Comorbid depression as a negative predictor of weight gain during treatment of anorexia nervosa: a systematic scoping review

Short title: Comorbid depression in anorexia nervosa

Mia Eskild-Jensen, BA1 Orch iD 0000-0002-2318-8523.
Rene Klinkby Støving, MD, PhD2,3,4 Orch iD 0000-0002-4255-5544.
Christopher Fay Flindt, MD5 Orch iD 0000-0002-2108-2768.
Magnus Sjøgren, MD, PhD5,6 Orch iD 0000-0003-2060-1914.

1 University of Copenhagen, Denmark.
2 Center for Eating Disorders, Odense University Hospital, Denmark.
3 Endocrine Research Unit, Odense University Hospital & Clinical Institute, University of Southern Denmark.
4 Mental Health Services in the Region of Southern Denmark.
5 Eating Disorder Unit, Mental Health Center Ballerup, Ballerup, Denmark.
6 Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

Corresponding author:
Magnus Sjögren, MD, PhD, Associate Professor, Psychiatrist
Psychiatric Center Ballerup and Copenhagen University
2750 Ballerup, Denmark
Email: jan.magnus.sjoegren@regionh.dk
Phone: +45 51 43 18 96

Conflict of Interest statement
The authors (MEJ, RKS, CFF, and MS) have no conflict of interests to declare.

Funding
There is no funding for this literature study.

Abstract
This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/erv.2787

This article is protected by copyright. All rights reserved.
**Background:** Anorexia nervosa (AN) is a serious mental illness with high rates of relapse and mortality. Psychiatric comorbidities are common but their impact on the prognosis is largely unknown.

**Objective:** The aim was to investigate the influence of psychiatric comorbidity on weight gain during treatment of AN.

**Methods:** A systematic search was performed in PubMed/MEDLINE, EMBASE and PsycINFO. Studies evaluating psychiatric comorbidity as a predictor for treatment outcome (weight gain) were included, however, comorbid alcohol/drug addiction was excluded from this review study.

**Results:** 4526 publications were identified from which 15 were included. The majority of the included studies had a prospective open naturalistic study design, a short-term follow-up period, and were based on small populations of primarily adolescent and adult women. Four studies indicate depression, and two obsessiveness as negative prognostic factors, while one study indicated moderate depression and yet another, neuroticism, as positive predictors for weight gain.

**Discussion:** The systematic scoping review found a large number of publications whereof only few directly described the influence of psychiatric comorbidity on weight gain in AN. Overall, studies were heterogeneous in design, purpose and outcome making comparisons difficult. Findings were divergent but depression had a negative influence on weight gain in four studies.

**Highlights**
- Several studies suggest psychiatric comorbidity as a negative prognostic factor in Anorexia nervosa, however only a few studies considered the influence on weight gain.
- The majority of the published studies had an open naturalistic study design, a short-term follow-up period, and included a small number of patients.
- Critical appraisal: four well-designed studies find that depression is a negative factor for weight gain, albeit one other study found moderate depression to be a positive predictor.

**Keywords:** anorexia nervosa, weight gain, comorbidity, systematic review.
1. INTRODUCTION

Anorexia nervosa (AN) is a serious psychiatric disorder characterized by failure to maintain normal body weight (BW) alongside an intense fear of gaining weight. Despite short-term weight gains from standard treatment in AN, frequently this gain does not last (Murray, 2019), while the long-term prognosis is often poor with severe physical and psychological complications. In a recent systematic review, the relapse frequency after treatment was found to be 31% (Berends, 2018) and in a large German long-term follow-up study, the standardized mortality rate was reported to be 5 (Fichter, 2016). Since the response to treatment in AN varies substantially between individuals, and treatment often is required for longer periods of time, which is multimodal and costly, identifying prognostic factors that would tailor treatment would be of great value (Keski-Rahkonen, 2014).

Psychiatric comorbidity is very common in AN. Among 2436 female inpatients, 97% were diagnosed with at least one psychiatric comorbidity (Blinder, 2006), and the likelihood of getting a comorbid diagnosis increases with duration of illness, a phenomenon that applies to almost all psychiatric disorders (Plana-Ripoll, 2019). In AN, comorbid anxiety disorders including obsessive-compulsive disorders (OCD), phobias, and also affective disorders and personality disorders are common. In addition, schizophrenia and autism spectrum disorders are sometimes found. The presence of these comorbidities is believed to significantly influence the course and mortality rate (Kask, 2016).

Weight gain is a key outcome in the treatment of AN. In view of its high prevalence, it is essential to explore the influence of comorbidities on weight gain in the treatment of AN (Marcoulides, 2012). Identification of confounders such as comorbidities, could lead to more individualized treatment associated with improved outcome and prognosis. However, evidence is scarce, and current knowledge relies on a few heterogenic studies where frequently the influence of co-morbidity on weight gain has been of secondary interest. Thereby, there is a need for a systematic evaluation of the current state of knowledge based upon published studies that have investigated the influence of psychiatric co-morbidity on weight gain in the treatment of AN. This was the aim of the current scoping review, an approach which has been found to be particularly useful when a topic has not yet been extensively reviewed or is of a complex or heterogeneous nature (Munn, 2018; Pham, 2014).

2. MATERIAL AND METHODS

This systematic scoping review was conducted in accordance with established scoping review standards (Peters, 2015; Tricco, 2018) following the PRISMA-ScR Guidelines. The study was preregistered in PROSPERO (PROSPERO identification number 161613).

2.1 Eligibility criteria
Eligible for inclusion were original studies in which patients with AN were undergoing weight restoration and either a) the impact of additional psychiatric disorders other than an eating disorder was investigated or b) possible to deduce as based on the presented data. See inclusion and exclusion criteria below.

2.2 Data sources
All studies were identified using the MEDLINE (via PubMed), EMBASE, and PsycInfo databases. The search included articles published before 1st December 2018, and the search strategy was developed including both indexed terms (e.g., MESH terms) and text words. The search strings were broad to ensure that that no relevant studies were overlooked.

2.3 Search Strategy
For details, please see Supplementary_search_strategies.

Inclusion criteria:
1. Anorexia nervosa according to DSM IV/V or ICD10 or corresponding diagnostic criteria.
2. Pharmacological and/or non-pharmacological treatment.
3. Studies with a primary aim of investigating the impact of psychiatric comorbidity on treatment outcome.
4. Studies that included the effect on body weight as one of the outcomes.
5. All ages.
6. All genders.

Exclusion criteria:
7. Studies including less than 10 individuals.
8. Animal studies.
9. Studies describing or investigating the effects of alcohol/drug dependency or addiction.
10. Case reports, editorials, commentaries, guidelines, book chapters, conference proceedings or narrative reviews.

2.4 Review and study selection process
4526 publications were identified in the three databases and transferred to Endnote reference software whereof 1059 duplicates were identified and removed (Figure 1: PRISMA flow chart). The remaining publications were thereafter transferred to the Covidence online software for systematic reviews for further
reviewing. Publications were screened independently by two authors (MEJ and CFF) starting with title/abstract screening which covered 3467 publications. Any disagreements were first resolved via consensus, and if this was not possible, resolved by the senior scientist (MSj). The publications were excluded based on inclusion and exclusion criteria (see above). This title/abstract review led to an identification of 155 publications, which were included for full text review, of which 140 full texts were excluded since they did not meet the inclusion criteria or met one or more of the exclusion criteria. Thereby, fifteen (n=15) unique publications remained, which were all included for data extraction. For details, see Supplementary_PRISMA-ScR-Fillable-Checklist_Comorbid_AN2020.

As preliminary screening showed that many different psychiatric disorders were considered as comorbid disorders, we chose broad search criteria to avoid overlooking any relevant study. Consequently, many studies were identified where psychiatric comorbidity was not investigated as a primary aim but merely stated as supplementary observations.

2.5 PRISMA flow diagram:
Figure 1 shows the steps in the literature review process following the PRISMA guideline (Moher, 2009).

2.6 Data extraction
The following data were extracted from each of the selected publications into a data extraction table (Table 1): study population and size, year, study design, objective, follow-up period, intervention, diagnostic instrument for primary diagnosis and comorbidities, psychiatric comorbidity, outcome measure, body weight gain, rate of completers, and study results. Discrepancies were resolved via consensus (MEJ and CF), and if not possible, after consultation with the senior scientist (MSj).

2.7. Risk of Bias
Risk of bias was assessed using the Newcastle-Ottawa Scale for non-randomized studies (Deeks, 2003).

3. RESULTS
Table 1 shows the data extracted for each of the 15 included studies on comorbid disorders and/or psychopathologic personality traits.

3.1 Study design
The majority of the 15 included studies used a prospective, open, naturalistic study design. Twelve studies had a short-term follow up of which the longest was 12 months. Three studies had long-term follow up of which the longest was 21 years. Four short-term studies included adolescent patients, seven adults, and one short-term study included a mix of adolescents and adults. Two of the long-term studies included adults and only one included adolescents. As displayed in Table 1, the specific comorbidities and included diagnostic tools varied considerably. In one study the type of comorbidity was not specified (Berona, 2018), and in two studies, comorbidity was assessed only by means of a self-report questionnaire, the BSI (Lockwood, 2012; Marcoulides, 2012). In one of the short-term studies, patients with psychotic symptoms were excluded (Kuipers, 2017). In the three long-term studies, comorbidity was included as a premorbid or life-time diagnosis, whereas it was assessed at inclusion in the short-term studies.

3.2 Setting

In six studies, the patients followed an in-patient treatment program, in four studies an out-patient treatment program, and in one study, a partial hospitalization treatment program was followed. In three studies, the treatment setting was not specified.

3.3 Sample size and considerations for statistical analyses

Most studies included a small number of participants; 13 studies included from 32 to 435 participants, while one study included 2882 participants. Five studies considered population size in the statistical analyses and interpretation of the results (Kuijpers, 2017; Lock, 2006; Marcoulides, 2016; Schlegl, 2014; Sebastian, 2019).

3.4 Intervention

Despite a great variety in treatment approaches/interventions, the majority of the included studies used a multimodal treatment approach for weight gain in AN. Two studies used CBT, three used FBT and one used cyproheptadine as interventions.

In two studies, concomitant medication was considered and adjusted for in the statistical assessment of influence on weight gain (Lock, 2006; Schlegl, 2016).

3.5 Assessment of Bias

The results of the assessment of bias according to the Newcastle-Ottawa Scale for non-randomized studies (Deeks, 2003), are presented in Table 2.
3.6 Synthesis of the data analysis of the influence of comorbidity on weight gain in AN

Table 2 summarizes the assessment of bias and the level of evidence for each included study, and, provides a synthesis of both for each study. Four short-term studies (Fischer, 2017; Lock, 2006; Schlegl, 2016; Schlegl, 2014) and two long-term studies (Carrot, 2017; Keski-Rahkonen, 2014) had a low bias and a high level of evidence, and were consequently ranked the highest in terms of scientific value for the results assessment.

Overall, not taking level of evidence and bias into account, five studies found that depression was a negative predictor of weight gain (Lock, 2006; Schlegl, 2014; Schlegl, 2016; Keski-Rahkonen, 2014; Berona, 2018), while one study found that moderate depression (Schlegl, 2014) was a positive predictor. Yet another study found that a depressive trait (Signorini, 2003) was a positive predictor of weight gain. Four studies found that anxiety, including phobia, was a negative predictor of weight gain (Lock, 2006; Kuipers, 2017; Lockwood, 2012; Yackobovitch-Gavan, 2009). One study found that OCD was a negative predictor (Carrot, 2017) and two studies found that obsessiveness was a negative predictor (Lock, 2006; Yackobovitch-Gavan, 2009) of weight gain. Yet another study found that among personality traits, neuroticism was positively correlated with weight gain (Fischer, 2017).

Based on the combination of high level of evidence and low bias, depression in the short-term, especially severe depression (Lock, 2006; Schlegl, 2016; Schlegl, 2014), and depressive symptoms (Keski-Rahkonen, 2014), obsessiveness (Lock, 2006) and OCD (Carrot, 2017) in the long-term, had a negative influence on weight gain. Moderate depression with an associated milder ED psychopathology (Schlegl, 2014) and a neuroticism personality trait (Fischer, 2017) were positive predictors of weight gain.

4 DISCUSSION

4.1 Implications of comorbidity on weight gain in the treatment of anorexia nervosa

To our knowledge this is the first systematic scoping review on the influence of psychiatric comorbidity concerned with weight gain in AN. Overall, depression was the comorbid disorder that most clearly had a negative influence on weight gain, both in the short-term and long-term studies (Lock, 2006; Schlegl, 2016; Schlegl, 2014; Keski-Rahkonen, 2014). In one and the same study, severe depression was a negative predictor, while moderate depression was a positive predictor of weight gain (Schlegl, 2014). This latter study described additional differences between moderate and severe depression specifically in terms of a) more amplified eating disorder psychopathology in severe depression, and, b) milder symptoms at the onset of treatment in AN patients with more positive outcomes. Taken together, depression may influence general psychopathology in AN, thereby providing one potential explanation as to why it is a negative prognostic factor for weight gain.
In addition to this potential effect, depression may also influence motivation and thereby negatively influence the process of recovery. Furthermore, depression may also have more general biological effects on appetite. Apart from depression, OCD and obsessiveness were also found to be negative predictors of weight gain in AN (Lock, 2006; Carrot, 2017). Overall, a greater emphasis on comorbidity is warranted in the clinical praxis aiming at treating these negative predictors effectively at first, to pave the way for more focused treatment efforts on weight gain in AN.

The majority of the included studies considered the effect of comorbidities jointly, and our analysis may thereby have overlooked any selective effects the individual comorbidities may have had on weight gain. As a contrast to this, one study explored the selective effects of comorbid psychopathologies and found depressive traits to be correlated to weight gain, narcissistic traits to weight loss, and psychotic traits to weight stability (Signorini, 2003).

Studies that investigated the effect of comorbid alcohol or drug abuse were excluded since the presence of these comorbid disorders often leads to radical clinical decisions such as early discharge from treatment, and the initiation of specialized care. Moreover, in some patients, the abuse may be a result of attempts to self-medicate the symptoms of AN (Bizzarri, 2009). Overall, it is expected that abuse will impair compliance and therapeutic treatment alliance, and there is evidence that abuse in psychiatric patients is strongly related to an increased mortality (Tidemalm, 2008).

4.2 Differences between the included studies, and limitations
Overall, the studies were heterogeneous in design, purpose and analyses of outcome, making direct comparison challenging. This heterogeneity hampers firm conclusions, apart from the negative influence on weight gain of depression and OCD. Furthermore, many patients are frequently diagnosed with several comorbidities, and the individual combination of these comorbid disorders could affect the way in which a patient responds to a given treatment. Moreover, the therapeutic interventions varied considerably with different, more or less well-defined, in- and out-patient treatment programs. In three studies investigating the effects of FBT, the influence of depression was negative in two (Berona, 2018; Lock, 2006) whereas no significant effect could be detected in one of these studies (Agras, 2014). In two other studies using CBT, anxiety had a negative effect on weight gain in one (Lockwood, 2012), whereas it had no effect in the other study (Marcoulides, 2012). Thus, in order to improve the current status of knowledge, studies with narrow inclusion criteria, harmonized study designs, interventions-, and statistical approaches to analyze the data, are needed to increase our understanding of the influence of a specific comorbidity on weight gain in AN.
Most studies did not thoroughly control for confounding factors such as higher compliance, longer stay in treatment, or AN subtypes, when comparing the effects of comorbidity on weight gain. Furthermore, a potential confounder may be the inherent difficulty in separating psychiatric comorbidity from symptoms related to AN. For example, deciding on whether depressive symptoms are related to comorbid depression, secondary to malnutrition, or an effect of long-term social isolation caused by AN (Laessle, 1988), may be challenging. In addition, in cases of treatment refractory AN, clinicians may be prone to assign a comorbid diagnosis to explain the long duration of the disease. This systematic scoping review therefore unequivocally emphasizes that more well-designed, well-powered studies are warranted to further explore the potential impact of psychiatric comorbidities on weight gain in AN. This could lead to more individualized treatment programs in the future and an improved prognosis for this devastating disease.

4.3 Conclusion and critical appraisal

Four well-designed studies were found indicating depression, and in two studies OCD and obsessiveness, as negative factors for weight gain in AN. Neuroticism and short-term moderate depression may be positive predictors of weight gain. Early identification of psychiatric comorbidities and the initiation of proper treatment is recommended.

Abbreviations

AN = Anorexia Nervosa
ADHD = Attention Deficit Hyperactivity Disorder
BD = Body Dissatisfaction
BDI = Beck Depression Inventory
BMI = Body Mass Index
BN = Bulimia Nervosa
BSI = Brief Symptom Inventory
CBT = Cognitive Behavioral Therapy
CSC = Clinically Significant Change
CY-BOCS = Children’s Yale-Brown Obsessive Compulsive Scale
ED = Eating Disorder
EDE = Eating Disorder Examination
EDE-Q = Eating Disorder Examination Questionnaire
Comorbid depression in anorexia nervosa

EDFHI = Eating Disorder Family History Interview
EDNOS = Eating Disorder Not Otherwise Specified
EDI = Eating Disorder Inventory
EOT = End Of Treatment
FBT = Family Based Treatment
FT = Family Therapy
HSCL = Hopkins Symptom Checklist
IBW = Ideal Body Weight
ICD-10 = International Classification of Disorders
KSADS = Kiddie-Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version
Mens. = Menstruation
MFC = Motivation For Change
MINI (MINI-KID) = Mini-neuropsychiatric Interview
MMPI = Minnesota Multiphasic Personality Inventory
Mo = Months
MPS = Multidimensional Perfectionism Scale
NOS = Naturalistic Observation Study
OCD = Obsessive Compulsive Disorder
PBS = Population Based Study
PHP = Partial Hospitalization Program
PMID = PubMed Identity=
PTSD = Post Traumatic Stress Syndrome
RC = Reliable changes
RMS = Raskin Mood Scale
RCT = Randomized Clinical Trial
SCID-I/-II = Structured Clinical Interview for DSM-IV-Axis I/II Disorders
STAI = State-Trait Anxiety Inventory
SyFT = Systematic Family Therapy
Symp. = Symptoms
W = weeks
Y-BOCS = Yale-Brown Obsessive-Compulsive Scale
YBOC-ED = Yale-Brown-Cornell Obsessive Compulsive-Eating Disorder Scale

This article is protected by copyright. All rights reserved.
COMPLIANCE WITH ETHICAL STANDARDS:
Conflict of Interest: All Authors declare that he/she has no conflict of interest. Ethical approval: This article does not contain any studies with human participants or animals performed by any of the authors. No funding was provided to enable this study.

REFERENCES


Fichter, MM., Quadflieg, N. (2016) Mortality in eating disorders - results of a large prospective clinical
Comorbid depression in anorexia nervosa


*Comorbid depression in anorexia nervosa*

This article is protected by copyright. All rights reserved.

Comorbid depression may influence weight gain during treatment of anorexia nervosa: a systematic scoping review

Short title:
Comorbid depression in anorexia nervosa

Mia Eskild-Jensen, BA1 Orch iD 0000-0002-2318-8523.
Rene Klinkby Støving, MD, PhD2,3,4 Orch iD 0000-0002-4255-5544.
Christopher Fay Flindt, MD5 Orch iD 0000-0002-2108-2768.
Magnus Sjøgren, MD, PhD5,6 Orch iD 0000-0003-2060-1914.

1 University of Copenhagen, Denmark.
2 Center for Eating Disorders, Odense University Hospital, Denmark.
3 Endocrine Research Unit, Odense University Hospital & Clinical Institute, University of Southern Denmark.
4 Mental Health Services in the Region of Southern Denmark.
5 Eating Disorder Unit, Mental Health Center Ballerup, Ballerup, Denmark.
6 Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

Corresponding author:
Magnus Sjögren, MD, PhD, Associate Professor, Psychiatrist
Psychiatric Center Ballerup and Copenhagen University
2750 Ballerup, Denmark
Email: jan.magnus.sjoegren@regionh.dk
Phone: +45 51 43 18 96

Conflict of Interest statement
The authors (MEJ, RKS, CFF, and MS) have no conflict of interests to declare.

Funding
There is no funding for this literature study.
Records identified through database searching (n = 4526)

Duplicates removed (n = 1059)

Records screened after duplicate removal (n = 3467)

Records excluded (n = 3312)

Full-text articles assessed for eligibility (n = 155)

Full-text articles excluded, with reasons (n = 433)
- #1: Non-english (n = 30)
- #2: Other study type (n = 27)
- #3: Non inclusion (n = 73)
- #4: 10 patients or less (n = 5)
- #5: No access (n = 5)

Studies included in qualitative synthesis (n = 15)

Figure 1. PRISMA flow diagram modified to fit the present material. Exclusion reasons #1 non-english studies, #2 case reports, editorials and commentaries, reviews and meta-analyses, guidelines, book chapters, or conference proceedings, #3 studies that did not meet inclusion criteria, #4 studies involving 10 patients or less, #5 no access.
<table>
<thead>
<tr>
<th>Publication</th>
<th>Population (n, diagnosis, and gender)</th>
<th>Age</th>
<th>Study design</th>
<th>Objective</th>
<th>Follow up period</th>
<th>Intervention</th>
<th>Diagnostic instrument and system for ED</th>
<th>Comorbidities (Diagnostic instrument)</th>
<th>Outcome measure:</th>
<th>Body weight gain (%)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short term follow up studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Adolescents upfront</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lock, 2006</td>
<td>AN = 86, (91% female, 19% AN-BP),</td>
<td>Completers:</td>
<td>RCT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1. Primary results</td>
</tr>
<tr>
<td>PMID: 16927385</td>
<td>Duration 11 (2-48) months</td>
<td>15.1 ± 1.6 y</td>
<td>Data from study comparing short vs long term FT</td>
<td>12 months</td>
<td>10 or 20 sessions of FBT</td>
<td>not stated EDE, YBC-ED</td>
<td>K-SADS</td>
<td>1. Drop-out (&lt;80% completed sessions)</td>
<td>1. n=15 (35%) dropouts</td>
<td>2. 62 % (n=42) fully remitted.</td>
<td></td>
</tr>
<tr>
<td>DOI: 10.1002/eat.20328</td>
<td></td>
<td>Non-completers:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2. Psychiatric co-morbid disorder (including comorbid symptoms of depression, anxiety and obsessiveness), being older, and problematic family behaviour less likely to remit.</td>
</tr>
<tr>
<td>Agras, 2014</td>
<td>AN = 164, Medically stable.</td>
<td>15.3 ± 1.7 y</td>
<td>RCT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1. Comorbid disorder and long term FT predicted drop-out.</td>
</tr>
<tr>
<td>PMID: 25250660</td>
<td>(12-18)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2. Younger patients (P = .04), shorter duration of illness (P = .04) gained more weight.</td>
</tr>
<tr>
<td>DOI: 10.1001/jamapsychiatry.2014.1025</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Schlegl, 2016
**PMID:** 26603278  
**DOI:** 10.1002/e rv.2416

| AN = 238, female, Inpatients. Antidepressants considered. | 15.7 ± 1.1 y (13–17) | Prospective open naturalistic study, 1. predictors of outcome 2. At discharge Multi-modal ICD-10-criteria Depression (BDI-I and II) BSI EDI-2 | 1. BMI change 2. CSC (symptom and weight change) | 12 mo 40.7% SyFT: 1. IBW EOT 91.1% 12 mo 93.3% (baseline 81.7). 2. 25.3% remission, 39% at 12 mo. |

### Berona, 2018
**PMID:** 30058155  
**DOI:** 10.1002/eat.22922

| AN = 102, Both genders. | 16.4 ± 2.9 y (11–24) | Prospective, open naturalistic study Weight gain trajectories 6 w FBT PHP DSM-IV-criteria EDE-Q | 1. Rate of weight gain 2. Predictors of rate of weight gain | All rapid responders (15.7%) gained at least 1.8 kg first 4 weeks, compared to 86.1% of moderate and 51.2% of slow responders. Rapid weight gain trajectory averaged 7.6 kg compared to 4 kg in the moderate class and 1.4 kg in the slow class. |

1. Length of stay, depression and body dissatisfaction were negative predictors of CSC

Add: No difference between FBT and SyFT. FBT faster weight gain first 8 weeks.
<p>| Study | PMID | DOI | AN | BN | ED- NOS | Both genders | Mean age (range) | Study design | Relationship | 5-year period | Multi-modal | DSM IV-criteria | Diagnosis | Readmission | Rate of weight gain, g/day | Recovery rate | Attachment and mentalization scores | Mental health outcomes |
|-------|------|-----|----|----|-------|-------------|----------------|----------------|--------------|--------------|-------------|-------------|---------------|-----------|-------------|---------------------------------|--------------|---------------------------------|---------------------|
| Sebastian, 2019 | 30807289 | 10.1515/jamh-2018-0228 | AN = 54 (66%), BN=3, ED- NOS=25 | | | Both genders | Mean 14.8 y (13.5–16.8) | Retrospective, review of medical records | Relationship between rate of weight gain and readmission | | Multi-modal | Depression, anxiety, obsessive compulsive traits, OCD, bipolar disorder, ADHD, substance use (Not specified) | 1. Readmission | 2. Rate of weight gain, g/day | | | | 1. Rapid weight gain and psychiatric co-morbidities increased risk of readmission. |
| Kuipers, 2017 | 28643289 | 10.1007/s40519-017-0405-x | AN = 27, BN= 4 EDNOS=7 | Women | Daycare unit | | 22.2 ± 3.5 y | Prospective, | Influence of pre-treatment attachment and/or mentalization on recovery | | Multimodal | DSM-IV-TR-criteria | Anxiety (STAI), depression (SCID-I), personality disorders (SKID-II) | 1. Recovery rate | 2. Attachment and mentalization scores | | | | 1. State and trait anxiety, and personality disorder were related to persistence of ED at 18 months. 2. Recovery at 12 and 18 mo was related to higher levels of mentalization. |
| Fischer, 2017 | 27775490 | 10.1080/10640266.2016.1241056 | AN-R=64 (30%), AN-BP= 118 (56%), EDNOS=12, ARFID=, BM=4 | Total = 211 | | | 31.9 ± 12.8 y | Prospective open naturalistic study | Impact of personality on weight restoration | average 57 days | Multi-modal | DSM-IV-criteria | Neuroticism (NEO-FFI), depression (BDI) | 1. Neuroticism score | 2. Rate of weight gain, BMI | Rate of inpatient weight gain averaged 1.9 kg per week (SD = 0.81) and partial hospital rate of weight gain averaged 1.5 kg per week (SD = 0.71). Completers/recovery: 62% achieved BMI &gt;20 kg/m2, | | 1. Neuroticism positively associated with weight restoration. Longer length of stay and high neuroticism, higher likelihood of weight restoration. |</p>
<table>
<thead>
<tr>
<th>women inpatients</th>
<th>Predictors of CSC</th>
<th>5 year period</th>
<th>Multi-modal</th>
<th>ICD-10-criteria</th>
<th>Depression (BDI-2), BSI, EDI-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schlegl, 2014 (Schlegl et al., 2014)</td>
<td>AN = 435, women inpatients</td>
<td>26.4 ± 9.0 y (18 – 70)</td>
<td>Prospective open naturalistic study</td>
<td>6-260 days treatment</td>
<td>1. CSC - BMI, ED symptoms, general psychopathology, depression. 2. Comorbidity as predictor of CSC</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean BMI gain 14.56 kg/m² (SD = 1.74) to 17.18 kg/m² (SD = 1.86) (ES = 1.51). Mean weight gain per week 0.84 kg (SD = 0.56), 52.2%. Normal BMI, EOT n = 108 (24.8%; BMI ≥ 18.5) at discharge. CSC=34,1-55.3%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1. Moderate depression positive predictors of CSC Severe depression and PTSD were negative predictors Treatment duration significantly contributed to pre-post change in body weight.</td>
</tr>
<tr>
<td>Schlegl, 2014 (Schlegl et al., 2014)</td>
<td>AN = 40, women, outpatient</td>
<td>28.0 ± 5.7 y (20 – 42)</td>
<td>Prospective naturalistic</td>
<td>8 mo period</td>
<td>1. Treatment drop-out (termination of treatment before 10th CBT session) 2. Weight change, BMI</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean weigh gain 2.12 kg (SD = 2.08), range = - 1.20 to + 9.95 At session 1, the mean was 44.6 kg (SD = 5.75), rising to 45.9 kg (SD = 5.77) by session 6, and 46.7 kg (SD = 5.66) by session 10.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1. Higher initial anxiety and phobia slower weight gain.</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Study Design</td>
<td>Participants</td>
<td>Intervention</td>
<td>Follow-Up</td>
</tr>
<tr>
<td>--------</td>
<td>------</td>
<td>--------------</td>
<td>--------------</td>
<td>-------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Marcoulides, 2012</td>
<td>(Marcoulides &amp; Waller, 2012)</td>
<td>AN = 32, women, outpatient</td>
<td>26.1 ± 8.7 y</td>
<td>Prospective naturalistic</td>
<td>Psychological predictors of weight gain</td>
</tr>
<tr>
<td>Signorini, 2003</td>
<td></td>
<td>AN = 58, women, AN-R=44, AN-BP=14, outpatient</td>
<td>20.5 ± 5.6 y</td>
<td>Longitudinal follow-up study</td>
<td>Predictors of clinical outcome</td>
</tr>
<tr>
<td>Eckert, 1982</td>
<td></td>
<td>AN = 105, women, inpatient</td>
<td>No information</td>
<td>RCT</td>
<td>Effect of cyproheptadine on depression</td>
</tr>
</tbody>
</table>

1. Higher comorbid pathology slower weight gain in the later part of the study (session 6 to 20)
### Long term follow up studies

**Including adolescents upfront**

<table>
<thead>
<tr>
<th>Author</th>
<th>PMID</th>
<th>AN</th>
<th>Age at follow up</th>
<th>Study Design</th>
<th>Interview Timing</th>
<th>DSM-IV Criteria</th>
<th>Lifetime Psychiatric Comorbidity</th>
<th>Clinical Assessment</th>
<th>Follow-up</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carrot, 2017</td>
<td>28258321</td>
<td>181 women</td>
<td>16.6 ± 1.6 y (13 – 22)</td>
<td>Retrospective, interviews conducted from 6 to 12 years after hospitalization</td>
<td>6-12 y</td>
<td>Multi-modal</td>
<td>DSM-IV criteria</td>
<td>Clinical assessment</td>
<td>Follow-up: Good or intermediate: 62.9% (n=61/97)</td>
<td>1. INSERM weight/height growth curve, long term outcome Morgan-Russell. Good = &gt;10th perc. + menstruate. Intermed. = weight &gt;10th perc. - menstruate. Poor = &lt;10th perc. - menstruate and/or bulimic.</td>
</tr>
<tr>
<td>Yackovitch-Garan, 2009</td>
<td>AN = 60, (36 remitted, 24 non-remitted)</td>
<td>Remitted: 22.0 ± 2.9 y Non-remitted: Case-control, retrospective interviews</td>
<td>Factors influencing course of AN</td>
<td>9-21 y post hospitalization</td>
<td>Multi-modal</td>
<td>DSM-IV criteria</td>
<td>Lifetime psychiatric comorb., SKID-Remission</td>
<td>Remission</td>
<td>16 (26.7%) complete remission</td>
<td>1. Anxiety and eating related obsessiveness associated with non-</td>
</tr>
<tr>
<td>Keski-Rahkonen, 2014 PMID: 24488835 DOI: 10.1002/eat.20624</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AN = 55 women.</td>
<td>Recovered 25.1 ± 1.3 y Unrecovered 25.0 ± 1.4 y</td>
<td>Populations based cohort study (PBS, NOS)</td>
<td>Factors associated with outcome at age 16, 17, 18, and 22-28 years</td>
<td>No</td>
<td>DSM-IV-criteria SCID, EDI</td>
<td>Pre-morbid depressive or OCD symptoms (SCID)</td>
<td>1. Recovery from AN</td>
<td>71 % (n=39) recovered. Unrecovered more likely depressive symptoms prior to ED onset (18.8% vs. 2.6%, p=0.04).</td>
<td>1. Pre-morbid depressive symptoms only factor associated with poorer outcome of AN</td>
<td></td>
</tr>
</tbody>
</table>

| non-remitted, women, inpatient | 23.3 ± 3.4 y | Controls: 31 healthy females | EDFHI, I/P, Y-BOCS, YBC-ED, BDI, STAI, MPS | 20 (33.3%) partial remission | remission. |
Table 2. Risk of bias assessed using Newcastle-Ottawa Scale for non-randomized studies.

<table>
<thead>
<tr>
<th>Publication</th>
<th>Case Definition Adequate</th>
<th>Representativeness (e.g. all cases in time period)</th>
<th>Selection of Controls, same population</th>
<th>Comparability (matched in design)</th>
<th>Exposure ascertainment</th>
<th>Level of evidence</th>
<th>Synthesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sebastian, 2019 (Sebastian &amp; Hergenroeder) PMID: 30807289 DOI: <a href="http://10.1515/ijamh-2018-0228">10.1515/ijamh-2018-0228</a></td>
<td>*</td>
<td>*</td>
<td>* (definition) (selection)</td>
<td>* (age) + (other)</td>
<td>*</td>
<td>2b</td>
<td>5 stars bias; 2b evidence level; Objective - Weight gain and readmissions Low scientific value for evaluation of impact of comorbidity on weight gain</td>
</tr>
<tr>
<td>Berona, 2018 (Berona et al., 2018) PMID: 30058155 DOI: <a href="http://10.1002/eat.22922">10.1002/eat.22922</a></td>
<td>*</td>
<td>+</td>
<td>* (definition) (selection)</td>
<td>+ (age) * (other)</td>
<td>*</td>
<td>2b</td>
<td>4 stars bias; 2b evidence level; Objective – predictors of weight trajectories Moderate (due to bias) scientific value for evaluation of impact of comorbidity on weight gain</td>
</tr>
<tr>
<td>Kuipers, 2017 (Kuipers et al., 2017) PMID: 28643289 DOI: <a href="http://10.1007/s40519-017-0405-x">10.1007/s40519-017-0405-x</a></td>
<td>*</td>
<td>+</td>
<td>* (definition) (selection)</td>
<td>* (age) * (other)</td>
<td>*</td>
<td>2b</td>
<td>5 stars bias; 2b evidence level; Objective – Prognostic value of attachment and mentalization Low scientific value for evaluation of impact of comorbidity on weight gain</td>
</tr>
<tr>
<td>Fisher, 2016 (Fischer et al., 2017) PMID: 27775490 DOI: <a href="http://10.1080/10640266.2016.1241056">10.1080/10640266.2016.1241056</a></td>
<td>*</td>
<td>*</td>
<td>* (definition) (selection)</td>
<td>* (age) * (other)</td>
<td>*</td>
<td>2b</td>
<td>6 stars bias; 2b evidence level; Objective – Prognostic value of personality on weight gain High scientific value for evaluation of impact of comorbidity on weight gain</td>
</tr>
<tr>
<td>Schlegl, 2015 (Schlegl et al., 2016) PMID: 26603278</td>
<td>*</td>
<td>*</td>
<td>* (definition) * (age)</td>
<td>* (other)</td>
<td>*</td>
<td>2b</td>
<td>6 stars bias; 2b evidence level; Objective – Predictors of weight gain</td>
</tr>
</tbody>
</table>

This article is protected by copyright. All rights reserved.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Scientific Value</th>
<th>Evidence Level</th>
<th>Objective</th>
<th>Impact of Comorbidity on Weight Gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agras, 2014 (Agras et al., 2014)</td>
<td>High</td>
<td>6 stars</td>
<td>Compare FBT with SyFT</td>
<td>Bias 1c Evidence Level: Compare FBT with SyFT</td>
</tr>
<tr>
<td>Schlegl, 2014 (Schlegl, Quadflieg, Lowe, Cuntz, &amp; Voderholzer)</td>
<td>Moderate</td>
<td>6 stars</td>
<td>Prognostic value of personality on weight gain</td>
<td>Bias 2b Evidence Level: Prognostic value of personality on weight gain</td>
</tr>
<tr>
<td>Lockwood, 2012 (Lockwood et al., 2012)</td>
<td>Low</td>
<td>3 stars</td>
<td>Prognostic value of clinical characteristics on outcome of CBT</td>
<td>Bias 2b Evidence Level: Prognostic value of clinical characteristics on outcome of CBT</td>
</tr>
<tr>
<td>Marcoulides, 2012 (Marcoulides &amp; Waller, 2012)</td>
<td>Moderate</td>
<td>4 stars</td>
<td>Prognostic value of personality on weight gain</td>
<td>Bias 2b Evidence Level: Prognostic value of personality on weight gain</td>
</tr>
<tr>
<td>Lock, 2006 (Lock et al.)</td>
<td>High</td>
<td>6 stars</td>
<td>Prognostic value of personality on weight gain</td>
<td>Bias 2b Evidence Level: Prognostic value of personality on weight gain</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Title</td>
<td>Scientific Value</td>
<td>Evidence Level</td>
</tr>
<tr>
<td>------------------------</td>
<td>-----------------------</td>
<td>-----------------------------------------------------------------------</td>
<td>------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>Signorini, 2003</td>
<td>(Signorini et al., 2003)</td>
<td>PMID: 12880196 DOI not available</td>
<td>Low</td>
<td>2b</td>
</tr>
<tr>
<td>Eckert, 1982</td>
<td>PMID: 7079420 DOI not available</td>
<td>Objective – Prognostic value of depression and cyproheptidine treatment on weight gain</td>
<td>Low</td>
<td>2b</td>
</tr>
<tr>
<td>Carrot, 2017</td>
<td>(Carrot et al., 2017)</td>
<td>PMID: 28258321 DOI: [10.1007/s00787-017-0963-5]</td>
<td>High</td>
<td>2b</td>
</tr>
<tr>
<td>Keski-Rahkonen, 2013</td>
<td>(Keski-Rahkonen et al., 2014)</td>
<td>PMID: 24488835 DOI: [10.1002/eat.22168]</td>
<td>High</td>
<td>2b</td>
</tr>
<tr>
<td>Yackovitch-Garan, 2008</td>
<td>(Yackobovitch-Gavan et al., 2009)</td>
<td>PMID: 19040269 DOI: [10.1002/eat.20624]</td>
<td>Low</td>
<td>4</td>
</tr>
</tbody>
</table>