopathology and psychosocial impairment in patients treated at a Singapore eating disorders treatment programme. *Singapore medical journal*, *59*(1), 33–38. https://doi.org/10.11622/smedj.2017042
- Nicholls, D. E., Lynn, R., & Viner, R. M. (2011). Childhood eating disorders: British national surveillance study. *The British journal of psychiatry : the journal of mental science*, *198*(4), 295–301. https://doi.org/10.1192/bjp.bp.110.081356
- O'Hara, Caitlin & Schmidt, Ulrike & Campbell, Iain. (2015). A reward-centred model of anorexia nervosa: A focussed narrative review of the neurological and psychophysiological literature. Neuroscience and biobehavioral reviews. 52. 10.1016/j.neubiorev.2015.02.012.
- Norman RM, Lewis SW, Marshall M. Duration of untreated psychosis and its relationship to clinical outcome. Br J Psychiatry Suppl. 2005 Aug;48:s19-23. doi: 10.1192/bjp.187.48.s19. PMID: 16055802.
- Paris J. (2002). Implications of long-term outcome research for the management of patients with borderline personality disorder. *Harvard review of psychiatry*, 10(6), 315–323. https://doi.org/10.1080/10673220216229
- Paris J. (2003). Personality disorders over time: precursors, course and outcome. *Journal of personality disorders*, 17(6), 479–488. https://doi.org/10.1521/pedi.17.6.479.25360
- Penttilä M, Jääskeläinen E, Hirvonen N, Isohanni M, Miettunen J. Duration of untreated psychosis as predictor of long-term outcome in schizophrenia: systematic review and meta-analysis. *British Journal of Psychiatry*. Cambridge University Press; 2014;205(2):88–94.
- Perris, F., Sampogna, G., Giallonardo, V., Agnese, S., Palummo, C., Luciano, M., Fabrazzo, M., Fiorillo, A., & Catapano, F. (2021). Duration of untreated illness predicts 3-year outcome in patients with obsessive-compulsive disorder: A real-world, naturalistic, follow-up study. *Psychiatry research*, *299*, 113872. https://doi.org/10.1016/j.psychres.2021.113872
- Perry JC, Banon E, Ianni F. Effectiveness of psychotherapy for personality disorders. *Am J Psychiatry*. 1999;156(9):1312-1321. doi:10.1176/ajp.156.9.1312

- Poulsen, S., Lunn, S., Daniel, S. I., Folke, S., Mathiesen, B. B., Katznelson, H., & Fairburn, C. G. (2014). A randomized controlled trial of psychoanalytic psychotherapy or cognitive-behavioral therapy for bulimia nervosa. *The American journal of psychiatry*, *171*(1), 109–116. https://doi.org/10.1176/appi.ajp.2013.12121511
- Poyraz CA, Turan Ş, Sağlam NG, Batun GÇ, Yassa A, Duran A. Factors associated with the duration of untreated illness among patients with obsessive compulsive disorder. *Compr Psychiatry*. 2015;58:88-93. doi:10.1016/j.comppsych.2014.12.019
- Richardson, C., & Paslakis, G. (2021). Men's experiences of eating disorder treatment: A qualitative systematic review of men-only studies. *Journal of psychiatric and mental health nursing*, *28*(2), 237–250. https://doi.org/10.1111/jpm.12670
- Robinson, L., Aldridge, V., Clark, E. M., Misra, M., & Micali, N. (2017). Pharmacological treatment options for low Bone Mineral Density and secondary osteoporosis in Anorexia Nervosa: A systematic review of the literature. *Journal of psychosomatic research*, *98*, 87–97. https://doi.org/10.1016/j.jpsychores.2017.05.011
- Sansfaçon, J., Steiger, H., Gauvin, L., Fletcher, É., & Israël, M. (2017). Does level of motivation for change impact post-treatment outcomes in the eating disorders? Protocol for a systematic review with quantitative analysis. *Journal of eating disorders*, *5*, 17. https://doi.org/10.1186/s40337-017-0147-1
- Saravanan B, Jacob KS, Johnson S, Prince M, Bhugra D, David AS. Assessing insight in schizophrenia: East meets West. *British Journal of Psychiatry*. Cambridge University Press; 2007;190(3):243–7.
- Schlegl, S., Hupe, K., Hessler, J. B., Diedrich, A., Huber, T., Rauh, E., Aita, S., Gärtner, T., & Voderholzer, U. (2019). Wege in die Versorgung und Behandlungslatenzen bei stationären Patienten mit Anorexia und Bulimia nervosa [Pathways to Care and Duration of Untreated Illness of Inpatients with Anorexia and Bulimia nervosa]. *Psychiatrische Praxis*, *46*(6), 342–348. https://doi.org/10.1055/a-0922-5651
- Schmidt, U., Wade, T. D., & Treasure, J. (2014). The Maudsley Model of Anorexia Nervosa Treatment for Adults (MANTRA): Development, Key Features, and Preliminary Evidence. *Journal of cognitive psychotherapy*, *28*(1), 48–71. https://doi.org/10.1891/0889-8391.28.1.48
- Schneider, M.R., DelBello, M.P., McNamara, R.K., Strakowski, S.M. and Adler, C.M. (2012), Neuroprogression in bipolar disorder. *Bipolar Disorders*, 14: 356-374. https://doi.org/10.1111/j.1399-5618.2012.01024.x
- Shakeel Khan M. K. (2021). Sibutramine and its cardiovascular effects: A deadly combination. *JPMA. The Journal of the Pakistan Medical Association*, *71*(12), 2850. https://doi.org/10.47391/JPMA.4004
- Shu, C.Y., Limburg, K., Harris, C. *et al.* Clinical presentation of eating disorders in young males at a tertiary setting. *J Eat Disord* **3,** 39 (2015). https://doi.org/10.1186/s40337-015-0075-x
- Smink, F. R., van Hoeken, D., & Hoek, H. W. (2012). Epidemiology of eating disorders: incidence, prevalence and mortality rates. *Current psychiatry reports*, *14*(4), 406–414. https://doi.org/10.1007/s11920-012-0282-y
- Smith, T.O., Davies, L. & Hing, C.B. Early versus delayed surgery for anterior cruciate ligament reconstruction: a systematic review and meta-analysis. *Knee Surg Sports Traumatol Arthrosc* 18, 304–311 (2010). https://doi.org/10.1007/s00167-009-0965-z
- Solmi, M., Collantoni, E., Meneguzzo, P., Degortes, D., Tenconi, E., & Favaro, A. (2018). Network analysis of specific psychopathology and psychiatric symptoms in patients with eating

disorders. *The International journal of eating disorders*, *51*(7), 680–692. https://doi.org/10.1002/eat.22884

- Souaiby, L, Gauthier, C, Kazes, M, et al. Individual factors influencing the duration of untreated psychosis. *Early Intervention in Psychiatry*. 2019; 13: 798– 804. https://doi.org/10.1111/eip.12562
- Steinhausen H. C. (2002). The outcome of anorexia nervosa in the 20th century. *The American journal of psychiatry*, *159*(8), 1284–1293. https://doi.org/10.1176/appi.ajp.159.8.1284
- Steinglass, J. E., Eisen, J. L., Attia, E., Mighter, L., & Walsh, B. T. (2007). Is anorexia nervosa a delusional disorder? An assessment of eating beliefs in anorexia nervosa. *Journal of psychiatric practice*, *13*(2), 65–71. https://doi.org/10.1097/01.pra.0000265762.79753.88
- Steinglass, J.E., Walsh, B.T. Neurobiological model of the persistence of anorexia nervosa. *J Eat Disord* **4,** 19 (2016). https://doi.org/10.1186/s40337-016-0106-2
- Treasure, J., Stein, D., & Maguire, S. (2015). Has the time come for a staging model to map the course of eating disorders from high risk to severe enduring illness? An examination of the evidence. *Early intervention in psychiatry*, *9*(3), 173–184. https://doi.org/10.1111/eip.12170
- Treasure, J., Oyeleye, O., Bonin, E. M., Zipfel, S., & Fernandez-Aranda, F. (2021). Optimising care pathways for adult anorexia nervosa. What is the evidence to guide the provision of high-quality, cost-effective services?. *European eating disorders review : the journal of the Eating Disorders Association*, *29*(3), 306–315. https://doi.org/10.1002/erv.2821
- Vocks, S., Tuschen-Caffier, B., Pietrowsky, R., Rustenbach, S. J., Kersting, A., & Herpertz, S. (2010). Meta-analysis of the effectiveness of psychological and pharmacological treatments for binge eating disorder. *The International journal of eating disorders*, *43*(3), 205–217. https://doi.org/10.1002/eat.20696
- Volpe, U., Tortorella, A., Manchia, M., Monteleone, A. M., Albert, U., & Monteleone, P. (2016). Eating disorders: What age at onset?. *Psychiatry research*, *238*, 225–227. https://doi.org/10.1016/j.psychres.2016.02.048
- Volpe, U, Monteleone, AM, Ricca, V, et al. Pathways to specialist care for eating disorders: An Italian multicentre study. *Eur Eat Disorders Rev*. 2019; 27: 274– 282. https://doi.org/10.1002/erv.2669
- Von Ranson, K. M., Wallace, L. M., & Stevenson, A. (2013). Psychotherapies provided for eating disorders by community clinicians: infrequent use of evidence-based treatment. *Psychotherapy research : journal of the Society for Psychotherapy Research*, *23*(3), 333–343. https://doi.org/10.1080/10503307.2012.735377
- Waller G. Treatment protocols for eating disorders: clinicians' attitudes, concerns, adherence and difficulties delivering evidence-based psychological interventions. Curr Psychiat Rep 2016; 18:1–8.
- Weigel, A., Rossi, M., Wendt, H. *et al.* Duration of untreated illness and predictors of late treatment initiation in anorexia nervosa. *J Public Health* **22,** 519–527 (2014). https://doi.org/10.1007/s10389-014-0642-7
- Wilson, G. T., & Zandberg, L. J. (2012). Cognitive-behavioral guided self-help for eating disorders: effectiveness and scalability. *Clinical psychology review*, *32*(4), 343–357. https://doi.org/10.1016/j.cpr.2012.03.001
- Working Group of the Clinical Practice Guideline for Eating Disorders. Clinical practice guideline for eating disorders. In: Quality plan for the national health system of the ministry of health and consumer affairs. Madrid: Catalan Agency for Health Technology Assessment and Research; 2009; Available at: www.guiasalud.es/egpc/traduccion/ingles/conducta_alimentaria/completa/apartado00/preguntas.html.

- Yager J, Devlin MJ, Halmi KA, et al. Guideline watch (August 2012): practice guideline for the treatment of patients with eating disorders. 3rd ed. Washington, DC: APA; 2012; Available at: psychiatryonline.org/pb/assets/ raw/sitewide/practice_guidelines/guidelines/eatingdisorders-watch.pdf.
- Zipfel, S., Wild, B., Groß, G., Friederich, H. C., Teufel, M., Schellberg, D., Giel, K. E., de Zwaan, M., Dinkel, A., Herpertz, S., Burgmer, M., Löwe, B., Tagay, S., von Wietersheim, J., Zeeck, A., Schade-Brittinger, C., Schauenburg, H., Herzog, W., & ANTOP study group (2014). Focal psychodynamic therapy, cognitive behaviour therapy, and optimised treatment as usual in outpatients with anorexia nervosa (ANTOP study): randomised controlled trial. *Lancet (London, England)*, *383*(9912), 127–137. https://doi.org/10.1016/S0140-6736(13)61746-8.