Funen Anorexia Nervosa Study

a follow-up study on outcome, mortality, quality of life and body composition

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2. Winkler L, Frølich JS, Gudex C, Bilenberg N, Hørder K, Støving RK. Patient- and clinician reported outcome in eating disorders. Psych Res. 2017; 247:230-235.
3. Winkler L, Bilenberg N, Hørder K, Støving RK. Does specialization of treatment influence mortality in eating disorders? - A comparison of two retrospective cohorts. Psych Res. 2015; 230(2):165-71.
4. Winkler L, Schulpen M, Frölich JS, Støving RK. Body composition and menstrual status in adult patients with a history of anorexia nervosa - at what fat percentage is the menstrual cycle restored? Int J Eat Dis. July 17th 2016.

Introduction

Eating disorders

EDs are not new phenomena, but are attracting increasing attention in both clinical and research settings. AN was first described in the 13th century and reports of religious fasting continued up through the Victorian era. However, it was not until 1873 that two neurologists independent of each other described AN (1). In the late 1970's bulimia nervosa (BN) was first described with the publication of 30 case reports (2) and was included as a separate disease from AN in the Diagnostic and Statistical Manual of Mental disorders, third edition (DSM-III) (3) in 1980. EDs most commonly affects young women (1:8) between the ages of 15-19, but an increase in earlier debut has been detected (4). EDs constitute a group of disorders that cause severe psychological and physical distress. It involves a disturbed body image and is associated with eating difficulties and/or weight loss. EDs remain relatively rare in the general population and epidemiological studies are complicated by patients concealing their illness, hence avoiding professional help with a high number of patients dropping out of treatment and clinical studies. Further challenges in prevalence studies include numerous changes in diagnostic criteria. Prevalence rates, therefore, vary, but are reported to be approximately 0.3% for AN and significantly higher for BN and eating disorder not otherwise specified (EDNOS) (1-3%) (5, 6). EDs are diagnosed according to either the International Classification of Diseases (ICD) by WHO (7) or the Diagnostic and Statistical Manual of Mental Disorders (DSM) by the American Psychiatric Association. The specified EDs include AN, characterized by restrictive energy intake, weight loss, fear of gaining weight and a disturbed body image and BN is characterized by repeated episodes of binge eating followed by compensatory behavior. In addition, patients suffering from BN have an excessive emphasis on body shape and weight. Patients not fulfilling the diagnostic criteria for AN or BN, were diagnosed with EDNOS. Despite EDNOS being the most common ED in both clinical and community setting (>50%) (8), the diagnostic group has been neglected in ED research due to the lack of specific criteria. EDNOS comprised a heterogeneous group with similar disabilities and comorbidities as the specified EDs (9). In 2013, APA published a revised edition of the DSM (DSM-5) including several alterations in the classification of EDs. It was, among other things, designed to reduce the preponderance of EDNOS diagnoses. In the DSM-5, BED was introduced as a new diagnosis, the amenorrhea criterion was removed from the AN criteria and the frequency of binge-eating/compensatory behavior was reduced for BN. Furthermore, the EDNOS diagnosis was omitted and replaced with other specified feeding and eating disorders (OSFED) and unspecified feeding and eating disorders (UFED). It is well-established that the introduction of the DSM-5 led to a substantial reduction (approximately 20-60%) of the unspecified disorders compared to the previous EDNOS diagnosis (8, 10, 11). The removal of the amenorrhea criterion was the leading cause of this reduction, with formerly diagnosed EDNOS patients now being diagnosed with AN. This reduction in the unspecified disorders and increase in AN has inevitably led to a change in the prevalence of EDs (12).

Health Related Quality of Life (HRQoL)

The severe physical and psychological implications of an ED,

affects patients' everyday life and impacts on physical, mental and social aspects. These implications are reflected in the Global Burden of Disease (GBD) study, where the term disability adjusted life years (DALY) was introduced in 1990 as a sum of years of life lost (YLL) and years lived with disability (YLD). The GBD study has ranked EDs in the "top 20" disorders for women, similar to schizophrenia and above, for instance, psychoses and rheumatoid arthritis (13). EDs cause impairments in many aspects of patient's lives; physically, mentally and socially. Patients tend to become reclusive and with increasing symptomatology they withdraw from everyday activities, in part due to physical deterioration. As the physical deterioration continues, patients often start to feel depressed, loose their ability to concentrate and become feckless. They tend to withdraw from activities previously enjoyed by the patient, having the disease slowly assume their lives. The physical implications of severe malnutrition can cause depression, lack of concentration, sleeplessness etc. As the disease becomes all-encompassing, the vicious cycle is difficult to break. The term quality of life (QoL) refers to the general well-being of an individual under the circumstances he or she lives in. It is, therefore, a very subjective measure with multiple facets playing a role. To investigate QoL it is important to enquire about many different aspects of their lives, as physical well-being, job, house, family, social well-being etc. all have an impact. However, every person attaches importance to different areas, thus QoL has a different meaning and definition for everyone. Health related QoL (HRQoL) is used in health care as a measurement of how affected a patient's QoL is by a disease, hence how big a share physical well-being undertakes of QoL. Several studies have reported the impaired HRQoL in ED patients (14, 15). A large literature review from 2011 found that, not only had patients with active disease an impaired HRQoL, also patients with subclinical symptoms or threshold cases reported impaired HRQoL (16). Patients were more impaired on the psychological aspects of their HRQoL than the physical aspects and impairment increased with symptomatology. The literature review examined the differences across the diagnostic groups and found a tendency towards BED having worse HRQoL than the other EDs, but that further research was needed to establish potential differences. Not just patients with active disease have impaired HRQoL, also former patients report poorer HRQoL compared to a normal reference group (15). The poor HRQoL observed in EDs is comparable to other serious diseases, i.e. angina (17), anxiety disorders (18) and patients with EDs report even poorer HRQoL than clinically depressed patients (15).

HRQoL can be measured in different ways. Generic questionnaires such as the Short Form-36 (SF-36) have been developed for use in any population and can be used as health surveys or to compare different diseases. In more recent years, several disease-specific questionnaires have been developed taking into account the nuances of the specific disease. A few HRQoL questionnaires have been developed and validated for use in ED patients, but none have yet been translated and validated in Danish. It has been proposed that HRQoL measures need to be disease-specific when examining the egosyntonic-dystonic diseases within EDs (19, 20). However, one study found that the generic questionnaire SF-36 was applicable in this patient group (21). A review from 2010 aimed to evaluate the validation studies of four disease-specific questionnaires (22). The tentative conclusion was that the questionnaires were adequate in evaluating HRQoL in EDs, but the authors called for further research in the area, in particular research aiming to capture the variation in HRQoL in EDs and evaluate the HRQoL with other correlated measurements (i.e. comorbidity or severity of the disease). When measuring HRQoL, the patient is the only one who holds the answers, with the patients themselves always report HRQoL assessment.

One of the major obstacles in particular, AN treatment is the egosyntonic nature of the disorder. An egosyntonic disorder is characterized by behaviors consistent with one's self. Patients cannot distinguish their thoughts/feelings/behaviors as pathological and instead embrace it as part of their self. They are threatened by treatment as they feel it will eliminate their self. AN patients will often not seek treatment until relatives convince them to or their physical state is so severe that they have an acute medical complication.

Motivation to treat is often low and achieving compliance and patient-clinician alliance is difficult. Patients with BN, on the contrary, are often very ashamed of their thoughts and behaviors. This is characteristic of an egodystonic disease, where patients disassociate with their behavior. They often wish to improve, but are so ashamed of their disease that this can hinder treatment. Patients with BN have often been sick significantly longer than patients with AN when they seek treatment (23). Studies suggest that the thoughts of the patients are not fully egosyntonic or egodystonic, rendering large variations across patients. This aspect is not easy to handle in research studies, which can cause great variation in study results (24).

Outcome

EDs remain relatively rare in the general population but it has a profound impact on those affected and their surroundings. So far, no treatments have provided a quick rehabilitation and outcome remains poor. A large literature review from 2002 comprising a total of 5590 AN patients found that only 46.9% of patients made a full recovery, 33.5% recovered partially and 20.8% continued down a chronic path (25). Results are approximately similar for BN (14) and ED-NOS (26), with no indication of the prognosis improving (27). A complicating factor in treatment is the large proportion (approx. 30%) that relapse (28) after attaining full recovery. A number of possible predictors for outcome have been suggested (i.e. diagnosis, age, duration of disease, psychiatric comorbidity, drop out, length of follow-up time, body mass index (BMI)) (29), but results are inconsistent.

Remission

One of the major obstacles in ED research is the lack of a clear consensus on what defines remission from an ED. Many different definitions of remission have been proposed and are used in both research and clinical settings (30). A unilateral definition of recovery would facilitate comparisons across studies. However, patients with an ED and clinicians may not define recovery the same. In depressive disorders, patients viewed other aspects important of remission than those defined by the clinician (31).

Patient-reported outcome (PRO)
The use of self-assessed questionnaires is gaining footing within the medical field. During the last few decades, research and treatment settings have relied increasingly on PRO measures. The incentive to apply PRO was to increase the understanding of the patients, help align treatment expectations and monitor progress imperative to the patient. PRO measures are able to report symptoms only known to the patient and enhance the patient's feelings of self-determination in treatment. By exploring PRO, the clinicians gain valuable information not otherwise apparent when conducting clinical assessments. Inclusion of PRO, compels patients to take ownership regarding their treatment and can lead to a higher motivation to change, which in turn predicts positive treatment outcome (32). Studies in other medical fields, especially cancer research, have demonstrated discrepancies between clinician-assessed outcome and PRO (25, 33). In obsessive-compulsive disorders (OCD), it has been demonstrated that PRO measures predict outcome better than clinician-reported measures (34). Integrating PRO measures in clinical assessment can improve the clinician-patient communication and provide treatment strategies more suitable for the individual patient, in the hope of minimizing drop-out and improving outcome. Aligning expectations so that the clinician and patient are at the same stage might increase the chance of a successful treatment.

Mortality
It is well-established that the prognosis for EDs is dire, with approximately one-fifth of patients following a chronic path (27). On top of that, AN has the highest mortality rate of any psychiatric disease (35). Mortality rates have fluctuated with reports of an increased mortality rate as high as 18 times the expected (36). No clear consensus of the increased risk has been established, with a few studies reporting no increased mortality risk (37). Predictors for mortality have not been examined as thoroughly as for outcome, but have often been classified under "poor" outcome. Predictors for poor outcome prevail for mortality and have been determined as higher age at debut, lower BMI, purging behavior and psychiatric comorbidity (38). A majority of fatalities are caused by suicide (38); however causes of death reported by death certificates are highly unreliable.

Body composition & menstrual status
Several studies have investigated the association between amenorrhea and body composition in AN patients. So far, no clear consensus has been established as to which minimum weight is required to maintain a regular menstrual cycle. Several factors are involved in the establishment and maintenance of a regular menstrual cycle. Amenorrhea was formerly a diagnostic criterion for AN, but was eliminated from the 2013 DSM-5 edition. It is, however, often still used in clinical practice as an indicator of physical recovery (39, 40). Amenorrhea occurs in most AN patients, but may be disguised, as this patient group has a high prevalence of using oral contraceptives. Many factors cause amenorrhea observed in AN patients and include, among others, weight loss, starvation, malnourishment and body composition. Patients with AN have hypothalamic hypogonadism with impaired gonadotropin-releasing hormone (GnRH) and decreased levels of FSH and LH. Studies have found that patients have a prepubescent pulsatile secretion of LH, suggesting a regression of the hypothalamic-pituitary-ovarian axis (41). The amount of body fat also plays an important in role in the onset and maintenance of menses. Already in the 19 70's authors suggested a minimum threshold of 17% for menarche and 22% as a minimum for the maintenance of menses (42). Whether these thresholds are applicable to patients with AN have not yet been determined, as results are varying, indicating that other factors and thresholds may be applicable in this specific patient group. Published studies examining amenorrhea in patients with AN have found an association between weight and menses, but the results are ambiguous, with differing body mass indexes (BMI) values for the resumption of menses. Published studies have determined that patients with a resumed menstrual function have higher BMI and body fat% than their amenorrheic counterparts (Table 1). Lower premorbid BMI have also been suggested to have a positive association with the resumption of menses (ROM), which is supported by other studies finding that higher premorbid weight is associated with continued amenorrhea (43). The role of weight gain is ambiguous as some studies found larger ΔBMI leading to the ROM, while others found smaller ΔBMI resulting in ROM. Most studies were performed on small sample sizes and only a few involved dual energy x-ray absorptiometry (DXA) scans, despite these being the most accurate in determining body composition (44, 45).

Table 1: Studies examining the association between body composition and menstrual status in AN.

Author	Year	n	Age - yrs (amenorrheic)	Age – yrs (menstrual recovery)	Measures	Outcome
Dei	2008	77	23.0 (17;28)	21.5 (18,26)	BMI & DXA	Lower premorbid BMI (19.2±1.8) & smaller ΔBMI (-0.14±1.4) in patients with resumed menses. No difference in body fat or lean body mass.
Dempfle	2013	172	14.9 (1.6)	15.4 (1.3)	BMI	Higher %IBW (91.1±8.7) & BMI (18.8±1.7) in patients with resumed menses.
Ghoch	2016	54	25.0 (7.1)	25.7 (8.0)	BMI & DXA	Higher body fat percentage (27.7±5.7) in patients with resumed menses.

Golden	1997	100	16.4 (2.4)	17.4 (3.0)	BMI & skinfold measurements	Higher baseline weight (44.4±5.5) and body fat (17.2±3.8) associated with resumed menses.
Golden	2008	56	16 (1.7)	16 (1.7)	BMI	BMI between 14th-39th percentiles associated with ROM within 3-6 months.
Martini	2015	115	Not reported		BMI	Higher BMI associated with resumed menses (OR=0.7 95%CI:0.6-0.8)
Pitts	2014	37	18 (1.7)	18 (3.1)	BMI & DXA	Higher BMI (~20), body fat percentage (23.1) and larger ΔBMI associated with resumed menses.

BMI= Body mass index (kg/m2). DXA=dual energy x-ray absorptiometry scan. IBW=ideal body weight. ROM=resumption of menses.

Aim of the thesis

The aim of this thesis was to contribute to the research in the field of EDs. The thesis aimed to investigate areas that remain unclear and contribute with new knowledge regarding mortality, quality of life, outcome and body composition in a field where research results often are ambiguous.

Objectives

Study 1 HRQoL

- To report HRQoL in EDs in a large Danish cohort and determine potential predictors for poor HRQoL.
- To investigate potential differences in HRQoL, between the diagnostic groups by performing meta-analysis on existing literature.

Study 2 Outcome

- To report ED pathology (measured by the Eating Disorder Inventory – 2 (EDI-2)), clinical outcome (measured by the Morgan Russell Outcome Schedule (MROS)) in a large Danish cohort and determine predictors of high symptom score (EDI-2) and poor outcome (MROS).
- To evaluate the correlation between the patient-reported EDI-2 and SF-36 and clinician-assessed characteristics (BMI and remission status).

Study 3 Mortality

- To calculate mortality rates in a large cohort of ED patients (n=998) including AN, BN and EDNOS with a long follow-up time.
- To compare the results to data from the same catchment area published prior to the establishment of a multidisciplinary ED center.

Study 4 Body composition & menstrual status

- To examine the association between body composition measures and amenorrhea in an adult cohort of patients with a history of AN and calculate predicted probabilities for the resumption of menses.
- To investigate the association between DXA scans and BMI, to determine whether body composition measures were superior to DXA scans in predicting the resumption of menses.

Materials and methods

This thesis was based on data from the Funen Anorexia Nervosa Study (FANS), which included all patients with an ED diagnosis referred to the Centre for Eating Disorders, Odense University Hospital (Denmark) between January 1994 and December 2004. The study was approved by the local Ethics Committee and was declared in ClinicalTrials.gov (identifier: NCT00267228).

Study population

The Centre for Eating Disorders was established as a multidisciplinary centre at Odense University Hospital (Denmark) in 1994. The centre is the primary referral centre for patients with an ED on the island of Funen and is the only specialized unit for EDs in the county. Funen constitutes 9.7% of the Danish population and represents the Danish population both demographically and socioeconomically (46). Before 1994, patients referred to the hospital from their general practitioners, were treated at either the psychiatric or the somatic department (adult or child/adolescent depending on age). The departments did not have a structured collaboration and patients received the treatment deemed necessary. After 1994, all referrals were centralized in the Centre for Eating Disorders and consist of an interdisciplinary cooperation between endocrinologists, pediatricians and psychiatrists. When patients are referred to the centre they are invited to a preadmission assessment conducted by health professionals from both departments. The preadmission assessment entails a detailed history, a physical exam and the clinicians conducting the assessment establish a diagnosis and treatment course. Treatment offered in the centre consists of psychotherapy performed by psychologists or psychiatrists (cognitive, systemic or psychodynamic). Psychotherapy is either on individual level, in groups, as family therapy or as multi-family therapy. Uniformly nutritional treatment is provided and patients are monitored by an endocrinologist/paediatrician, dieticians and trained nurses. Twice a month staff meet to discuss patient progress.

All patients referred to the centre between the years of 1994-2004, who received an ED diagnosis, were identified through an electronic patient administrative system (FPAS) and included in the FANS database. All diagnostic categories were converted into the DSM-IV terminology for uniformity and included AN, BN and EDNOS. All medical charts were

systematically reviewed to obtain clinical data. The following clinical data were extracted from the medical charts:

- Age at referral
- Year of referral
- Duration of disease at referral
- BMI at referral
- Lowest recorded BMI
- Psychiatric comorbidity
- Inpatient treatment (yes/no)

In 2008, all patients identified with an ED diagnosis through FPAS, were contacted and invited to participate in the present study. Patients referred from outside of Funen County were excluded from the study as they represent a highly selected group, with severe and intractable diseases. These patients have often been through a long treatment course in their home county before being referred to the Centre for Eating Disorders in Odense. The invitations included information about the study, consent forms, the Morgan Russell Outcome Scale (MROS), the Eating Disorder Inventory-2 (EDI-2) and the Short-Form 36 (SF-36). Furthermore, it included an invitation to undergo a clinical assessment including a DXA scan. Patients who did not respond to the initial invitation within three weeks were contacted by telephone up to three times. Patients who declined the invitation or were unreachable are in this thesis referred to as non-responders. A flowchart of the participant inclusion procedure can be seen in the results section. To investigate mortality rates in the cohort we obtained data from the *"Danish national cause of death register".* All persons living in Denmark with citizenship or residence permit are assigned a personal 10-digits civil identification number. This has been mandatory by law since 1968. Since 1871 it has also been mandatory by law in Denmark to complete a death certificate in any case of death. After 1970 this registry has been fully computerized (*The Danish national cause of death register*) and include data on all deaths among Danish residents (47). At the beginning of 2012 we contacted the registry and requested information on deaths and causes hereof of all patients included in FANS. Patients were identified by their 10-digit civil identification number.

MROS

Morgan and Russell developed, in the 1970's, an assessment scale to evaluate outcome in AN. The MROS has since been used in numerous publications to assess outcome in AN. It combines information from the patient on eating behaviour, body weight, menstrual state, sexual adjustment and socioeconomic status with information on clinical status (weight and mental health) within the preceding six months to generate a general and an average outcome score (48). The general outcome score is categorized as good, intermediate or poor outcome based solely on weight and menstrual status. The average outcome score is a quantitative score ranging from 0-60 that also considers the other three areas. Although much of the information is provided by the patient, overall assessment of the information is performed by the clinician. In this study, patients were invited to complete the MROS. The MROS was developed to use in a structural clinical interview, but has previously been used retrospectively through medical chart review (49). A higher score indicates better outcome. Good inter-rater reliability has been reported for the Danish version of the scale (50).

EDI-2

The EDI was developed in the 1980's by Garner et al. (51) as a tool to assess the pathology of AN and BN. It was not developed as a tool to diagnose EDs, but as an aid in evaluating the burden of symptoms. It provides clinical information regarding the psychological and behavioral dimensions of EDs. In 1991 a revised version (EDI-2) with three additional subscales was published (52). The EDI has been used in numerous studies and in clinical practice. The questionnaire has been validated in Danish samples (53). It is a self-report measure and contains 91 items across 11 subscales measuring (1) drive for thinness, (2) bulimia, (3) body dissatisfaction, (4) ineffectiveness, (5) perfectionism, (6) interpersonal distrust, (7) interoceptive awareness, (8) maturity fears, (9) asceticism, (10) impulse regulation and (11) social insecurity. Each item is scored between 0 and 3, with 0 representing a non-problematic response. Thus, a higher total score represents a higher level of symptomatology.

SF-36

The SF-36 is a generic, self-report questionnaire measuring HRQoL. It was developed in 1992 by Ware & Sherbourne (54) and has been used extensively in ED studies, with high internal consistency reliability coefficients reported for all subscales (55). It consists of eight subscales that assess physical functioning (PF), role limitations due to physical health problems (RP), bodily pain (BP), general health perception (GH), vitality (VT), social functioning (SF), role limitations due to emotional problems (RE) and general mental health (MH). The sum for each subscale is transformed into a 0-100 scale with higher scores indicating better HRQoL. The scores can be transformed into t-scores and summarized in a mental component scale (MCS) and physical component scale (PCS), where a score of 50 represents the general population.

Clinical assessment (including DXA scan)

The clinical assessment performed at the DXA scan, was performed by a trained health professional and included height and weight measurement as well as assessment of remission status. Height was measured using a wall-mounted stadiometer and weight was measured on a calibrated platform scale. As no strict consensus has been agreed upon regarding remission status in patients with EDs (56), this study defined remission stringently with patients regarded as being in full remission when the following three criteria were met: 1) % ideal body weight (IBW) consistently above 85%, 2) no bulimic or purging episodes within the last six months and 3) no treatment with psychotropic drugs or psychotherapy within the last six months. Body composition measures, including lean body mass, total fat mass and fat percentage, were obtained by a DXA scan (Hologic, Discovery, Waltham,

MA, US) in fan bean mode. The coefficient of variation (CV) was 1.5% in our unit.

Search strategy for the meta-analysis on HRQoL

A systematic review of the existing literature was conducted using a keyword-based search in the databases PubMed and PsychInfo using the following search terms: anorexia OR bulimia OR EDNOS OR eating disorders OR binge eating AND quality of life OR QoI AND SF-36. The search terms were built from a preliminary review of the existing literature. Prior to limiting the search to the generic questionnaire SF-36, a literature search was performed on two disease-specific questionnaires (the Eating Disorders Quality of Life instrument (57) and the Health Related Quality of Life Eating Disorders questionnaire (58)), but was discarded due to an insufficient number of studies to be able to perform a meta-analysis.
The search was limited to English or Danish linguistic studies. After removing duplicates, titles and abstracts were reviewed to identify which studies were applicable for further investigation. Full-text reviews of the remaining papers were conducted, to include eligible papers. Studies were included if they:

- Included patients with an ED diagnosis
- Used the SF-36 to measure HRQoL
- Reported raw mean scores for all eight subscales of the SF-36
- Reported SF-36 as a baseline or cross-sectional value (not post-intervention)

The authors of three studies, only including summarized SF-36 scores, were contacted in the hope of obtaining the raw scores, but unsuccessfully. The authors discussed and evaluated the process on a regular basis. The first author carried out the identification of studies, data extraction and assessment. A flowchart of the selection procedure can be seen in the results section.

Statistical analyses

All statistical analyses were conducted using STATA – Data analyses and statistical software version 13.1, except the meta-analysis, which was performed using the statistical analysis software (SAS) version 9.2. Methods for statistical calculations are described separately in each paper. For unpublished results included in this thesis, the following statistical methods were applied.
Normality of data was evaluated by the Shapiro-Wilk test and visually by normal probability plots for the continuous variables. Chi^2 tests were used to assess the distribution of categorical variables. Non-normal distributed data were further evaluated with histograms, to determine distribution. Data are presented as mean +/- standard deviation (SD) for normally distributed data or median and interquartile range (IQR) for non-normally distributed data. Student's t-test, one-way ANOVA, Mann-Whitney U or Kruskal-Wallis tests were performed for comparisons, as appropriate.

Study 1 HRQoL

SF-36 subscale and component summary scores were calculated for all diagnostic groups in the cohort. Kruskal-wallis tests were performed to compare medians between the diagnostic groups. To compare the SF-36 scores from our cohort with a norm population we performed a Mann-Whitney U test. Subsequent predictor analyses were performed on all patients as one combined group. Simple regression analyses were performed to determine predictors for HRQoL, with the component summary scores as dependent variables and BMI (at referral, DXA scan, lowest recorded), age at referral, duration of disease, psychiatric comorbidity and inpatient treatment as independent variables. Subsequently, multiple regression analysis was performed to estimate the most pivotal predictor.
We investigated potential differences between HRQoL in AN, BN, EDNOS and BED in existing literature through meta-analysis. The statistical method is described in paper 1.

Study 2 Outcome

EDI scores were calculated for the cohort and medians (IQR) are reported for the three diagnostic groups. MROS outcome scores were calculated and results for patients with AN are displayed in the results section.
To determine predictors for high symptom score and poor outcome at follow-up, simple linear regression was performed with EDI-2 scores and MROS average scores as the dependent variables. BMI (at referral, at DXA scan, lowest recorded), age at referral, duration of disease, psychiatric comorbidity and inpatient treatment were used as independent variables. Subsequently multiple regression analysis was performed to estimate the most pivotal predictor. Regression analysis for MROS was only performed for AN, as the assessment tool has not been validated for BN and EDNOS.
The statistical methods applied to examine the correlation between patient-reported symptomatology (EDI-2), HRQoL (SF-36) and clinical characteristic (BMI and remission status) are described in paper 2.

Study 3 Mortality

The *"Danish national cause of death register"* was contacted at the beginning of 2012, to determine the number and causes of death in the study population. December 31st 2011 was defined as the cut-off date. Statistical methods, for calculating the standardized mortality ratios (SMRs) and comparing the results to a previously published cohort, are described in paper 3.

Study 4 Body composition and menstrual status

Statistical methods are described in paper 4.

Results

Brief summaries of the results of each study are presented below. More detailed results are available in papers 1-4.

Study participants

A total of 1064 patients were identified through FPAS as having been referred with an ED diagnosis to the Centre for Eating Disorders between 1994 and 2004. Of those, 66 patients had been referred from outside of Funen County and were excluded. Of the remaining 998 patients, 39 were male (~4%). Invitations were sent out to the remaining 998 patients, and 284 patients responded initially with only 10 patients declining the invitation. The initial non-responders (n=722) were sent written reminders, which yielded an addi-

tional 254 responses. Patients still not responding were attempted to be reached by telephone, however it was not possible to establish contact with 469 (non-responders) of the patients (47%), whereas a total of 544 patients completed at least one of the questionnaires and/or the clinical assessment (responders) (Figure 1). Responders only differed in age at referral for AN. On all other included variables responders resembled non-responders (Table 2).

Figure 1: Flowchart of participant inclusion in Funen Anorexia Nervosa Study (FANS).

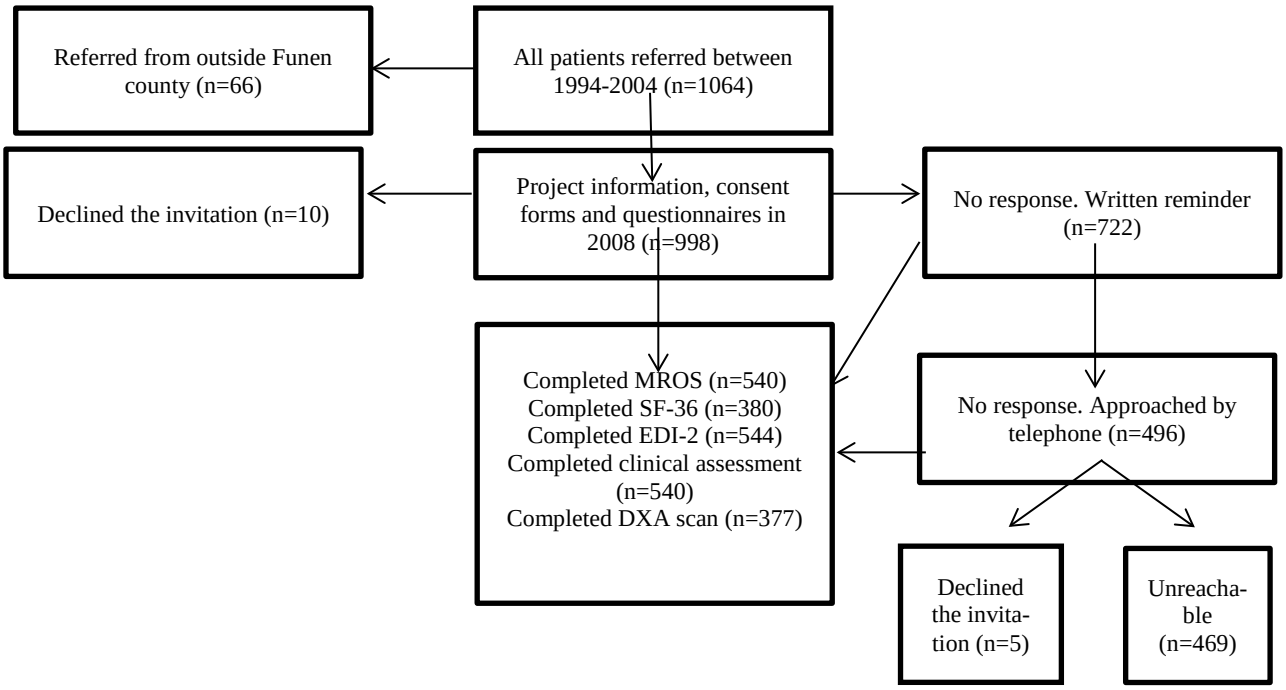


Table 2: Study characteristics divided into diagnostic groups. Two-sampled t-test (significance level p<0.05) and percentage of missing values.

	AN responders (n=217)	AN non-responders (n=176)	p-value	Missing values (%)
Age at referral	19.1 (6.0)	21.1 (9.2)	0.01	0%
BMI at referral	16.3 (2.2)	16.2 (2.8)	0.35	0%
Duration of disease	3.4 (4.4)	4.2 (6.6)	0.16	0%
Lowest recorded BMI	14.9 (2.3)	14.6 (2.4)	0.22	4%
Psychiatric comorbidity	23%	26%	0.47	14%
Inpatient treatment	50%	43%	0.22	0%
BMI at clinical assessment	18.4 (2.7)			
Full remission	52%			
	BN responders (n=204)	**BN non-responders (n=156)**	**p-value**	**Missing values (%)**
Age at referral	22.3 (6.2)	22.2 (5.8)	0.89	
BMI at referral	22.1 (4.8)	22.2 (4.5)	0.84	
Duration of disease	5.0 (4.8)	4.7 (3.8)	0.52	
Lowest recorded BMI	19.4 (3.3)	19.4 (3.5)	1.0	30%

Psychiatric comorbidity	22%	18%	0.38	16%
Inpatient treatment	10%	6%	0.23	0%
BMI at clinical assessment*	22.3 (4.0)			
Full remission	26%			
	EDNOS responders (n=118)	**EDNOS non-responders (n=125)**	**p-value**	**Missing values (%)**
Age at referral	21.2 (8.2)	20.2 (7.2)	0.32	
BMI at referral	19.9 (4.2)	19.5 (4.4)	0.47	
Duration of disease	4.0 (4.6)	3.5 (4.2)	0.38	
Lowest recorded BMI	18.7 (4.5)	18.1 (3.1)	0.28	12%
Psychiatric comorbidity	43%	48%	0.84	6%
Inpatient treatment	14%	18%	0.36	0%
BMI at clinical assessment	21.0 (4.9)			
Full remission	48%			

Study 1HRQoL

Study 1 aimed to report HRQoL in EDs in a large Danish cohort and determine potential predictors for poor HRQoL.

A total of 380 patients completed the SF-36 questionnaire. Of these, 180 patients were in remission and 200 were not in remission. SF-36 scores, stratified by diagnostic groups and remission status, are presented in Paper 2. There was no statistically significant difference in HRQoL between the diagnostic groups in our cohort as determined by Kruskal-Wallis tests (p-value>0.05). The scores were compared to a population norm (59), revealing significantly lower scores for our population on all subscales, except for PF and BP (p<0.05) (59). A visual presentation of these results can be seen in Paper 2.

Based on our data the following factors predict poor HRQoL, determined by simple regression analyses: lower BMI (at referral/lowest/clinical assessment), higher age at referral, psychiatric comorbidity and duration of disease at referral. When testing the variables in a multivariable regression model we found that psychiatric comorbidity and duration of disease were the most prominent predictors for poor HRQoL (R-squared 0.17).

Meta-analysis:

In study 1 we also aimed to investigate potential differences in HRQoL between the diagnostic groups, examined through meta-analysis on existing literature. Using the search terms described in the method section, 102 citations were identified as potentially eligible. The final number of articles for examination was reduced to seven after thorough consideration and elimination (flowchart of study inclusion can be seen in Paper 1). Across the selected studies 757 patients had an ED diagnosis; 227 with AN, 216 with BN, 166 with EDNOS and 148 with BED. The mean etimate scores for all eight subscales of the SF-36 are listed in table 3. AN was held as baseline and the estimates for BED, BN and EDNOS are reported (as well as the p-value) in relation to the baseline value.

Table 3: Mean estimate scores for AN (held as baseline) with corresponding p-values.

	Mean AN	BED (Estimated deviation from AN)	p-value	BN (Estimated deviation from AN)	p-value	EDNOS (Estimated deviation from AN)	p-value
PF	85.0	-17.5	0.1	3.1	0.8	1.2	0.9
RP	44.8	-5.9	0.8	11.8	0.6	15.5	0.6
BP	62.8	-10.8	0.5	3.9	0.8	3.5	0.8
GH	49.1	2.9	0.8	0.6	0.9	1.6	0.9
VT	37.5	-5.9	0.6	-0.7	0.9	0.9	0.9
SF	55.2	3.5	0.8	1.3	0.9	-2.7	0.9
RE	40.2	1.8	0.9	-9.3	0.7	-11.9	0.7
MH	44.4	13.4	0.3	-2.3	0.9	-1.9	0.9
PCS	60.9	-4.5	0.7	9.2	0.5	7.5	0.7
MCS	44.3	4.7	0.8	-2.5	0.4	-2.7	0.3

The mean scores and CI for the four diagnostic groups, for ED combined and for the norm were plotted in forest plots, to visualise overlapping CI. The forest plots can be seen in paper 1. We found no significant differences in HRQoL, measured by SF-36, between the diagnostic groups and found a significantly lower HRQoL in EDs compared to a population norm.

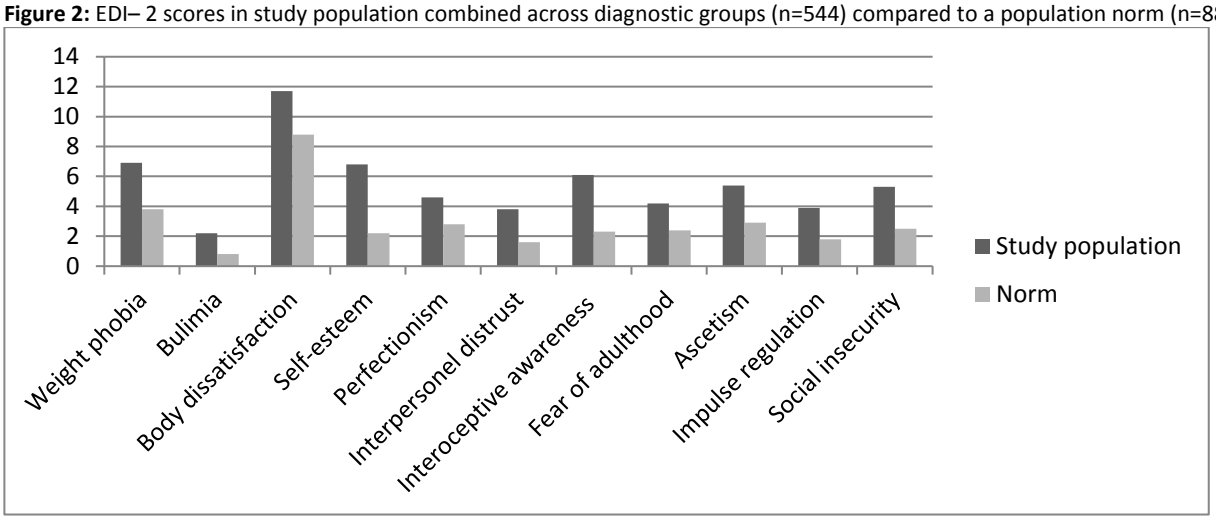
Study 2 Outcome

Study 2 was a cross-sectional study aiming to investigate ED pathology (measured byEDI-2) and clinical outcome (measured by MROS) in a large Danish cohort. We wanted to determine predictors for high symptom score (EDI-2) and poor outcome (MROS). Furthermore, we aimed to evaluate the correlation between the patient-reported EDI-2 and SF-36 and clinician-assessed characteristics (BMI and remission status).

EDI-2: More than half of the identified patients (n=544, ~55%) completed the EDI-2 questionnaires. Scores for the 11 EDI subscales (& total score) are reported in Paper 2, stratified by diagnoses and remission status, as well as results from Kruskal-Wallis rests. Two of the eleven subscales had results with significant differences between the diagnostic groups. The bulimia subscale score was higher in the BN group and fear of adulthood was higher in AN than BN.

The EDI-2 scores (for the total cohort) were compared to a population norm (53), revealing significantly increased EDI-2 scores in our population (figure 2), regardless of remission status (p-value=0.006).

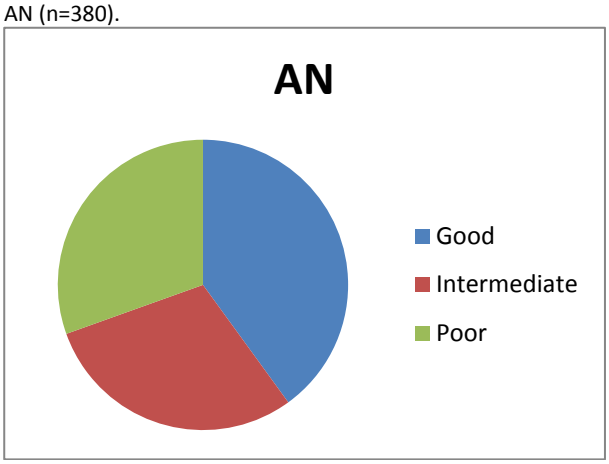
Figure 2: EDI– 2 scores in study population combined across diagnostic groups (n=544) compared to a population norm (n=881).



Simple regression analyses revealed the following factors to predict high symptom score: lower BMI (at referral/lowest/clinical assessment), duration of disease and psychiatric comorbidity. Psychiatric comorbidity was the most prominent predictor for high symptom score, determined by multivariable regression analysis, however only a weak predictor (R2=0.07).

MROS: 540 (~54%) participants completed the MROS questionnaire (of these 380 patients were diagnosed with AN). The average outcome score for AN had a mean of 42.4 (12.9). The general outcome score for AN is displayed in the following pie chart. As the MROS is only validated for use in AN, the general outcome scores for BN and EDNOS was not reported.

Figure 3: Morgan Russell Outcome Scale general score for AN (n=380).



The following factors predicted poor outcome for AN: inpatient treatment, psychiatric comorbidity, longer duration of disease, higher age at referral and lower BMI. Higher age at referral and admittance to inpatient treatment were the most prominent predictors for poor outcome, determined by multivariable regression analysis (R^2= 0.19). As would be expected, patients classified as being in full remission had significantly lower symptomatology and better outcome (p<0.01).

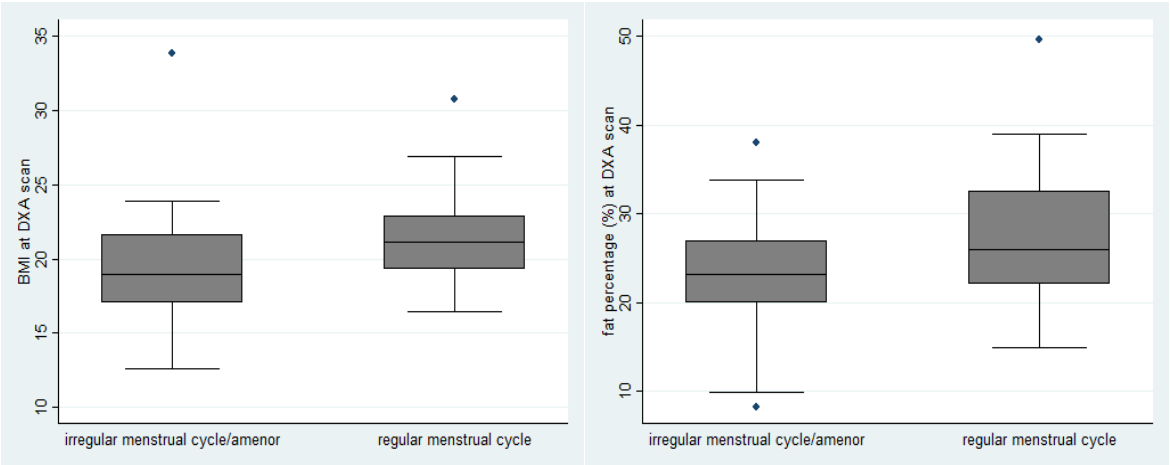
In paper 2 we investigated the correlation between PRO, measured by SF-36 and EDI-2, and clinical characteristics (BMI and remission status). There was a positive correlation between EDI score and BMI, regardless of remission status, for AN and EDNOS, representing an increase in EDI score with increasing BMI values. This was not true for BN. We found no association between clinical characteristics (BMI and remission status) and HRQoL.

Study 3 Mortality
Mortality rates for the cohort was investigated in study 3 and compared to previous published results from the same catchment area. A total of 21 patients from FANS had died by the end of 2011. When divided into diagnostic groups, reported SMRs for AN was 2.89, for BN 2.37 and for EDNOS 1.14. These ratios were significantly lower than mortality rates published by Jorgensen et al. in 1992 (60) from the same catchment area. The ratios were adjusted continuously for age and BMI by restricted cubic spline with three degrees of freedom (61) for comparison, revealing a decrease in mortality of >50%.

Study 4 Body composition and menstrual status Study 4 was a cross-sectional study aiming to investigate the association between body composition measures and menstrual status in AN. All AN responders were included, excluding patients using oral contraceptives or patients with primary amenorrhea (n=113). Characteristics of these patients were similar to the entire AN cohort on the following baseline parameters: age at referral, duration of disease at referral and BMI at referral. A total of 52 patients had amenorrhea (or irregular menstrual bleeds) at the time of the DXA scan and 61 had a regular menstrual cycle. The amenorrheic patients had significantly lower BMI and fat percentage at the DXA scan compared to patients with a regular menstrual cycle, as visualized below.

BMI and fat percentage were significant predictors of the recovery of menstrual function. Fifty percent of patients were expected to resume their menstrual function at a BMI of 19 kg/m^2 or a fat percentage of 23%. Twenty-five percent of patients were expected to resume their menstrual function at BMI 14 kg/m^2 or fat percentage 11%. Fat percentage and BMI were equally capable of predicting the resumption of menses.

Figure 4: BMI and fat percentage visualized by boxplot for the two outcome groups.



Thesis at a glance

	Study design	Sample	Methods	Aim	Conclusion
Study 1	• 1) Cross-sectional cohort study. • 2) Meta-analysis on existing literature.	I. 1) 380 patients with AN, BN and EDNOS from FANS. II. 2) Seven published studies (n=757) measuring HRQoL assessed by SF-36 in AN, BN, EDNOS and BED.	I. 1) SF-36 and clinical characteristics. II. 2) Meta-analysis.	I. 1) To report HRQoL and determine predictors of poor HRQoL. II. 2) To investigate potential differences in HRQoL between the diagnostic groups.	I. 1) HRQoL was impaired in a large Danish ED cohort compared to a norm population. No differences between the diagnostic groups. Predictors of poor HRQoL: Psychiatric comorbidity and longer duration of disease. II. 2) HRQoL in EDs impaired compared to a norm population, but no differences between the diagnostic groups.

Study 2	Cross-sectional cohort study.	540 patients with AN, BN and EDNOS from FANS.	SF-36, EDI-2, MROS and clinical characteristics.	I. 1) To report ED pathology and clinical outcome and determine predictors hereof. II. 2) To evaluate the correlation between PRO and clinical characteristics.	I. 1) High symptom score and poor outcome in a large Danish cohort, similar to previous publications. Predictors of poor outcome: Psychiatric comorbidity, higher age at debut or the presence of inpatient treatment. II. 2) EDI scores correlated with BMI, regardless of remission status for AN and EDNOS.
Study 3	Retrospective cohort study.	996 patients with AN, BN and EDNOS from FANS.	SMR, crude ratios adjusted by cubic spline.	To investigate mortality rates in a large, retrospective Danish cohort and compare these with previous published results.	SMR for AN: 2.89; BN:2.37; EDNOS: 1.14. Results significantly lower than previous mortality data from same catchment area.
Study 4	Cross-sectional cohort study.	113 patients from FANS with AN.	DXA scan, BMI, clinical characteristics.	To investigate the association between body composition measures and menstrual status.	BMI and fat % predict the recovery of menses. DXA not superior to BMI in predicting the resumption of menses. Approx. 50% of patients expected to resume their menses at BMI 19kg/m2 or fat % 23%.

FANS=Funen Anorexia Nervosa Study include all patients referred to the Centre for Eating Disorders, Odense, between 1994-2004.

General discussion

Study 1 HRQoL

In study 1, we established that HRQoL was decreased in a large Danish cohort of patients with EDs compared to the general population in all patients, regardless of remission status. These findings are in line with previous publications (15), finding significantly impaired HRQoL in patients with EDs, as well as patients recovered from an ED. In this study we defined remission stringently, expecting patients in the remission group to resemble the general population. The results of study 1 (paper 2), concludes that despite the stringent definition, patients in remission are still affected by their former disease in HRQoL. We found no significant differences between the diagnostic groups. This finding is supported by our meta-analysis, confirming no difference between the diagnostic groups (62). Our data did not include information regarding binge-/purging behavior, which have previously been reported to predictor HRQoL (63, 64). When examining predictors for HRQoL, we found lower BMI, higher age, psychiatric comorbidity and longer duration of disease to predict poor HRQoL. This is in accordance with previous published results (65, 66). Especially comorbid psychopathology plays a pivotal role in patients' everyday life, why one of the major limitations of the meta-analysis was not being able to adjust for psychiatric comorbidity. It is likely that the diagnostic groups included differed from one another in terms of comorbid depression, anxiety, substance abuse, dysfunctional personality traits, etc. However, it seems that psychiatric comorbidity is equally prevalent across the diagnostic groups (67). With no apparent difference in prevalence of comorbid pathology, the variable would possibly not contribute to detecting differences in HRQoL, why we argue that our findings of HRQoL are still plausible despite not adjusting for comorbid psychopathology. Axis 1 disorders are the most common psychiatric comorbidities in EDs, with more than half of the patients suffering from major depression (68). The depression experienced in patients with EDs is often linked to the under-/malnourishment. However, Braun et al. found that almost half of their study sample experienced depressive symptoms prior to the debut of an ED (69). However, results from that study found that patients with AN were more likely than patients with BN to debut their ED prior to their depressive symptoms. This supports the fact that the severe undernourishment in AN is a direct cause of the depression. Nonetheless, data regarding psychiatric comorbidity was not available for inclusion in the meta-analysis examining potential differences between the diagnostic groups, but findings from our Danish cohort and several other publications support the fact that psychiatric comorbidity is prevalent in EDs and do contribute to poor HRQoL. In the meta-analysis we were not able to establish any differences in HRQoL between the diagnostic groups (62). This is contrary to previous reports of BED showing the most impaired HRQoL among the diagnostic groups (65). Our meta-analysis is the first, to our knowledge, that has pooled data from existing HRQoL studies performed in EDs. Our results support the inclusion of BED as a diagnosis in the DSM-5, as patients with BED report impaired HRQoL comparable to the other EDs. The inclusion of BED as an independent diagnosis

can facilitate health legislations in providing treatment for this patient group in line with well-established treatments provided for AN, BN and EDNOS. The methodology regarding the included studies in the meta-analysis is problematic due to the heterogeneity of the studies. Participants were recruited for the studies under different circumstances. Some participants were likely drawn from groups with generally worse health and/or worse psychopathology than others and this questions their comparability. Some of the included studies relied on self-reported ED symptoms to form the basis of the diagnosis, however data have been published to support the validity of self-reported ED symptoms (70). Comparing patients diagnosed via self-report with someone diagnosed by an expert in EDs is problematic, however the heterogeneity of included studies represent an invincible inherent limitation of meta-analysis in general. Data from our cohort and the meta-analyses supports the fact that patients with EDs have impaired HRQoL. Psychiatric comorbidity, BMI, age and duration of disease predict HRQoL in EDs and no significant differences could be detected between the diagnostic groups, neither in data from a large Danish cohort nor through meta-analysis on existing literature.

Study 2 Outcome

In study 2 we examined the outcome (assessed by the MROS) and ED symptomatology (measured by EDI-2) in a large Danish cohort. We found, despite 41% of our cohort being in complete remission at the time of the assessment, ED symptomatology was significantly increased compared to a population norm. This increase was present, regardless of remission status. We measured outcome by the MROS which has been used in numerous publications to determine outcome in AN since its publication in the 1970's. We found that 41% of our AN patients had a good general outcome score at the final assessment, 28% had an intermediate outcome score and 31% had poor outcome. This is in line with previous publications (27). We also examined outcome assessed by MROS for BN and EDNOS which revealed quite different results than for AN with a higher proportion of good outcome. The MROS has not been validated for use in BN or EDNOS and was developed for assessing AN only. Therefore, we have chosen not to report the outcomes assessed by MROS for BN and EDNOS as these outcomes should not be taken into account.

We also wanted to examine the correlation between PRO, assessed by EDI-2 and SF-36 and clinical characteristics. To perform these analyses we correlated EDI-2 and SF-36 scores with BMI and remission status determined by a clinician.

We found a high association between EDI-scores and BMI for AN and EDNOS, independent of remission status, representing an increase in symptomatology with increasing BMI. This supports the low level of agreement between PRO and clinical observations reported in other medical fields (34, 71). Including PRO in the assessment of patients is gaining momentum and our study supports the continued use of PRO measures, as clinical data does not clarify all aspects of outcome in EDs. Therapeutic alliance is crucial for a good treatment outcome (72). Gaining knowledge regarding the patient's perception of their disease and how this correlates to clinician assessed characteristics is valuable in enhancing this alliance. Detecting discrepancies between good clinical characteristics and poor PRO, provides the clinician with information that despite good objective markers, the patient might not perceive the outcome as good. These discrepancies can result in treatment drop-out or relapse. Identifying patients with poor PRO, despite being categorized as in remission by the clinician, can potentially prevent relapse with enhanced treatment focus on these patients. The results of this study supports incorporating PRO in future research and clinically when assessing outcome.

Study 3 Mortality

In study 3, our data revealed an increased risk of premature death close to three times the expected (73). Our results were lower than those published recently in a large prospective study by Fichter et al. including 5839 patients who had received inpatient treatment for a minimum of 21 days (74). The authors found an increased risk of premature death for AN of almost six times the expected, which differed from our SMR of 2.86 for AN. The inclusion of solely inpatient treated patients may explain the difference between the two SMRs, as patients receiving inpatient treatment often have a more severe course of their disease. We compared our results to previously published data (Joergensen et al.) from the same catchment area and found a significant decrease in mortality over time (60). The interesting aspect of comparing these two cohorts was the establishment of a specialized ED centre in the latter cohort. Patients in the Joergensen cohort were significantly older, had lower BMI and the cohort consisted of fewer participants. The increase in incidence in our cohort could be due to increased awareness of EDs during the later period, which may have brought less severe cases to care. This is supported by Smink et al. who found a stable incidence rate over the past decade, but an increase in the 15-19 year old girls (6). It is not clear if the increase in this age group is due to the increased awareness surrounding EDs or an earlier debut age. The decrease in age and increase in BMI in our cohort hints that the participants had less severe symptomatology. Unfortunately we did not have data from either cohort regarding severity of disease. It would have strengthened the study considerably had we obtained e.g. EDI or other psychopathology measurements to compare the patient's psychopathology. We attempted to respond to this limitation by adjusting for BMI as an indicator of disease severity. When comparing mortality rates in the two cohorts we adjusted for BMI, age and diagnoses and found that the decrease was still significant and noticeable. Many other factors may have impacted the decrease in mortality, but due to the limitation in data these were not tested. However, the obvious cause of higher age and lower BMI in the Joergensen cohort could not explain the difference. So the conclusion remains, that the striking difference in SMR partly could be attributable to the organizational changes in treatment, similar to what others have suggested (75-77).

Study 4 Body composition and menstrual status

The correlation between body composition measures and menstrual status was investigated in study 4, as well as predicted probabilities of resuming a regular menses. In study 4,

we found that fat percentage and BMI were the most prominent predictors of the resumption of menstrual status in a cross-sectional study with retrospective data of 113 adult AN patients. These findings are in line with previous publications stating these factors as pivotal in regaining menstrual function (78, 79). However, numerous other factors impact ovarian function, which is demonstrated by the low R-squared value (0.14) obtained by the regression analyses. We conducted post-estimation predictions in order to provide clinicians with cut-off values for BMI and fat percentage. Based on data from our study, half of the patients were predicted to resume their menses at BMI 19/fat percentage 23. These findings differ from previously published results (80, 81), as our threshold for the resumption of menses was higher. Our patients were older than patients included in the aforementioned studies and had a longer duration of disease, which might impact the differing results. Clinicians may observe a resumed menstrual status despite the patient being severely underweight. This is supported by our results, with as many as 25% of patients were predicted to resume their menstrual status at BMI 14/fat percentage 11. In a clinical setting, BMI is easy, quick and inexpensive to obtain. The general perception has been that body composition assessed by imaging would provide a more accurate estimate. In study 4, we determined that DXA scans were not superior to BMI in predicting the recovery of menstrual status. This is valuable information as many amenorrheic patients are eager to know when they can expect their menses to return. Providing them with an easily available cut-off, such as the reported BMI, is valuable.

Strengths and limitations

- To our knowledge, we were the first to perform a meta-analysis on HRQoL in EDs
- Our data included a large number of patients (n=998)
- Our data included patients with AN, BN and EDNOS, whereas most studies have predominantly focused on AN.
- From time of referral to final clinical assessment we had a mean time of 8.9 years. Due to the persistent and often chronic course of an ED, a minimum observation time of 4-5 years is recommended in follow-up studies (27). Research performed on EDs often has limited follow-up time.
- We were able to compare mortality data from our cohort to previously published data from the same catchment area.
- Large cohort of AN patients participated in the DXA scan.
- The generic questionnaire SF-36 was used to assess HRQoL. This may have been inferior in catching the nuances of an ED. This limitation was, however, unavoidable, as disease-specific questionnaires have not yet been validated in Danish.
- More than half (54%) of the referred patients participated in the final assessment. The large number of drop-out is common in ED research and may be explained by the patients' considering themselves to be treatment completers and not wanting to participate in anything reminding them of their disease.
- We had limited clinical data available both at baseline and at the final assessment. It is likely that many other variables could affect the investigated outcomes.
- Only 28% of our entire ED sample reported psychiatric comorbidity, which is low compared to previous reported rates (82). This large variance is most likely due to methodological differences, and a limitation of our study was the non-systematic approach in collecting data on comorbidity, reflected in the 14% missing values.
- Biomarkers, information regarding exercise and nutritional information would have strengthened study 4. The lack of these variables is regarded as a limitation and may explain why only 14% of the variation in menstrual recovery could be explained by the tested independent variables.

Future perspectives

Awareness of EDs has increased over the last decades, which has led to more research in the area. There are still a lot of unknown factors regarding the etiology, outcome and prognosis. This study has contributed with results regarding HRQoL, outcome, mortality and menstrual status. However, more research is warranted to facilitate treatment strategies in the quest of improving prognosis. So far, prognosis is poor with a large proportion of patients following a chronic course. These patients may be helped better by focusing on increasing HRQoL instead of striving towards complete remission. To assess HRQoL, future studies should use disease-specific questionnaires, developed to catch the different nuances of EDs. Results from our study support the continued use of PRO and recommend the incorporation of these in future outcome assessments and remission definitions. Our study found that mortality rates were decreased after the formation of a specialized unit. A future study might be able to include other variables that could have impacted the results, to determine the effect of specialized treatment on mortality. Prospective studies should be conducted to determine other factors influencing the recovery of menstrual status.

Summary

Eating disorders (EDs) comprise a wide range of symptoms, with severe psychological and physical implications for the patient. EDs include anorexia nervosa (AN), bulimia nervosa (BN) and until 2013 eating disorder not otherwise specified (EDNOS), if criteria for AN or BN were not met. Patients suffering from an ED have poor prognosis, with more than half of AN patients not obtaining complete remission. One-fifth develops a chronic disease. EDs have an increased risk of premature death and patients with EDs report poorer quality of life (QoL) compared to both the general population and other psychiatric/somatic diseases. Patients who, apparently, obtain complete remission will still be affected in QoL when compared to a healthy reference group. Treatment is complicated by high drop-out rates, hence making large retrospective follow-up studies difficult to conduct. The multiple endocrine disturbances as a result of the severe malnourishment in AN often result in amenorrhea and a weight goal for remenorrhea has been ambiguous.

This thesis encompasses results from four studies examining the abovementioned challenges and is based on a large retrospective cohort of ED patients referred to a highly specialized ED treatment unit.

Study 1: QoL in EDs was reported for a large retrospective Danish cohort. Furthermore, meta-analysis on existing published literature was performed to determine potential differences between the diagnostic groups. QoL in EDs was significantly decreased compared to the general population and no difference between the diagnostic groups was established.

Study 2: ED pathology (measured by the Eating Disorder Inventory – 2 (EDI-2)) and outcome (measured by the Morgan Russell Outcome Schedule (MROS)) was reported for a large retrospective Danish cohort. The correlation between the patient-reported measurements (SF-36 & EDI-2) and clinician-assessed characteristics (BMI and remission status) was investigated in a group of ED patients (n=383). A high association between EDI scores and BMI was observed in AN and EDNOS, despite remission status, representing an increase in symptomatology with increasing BMI. This was not present in BN. We found no association between HRQoL and BMI in any of the diagnostic groups.

Study 3: Mortality rates were calculated in a large group of ED patients (n=998) including AN, BN and EDNOS with a long follow-up time. We found a SMR of 2.9 for AN, which was considerably lower than previous published results. We compared the results to data from the same catchment area published prior to the establishment of a multidisciplinary ED center. Patients with EDs had a significantly increased risk of premature death compared to the general population; however the mortality rates had decreased since the formation of the ED unit.

Study 4: The association between body composition measures and amenorrhea was studied in a cohort of adult patients with a history of AN (n=113) and predicted probabilities for the resumption of menses was determined. We found a high association between DXA scans and BMI in predicting the resumption of menses. Half of the patients were predicted to resume their menstrual status at BMI 19/fat percentage 23, however at BMI 14/fat percentage 11 still 25% of patients were predicted to resume their menses.

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