HEALTH-RELATED QUALITY OF LIFE AND COST-UTILITY IN BULIMIA NERVOSA AND ANOREXIA NERVOSA IN WOMEN

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ABSTRACT

Pohjolainen Veera. Health-related quality of life and cost-utility in bulimia nervosa and anorexia nervosa in women.

Eating disorders (ED) are serious medical conditions leading to high mortality and having a major impact on the health-related quality of life (HRQoL) of the sufferers. HRQoL is the most commonly used measure of the quality of life subconcept, assessing one’s life specifically in relation to health. In addition, the costs of treating EDs are considered high. Despite these facts, the cost-effectiveness of treatment in terms of quality-adjusted life years (QALYs) (i.e. cost-utility) has not previously been studied. There is no information on the long-term quality of life in eating disorders, and the prognostic factors regarding HRQoL are undetermined.

The aims of this naturalistic follow-up study were to measure the cost-utility (i.e. the cost per QALY) of the treatment of bulimia nervosa (BN) (Study I) and anorexia nervosa (AN) (Study II), to identify prognostic factors related to HRQoL in AN using the Bayesian method (Study III) and to measure the long-term development of HRQoL in AN and BN (Study IV). The study participants comprised 72 AN (mean age 23 SD 7.3) and 110 BN (mean age 25 SD 6.3) patients, who were mainly young females, entering treatment in the Eating Disorder Unit of Helsinki University Central Hospital, Finland, from June 2002 to December 2003. The Eating Disorder Unit provides treatment at the tertiary care level for adult ED patients within a catchment area of approximately 1.5 million people. Most treatment is provided at the outpatient level, but day patient treatment and inpatient wards are also available. The patients were asked to complete the 15D HRQoL questionnaire and the Eating Disorder Inventory (EDI) questionnaire, as well as a specific questionnaire developed for the needs of this study before the start of treatment. Follow-up questionnaires were mailed at 6 months, 2 years and approximately 8 years after the beginning of the treatment. All patients received normal hospital treatment and were followed up in a naturalistic setting in order to gain more information on the everyday-life effectiveness of ED treatment. Direct hospital costs concerning the treatment of individual patients in the Eating Disorder Unit were obtained from the clinical patient administration system (Ecomed®).

The quality-adjusted life years (QALYs) gained were calculated and the cost-utility was assessed. Two assumptions based on the development of HRQoL in eating disorders were made: the best-case scenario (i.e. the most optimistic scenario) and the base-case scenario (i.e. the most pessimistic scenario). Prognostic factors concerning AN were investigated based on a
Bayesian approach, which allows the analysis of small data sets, and was performed using a naïve Bayes classifier.

The baseline HRQoL of BN and AN patients was poor, but improved during the follow-up (6 months in BN, 2 years in AN). The cost per QALY in BN varied from €1455 (best-case scenario) to €16 481 (base-case scenario) (€4428 to €19 663 discounted 5%). In AN, the cost per QALY varied from €5296 (best-case scenario) to €64 440 (base-case scenario) (€11 559 or €71 600 discounted 3%), depending on the assumptions used in the analysis.

In Study III, a set of prognostic factors was identified in AN. An impaired follow-up HRQoL score was associated with three baseline risk factors: low self-reported vitality (15D), high scores in eating control and a poor self-reported health status. A low baseline body mass index (BMI) and a high need for support in the eating dimension of the 15D predicted a low follow-up BMI.

In Study IV, the 8-year health-related quality of life in AN and BN continued to improve, but did not achieve the level of the normal population.

In conclusion, the costs of treating AN have been considered high, but in our study, the cost-utility was in the same range as other interventions investigated in our hospital. The cost per QALY in BN was less than the guidelines recommend, and in AN the cost per QALY was in the range the commonly cited guidelines recommend for the adoption of health care interventions, indicating that the treatment of AN and BN in young women is cost-effective and worthwhile. A set of prognostic factors regarding HRQoL was identified and the long-term HRQoL was studied. However, the participants were all female, so the conclusions can only be generalized to female samples, although this is usually the case in research regarding eating disorders. The assessment of HRQoL in ED patients can be a valuable measurement when taking into consideration the long-lasting impact of the disorder on HRQoL. More information on the everyday-life effectiveness of different treatment options should be gathered.

**Keywords:** health-related quality of life, quality-adjusted life year, cost-utility, anorexia nervosa, bulimia nervosa, eating disorders, adolescent, female, woman, youth
TIIVISTELMÄ

Pohjolainen Veera. Ahmimishäiriötä ja laihuushäiriötä sairastavien naisten elämänlaatu ja
hoidon tuloksellisuus

Syömishäiriöt ovat vakavia sairauksia, joihin liittyv korkea kuolleisuus sekä heikentynyt
terveyteen liittyvä elämänlaatu. Syömishäiriöiden hoitoa on pidetty kalliina, mutta
syömishäiriöiden hoidon kustannusvaikuttavuutta ei ole aiemmin mitattu käyttäen
laatupainotteisia elinvuosia (Quality adjusted life year eli QALY). Syömishäiriöpotilaiden
elämänlaadun pitkääikaiskehityksestä ei ole tietoa, eikä myöskään tunneta terveyteen liittyvän
elämänlaadun muutosta ennustavia tekijöitä.

Tutkimuksen tavoitteena oli mitata ahmimishäiriön ja laihuushäiriön hoidon
tuloksellisuutta käyttäen mittarina laatupainotteisia elinvuosia (QALY) ja niiden kustannuksia
(osatyöt I ja II). Osatyössä III laihuushäiriön osalta kartoitettiin tekijöitä, jotka ennustivat
laihuushäiriöstä kärsvien terveyteen liittyvän elämänlaadun ja painoindeksin (BMI)
korjautumista hoidon avulla. Tässä käytettiin apuna Bayesilaista ennustamista. Yhtenä
tavoitteena oli myös mitata syömishäiriöpotilaiden terveyteen liittyvän elämänlaadun
pitkääikaiskehitystä (osatyö IV).

Tutkimukseen osallistui 72 laihuushäiriöpotilasta (keski-ikä 23 vuotta) ja 110
ahmimishäiriöpotilasta (keski-ikä 25 vuotta). Tutkimukseen kutsuttiin ne potilaat, jotka olivat
aloittamassa hoitoa Helsingin ja Uudenmaan sairaanhoitopiirin (HUS) syömishäiriöyksikkössä
Syömishäiriöyksikkö on yli 18-vuotiaita hoitava syömishäiriöpotilaiden erityishoidon yksikkö,
joka tuottaa palveluita ensisijaisesti HUS-alueen väestölle (väestömäärä on noin 1,5 miljoonaa).
Hoito on avoitoportunotteista, mutta myös sairaala- ja päiväsairaalahoitoa voidaan tarjota.
Ennen hoidon algua potilaat vastasivat terveyteen liittyvään elämänlaadun kyselyyn (15D),
syömishäiriöoireita kartottavaan kyselylomakkeeseen (EDI) sekä tutkimusta varten
kehitetyn seurantalomakkeeseen. Seurantalomakkeet postitettiin 6 kuukauden, 2 vuoden ja 8
vuoden kuluttua hoidon alkamisesta. Seurannan aikana potilaat saivat tavanomaista hoitoa
syömishäiriöyksikössä, lisäksi hoidon kustannukset poimittiin tietokannasta, johon ne
tallentuivat (Ecomed®). Tarkoituksena oli saada lisätietoa syömishäiriöyksikön tavanomaisen
hoidon tuloksellisuudesta.

Tutkimustulosten mukaan ahmimishäiriö- ja laihuushäiriöpotilaiden terveyteen liittyvä elämänlaatu oli ennen hoitoa heikentynyt, mutta parani merkitsevästi seurannassa. Ahmimishäiriöpotilaita seurattiin 6 kuukautta(osatyö II) ja laihuushäiriöpotilaita 2 vuotta (osatyö II). QALY:n hinnaksi muodostui ahmintahäiriössä €1,455 (optimistisin laskelma) ja €16,481 (pessimistisin laskelma) (5% diskontatut hinnat €4,428 ja €19,663) ja laihuushäiriössä €5 296 (optimistisin laskelma) ja €64 440 (pessimistisin laskelma) (diskontattuna 3% vastaavat luvut €11 559 tai €71 600).

Osatyössä III löydettiin laihuushäiriöön liittyviä ennustetekijöitä: heikentynyt energisyynen kokemus, runsas syömisen kontrollointi ja kokemus huonosta terveydentilasta hoidon aluksi ennustivat, että terveyteen liittyvä elämänlaatu oli edelleen heikentynyt seurannassa. Alku vaiheen matala painoindeksi ja lisääntynyttä joustavuutta (15D) ennusti sitä, että painoindeksi ei saavuttanut normaaliarvoa seurannassa.

Osatyössä IV seurattiin syömisähiriöpotilaiden terveyteen liittyvää elämänlaatuja 8 vuoden kuluttua hoidon alkamisesta. Terveyteen liittyvä elämänlaatu koheni seurannassa, mutta oli edelleen heikentynyt verrattuna normaaliarvoa seurannassa.


Yhteenvetona voidaan todeta, että vaikka syömisähiriöpotilaiden hoitoa on pidetty kalliina, oli se QALY-jen laskennan avulla kustannusvaikuttavaa. Laihuushäiriössä löydettiin terveyteen liittyvän elämänlaadun ennustetekijöitä ja elämänlaadun pitkääikaiskehityksestä saatii lisätietoa. Tutkimuksen osallistuneet potilaat olivat naisia, joten tuloksia ei voi yleistää miehiin. Elämänlaatumuittausten käytännön syömisähiriöpotilaiden hoidossa voi antaa lisätietoa sairaudesta varsinkin kun tämän potilasryhmän terveyteen liittyvää elämänlaatua oli vielä kahdeksan vuoden kuluttua hoidon alkamisesta heikentynyt. Lisää tietoa tarvitaan erilaisten hoitojen arvikaikututtavudesta syömisähiriöissä.
Avainsanat: ahminishäiriö, laihuushäiriö syömishäiriöt, laatupainotteinen elinvuosi (QALY), kustannusvaikuttavuus, elämänlaatu, nuoruusikä
LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original studies, referred to in the text by their Roman numerals I–IV.


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# ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AN</td>
<td>Anorexia nervosa</td>
</tr>
<tr>
<td>BN</td>
<td>Bulimia nervosa</td>
</tr>
<tr>
<td>BED</td>
<td>Binge-eating disorder</td>
</tr>
<tr>
<td>BMI</td>
<td>Body-mass index</td>
</tr>
<tr>
<td>CBT</td>
<td>Cognitive-behavioural therapy</td>
</tr>
<tr>
<td>CEA</td>
<td>Cost-effectiveness analysis</td>
</tr>
<tr>
<td>COI</td>
<td>Cost-of-illness study</td>
</tr>
<tr>
<td>DSM</td>
<td>Diagnostic and Statistical Manual of Mental Disorders</td>
</tr>
<tr>
<td>ED</td>
<td>Eating disorder</td>
</tr>
<tr>
<td>EDI</td>
<td>Eating disorders inventory</td>
</tr>
<tr>
<td>EDNOS</td>
<td>Eating disorder not otherwise specialized</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td>HRQoL</td>
<td>Health-related quality of life</td>
</tr>
<tr>
<td>ICD</td>
<td>International Statistical Classification of Diseases and Related Health Problems</td>
</tr>
<tr>
<td>IPT</td>
<td>Interpersonal therapy</td>
</tr>
<tr>
<td>PRO</td>
<td>Patient-reported outcome</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized controlled trial</td>
</tr>
<tr>
<td>SSRI</td>
<td>Serotonin-specific reuptake inhibitors</td>
</tr>
<tr>
<td>SMR</td>
<td>Standardized mortality ratio</td>
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<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>QALY</td>
<td>Quality-adjusted life year</td>
</tr>
<tr>
<td>QoL</td>
<td>Quality of life</td>
</tr>
<tr>
<td>15D</td>
<td>15D instrument</td>
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1 INTRODUCTION

Eating disorders (ED) usually start at the age of 12–24 years and affect adolescent girls and young adult women. EDs are divided into three categories: anorexia nervosa (AN), bulimia nervosa (BN) and atypical eating disorders (EDNOS). Binge-eating disorder (BED) is typically considered to be an EDNOS (Fairburn and Harrison, 2003). Increased mortality (Agras, 2001; Crow et al., 2009; Suokas et al., 2013; Chesnye et al., 2014), severe physical and psychosocial morbidity (Fairburn and Harrison, 2003; Treasure et al., 2010) are often associated with EDs.

Several studies have investigated the treatment and outcome in EDs. However, the functional impairment caused by EDs has previously been overlooked. In the last two decades, there has been increased interest in examining the health-related quality of life (HRQoL) in EDs. QoL comprises many areas and health is only one of its determinants (Bowling, 1996). The health-related quality of life (HRQoL) is a subconcept of QoL. The measurement of HRQoL directly reflects the patient’s viewpoint and not that of health-care professionals. HRQoL is often considered in terms of how it is negatively affected, with illness causing impairment and functional limitation and finally disability (Verbrugge and Jette, 1994).

ED patients suffer from impaired HRQoL compared to the general population (Padierna et al., 2000; de la Rie et al., 2005, Abraham et al., 2006, McHugh et al 2007, Jenkins et al., 2011). Although there has been increasing interest in studying HRQoL in EDs, to our knowledge, no studies have followed patients for longer than three years after the start of treatment. Long-term data on the development of HRQoL after treatment are lacking. There is also limited information on the prognostic factors that may predict the treatment outcome measured with the HRQoL. Furthermore, the role of the baseline HRQoL in predicting the AN outcome is poorly understood.

The economic burden of eating disorders is substantial (Simon et al., 2005), although the available information probably underestimates the costs (Stuhldreher et al., 2012). Cost-utility analysis is a type of cost-effectiveness analysis that examines the costs and effectiveness of therapies by using the quality-adjusted life year (QALY) gained as its unit of effectiveness. Cost-utility analyses are therefore considered as important measures both for reporting cost-effectiveness results in the literature and for informing policy decisions on the allocation of health care resources (Pirraglia et al., 2004). The calculation of cost per quality-adjusted life year (QALY) is based on HRQoL scores and the costs of treatment.
To our knowledge, no studies so far have used QALYs as an outcome measure in AN or BN in a naturalistic treatment setting. The aim of Studies I and II was to measure the cost per QALY in BN and AN and compare this with other somatic treatments investigated in our hospital. In Study III, the aim was to find prognostic factors in AN using a Bayesian method. In Study IV, the long-term quality of life of eating disorder patients was measured.

2 REVIEW OF THE LITERATURE

2.1 Bulimia nervosa

Bulimia nervosa (BN) was first named and described by Gerald Russell in 1979 (Russell, 1979), and first included in the Diagnostic and Statistical Manual of Mental Disorders in 1980 (DSM-III, American Psychiatric Association 1980). BN is characterised by recurrent episodes of binge eating and secondly by inappropriate compensatory behaviour (vomiting, purging, fasting or exercising, or a combination of these) in order to prevent weight gain. In BN, self-evaluation is strongly influenced by body shape and weight. People with BN also suffer from a subjective feeling of loss of control over eating when they are binge eating (NICE Guideline, 2004).

2.1.1 Diagnosis of bulimia nervosa

The central features of BN, according to the diagnostic criteria of ICD-10 (10th version of the International Statistical Classification of Diseases and Related Health Problems), are recurrent episodes of overeating in which large amounts of food are consumed in short periods of time (at least twice a week for 3 months), preoccupation with eating and a strong desire or a compulsion to eat, attempts to counteract the fattening effects of food, for instance by self-induced vomiting, the use of appetite suppressants, alternating periods of starvation, and in addition, BN patients have a self-perception of being too fat, with an intrusive dread of fatness.
In atypical bulimia nervosa (BN), the same criteria apply as in BN, but not all of the criteria must be fulfilled. In the literature, atypical BN is often described as “broad BN”.

2.1.2 Prevalence

Bulimia nervosa usually starts in young adolescence (age 10–19 years) (Currin et al., 2005). The prevalence of BN in the literature varies depending on the screening method, population and the diagnostic criteria used. In women, the estimated lifetime prevalence is from 0.9 to 2.9% (Wade et al., 2006; Hudson et al., 2007; Preti et al., 2009). In a large gender-mixed community sample of 14- to 24-years-olds (n = 3021), the cumulative lifetime incidence of BN was 1.2 (Nagl et al., 2016). A Finnish twin study reported the prevalence of bulimia to be about 2.3% in a community sample (n = 2881) (Keski-Rahkonen et al., 2009). In a Finnish sample of adolescents (n = 595), the lifetime prevalence for females age 18 was 0.4% for bulimia nervosa (BN) (Isomaa et al., 2009). In men, the lifetime prevalence of BN has been 0.1–0.5% (Hudson et al., 2007; Woodside et al., 2001). In a large (n = 2230) community cohort of adolescent women, the lifetime prevalence of DSM-5 BN was 0.8% (Smink et al., 2014).

2.1.3 Medical complications of compensatory behaviours

In both AN and BN, severe problems can be caused by compensatory behaviours. For example, purging can cause severe electrolyte and acid-base alterations. Excessive vomiting can result in persistent gastric acid reflux, leading to dysphagia and dyspepsia (Westmoreland et al., 2016), and oesophageal malignancy in BN has even been reported (Dessureault et al., 2002). The repeated exposure to stomach acid can cause dental erosion (Uhlen et al., 2014). Parotid gland enlargement, sialadenosis, is a common feature of self-induced vomiting (Coleman, 1998).

The most dangerous medical complication of self-induced vomiting relates to electrolyte and acid-base changes. Metabolic alkalosis and hypokalaemia are the most common abnormalities. With vomiting, this is due to the loss of both acid and potassium in the vomitus. The potentially severe degrees of hypokalaemia can cause cardiac arrhythmias and can be one of the causes of mortality in BN (Crow et al., 2009; Westmoreland et al., 2016). BN patients can also abuse syrup of ipecac to accomplish vomiting. Ipecac contains a cardiac toxin (emetine)
that can cause irreversible cardiomyopathy and severe congestive health failure (Ho et al., 1998).

Excessive laxative abuse can cause hypokalaemia. In addition, laxative abuse can cause rectal prolapse, diarrhoea, haemorrhoids and haematochezia (Xing et al., 2001; Malik et al., 1997). Chronic laxative abuse can result in permanent harm to the peristalsis of the colon. Consequently, the colon is converted into an inert tube and severe constipation ensues, which may necessitate a colectomy (Joo et al., 1998).

### 2.1.4 Psychiatric comorbidities

In a large, nationally representative, population-based study conducted by Hudson et al. (2007), it was found that among individuals with an eating disorder, those with BN were at highest risk of a comorbid disorder (94.5% of the individuals with BN had at least one comorbid disorder). BN is often associated with affective disorders (McElroy et al., 2006), with 80–90% reporting at least one episode during their lifetime (Godart et al., 2015), and with alcohol misuse (Gadalla et al., 2007; Bulik et al., 2004a).

There is also an association with personality disorders (Braun et al., 1994, van Hanswijck de Jonge et al 2003). In a study of BN and personality disorders in college women, 61% of BN met the criteria for a personality disorder. The most typical of these was borderline personality disorder (34.7%) (Schmidt and Telch, 1990). Evidence suggests that the course of illness (Thompson-Brenner et al., 2008) and treatment outcomes in BN (Hayes et al., in press) are associated with personality constructs. Researchers have also identified a “multi-impulsive BN group” (Lacey and Evans, 1986; Fichter et al., 1994) categorized by three or more risky behaviours (alcohol abuse, drug abuse, self-harm, suicide attempts, stealing and/or sexual promiscuity) (Myers et al., 2006).

### 2.1.5 Mortality

In a meta-analysis, the weighted mortality rate (i.e., deaths per 1000 person-years) in BN has been 1.7 and the standardized mortality ratio 1.93 (Arcelus et al., 2011). In a Finnish study, the hazard ratio (HR) for suicide was elevated in broad BN (HR 6.07; 95% CI 2.47–14.89) (Suokas et
al., 2013). In a study conducted in the US, the crude mortality rate for BN was 3.9 and the mortality rate was elevated both for all causes and suicide (Crow et al., 2009).

2.1.6 Treatment of bulimia nervosa

There is a strong evidence-base that in BN, cognitive-behavioural therapy (CBT) and interpersonal psychotherapy (IPT) reduce binge eating (Hay et al., 2009). However, the binge remission rates at the end of CBT are only 30–40% (Hay et al., 2009). IPT is as efficacious as CBT, but it has shown a slower response of symptom change than CBT (Shapiro et al., 2007; Hay et al., 2009). Both group and individual therapy are effective. People over 18 years old who receive CBT will probably benefit from taking serotonin-specific reuptake inhibitors (SSRI) (NICE Guideline, 2004; Hay et al, 2001). SSRI medication during 8 weeks can reduced binge eating by 50% (Balcaltchuk and Hay, 2003). Self-help approaches that used highly structured CBT treatment manuals have been promising (Hay et al., 2009).

2.1.7 Prognosis of bulimia nervosa

Only a minority of BN cases are detected by healthcare providers (Mustelin et al., 2015; Keski-Rahkonen and Mustelin, 2016). Keel and Brown (2010) examined studies conducted between 2004–2010 and found that the remission rates for bulimia nervosa vary considerably depending on the length of the follow-up period. The lowest rates (27–28%) were reported with a one-year follow-up, and the highest rates (up to 74%) were reported in studies with a 5- to 20-year follow-up. One study (Ben-Tovim et al, 2001) assessed the five-year outcome based on the Morgan-Russell-Hayward criteria: on follow-up, 76% of those with a history of treatment had a good outcome and only 2% had a poor outcome. In a twelve-year follow-up study by Fichter and Quadflieg (2004), it was found that the majority of patients (70%) were in remission, while 23.3% suffered from an eating disorder. They also found the total EDI scores to be worse at the two-year follow-up than on discharge, but the scores had reached the discharge level at six years and had significantly further improved at the 12-year follow-up. In a study by Keel and
colleagues following 222 BN patients for a mean of 11 years, about 70% of the patients were in full or partial remission, but 11% still met the criteria for BN (Keel et al., 1999). In a population-based study by Fairburn and colleagues (2000) examining the natural course of BN, there was a significant improvement in the EDE score over a period of five years.

Across studies on BN, psychiatric comorbidity and general psychiatric symptom severity have emerged as poor prognostic indicators (Fichter et al., 2004; Clausen, 2008). Avoidant personality disorder (Grilo et al., 2007) and a family history of alcohol abuse (Bogh et al., 2005) have predicted a worse outcome.

2.2 Anorexia nervosa

Anorexia nervosa-like syndromes date to the practice of fasting by medieval saints, but the clinical description first appeared in the 17th century by Morton (Silverman, 1983). The British physician William Gull and the French physician Henri Laseque provided the first modern accounts of the condition, the essential features of which have remained unchanged to this day.

People suffering from anorexia nervosa (AN) have a drive to thinness, which results in weight loss and a refusal to maintain a normal body weight. In AN, a widespread endocrine disorder develops as a consequence of poor nutrition (NICE Guideline, 2004). AN patients additionally suffer from many medical problems, such as osteoporosis, cardiovascular problems and psychological problems (Agras, 2001).

2.2.1 Diagnosis of anorexia nervosa

The central features of AN, according to the ICD-10 diagnostic criteria, are weight loss, or a lack of weight gain in children, leading to a body weight at least 15% below the normal or expected weight. The weight loss is self-induced, the patients suffer from a self-perception of being too fat and a dread of fatness, and in addition, a widespread endocrine disorder occurs, manifesting in females as a amenorrhea and in males as a loss of sexual interest and potency.

The diagnosis of atypical anorexia nervosa in the ICD-10 (F50.1) follows the same criteria as AN (F50.0), but the patients need not fulfil all the criteria. Several studies have found that the distinction between AN (50.0) and atypical AN (F50.1) is associated with differences in the
treatment outcome, clinical presentation and mortality (Dellava et al., 2011; Suokas et al., 2013; Silen et al., 2015).

2.2.2 Prevalence

AN usually develops during adolescence and the highest incidence occurs at the age of 10–19 years (Currin et al., 2005). In a large community-based study (n = 3021), the earliest onset of EDs appeared in those with symptomatic AN, with a considerable proportion of individuals already showing symptoms before 13 years of age (Nagl et al., 2016). Estimates of the prevalence and incidence of AN depend on the screening method, the population in question and the diagnostic criteria used. In the literature, the lifetime prevalence of AN among women has varied from 0.3–0.9% (Hudson et al., 2007; Preti et al., 2009; Swanson et al., 2011; Smink et al., 2012), but higher estimates (1.2–2.2%) have also been reported. In twin studies, the prevalence has been higher (Keski-Rahkonen et al., 2007; Smink et al., 2012), and in a Finnish population-based sample (n = 1863), the prevalence of AN was 2.1% (Lähteenmäki et al., 2014). In a large gender-mixed community sample of 14- to 24-year-olds (n = 3021), the cumulative lifetime incidence of AN was 1.7% (Nagl et al., 2016). In adolescents (n = 595), the lifetime prevalence for females aged 18 years was 2.6% for anorexia nervosa (AN) (Isomaa et al., 2009). In men, the lifetime prevalence of AN was estimated to be 0.24% (Raevuori et al., 2009). However, changes in diagnostic definitions and different operationalizations can have an impact on the prevalence (Brown, 2014). In a large (n = 2230) community cohort of adolescent women, the lifetime prevalence of DSM-5 anorexia nervosa was 1.7% (Smink et al., 2014).

2.2.3 Medical complications in AN

Weight loss and malnutrition in AN can cause complications in almost every body system (Westmoreland et al., 2016). Complications related to purging are also common in AN, and are discussed in the section concerning complications related to BN.

Sudden cardiac death along with other medical complications and suicide account for approximately 60% of AN-related deaths (Westmoreland et al., 2016). In the cardiac system, bradycardia is noted and hospitalization is recommended for a heart rate of less than 40 beats
per minute (käypä hoito, 2014). Patients may additionally suffer from prolongation of the QTC interval (<500 ms) in electrocardiography, but this has actually been quite rare in the absence of contributing factors (Faccini et al., 2006; Krantz et al., 2011). Severe anorexia nervosa can lead to left ventricular atrophy and pericardial effusions, which are generally reversible with refeeding. However, one MRI study demonstrated a myocardial scar in AN patients, which can lead to malignant arrhythmias (Oflaz et al., 2013). In the gastrointestinal system, slowed gastric emptying, gastroparesis, acute gastric dilatation and even superior mesenteric artery syndrome have been demonstrated in AN (Benini et al., 2004; Mascolo et al., 2015). In addition, elevated liver transaminases frequently occur as a result of malnutrition (Miller et al., 2005).

The effects of AN on the haematological system cause anaemia, leukopenia and thrombocytopenia (Hutter et al., 2009). Osteoporosis is also common in AN, increasing the risk of bone fractures later in life (Lucas et al., 1999). Unfortunately, no treatments are currently specifically approved for osteoporosis in AN; however, weight gain and the resumption of menses are associated with improved bone density (Miller et al., 2006). Osteoporosis is one of the complications of AN, and may be lead to irreversible damage even after recovery (Westmoreland et al., 2016). The effects on the endocrine system increase the risk of amenorrhea and can cause infertility (Jacoangeli et al., 2006). Hypoglycaemia can occur in severe AN as a result of depleted hepatic glycogen stores, and is a poor prognostic sign (Rich et al., 1990). The medical complications related to purging are discussed in detail in the section concerning medical complications in BN.

A significant global loss of brain volume has also been observed in AN in both grey matter and white matter in several studies, including two recent meta-analyses (Titova et al., 2013; Seitz et al., 2014). The mechanisms of brain volume reduction are largely unknown (Seitz et al., 2015). During weight gain, however, a significant volume recovery has been noted (Ehrlich et al., 1998; Mainz et al., 2012).

In the nutritional rehabilitation in AN, a rare side effect of refeeding syndrome should be carefully considered (Marzola et al., 2013). Refeeding syndrome is caused by the rapid refeeding of someone in a state of starvation (BMI under 12), and is characterized by hypophosphataemia, hypomagnesaemia, hypokalaemia, glucose intolerance, fluid overload and thiamine deficiency. The clinical consequences can include cardiac arrhythmia, hypotension, rhabdomyolysis, respiratory failure and coma (Hearing, 2004).

Many of the cognitive deficits in anorexia nervosa are restored after weight recovery. However, some abnormalities in executive function remain after weight restoration (Tchanturia
et al., 2002). In addition, reproductive health outcomes are compromised in women with a history of EDs (Linna et al., 2013).

2.2.4 Psychiatric comorbidities

There is a significant comorbidity of affective and anxiety disorders with anorexia nervosa (Halmi et al., 1991; Jacobi et al., 2004b; Blinder et al., 2006; Hudson et al., 2007; Lähteenmäki et al., 2014). In a female inpatient sample, 97% evidenced one comorbid diagnosis. Comorbid mood disorder was the most common (94%), while 56% of inpatients evidenced anxiety disorders and 22% evidenced substance use disorders. There were no differences across eating disorders in depression or anxiety disorder, but alcohol abuse/dependence was twice as likely with BN (Blinder et al., 2006). The National Comorbidity Survey Replication (NCS-R) revealed that more than half (56.2%) of respondents with AN met the criteria for at least one other mental disorder (Hudson et al., 2007), and similar results have been found in a Finnish study (Lähteenmäki et al., 2014).

AN patients also suffer from autistic spectrum disorders, attention-deficit hyperactivity disorder (Wentz, 2005) and personality disorders (typically C-cluster: obsessive-compulsive, dependent, and avoidant personality) (Johnson and Wonderlich, 1992). In a sample of ED individuals, 35% of those with AN met the criteria for obsessive-compulsive disorder (OCD) (Thornton and Russell, 1997). The prevalence in ED samples of personality disorder varied from 21% to approximately 90% for AN and BN in a meta-analysis (Rosenvinge et al., 2000).

2.2.5 Mortality

AN patients suffer from one of the highest mortality rates of all psychiatric disorders (Chesnye et al., 2014). In a meta-analysis, the standardized mortality rate in AN was 5.86 (Arcelus et al., 2011) and in a large prospective clinical longitudinal study it was 5.35 (Fichter and Quadflieg, 2016). Most deaths due to AN are a direct consequence of starvation-related complications, while one in five deaths in AN result from suicide (Royal College of Psychiatrists, 2012). In a follow-up study in the Helsinki and Uusimaa Eating Disorder Clinic, the mortality risk (hazard
ratio, HR) in broad anorexia of all causes was 6.51 and the risk of suicide was elevated (HR 5.07) (Suokas et al., 2013).

2.2.6 Treatment of anorexia nervosa

Evidence-based recommendations for the treatment of AN are scarce. These recommendations emphasise the importance of a multidisciplinary approach, including medical, nutritional, social and psychological components (NICE Guideline, 2004; American Psychiatric Association Practice guidelines for the treatment of patients with eating disorders., 2006; Käypä hoito 2014).

Evidence also suggests that in AN, weight should be restored to the level of the resumption of menses (90% of standard body weight) to have a better prognosis (Golden et al., 1997). The guidelines agree that most people with AN can be treated as outpatients, but that day-patient and inpatient services are needed for those with more severe illness and those who do not improve with outpatient care. In a multicentre randomized trial, Herpertz-Dalman and colleagues (2014) reported that a stepped care approach including day-patient treatment was equally effective and less costly compared to inpatient treatment in non-chronic adolescent AN.

In adolescent patients with AN, there is clear and growing evidence to support the efficacy of family treatment compared with individual-based approaches (Lock, et al., 2010, 2015). The evidence supports family-based treatment with a focus on eating disorder behaviour and weight gain (Lock, 2015).

In adult patients with AN, several treatment studies have been published, reporting substantial weight gain and improvements in the eating disorder and general psychopathology at the end of treatment and on follow-up (Whitney et al., 2012; Schmidt et al., 2012, 2015; Zipfel et al., 2014, 2015). The largest of these trials compared three different treatments: focal psychodynamic psychotherapy (FPT), enhanced cognitive behaviour therapy (CBT-E) and optimized treatment as usual, including psychotherapy as well as medical care by the family doctor (Zipfel et al., 2014). Weight gain was similar in all three groups, but in FPT it proved advantageous in terms of recovery at 12 months, while CBT-E was more effective with respect to the speed of weight gain. A novel anorexia nervosa-specific outpatient therapy (Maudsley Model of Anorexia Nervosa Therapy for Adults, MANTRA) has been compared with Specialist
Supportive Clinical Management (SSCM) (Schmidt et al. 2012). The overall outcome did not differ between groups, but patients preferred MATRA to SSCM, and patients with more severe illness experienced a greater weight gain in the MANTRA group (Schmidt et al., 2015). In summary, the evidence base for the treatment of adults with anorexia nervosa is advancing, but no specific approach has shown clear superiority (Hay et al. 2015). The common elements of the AN psychotherapeutic approach are focused on weight regain and nutritional rehabilitation (Hay 2014).

The evidence regarding pharmacotherapies is scarce. No strong evidence lends support to drug treatment in either the acute or maintenance phases of the illness. Studies have investigated fluoxetine in the prevention of relapse in AN, but the evidence base for this is weak (Walsh, 2006; NICE Guideline, 2004). There has been interest in the potential use of atypical antipsychotic drugs. The idea is that by reducing anxiety symptoms and distorted cognition, resistance to weight gain decreases. Small initial randomised studies have reported decreases in obsessive symptoms and an increased rate of weight gain (Bissada et al., 2007; Bissada et al., 2008). However, larger trials are necessary determine whether these drugs are beneficial, despite the potential increase in the QTc interval with the concomitant risk of cardiac arrhythmias.

### 2.2.7 Prognosis of anorexia nervosa

The course of anorexia nervosa is very variable (Treasure and Schmidt, 2002). Many people with eating disorders who have been detected in community studies have not sought treatment (Hudson et al., 2007, Keski-Rahkonen et al. 2007). There is no good evidence on the prognosis of those AN patients who do not access formal medical care (Treasure and Schmidt, 2002).

Steinhausen (2002) summarised 119 treatment studies covering 5590 patients, finding that, on average, only 46.9% of the surviving patients fully recovered, while 33.5% improved and 20.8% developed a chronic course of the disorder (Steinhausen, 2002). A one-third crossover to BN has also been observed in AN (Eddy et al., 2008). The crude mortality rate was 5.0 in the study by Steinhausen et al. (2002). The SMR in AN appears to be higher than in schizophrenia, bipolar or unipolar depression (Arcelus et al., 2011), and one of the highest in the field of psychiatry (Chesny et al. 2014).

In AN, few prognostic factors have reliably been identified. Negative prognostic factors for AN are a longer duration of illness before treatment and a longer duration of treatment or need
for inpatient treatment (Fichter et al., 2006; Eisler et al., 2007; Papadopolous et al., 2009). Prognostic indicators for AN appear to be closely associated with the severity and duration of AN (Keel et al., 2010). Premorbid depressive symptoms in AN are also associated with a poor outcome in the general population (Keski-Rahkonen et al., 2014). Since the highest incidence of AN occurs between 10 and 19 years of age (Currin et al., 2005), this condition can potentially disrupt optimum growth and development. AN can also cause educational disturbances (Byford et al., 2007), which can lead to difficulties in independent living in 20% of cases up to 10–20 years after the onset of the illness (Hjern et al., 2006).

2.3 Other eating disorders

Some people suffer from eating disorders that do not meet the precise diagnostic criteria for AN or BN, but closely resemble these conditions (Fairburn and Harrison, 2003). In Europe, these are often termed 'atypical eating disorders' (Fairburn and Harrison, 2003), the equivalent American term being 'eating disorders not otherwise specified' (EDNOS) (American Psychiatric Association, 1994). EDNOS comprises the most common subgroup of eating disorders in both clinical and community samples (Smink et al., 2013). Binge-eating disorder (BED) is typically considered a part of EDNOS, and is the most common eating disorder in the EDNOS subgroup (Fairburn and Harrison, 2003).

2.3.1 Binge-eating disorder (BED)

The occurrence of binge-eating episodes in the absence of compensatory behaviours is the core feature of BED. The disorder is often seen in obese individuals, but it differs from obesity in terms of psychopathology and weight and shape concerns (Wonderlich et al., 2009). In BED, the lifetime prevalence varies from 1.9 to 3.5% (Hudson et al., 2007; Preti et al., 2009; Swanson et al., 2011). In men, the prevalence varies from 1.1–3.1% (Hudson, 2007; Striegel-Moore and Franko, 2003). In a Finnish community-based study concerning young adult women (ages 22–27), the lifetime DSM-5 prevalence was 0.7% (Mustelin et al., 2015). The mortality risk in BED is elevated and an SMR of 2.3 is described in the literature (Fichter et al., 2008).
2.4 Aetiology of eating disorders

The aetiology of eating disorders is considered to be multifactorial (Cooper and Steere, 1995). It depends on individual vulnerability, consequent on the presence of biological or other predisposing factors, their exposure to particular provoking risk factors (Jacobi et al., 2004a) and on the operation of protective factors, whether or not a person develops an eating disorder (NICE Guideline, 2004).

2.4.1 Genetic risk factors

Behavioural genetic data have consistently indicated that both genetic and environmental influences contribute to eating symptoms (Culbert et al., 2015). The division into genetic and environmental risk factors is somewhat artificial, because parental mental disorder, for example, is a genetic risk factor, but also an environmental factor in that it affects the emotional atmosphere in the family (Nomura et al., 2002). The combined genetic and environmental effect is called gene–environment interaction. The effects of environmental factors may also transfer without changes in the DNA sequence; this is called epigenetics (Foley et al., 2009; Liyanage et al., 2014).

Large twin studies have established that AN, BN and BED are heritable (Bulik et al., 2016). Yilmaz et al. (2015) reported the replicated twin-based heritability estimates for AN (0.48–0.74) and BN (0.55–0.62). Nonshared environmental effects generally account for the remaining variance (Culbert et al., 2015).

Despite significant methodological advances in the study of genetic associations over the past two decades, we still know relatively little about the specific genes that contribute to eating disorders. Five genome-wide association studies (GWAS) have been conducted for AN or disordered eating (Wade et al., 2013; Culbert et al., 2015), but no gene variant has met the significance threshold for multiple comparisons. Candidate gene association studies have been used to examine genes in neurobiological systems (e.g. serotonin (5HT), dopamine, brain-derived neurotrophic factor) (Culbert et al., 2015). Possible polymorphisms of the 5-HT2A (Gorwood et al., 2003) and 5-HTTLPR polymorphic region of the serotonin transporter gene (Calati et al., 2011) appear robust candidates for AN. Evidence for genetic and environmental effects has also
emerged from developmental twin studies. The magnitude of genetic influences on disordered eating symptoms in females varies according to *age and pubertal status.* Ovarian hormones have been proposed as a possible mechanism underlying developmental changes in the genetic risk in girls (Ostlund et al., 2003).

In a Swedish register-based study, it was found that when one or both parents had a *lifetime history of psychiatric disorder,* the offspring were at increased risk of developing an eating disorder (Bould et al., 2016). The nature of suicidality in eating disorders has also been examined in a Swedish population study (Yao, 2016). An increased risk of suicide attempts was recorded among individuals with eating disorders and among individuals without eating disorders who had a relative with an eating disorder, suggesting that *suicidality* may be due to familial liability for the association between eating disorders and suicide (Yao et al., 2016). The co-occurrence of eating disorders and other psychiatric conditions is partly due to shared genetic factors (Bulik et al., 2016).

**Gene–environment interplay**

Parental factors (e.g. *parental pressures and criticism; low parental contact*) and *abuse history* have been identified as retrospective correlates of eating pathology (Jacobi et al., 2004a). Abuse history is often considered a risk factor because of some retrospective reports, and childhood abuse was demonstrated to prospectively predict an elevated risk of disordered eating and eating disorder onset in a longitudinal study (Johnson et al., 2002). The interactions between these environmental experiences and biological factors have been explored in some studies. The short allele of 5-HTTLPR has been shown to interact with *parenting style,* e.g. *criticism,* *underinvolvement* and *physical abuse* in the prediction of AN, bulimic symptoms and the drive for thinness (Culbert et al., 2015). These data provide initial evidence that environmental experiences may serve to potentiate the risk of eating disorders, particularly in individuals who are biologically vulnerable. *Epigenetic alterations in dopaminergic functioning* may also be linked to eating disorders (Culbert et al., 2015; Groleau et al., 2014).
2.4.2 Environmental risk factors

2.4.2.1 Biological risk factors

Prenatal stress following maternal bereavement is associated with an increased overall risk of EDs in adolescent girls and young women (Su et al., 2016). Early insults to the central nervous system may contribute to the onset of AN, at least in a subpopulation of individuals (Favaro et al., 2011a; Cnattingius, 1999). Perinatal factors, e.g. pregnancy and delivery complications, hypoxia and signs of retarded foetal growth (Favaro, 2011b), as well as multiple births and a lower gestational age, have also been associated with an elevated risk of developing AN (Goodman, 2014). In BN, there is evidence that restricted growth and a smaller birth size predict later BN (Favaro et al., 2006). In a Swedish data set (Goodman et al., 2014), a contrary finding was that a higher birth weight predicted BN. This may reflect the significance of early metabolic programming in the tendency to gain weight, which is also relevant in BN (Skilton et al., 2014). The overall effect of prenatal/perinatal factors on the total risk of EDs appears to be relatively small. It is likely that if there are early prenatal/perinatal risk factors, they operate in conjunction with other individual or environmental factors and, depending on the combination of risk factors, the outcome varies (Raevuori et al., 2014a).

Puberty and adolescence are characterized by profound changes, vulnerabilities and the transition to adulthood, and they represent the period of first onset of AN (Zipfel, 2015). A possible explanation for the crucial role of puberty in the onset of AN might lie in hormonal changes and dysregulations that interact with neurotransmitter functioning, brain maturity and genetic factors (Herpertz-Dahlman et al., 2011).

The rate ratio of the lifetime prevalence of AN and BN in females is substantially higher than in males (sex ratio ranging from 1:10 to 1:16) (Hoek, 2006; Nagl et al., 2016). On the other hand, the risk of eating disorders has also been shown to be increased in some somatic illnesses, e.g. type 1 diabetes (Tiller, 1994; Jones et al., 2000; Arigo et al., 2012), and several autoimmune diseases with different genetic backgrounds (Raevuori et al., 2014b). There is a highly increased risk of type 2 diabetes in patients with binge eating disorder and bulimia nervosa (Raevuori et al., 2015). Paediatric autoimmune neuropsychiatric disorders associated with streptococcal
infection (PANDAS) is a process whereby a streptococcal infection leads to the onset of anorexia nervosa through a postulated autoimmune mechanism (Vincenzi et al., 2010).

### 2.4.2.2 Psychosocial risk factors

Personality traits have received significant attention in aetiological models of eating disorders (Lilenfelc et al., 2006). Negative emotionality predicts the development of eating pathology. Similarly to eating disorders, personality traits have been shown to be heritable. The remaining variance is typically explained by non-shared environmental factors (Polderman et al., 2015). Perfectionism also increases the risk of eating disorders. Perfectionism interacts with body dissatisfaction to predict the drive for thinness. Results from twin studies suggest that genetic, rather than environmental factors are most important (Wade and Bulik, 2007). Inhibitory control deficits appear to be correlates of EDs (Culbert et al., 2015). Neurocognitive flexibility is also impaired in AN, and it may persist (Tchanturia et al., 2012).

The environment also carries other risk factors. In a large register study in Sweden, a higher level of parental education independently predicted a higher rate of ED in females, but not in males (Ahren et al., 2013). However, in a Finnish study, adolescent eating disorders were not associated with the socio-economic status of the family (Litmanen et al., 2016). In addition, neglect and physical and sexual abuse increase the risk of developing an eating disorder (Treasure et al., 2010). Negative self-evaluation, elevated weight and shape concerns, general psychiatric morbidity (Jacobi et al., 2004), depressive disorder and generalized anxiety disorder (Sihvola et al., 2009) are also risk factors of EDs.

### 2.4.3 Sociocultural context

The increase in AN in low-income and middle-income countries suggests that cultural transitions associated with industrialisation, globalisation and urbanisation might be associated with environmental risk constellations for the development of AN (Smink et al., 2012). The adoption of the so-called Western lifestyle, including thin ideal internalisation, might be part of
this constellation. In addition, food-related and weight-related harmful experiences can have an influence on developing an ED. The rates of BN symptoms have also increased following exposure to Western influences (Becker et al., 2002). The excess value placed on thinness encourages extreme dieting and weight control practices. Criticism focused on shape, weight and food issues increases the risk of developing an eating disorder (Wade et al., 2007).

Despite these sociocultural pressures to be thin, the incidence of AN is relatively low (Schmidt, 2003). The adoption of thin ideal internalisation could simply increase the number of individuals engaging in strict dieting and excessive exercise, which can then trigger eating disorders in genetically susceptible individuals (Zipfel et al., 2015). Twin studies have demonstrated that internalization of the thin ideal is accounted for by individual differences in both genetic and environmental factors (Suisiman, 2012, 2014).

### 2.4.4 Neurobiological factors as a result of disordered eating behaviours

As a result of starvation and disturbed eating behaviours, many biological disturbances emerge. However, some biological findings are causally linked as risk or maintaining factors (Treasure et al., 2010). Starvation is associated with many behavioural and psychosocial disturbances. During starvation, the brain shrinks, causing rigidity, emotional dysregulation and social difficulties (Keys et al., 1950). There are profound disturbances of brain serotonin (Kaye et al., 2005), neuropeptide systems (Frank et al. 2005) and brain neurocircuitry (Muhlau et al., 2007). During weight gain and brain mass restoration, many symptoms resolve (Castro-Fornieles et al., 2009).

Abnormal changes in the central control of appetite have a role in the risk and maintenance of eating disorders (Treasure et al., 2010). In the models of binge eating in laboratory rodents, eating disorder behaviours have been seen to affect the drive system of the central control of appetite (Avena, 2007; Boggiano et al., 2007). In these studies, researchers have replicated the conditions implicated in the increase in binge eating and produced animals with an addiction to food.

Abnormalities in both illness-related (food and body shape) and non-illness-related information processing have been detected in eating disorders. An attentional bias is evident towards food and body shape (Lee, 2004) associated with increased activation in distributed
neural networks connected with self-regulation and hedonic motivation (Kaye et al., 2009; Van den Eynde and Treasure, 2009). These functional anomalies can maintain eating disorder behaviours. For example, impaired social and emotional regulation could cause isolation.

2.4.5 Protective factors

Protective factors identified in studies include low BMI, healthy eating attitudes (Westerberg-Jacobson, 2010), an accepting attitude towards body size and a positive self-evaluation (Gustafsson et al., 2009). Parent-adolescent connectedness and frequent family communication have also been identified as protective factors for adolescent dieting and eating disorder symptoms (Fonseca et al., 2002). Greater parent-adolescent connectedness and a greater family meal frequency have also been identified as significant prospective protective factors for dieting, binge eating and purging in adolescent girls (Berges et al., 2014; Haines et al., 2010).

2.5 Adolescence

Adolescence is a transitional stage from childhood into adulthood during which the individual undergoes many physiological, psychological, cognitive and social changes (Aalberg, 2016). Adolescence is initiated by pubertal onset and can be divided into three periods: early adolescence (12–14 years), middle adolescence (15–16 years) and late adolescence (17–22 years) (Richter, 1998). Each of these periods has certain developmental tasks, which are the achievement of biological and sexual maturity, the development of personal identity, the development of intimate sexual relationships, and the establishment of independence and autonomy (Christie and Viner, 2005). Adolescence is characterized by major changes in the neural systems that serve higher subcognitive functions, reasoning and interpersonal interactions, cognitive control of emotions, risk-versus-reward appraisal and motivation. It is precisely these changes that, when suboptimal in timing or magnitude, increase the risk of cognitive, affective and addictive disorders (Paus et al., 2008). In the field of EDs, studies have revealed that EDs are associated with early maturation, suicidal behaviour, body dissatisfaction and conflicts in family relationships, especially with BN, and psychosexual difficulties and few social contacts with AN (Ruuska, 2006).
In a Finnish study on adolescents, mid-adolescent girls showed significantly greater body dissatisfaction than boys. Adolescents with underweight appeared to be most satisfied and those with overweight and obesity most dissatisfied with their bodies. Body dissatisfaction and self-esteem were negatively correlated, and body dissatisfaction was associated with abnormal eating. (Mäkinen, 2015).

2.6 Quality of life

Modern medicine has traditionally focused on assessing patients through objective measures. However, outcomes cannot be solely assessed in objective terms, as such indicators do not explain how people perceive and experience their lives. Recently, the focus in medicine has been redirected to the broader personal and social context of the person with the disease (Higginson et al., 2001). Quality of life has become an important adjuvant and alternative tool in clinical assessment (Orley et al., 1998).

Since 1948, when the World Health Organization (WHO) defined health as being not only the absence of disease and infirmity but also the presence of physical, mental and social well-being, quality-of-life issues have become more important in health care practice and research (WHO, 1948). There has been a nearly exponential increase in clinical studies measuring quality-of-life since 1973 (Testa and Simonson, 1996). The World Health Organization (WHO) defines quality of life as "an individual's perceptions of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns" (The WHOQOL Group, 1998).

One of the reasons behind the rapid development of quality of life measures in healthcare has been the growing recognition of the importance of understanding the impact of healthcare interventions on patients' lives rather than just on their bodies (Addington-Hall and Kalra, 2001). Quality of life (QoL) is becoming an increasingly important outcome of healthcare for several reasons. Subjective valuations, autonomy and the needs of patients are increasingly respected (Saarni et al., 2010). Patients are interested in their quality of life after an intervention and they may actually appreciate this endpoint more than clinicians do. This has
led clinicians and researchers to quantify the impact of specific interventions (Spertus et al., 2002).

Defining and measuring quality of life is complicated. When trying to define and measure QoL, we need to take into account both objective life conditions and subjective personal appraisals. What is important to each person varies. A synthesis of these perspectives provides a model of quality of life, which integrates objective and subjective indicators and individual values across a broad range of life domains (Felce, 1997). Considerable agreement exists that quality of life is multidimensional. It can be categorised within five dimensions: physical well-being, material well-being, social well-being, emotional well-being, and development and activity (Felce and Perry, 1995).

2.7 Health-related quality of life

2.7.1 Theory of health-related quality of life

WHO supports the consensus view that health is more than a matter of the absence of a specific disease or injury. It is also the presence of certain threshold levels of the ability to carry out physical and mental actions and tasks in the current environment (WHO, 2002). During the last three decades, there has been general acceptance of an approach to describing health states of individuals in terms of multiple domains of health, and in developing self-report instruments that seek information on each of these domains (Hunt et al., 1981; Ware et al., 1993). In order to measure and report on the health of populations or individuals, under any of the three views outlined above, it is necessary to develop a valid, reliable and comparable way to measure the health status. This requires the following: a classification of the health state domains, and specification of a set of domains necessary and sufficient to describe health states for measurement purposes; specification of what we are measuring in each domain; a common understanding of what is full health versus exceptional talent in any given domain; and, if we wish to construct summary measures of the average level of population health, a method to place a single cardinal value on the overall level of health associated with a health state defined in multiple domains (WHO, 2002).
2.7.2 The concept of Health-related quality of life

Health-related quality of life (HRQoL) is a subconcept of QoL: HRQoL tries to capture the aspects of QoL that health and ideally also healthcare can influence. HRQoL is a fairly broad, multidimensional concept that includes symptoms of the disease or health condition, treatment side effects, and functional status across physical, social and mental health life domains (Revici et al., 2014). In addition to its multidimensional nature, a core component of the definition is the emphasis on the subjective, patient perspective. There is also increasing recognition that HRQoL is a subjective matter, and how these components are affected by illness and treatment should therefore be assessed by the individuals themselves (Slevin et al., 1988).

HRQoL outcomes are currently a large subset of an even broader set of outcomes that have come to be referred to as patient-reported outcome (PRO) measures (Revici, 2014). PROs are defined as any report of the status of a patient’s health condition or other clinical outcome that comes directly from the patient without interpretation from a clinician or anyone else. The use of PROs in research is well established (Black et al., 2016). There is a consensus that health outcome evaluations that include PROs along with clinician-reported outcomes and administrative data are necessary to inform clinical and policy decisions.

2.8 Health-related quality of life in eating disorders

Several studies have investigated the abnormal eating patterns in eating disorders, but studies also taking into account the patients’ perception have only in recent decades been under interest. Eating disorders are serious disorders (Klump et al., 2009) affecting young individuals for a long time, and it is crucial to gain more information on the overall well-being of these patients and how the treatment affects their HRQoL. The health-related quality of life of the caregivers of ED patients has also been under investigation in recent years (Martin et al., 2011).

Studies have shown that ED patients suffer from impaired QoL compared to the general population (Padierna et al., 2000; De la Rie et al., 2005) (Table 3). This impairment in QoL is
greater than in many psychiatric disorders (for example mood disorders) or physical conditions (for example coronary angina) (Keilen, 1994; De la Rie et al., 2005; Jenkins et al., 2011). There have not been any differences in diagnostic groups concerning HRQoL (Winkler et al., 2014), but impairments in HRQoL are associated with the severity of ED symptoms (Bamford and Sly, 2010). After the treatment of ED, former patients have still demonstrated lower QoL than population norms (de la Rie et al., 2005) (Table 4). In one study, patients’ QoL scores improved following treatment and were maintained at a one-year follow-up, but still remained poorer than those of a female student control group (Abraham et al., 2006). One reason for this could be that the changes seen immediately following treatment may be smaller than those reported on follow-up, reflecting a greater psychological change over the longer-term (Abraham et al., 2006). Binge eating and/or the use of purging behaviours has predicted a poorer quality of life in some studies (Jenkins et al., 2011; Gonzales-Pinto et al., 2004). Studies following patients after treatment completion are scarce (Table 4). A recent meta-analysis emphasised that AN, BN and BED have a serious impact on the patient’s HRQoL and are also associated with increased healthcare utilization and healthcare costs. According to the authors, the limited evidence suggests that further research is warranted to better understand the differences in long-term HRQoL and the economic burdens of AN, BN and BED (Agh et al., 2016).

2.9 Measurement of health-related quality of life

Health-related quality of life (HRQoL) is a multidimensional construct. It typically assesses the social, psychological and physical dimensions of health. HRQoL measures the patient’s perception of the impact of an illness and its treatment on these domains and overall well-being. It has been considered that the measurement of HRQoL is important, because it directly reflects the patient’s view on the effect of an illness on his/her well-being, and not that of a health care professional. With the help of HRQoL, we seek to measure the aspects of QoL that health and ideally also healthcare can influence. In general, two approaches to HRQoL measurement are available: specific instruments that focus on problems associated with single disease states, patient groups, and areas of function or individuals, and generic instruments that provide a summary of the health-related quality of life (Guyatt et al., 1993).
However, there are also some limitations when measuring HRQoL in EDs. There may be problems when using HRQoL as an outcome measure, as, for example, AN patients with an extreme lack of insight may not provide accurate information (Engel et al., 2009).

2.9.1 Disease-specific instruments

Disease-specific instruments have an important role in assessing the effectiveness of treatment, since generic instruments may lack sensitivity to important differences in health status that are essential for particular diseases.

In recent years, disease-specific HRQoL instruments have been developed for eating disorders. There are instruments such as the Eating Disorders Quality of Life Instrument (EDQOL) (Engel et al., 2006), the Eating Disorders Quality of Life Scale (EDQLS) (Adair et al., 2007) and the Health-Related Quality of Life in Eating Disorders Questionnaire (HeRQoLEDv2), (Las Hayas et al., 2006).

Few of the HRQoL studies in the ED field have used both generic and disease-specific measures. In these studies, the disease-specific measures have been more informative when trying to assess HRQoL in patients with EDs. These studies have also suggested that disease-specific measures provide a good indication of an improved quality of life on follow-up (Ackard et al., 2014). In one study, it was found that disease-specific HRQoL measures are important to use when comparing HRQoL in ED patients across treatments and outcomes, and these measures may have a greater sensitivity to detect meaningful differences in the diagnosis than generic instruments (Ackard et al., 2014).

2.9.2 Generic instruments

Generic instruments can be used for different patient groups independent of the underlying disability or disease. Well-known generic instruments include the Medical Outcomes Study, 36-item short form (SF-36) (Ware et al., 1993), the Nottingham Health Profile (Hunt et al., 1981), and the 15D (Sintonen, 2001). Generic instruments can be methodologically classified into profile and single index score measures. An example of a profile instrument is the SF-36, which describes the health state from the standpoint of various physical and emotional dimensions,
e.g. bodily pain and social function. A single index score instrument (e.g. 15D) produces a single index score on a 0–1 scale. This is a necessary requirement for the calculation of quality-adjusted life years (QALYs).

### 2.9.2.1 15D instrument

The 15D is a generic, 15-dimensional, standardized, self-administered HRQoL instrument that can be used both as a profile and a single index score measure. The dimensions used in the 15D are moving, seeing, hearing, breathing, sleeping, eating, speech, excretion, usual activities, mental function, discomfort and symptoms, depression, distress, vitality and sexual activity.

In the development of the 15-D generic HRQoL instrument, there have been many objectives. The first has been to evaluate the effectiveness and efficiency (cost-effectiveness/utility) of different health care programmes and technologies within disease categories in clinical trials or in average practice and across disease categories, and to thereby facilitate resource allocation decisions at the level of both clinical and health care policy. The second aim in population studies has been to describe and quantify the HRQoL of population groups and whole populations cross-sectionally and changes in the HRQoL over time (e.g. to assess the need for and effect of resource reallocation between regions). The third objective has been to assist and improve clinical practice and individual clinical decisions by pinpointing problems that need attention and to assess the clinical outcomes. Finally, the aim has been to describe the patient mix of various health care units (such as hospitals and health centres) and to standardise it when analysing and comparing the productivity of the units (Sintonen, 1994).

There have been several studies measuring HRQoL with the 15D. For example, it has been used for measuring HRQoL in several chronic conditions in the community, e.g. in pulmonary disorders, cardiovascular disorders, musculoskeletal disorders, hearing problems and psychiatric disorders (Saarni et al., 2006). Furthermore, several studies have measured HRQoL when assessing cost-effectiveness in secondary health care, e.g. in hip or knee replacement surgery (Räsänen et al., 2007), routine cataract surgery (Räsänen et al., 2006b) and routine neurosurgical spinal surgery (Räsänen et al., 2006a), but no studies to our knowledge have measured the HRQoL of ED patients using the 15D.
Table 3. Major cross-sectional studies on the HRQoL of AN or/and BN patients

(AN = anorexia nervosa, BN = bulimia nervosa, EDNOS = eating disorder not otherwise specified, BED = binge eating disorder, NHP = Nottingham Health Profile, SF-36 = Medical Outcomes Short-Form questionnaire, 36-item short form, EDQOL = Eating Disorders Quality of Life Instrument, WHOQoL-Bref = Abbreviated World Health Organization Quality of Life Questionnaire, QOL = quality of life, EAT-40 = Eating attitude test, PCS = correlated physical health, MCS = correlated mental health)
<table>
<thead>
<tr>
<th>Study</th>
<th>N Diagnosis Female (%)</th>
<th>Mean age (years)</th>
<th>Quality of life measure</th>
<th>Recruitment/Outpatient/inpatient</th>
<th>Control or reference</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keilen et al 1994, UK</td>
<td>52 AN 74 BN (100)</td>
<td>n/a</td>
<td>NHP</td>
<td>New referrals to ED treatment, n/a</td>
<td>Patients with somatic conditions and students</td>
<td>ED patients QoL worse than control group and lower than same than in e.g. coronary artery disease on domains related to emotional reactions, social isolation e.g.</td>
</tr>
<tr>
<td>Padierna et al 2000, Spain</td>
<td>116 AN 64 BN 17 BED (98)</td>
<td>23.4</td>
<td>SF-36</td>
<td>Outpatients of ED clinic</td>
<td>Scoring of General population</td>
<td>ED patients QoL worse than control, and QoL associated with severity of EAT-40</td>
</tr>
<tr>
<td>Gonzales-Pinto et al 2004, Spain</td>
<td>47AN (82.7)</td>
<td>20</td>
<td>SF-36</td>
<td>ED outpatient center</td>
<td>No control</td>
<td>Predictive values for pcs: poor outcome in previous year, comorbidity and female; for mcs: comorbidity and purging</td>
</tr>
<tr>
<td>Mond et al 2005, Australia</td>
<td>19 ANR 15 ANP 40 BN 10 BED n/a</td>
<td>ANR19 ANP25 BN 23 BED34</td>
<td>SF-36, WHOQOL-BREF</td>
<td>Patients referred to ED treatment, outpatients</td>
<td>Female general population</td>
<td>ED patients had lower QoL and the subgroup of restrictive AN had better QoL than other eating disorder patients</td>
</tr>
<tr>
<td>De la Rie et al 2005, Netherlands</td>
<td>44AN (100) 41BN (95.3) 68EDNOS (96.7)</td>
<td>26.3 29.0 29.4</td>
<td>SF-36</td>
<td>ED patients and advertisement n/a</td>
<td>General population and mood disorder patients</td>
<td>the QOL of ED patients QoL worse than normal reference group and worse than the QOL of patients with mood disorder</td>
</tr>
<tr>
<td>Engel et al, 2006, United States</td>
<td>155 ED (100)</td>
<td>22</td>
<td>EDQOL</td>
<td>Recruited sample of students n/a</td>
<td>Non-ED subjects</td>
<td>ED patients had greater impairment in EDQOL than non-ED</td>
</tr>
<tr>
<td>Latner et al 2008, New Zealand</td>
<td>11AN 5BN 3BN 30EDNOS (100)</td>
<td>26</td>
<td>SF-36</td>
<td>ED outpatient center</td>
<td>General female population</td>
<td>ED patients had lower MCS. Qol general and PCS predicted by subjected bulimic episodes</td>
</tr>
<tr>
<td>Bamford and Sly, 2010, UK</td>
<td>80AN 40BN 36EDNOS (95)</td>
<td>26.7</td>
<td>EDQOL</td>
<td>In-and outpatients</td>
<td>Comparison across groups</td>
<td>AN&lt;BN and EDNOS on psychological and physical/cognitive domains</td>
</tr>
<tr>
<td>Baiano et al 2014, Italy</td>
<td>33AN 26BN 7 BED 14EDNOS (100)</td>
<td>28</td>
<td>WHOQoL-BREF</td>
<td>ED patients referred to ED clinic In-and outpatients</td>
<td>Comparison across groups</td>
<td>No difference in ED groups</td>
</tr>
</tbody>
</table>
Table 4. Major HRQoL studies on AN and/or BN with a follow-up.

(AN = anorexia nervosa, BN = bulimia nervosa, EDNOS = eating disorder not otherwise specified, BED = binge eating disorder, NHP= Nottingham Health Profile, SF-36 = Medical Outcomes Study 36-item short form, HeRQoLED = Health-Related Quality of Life for Eating Disorders, Qol ED = Quality of Life for Eating Disorders, EEE-C = eating and exercise examination score, EDQOL= Eating Disorders Quality of Life Instrument, QOL = Quality of life, EAT-40 = Eating attitude test, PCS = correlated physical health, MCS = correlated mental health)
<table>
<thead>
<tr>
<th>Study</th>
<th>N and Diagnosis, Female (%)</th>
<th>Quality of life measures</th>
<th>Recruitment, Mean age (years)</th>
<th>Control or reference</th>
<th>Duration of follow-up</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Padierna et al 2002, Spain</td>
<td>131 AN or BN, (98.5)</td>
<td>SF-36</td>
<td>Outpatients of ED clinic, 22.3</td>
<td>General populatio n</td>
<td>24 months</td>
<td>Significant improvement during follow-up in QoL and clinical outcome measures</td>
</tr>
<tr>
<td>Abraham et al 2006, Australia</td>
<td>71 AN 55 BN 80 EDNOS n/a</td>
<td>EEE-C QOL scores SF-12</td>
<td>In-patient in ED center, n/a</td>
<td>Baseline and discharge (LOS 34 or 59 days)</td>
<td>12 month follow-up</td>
<td>QoL improved during inpatient treatment and between admission and 12 months after discharge. ED patients had lower QoL than reference population.</td>
</tr>
<tr>
<td>McHugh, 2007, USA</td>
<td>65 AN (100)</td>
<td>SF-36</td>
<td>AN patients entering a specialist inpatient care, 16.0</td>
<td>Comparison with high and low readiness for change</td>
<td>Baseline and discharge (LOS 34 or 59 days)</td>
<td>QoL less than normal population. 81% discharged below average QoL</td>
</tr>
<tr>
<td>Munoz et al 2009, Spain</td>
<td>61 AN 47 BN 245EDNOS (96.6)</td>
<td>SF-36 HeRQoL ED</td>
<td>Patients entering outpatient treatment , 26.8</td>
<td>General populatio n</td>
<td>12 months</td>
<td>ED patients had lower QoL. After 1 year improvements in PCS</td>
</tr>
<tr>
<td>Adair et al 2010, Canada</td>
<td>56AN 39BN 35EDNOS (98.5)</td>
<td>EDQLS Quality of life inventory SF-12</td>
<td>ED treatment program, inpatient or outpatient, 25.6</td>
<td>QoL measures in different time points</td>
<td>3 and 6 months</td>
<td>EDQOL scores improved in 3 and 6 months</td>
</tr>
</tbody>
</table>
2.10 Prognostic factors in eating disorders

Understanding the factors that predict a favourable outcome following specialist treatment for an eating disorder may assist in improving treatment efficacy and in developing novel interventions.

A literature review identified many factors that may predict the treatment outcome. In AN, factors associated with a poor prognosis are premorbid psychiatric symptoms, e.g. depression (Keski-Rahkonen et al., 2014), rapid weight loss, bulimia nervosa, comorbid obsessive-compulsive disorder (OCD), vomiting and purging (Berkman et al., 2007; Steinhausen et al., 2002; Keski-Rahkonen et al., 2014). A favourable prognosis is associated with an early age at onset, short duration of illness, short treatment duration, a supportive relationship with the parents and a high socioeconomic status (Steinhausen et al., 2002; Berkman et al., 2007).

In bulimia, there has for most prognostic factors only been conflicting evidence (Steinhausen et al., 2009), but some studies have demonstrated that a young age of onset of BN and treatment are associated with favourable outcomes (Keel and Mitchell, 1997; Quadflieg and Fichter, 2003; Steinhausen et al., 2009).

In a recent meta-analysis, early symptom improvement in AN was revealed as a significant predictor of the outcome (Vall and Wade, 2015). In AN, results indicated that patients who had a higher weight on discharge had better outcomes on follow up. The authors suggested that ensuring that patients with severe pathology are not discharged from treatment before they have reached a satisfactory level of improvement may assist in achieving a better long-term outcome (Vall and Wade, 2015).

2.10.1 Health-related quality of life and prognostic factors

Eating disorder patients suffer from an impaired quality of life, and even after treatment the HRQoL of ED patients is lower than that of the normal population (Padierna et al., 2000). However, there is limited information on the prognostic factors that may predict the treatment
outcome measured with HRQoL. To our knowledge, no studies have sought to determine prognostic factors of HRQoL in eating disorders.

2.11 Economic evaluation in eating disorders

Increasing attention has been paid to the health care economics of eating disorders (Crow and Peterson, 2003). It has been considered in the literature that the treatment of EDs is expensive (Stuhldreher, et al. 2012). Consequently, some health insurance providers have limited the amount of treatment provided for EDs (Crow and Nyman, 2004). Health economic studies on the treatment of eating disorders have indicated that the costs of treating AN and BN are comparable to the treatment of schizophrenia. By comparison, costs for the treatment of AN and BN were significantly higher than those for the treatment of OCD (Striegel-Moore et al., 2000).

Studies have demonstrated that the utilization of general health care by care eating disorder patients is high (Mitchell et al., 2009). There is also a growing interest in studying the public health costs associated with eating disorders.

Illness-associated costs are a major concern in EDs, and in recent years, several studies have investigated these costs. These have included studies examining the national costs of ED, the third-party payer costs for ED treatment, societal costs of ED, and cost-effectiveness analysis of specific treatments. A number of further cost effectiveness analyses are planned, for instance concerning ED prevention costs (Crow, 2014).

Despite the interest in studying the costs of EDs, information regarding health care utilization, the costs of treatment and the cost-effectiveness of different treatments is still sparse (Stuhldreher et al., 2012). Knowledge of the cost-effectiveness and cost-utility of EDs is limited, and it is considered that this area will be a fertile one for continued study (Crow, 2014).

2.11.1 Treatment-related costs

2.11.1.1 Cost-of-illness studies
Cost-of-illness studies (COIs) are the most recommended instruments to assess the economic burden associated with EDs (Stuhldreher et al., 2012). COIs inform decision makers about the economic impact of certain diseases by providing a comprehensive assessment of the costs. The costs generally differ according to the perspective from which they are evaluated. These perspectives are typically the third-party payer or society. Direct costs include all medical costs. In the societal perspective, indirect costs are also incorporated (losses of productivity: reduced productivity, sickness absence, premature death) (Stuhldreher et al., 2012).

Direct costs in AN were compared in a systematic review by Stuhldreher et al. (2012). They inflated the costs to 2008 US$ using country-specific gross domestic product inflators and converted the figures to purchasing power parities (PPP). PPP account for differences in price levels between countries.

The analysis revealed substantial differences between the reviewed studies. In a study by Striegel-Moore et al. (2000), the disease-specific cost in AN was highest (US$8042 PPP in women, US$3653 PPP in men), but Krauth and colleagues (2002) calculated a considerably lower disease-specific cost of US$2291 PPP. The lowest excess costs (US$1288 PPP) were reported by Mitchell and colleagues (2009).

In BN, the direct costs have been more homogeneous, with reports of US$5016 PPP (Mitchell et al., 2009) and US$3941 PPP (Striegel-Moore et al., 2000) in women and US$5169 PPP in men. Krauth and colleagues (2002) reported low direct costs for BN of US$127 PPP.

In BED, reported direct costs have been US$3487 PPP (Dickerson et al., 2010) and US$2214 PPP (Grenon et al., 2010). Reported costs for EDNOS have almost been the same as in BN: US$5301 PPP (Mitchell et al., 2009) and US$4267 PPP (Striegel-Moore et al., 2000).

When comparing different economic analyses, there are several reasons for uncertainty. For example, most economic analyses have been clinical trials not representing the average ED patient, economic estimates have been inaccurate, sample sizes have been too small, and patient data have often been incomplete (Table 5). In a review on costs and cost-effectiveness, the methodological quality of studies was found to be heterogeneous, and most of the studies did not meet the criteria for a cost-of-illness study (Stuhldreher et al., 2012). The authors only included three cost-of-illness studies on AN or BN.
Table 5. Major studies describing the healthcare costs for anorexia and bulimia nervosa. There are several differences in the design and analysis of these studies, which reduces the comparability of the cost data.

(AN = anorexia nervosa, BN = bulimia nervosa, EDNOS = eating disorder not otherwise specified, BED = binge-eating disorder, BMI = body mass index, OCD = obsessive-compulsive disorder, CBT = cognitive-behavioural therapy)
<table>
<thead>
<tr>
<th>Study</th>
<th>Perspective</th>
<th>Country</th>
<th>N and diagnosis</th>
<th>Duration of the follow-up</th>
<th>Costs</th>
<th>Description</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>O'Brien, Patrick, 1998</td>
<td>Third party Payer</td>
<td>USA</td>
<td>AN=641&lt;br&gt;BN=326</td>
<td>Duration of inpatient stay AN=13 days&lt;br&gt;BN=days</td>
<td>Inpatient cost AN= 12 390 $&lt;br&gt;BN= 9120 $</td>
<td>Inpatient cost estimates, adjusted for medical inflation and cost-to-charge ratios were developed using data from all-payer discharge database</td>
<td>Cost of acute hospitalization for AN and BN was estimated</td>
</tr>
<tr>
<td>Krauth et al 2002</td>
<td>Society</td>
<td>Germany</td>
<td>Estimation of cases of AN=4600 and BN=590 in inpatient treatment per year</td>
<td>Estimation of total costs for society and annual cost per AN and BN</td>
<td>Inpatient, health insurance, rehabilitation pension insurance, inability to work. Cost of illness app 195 million euros, bulimia 124 million.€ in Germany. Annual cost per AN 5300€, bulimia 1300€.</td>
<td>Cost-estimates were projections derived from benefit data, pension insurance and from epidemiological studies (prevalence, mortality). Authors estimated the average cost of treating AN in cluding indirect costs (inability to work, mortality)</td>
<td>This study underlines the significance of indirect costs due to premature death, but also highlights the extremely cost-intensive treatment. The hospitalization cost per AN (12,800€)patient is markedly higher than the average hospitalization cost (3600€)</td>
</tr>
<tr>
<td>Striegel-Moore et al 2000</td>
<td>Third party payer</td>
<td>USA</td>
<td>AN= 517 (Female) 49 (Male)&lt;br&gt;BN= 725 (Female)&lt;br&gt;41 ( Male )&lt;br&gt;EDNOS= 756 ( Female )&lt;br&gt;176 ( Male)</td>
<td>One year</td>
<td>One year data from national insurance database from claims from ED patients and other patients</td>
<td>Treatment of AN or BN was comparable in cost of treatment of schizophrenia. ED costs were more than in the treatment of OCD</td>
<td>Striegel-Moore et al 2000</td>
</tr>
<tr>
<td>Mitchell et al 2009</td>
<td>Third party Payer</td>
<td>USA</td>
<td>ED diagnosis= 167</td>
<td>52.5 months</td>
<td>Hospital care, health care provider, prescription medication AN 3405 $&lt;br&gt;BN 6639 $&lt;br&gt;EDNOS 6887$ (Group1)</td>
<td>Health insurance database</td>
<td>Health care costs remained elevated after a diagnosis of an ED for an extended period of time</td>
</tr>
<tr>
<td>Haas et al 2012a</td>
<td>Costs of the hospitalization</td>
<td>Germany</td>
<td>AN=101&lt;br&gt;BN=95</td>
<td>The length of Inpatient stay during 2006-2009</td>
<td>Inpatient cost using micro costing AN= 5251€&lt;br&gt;BN=3265€</td>
<td>The aim of the study was to analyze if psych osomatic in patients treated for eating disorders could be reimbursed by a common per diem rate</td>
<td>The diagnosis of AN predicted higher costs. Predictors of high costs were found.</td>
</tr>
<tr>
<td>Crow, Nyman 2004</td>
<td>Third party Payer</td>
<td>USA</td>
<td>AN</td>
<td>Cost-modelling analysis was used to estimate the incremental cost-effectiveness of AN treatment</td>
<td>Adequate care (inpatient, partial hospitalization, outpatient psychotherapy, medication) and Usual care (limited intensity)</td>
<td>Adequate care $8119200&lt;br&gt;Usual care $36200 $&lt;br&gt;Adequate care model yeild a cost per year of life saved of only $30000</td>
<td>The comprehensive treatment of An appears to be quite cost-effective in terms of cost per year life saved.</td>
</tr>
<tr>
<td>Byford et al 2007</td>
<td>Third party Payer</td>
<td>UK</td>
<td>AN inpatient n=47&lt;br&gt;specialist outpatient n=45&lt;br&gt;general outpatient n=43</td>
<td>2 years</td>
<td>Inpatient 34531 €&lt;br&gt;Outpatient sp 26738 €&lt;br&gt;General 40 791€</td>
<td>There were no significant differences in clinical outcomes between groups, but specialists out-patient was less costly than inpatient and general out-patient treatment</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Funding Source</td>
<td>Country</td>
<td>Sample Size</td>
<td>Treatment Duration</td>
<td>Direct Costs</td>
<td>Indirect Costs</td>
<td>Cost Calculation</td>
</tr>
<tr>
<td>------------------------------</td>
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<tr>
<td>Lock et al 2008</td>
<td>Third party payer</td>
<td>USA</td>
<td>AN</td>
<td>39,686$</td>
<td>Medical hospital, outpatient family therapy, medication, doctor visit</td>
<td>Based on clinical records, the costs and effects of outpatient family therapy were evaluated</td>
<td>Most of the costs associated with outcome were secondary to medical hospitalization. Adolescent treatment costs appeared to be lower when families are used effectively to aid in treatment.</td>
</tr>
<tr>
<td>Haas et al 2012b</td>
<td>Costs of the hospitalization</td>
<td>Germany</td>
<td>AN=127</td>
<td>Patient treated from 1/2005 to 3/2009. Mean length of hospitalization (LOD) 28 days</td>
<td>Cost calculated based from actual consumption of resources by each patient 4,647€/6831US$</td>
<td>The aim was to calculate inpatient costs for average AN patient and to identify significant predictors of cost.</td>
<td>BMI predicted inpatient costs per day, also comorbidity did increase costs.</td>
</tr>
<tr>
<td>Toulany et al 2015</td>
<td>Costs of the hospitalization and caregiver perspective</td>
<td>Canada</td>
<td>AN=73</td>
<td>Inpatient stay during 2 years</td>
<td>Inpatient costs = 51,349 Can $</td>
<td>Total societal cost = 54,932 Can $</td>
<td>Micro-costing of cohort study involving adolescent patients admitted for treatment of anorexia nervosa at a tertiary care. Hospital costs and caregiver costs were determined</td>
</tr>
<tr>
<td>Stuhldreher et al 2015</td>
<td>Third party payer</td>
<td>Germany</td>
<td>AN=242</td>
<td>3 months</td>
<td>Direct costs (costs of the treatment) and indirect costs (disability)</td>
<td>Mean cost for 3-month was €5866, direct costs were 57%</td>
<td>To estimate direct and indirect costs of AN and to identify cost determinant</td>
</tr>
<tr>
<td>Koran et al 1995</td>
<td>Third party payer</td>
<td>USA</td>
<td>BN=71</td>
<td>Costs during 32 weeks</td>
<td>Costs were calculated by multiplying clinics professional fees by the number of visits and addid medication costs</td>
<td>Cost-effectiveness of CBT vs desipramine and combination</td>
<td>Medication appeared to be more cost-effective than CBT but the authors discuss the pitfalls and limitations of this study</td>
</tr>
<tr>
<td>Crow et al 2009</td>
<td>Society</td>
<td>USA</td>
<td>BN=128</td>
<td>Costs during 12 months</td>
<td>Costs of treatment and travel time for therapists and subjects. Unit costs were derived from the Medicare website,</td>
<td>Aim was to compare face-to-face CBT ($9324) vs telemedicine CBT ($7300)</td>
<td>Telemedicine and face-to-face CBT were similarly effective and costs in telemedicine substantially less underlining the usefulness of telemedicine in this treatment.</td>
</tr>
<tr>
<td>Crow et al 2013</td>
<td>Third party payer</td>
<td>USA</td>
<td>BN=293</td>
<td>Costs during treatment 4 months</td>
<td>Inpatient costs, outpatient and emergency room utilization and medication costs</td>
<td>Aim was to analyze the costs of stepped care ($12146) vs CBT($20317)</td>
<td>Stepped care appeared more cost effective than CBT</td>
</tr>
</tbody>
</table>
2.11.1.2 Cost-effectiveness analysis

Cost-effectiveness analysis (CEA) is applied to compare at least two alternative treatments regarding costs and outcomes. Using an incremental analysis (differences in costs are put in relation to differences in effects), they combine both parameters to determine the most efficient treatment. CEAs support the decision on how to allocate scarce resources in healthcare systems. CEAs can be conducted within clinical trials.

2.11.1.3 Cost-effectiveness analysis in BN

Crow et al. (2013) reported a cost-effectiveness analysis of a randomized controlled trial for BN treatment. BN patients were randomized into either a cognitive behavioural therapy treatment, potentially augmented by fluoxetine, or stepped care treatment (treatment beginning with guided self-help, then fluoxetine, then CBT). To account for uncertainty, cost-effectiveness ratios were examined with boot strapping and sensitivity analyses. According the study, the stepped care approach was both more effective and less costly. The cost per abstinent participant was US$12 146, while the CBT was US$20 317. In those participants who achieved abstinence from BN symptoms, the QoL improved significantly more (Crow, 2013) (Table 5).

2.11.1.4 Cost-effectiveness analysis in AN

In the literature, there are few recent studies examining specific costs related to the treatment of EDs. Stuhldreher et al. (2015) described the results of a cost-effectiveness analysis of AN treatment outpatients. They collected health care utilization data on all participants (225 of the 242 participants). Specifically, they also examined retrospective recall of costs over the three months preceding the study. The cost in the three months preceding trial entry was €5866 (€3374 direct, €2492 indirect). The main driver of costs was hospitalization for eating disorder treatment. A cost analysis involving 127 individuals with anorexia nervosa has also been conducted by Haas and colleagues (2012). In this study, the cost of services was calculated based on resource utilization using bottom-up microcosting from a hospital perspective. The mean cost was €4647 (US$6831) per case. The presence of psychiatric comorbidity and lower admission of BMI were predictive of a higher overall cost (Table 5).
2.11.1.5 Cost-effectiveness of prevention

A study by Wang et al. (2011) assessed the economic effect of the school-based obesity prevention programme Planet Health for preventing disordered weight control behaviours and determined the cost-effectiveness of the intervention. They estimated that with the help of the programme, one case of bulimia nervosa would have been prevented, indicating $33,999 in medical costs and 0.7 QALYs saved.

2.11.2 Quality-adjusted life year as an outcome measure

The quality-adjusted life year (QALY) is a metric that combines mortality and morbidity into a single index score. QALYs offer a broad definition of a successful medical care and treatment outcome (Jennet 1992). Cost-utility analysis is a type of cost-effectiveness analysis that examines the costs and effectiveness of therapies by using the calculation of cost per quality-adjusted life year (QALY) as a unit of effectiveness. Cost-utility analysis is considered the gold standard both for reporting cost-effectiveness results in the literature and for informing policy decisions on the allocation of health care resources (Pirraglia et al., 2004).

Many studies regarding eating disorders have focused on weight and eating behaviours, which may fail to capture the disability caused by the illness (Keilen et al., 1994). QALYs can be used in comparing different diseases and treatments (Keilen et al., 1994). Counting of the cost per QALY is based on QoL scores, statistical life expectancy and the costs of the treatment.

Very few studies have used QALYs as an outcome measure in eating disorders, although it is recommended in the literature to measure the cost per QALY (Stuhldreher et al., 2012). In a study by Lynch et al. (2010), a QALY was estimated for treating recurrent binge-eating disorder treatment. They compared one group receiving standard care with another group receiving both standard care and CBT group therapy. The latter was more expensive but produced more binge-free days, and the cost per QALY was $26,847 (Lynch et al., 2010).
### 2.12 Summary of the reviewed literature

BN and AN are serious medical conditions that usually start in young adolescence and mainly affect women. The prevalence of BN is estimated to range from 0.9 to 2.9% in women and from 0.1 to 0.5% in men. The prevalence of AN in women varies from 0.3 to 2.2%, while in men the prevalence of AN was estimated to be 0.24%. AN and BN result in high mortality and have a major impact on the health-related quality of life (HRQoL) of the sufferers. In a meta-analysis, SRM was 1.93 in BN and 5.86 in AN, being one of the highest in the field of psychiatry (Arcelus et al., 2011). BN and AN are heritable, but the aetiology of eating disorders is considered to be multifactorial (Cooper and Steere, 1995). Whether a person develops an eating disorder depends on individual vulnerability, consequent on the presence of biological or other predisposing factors, their exposure to particular provoking risk factors (Jacobi et al., 2004) and on the operation of protective factors (NICE Guideline, 2004).

The HRQoL of eating disorder patients has been poor, and even after treatment the HRQoL is less than that in the normal population. The costs of ED treatment have been considered high. No previous studies on eating disorders have measured the cost per QALY. The prognostic factors regarding HRQoL are unclear, and the long-term HRQoL of ED patients is undetermined.
3 AIMS OF THE STUDY

The aims of this study were to measure the cost-effectiveness of treatment in terms of quality-adjusted life years (QALYS) in BN and AN, to assess the prognostic factors in AN and to measure the long-term HRQoL in BN and AN.

The specific aims were as follows:

1) and 2) To investigate HRQoL and cost-effectiveness in terms of quality-adjusted life years (cost per QALY) in bulimia nervosa and anorexia nervosa treatment in a naturalistic treatment setting. (Studies I, II)

3) To assess the prognostic factors related to HRQoL in AN using a novel Bayesian method in patients treated at the Eating Disorder Unit. (Study III)

4) To measure the long-term quality of life of anorexia nervosa and bulimia nervosa patients after approximately 8 years from the start of treatment. (Study IV)
4 MATERIALS AND METHODS

4.1 Study design and participants

The subjects of this naturalistic follow-up study comprised of 72 consecutive patients diagnosed with AN and 110 patients diagnosed with BN entering treatment in the Eating Disorder Unit of Helsinki University Central Hospital from June 2002 to December 2003. The number of binge-eating disorder (BED) (n = 19) and eating disorder not otherwise specified (EDNOS) (n = 21) patients was so limited that they were not analysed in this study. The HRQoL of ED patients at baseline was compared with that of a representative sample of the general female population studied in the National Health 2000 Health Examination Survey (Aromaa et al., 2004). For comparison, the population sample was weighted to correspond to the age distribution of the patients.
Figure 1. The flow-chart of the study design

Participants entering treatment n=270

Missing data N=21

Missing diagnosis N=19

Participants with diagnosis N=230

Not diagnosed an eating disorder N=8

Diagnosed with an Eating disorder N=222

Anorexia nervosa N=72

Refused n=33

Follow-up at 2 years N=39 Study II, III

Refused n=25

Follow-up at 8 years N=47 Study IV

Bulimia nervosa N=110

Refused n=38

Follow-up at 6 months N=72 Study I

Refused n=56

Follow-up at 8 years N=54 Study IV

EDNOS N=21

BED N=19

Participants with diagnosis N=230

Not diagnosed an eating disorder N=8

Diagnosed with an Eating disorder N=222

Anorexia nervosa N=72

Refused n=33

Follow-up at 2 years N=39 Study II, III

Refused n=25

Follow-up at 8 years N=47 Study IV

Bulimia nervosa N=110

Refused n=38

Follow-up at 6 months N=72 Study I

Refused n=56

Follow-up at 8 years N=54 Study IV

EDNOS N=21

BED N=19
The diagnosis of AN and BN was based on clinical assessment (International Statistical Classification of Diseases and Related Health Problems ICD-10 criteria) by a psychiatric consultant or resident. The inclusion criterion was an ED diagnosis, and no exclusion criteria were introduced.

At baseline, the subjects completed the 15D HRQoL questionnaire (http://www.15d-instrument.net/15d, Sintonen, 2001) and the Eating Disorder Inventory (EDI) questionnaire (Garner et al., 1983), as well as a specific questionnaire developed for the needs of this study enquiring, for example, about the patients’ self-perceived health status and eating habits. Follow-up questionnaires were mailed to all subjects who had returned the first questionnaire. The follow-up questionnaires were mailed approximately six months, two years and eight years after the start of treatment at the Eating Disorder Unit. A reminder was sent if the participant did not respond to the first questionnaire mailing.

The study protocol was approved by the Ethics Committee of Helsinki University Central Hospital, Finland.
Table 6. Baseline characteristics of the bulimia nervosa and anorexia nervosa participants (with SDs) (BN = bulimia nervosa, AN = anorexia nervosa, EDI = Eating Disorder Inventory (the higher the score, the greater the eating disorder problems), BMI = body mass index, HRQoL score = health-related quality of life score

<table>
<thead>
<tr>
<th>Variable</th>
<th>Bulimia Nervosa 6 months follow-up (n=72)</th>
<th>Bulimia Nervosa 8 years follow-up (n=54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age, (SD)</td>
<td>25(6.0)</td>
<td>25.7(6.0)</td>
</tr>
<tr>
<td>Age range</td>
<td>(17-48)</td>
<td>(17-45)</td>
</tr>
<tr>
<td>Female %</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>HRQoL score</td>
<td>0.80 (0.09)</td>
<td>0.818 (0.088)</td>
</tr>
<tr>
<td>EDI score</td>
<td>80 (28)</td>
<td>82 (32)</td>
</tr>
<tr>
<td>BMI kg/m2</td>
<td>22 (3.9)</td>
<td>21 (7.3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>Anorexia nervosa 2 years follow-up (n=39)</th>
<th>Anorexia Nervosa 8 years follow-up (n=47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age, (SD)</td>
<td>22(5.0)</td>
<td>23(7.8)</td>
</tr>
<tr>
<td>Age range</td>
<td>(17-42)</td>
<td>(17-64)</td>
</tr>
<tr>
<td>Female %</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>HRQoL score</td>
<td>0.792 (0.12)</td>
<td>0.807 (0.123)</td>
</tr>
<tr>
<td>EDI score</td>
<td>73(27)</td>
<td>74 (29)</td>
</tr>
<tr>
<td>BMI kg/m2</td>
<td>16.5 (2.2)</td>
<td>16.4(2.1)</td>
</tr>
</tbody>
</table>
4.1.1 Drop-outs

Only approximately half of the patients responded to the follow-up and data were also missing from completed questionnaires. However, the patients were approached before the treatment even started, and many of the patients may have decided not to begin the treatment, since ED patients are usually very ambivalent about receiving treatment, and dropout rates from inpatient treatment for eating disorders are very high (Pham-Scottez et al., 2012). The representativeness of the present study group was tested in terms of age, HRQoL, BMI and EDI, and they did not differ from those individuals who did not respond to the follow-up.

4.1.2 Follow-up in bulimia nervosa

For participants diagnosed with BN who returned the first questionnaire (n = 110), the follow-up questionnaires were mailed after 6 months and approximately after 8 years from the start of treatment. Seventy-two BN patients (62%) returned the follow-up questionnaire at 6 months, and at 8 years, fifty-four patients (49%) responded and were thus available for analysis. Those who did not return the questionnaires did not differ statistically significantly regarding HRQoL or age compared to the responders (mean age 25.7 (SD 5.9) vs. 25.6 (SD 6.8), p = 0.937; mean 15D score 0.818 (SD 0.09) vs. 0.815 (SD 0.94), p = 0.861).

4.1.3 Follow-up in anorexia nervosa

Those who were diagnosed with AN and who returned the first questionnaire (n = 72) were mailed the follow-up questionnaires 2 years and 8 years following the start of treatment. At the 2-year follow-up, thirty-nine patients returned the questionnaire (53%), while at the 8-year follow-up, forty-seven AN patients (65%) returned the questionnaire. Those who returned only the baseline questionnaire did not differ significantly regarding age or HRQoL from those who also returned the 2-year or 8-year questionnaire (mean age 23.3 (SD 7.8) vs. 22.5 (SD 5.9), p = 0.682; mean 15D score 0.807 (SD 0.12) vs. 0.823 (SD 0.10), p = 0.565).
4.2 Clinical assessment

Patients were examined by a psychiatric resident or consultant when entering the Eating Disorder Unit. If needed, consultation with an internist and dietician was provided. After the consultations, interventions were adjusted to each patient’s needs by a multidisciplinary team.

4.3 Treatment interventions

The Eating Disorder Unit provides tertiary-care-level treatment. The Unit is part of Helsinki University Central Hospital and provides specialized assessment and treatment of adults with EDs within a catchment area of approximately 1.5 million people. Some tertiary referrals for inpatient treatment are also taken from other parts of Finland. Most treatment is provided at the outpatient level, but day patient treatment and inpatient wards are also available. The Eating Disorder Unit uses a cognitive-behavioural approach in the treatment. The treatment interventions during this study followed normal hospital procedures. When this study began, it was the first specialized ED Unit in Finland.

4.3.1 Treatment interventions in bulimia nervosa

In the Eating Disorder Unit, the treatment of BN patients followed the stepped-care programme. First, the patients received psychoeducational lectures including elements of cognitive behaviour therapy. Experienced dieticians and internists gave the lectures. After these, patients who still suffered symptoms were invited to cognitive-behavioural group (CBT) therapy (8 sessions). Therapy sessions were held by an experienced dietician and a psychiatric nurse. Patients who were still symptomatic after the group therapy received individual CBT provided by a psychiatric nurse (about 20 sessions). Short-interval treatment in the day hospital or on the inpatient ward was offered if the patients were unable to stop binging and purging in outpatient care. The patients also received psychopharmacological treatment and, if needed, individual nutritional counselling and social skills training.
4.3.2 Treatment interventions in anorexia nervosa

In AN, the treatment interventions consisted of psychoeducation, cognitive-behavioural group and/or individual therapy, motivational interviews, social skills training, nutritional counselling and psychopharmacological treatment. If the body mass index (BMI) was 16 kg/m² or lower, inpatient treatment was recommended. After the inpatient treatment, the patients were invited to a day hospital and they started a 40-session cognitive-behavioural therapy intervention after their BMI was 17 kg/m² or higher.

4.4 Baseline and follow-up measurements

4.4.1 HRQoL (15D instrument)

HRQoL was assessed using the 15D questionnaire (Sintonen, 2001). The valuation system of the 15D is based on the application of multi-attribute utility theory. A set of preference (or utility) weights, elicited from the general public through a three-stage valuation procedure, is used in an additive aggregation formula to generate the utility score (15D score, a single index number) over all dimensions (Sintonen, 1994a, 1995). The maximum score is 1 (indicating no problems in any dimension) and the minimum score 0 (being dead). The minimally important difference or change in the 15D score is 0.03, indicating clinical significance (Sintonen, 1994b; Alanne, 2015). In most of the important properties (reliability, content validity, discriminatory power and responsiveness to change), the 15D compares favourably with other similar HRQoL instruments (Stavem, 1999; Hawthorne, et al. 2001; Moock and Kohlman, 2008; Vainiola et al., 2010).

4.4.1.1 Age-adjusted comparison group from the female general population

The HRQoL of ED patients at baseline was compared with that of a representative sample of the general female population studied in the National Health 2000 Health Examination Survey
(Aromaa et al., 2004). For comparison, the population sample was weighted to correspond to the age distribution of the patients.

### 4.4.2 Clinical outcome measures

#### 4.4.2.1 Eating Disorder Inventory

The clinical outcome was measured using the Eating Disorder Inventory (EDI) (Gardner et al., 1983; Welch et al., 1990), and based on the self-reported weight and height, BMI was calculated accordingly. The Eating disorder Inventory (EDI) (Garner et al., 1983) is one of the most widely used self-report inventories for eating disorders. The EDI is designed to assess the psychological characteristics of AN and BN (Garner et al., 1983). It has repeatedly been shown to be a reliable and valid instrument (Garner et al., 1983; Welch et al., 1990). The EDI is comprised of 64 items divided into eight subscales. These subscales are Drive for Thinness, Perfectionism, Bulimia, Body Dissatisfaction, Interpersonal Distrust, Ineffectiveness, Interoceptive Awareness and Maturity Fears. In the EDI, there is a recognized cut-off for the total score of 42, above which respondents are regarded as being susceptible to a clinical eating disorder (Bennett and Stevens, 1997). According to preliminary data, the total initial EDI score is associated with a poor prognosis in AN patients (Bizeul, 2001).

ED patients self-report their current weight in the EDI. Eating disorder patients have been extremely accurate in self-reporting their weight, although AN patients slightly over-report their weight (McCabe et al., 2001). In the Eating Disorder Unit, where this study was carried out, a cut-off for each subscale of the EDI is in clinical use. This cut-off is 5 points, except for the subscale “Perfectionism”, for which the cut-off of 10 is used. The cut-off of the EDI (<46) represents the cut-offs of all the eight subscales combined, indicating an improvement in the psychological characteristics of EDs.

#### 4.4.2.2 Questionnaire developed for the needs of the study

A specific questionnaire developed for the needs of this study was also used. It assessed the self-reported health status of the patients and included questions about the eating habits, for example: “I control my eating” (scale 0–5: never, rarely, sometimes, quite often, always) or “I avoid eating”.
4.5 Cost-utility

Since 2002, HRQoL data have been collected on approximately 15 000 patients in approximately 20 different specialties before and after interventions performed at the hospitals of the Helsinki and Uusimaa Hospital District (Räsänen et al., 2005). The observed change in HRQoL is related to routinely collected cost data on specialist medical care provided to the patients in order to determine the cost-utility of these interventions. These results enable the comparison of the every-day cost-utility of a range of interventions. These results also offer decision-makers relevant information for the planning of future specialist healthcare services.

4.5.1 Costs of the treatment

The direct hospital costs of the treatment were obtained from the Ecomed® clinical patient administration system (Datawell Ltd., Espoo, Finland). All cost data concerning the treatment of individual patients in the Eating Disorder Unit are stored in this database. All speciality-relevant costs at the Eating Disorder Unit (interventions, ward, ambulatory visits, laboratory and radiology) cover the period from the start of treatment to the end of the 6-month (BN) and two-year (AN) follow-up. The costs are based on current prices in 2002–2005. We did not include productivity loss due to potential work disability or other non-healthcare costs. Medication costs during inpatient treatment are included in the costs, but other medication costs are not.

4.5.2 Cost-utility in bulimia nervosa

BN patients often can have relapsing course and many of the patients do not receive any treatment. We analysed two scenarios based on different sets of assumptions about the development of health outcomes when treated or not treated.

4.5.2.1 Best-case analysis in BN

In the best-case sensitivity analysis (i.e. the most optimistic scenario regarding cost-utility), we analysed a scenario in which HRQoL would not improve without treatment. We also assumed that the HRQoL gain from the treatment by 6 months would last until the end of the remaining
statistical life expectancy of each patient. After this, we calculated the QALYs gained by the treatment accordingly. By dividing the mean cost by the mean number of QALYs gained, we obtained the cost per QALY gained (the cost-utility) (Figure 2).

![Best-case analysis](image)

Figure 2. Best-case analysis in BN.

### 4.5.2.2 Base-case analysis in BN

In the base-case cost-utility analysis (i.e. the most pessimistic assumption), we assumed that even if the patients do not receive treatment, their HRQoL will improve linearly during 10 years to the same level as reached by the treated patients after 6 months of treatment. For those who received treatment, we assumed that the HRQoL gain by 6 months would persist until 10 years. After this, we calculated the QALYs gained by the treatment accordingly. The mean cost of the
treatment was then divided by the mean number of QALYs gained, giving the cost per QALY gained (Figure 3).

**Figure 3.** Base-case analysis in BN.

As the gain from treatment is expected to last many years, the cost per QALY is also reported using a discount rate of 5%, which is the typical approach used in health economics (Drummond et al., 2005).
4.5.3 Cost-utility in anorexia nervosa

The course of AN is highly variable, and we therefore analysed two scenarios based on different sets of assumptions about the development of health outcomes when treated or not treated.

4.5.3.1 Best-case analysis in AN

In the best-case sensitivity analysis, \textit{(i.e. the most optimistic scenario regarding cost-utility)}, we analysed a scenario where HRQoL would not improve without treatment. We also assumed that the HRQoL gain from the treatment by two years would last till the end of the remaining statistical life expectancy of each patient. The QALYs gained were then calculated. Dividing the mean costs of the treatment by the mean HRQoL gain gives the cost per QALY gained. This analysis assumes that the difference between treated and not-treated patients achieved during the first two years of treatment remains the same for the rest of life expectancy, but the HRQoL can improve in both groups over time \textit{(i.e. two years after start of treatment)} (Figure 4).

![Best-case analysis](image_url)

**Figure 4.** Best-case analysis in AN.
4.5.3.2 Base-case analysis in AN

In this analysis, we assumed that if we do not treat the patients, their HRQoL will improve linearly in 10 years to the same level as treated patients have achieved after two years from the start of the treatment (base-case cost-utility analysis i.e., the most pessimistic scenario regarding cost-utility). We also assumed that the HRQoL gain by two years would persist until 10 years for those treated. Dividing the mean costs by the mean HRQoL gain gives the cost per QALY gained (Figure 5).

![Base-case analysis](image)

**Figure 5.** Base-case analysis in AN.

The cost per QALY is also reported using discount rates of 3–5%, which is the typical approach used in health economics, as the gain following treatment is expected to last many years (Drummond et al., 2005).
4.6 Statistical methods

Data were analysed using the statistical software SPSS for Windows version 21.0 (SPSS Inc., Chicago, IL, USA). The results are presented as means and standard deviations (SDs) for continuous variables, and as percentages. The significance of differences between before and after treatment scores was analysed with the Student’s two-tailed paired t-test for dependent samples, and the difference between patients and the general population with the two-tailed independent samples t-test. P-values ≤0.05 were considered statistically significant.

4.6.1 Bayesian methods

The fundamental ideas of the Bayesian statistical paradigm have existed for centuries (Bayes, 1763), but only in recent decades have Bayesian statistics been applied in psychological research (Andrews and Baguley, 2013). The core idea behind Bayesian statistics is that a posterior distribution of a particular parameter can be generated as a function of both observed data and prior knowledge (Kruschke, 2011). The Bayesian approach therefore has the advantage of permitting researchers to incorporate prior knowledge into their data analysis, in contrast to traditional frequentist statistics. The creation of 95% credible intervals is also allowed by Bayesian data analysis, indicating that the probability that a particular parameter lies within the specified interval is 95%.

Bayesian statistics are widely used in medical statistics, including clinical trials, epidemiology and meta-analyses (Ashby, 2006). One advantage of the Bayesian method is that analysis can also be performed with small data sets, with certain limitations (Blomstedt et al., 2007; Ng and Jordan, 2002; Wang et al., 2004; Greenland et al., 2000; Bellazzi and Zupan, 2008; Soini et al., 2009). In terms of prediction accuracy (Blomstedt et al., 2007; Soini et al., 2009), variable selection and multiple performance measures (Soini et al., 2009), a web-based naïve Bayesian classifier (NBC) method equalled or outperformed logistic regression, especially with small data sets. If the data set is small, dependencies are weaker and the model found to be best may not be very much better than the second best (Myllymäki et al., 2002). Bayesian analyses can use informative priors based on previous comorbidity findings (Gallagher and Brown, 2015). The Bayesian method has previously been used in psychiatry, for example in mood and anxiety disorders (Gallagher and Brown, 2015) and in schizophrenia (Samara et al., 2016).
4.6.1.1 Bayesian method in our study

In our study, we aimed to determine the factors that may predict the treatment outcome in AN. We decided to use the Bayesian method, since it is a novel method in the field of eating disorders, and in addition it can be used on small sample sizes with certain limitations.

In our study, we aimed to use the Bayesian method to investigate the prognostic factors in AN. For the analysis, we formed four outcome variables as follows:

1. A patient reaching at least 0.85 on the HRQoL index score; variable referred to as QoL.
2. A patient reaching a BMI of at least 19 kg/m²; variable referred to as BMI
3. A patient reaching an EDI score of less than 46; variable referred to as EDI
4. A patient fulfilling at least two of the previous three criteria; variable referred to as sum.

For HRQoL, a cut-off of 0.85 was chosen on the basis that it represents the average HRQoL of psychiatric patients in Finland (Saarni et al., 2007). For BMI, a cut-off of >19 was applied to be sure that the patients had reached a normal weight, because the threshold for being underweight is BMI < 18.5 according to WHO (http://apps.who.int/bmi/index). The cut off for EDI was <46, which is in clinical use in the Eating Disorder Unit.

In this study, PREQ, a web-based naïve Bayesian classifier (NBC), was used. PREQ can use multidimensional priors, e.g. separate priors for the outcome variable in general and for the outcome variable according to each predicting variable. However, the data modelling was performed without informative a priori information (Ryynänen et al., XXXX). PREQ has been developed from its previous application, the B-Course tool (Myllymäki et al., 2002).

Relationships were assessed between class variables and predictors with posterior odds (PO). These equal the product of prior odds as well as the likelihood ratio, and also the estimated inversed probabilities, giving an idea of the predictor’s strength. The POs were determined by

\[
PO = \frac{P_{PC}}{P_{NPC}}
\]

in which \(P_{PC}\) represents the predicted class and \(P_{NPC}\) the non-predicted class. POs are not directly dependent on the amount of data (Soini et al., 2009).

In this preliminary study, the data were unfortunately so limited that it was not possible to form separate training and test sets. We wanted to avoid overfitting the model, and a new data set (\(n = 30\)) was therefore first formed by randomly removing nine cases. This procedure was repeated four times to obtain five randomly diminished training sets. After this, NBC prediction
was performed for all four outcome variables in all five training sets. Next, only those predictor variables that were present in at least three models were then selected, thus forming a final training set containing seven potential predictor variables.

For the total data set, final modelling was performed separately for all four outcome variables by using the set of seven predictor variables. The model was considered overfitted if a model with more than three predictor variables was obtained. Overfitting was noted by obtaining unrealistic models with high accuracy (up to 100%). When this occurred, the number of predictor variables was limited to a maximum of three.

The data set was tested using leave-one-out cross-validation (LOOCV) (Soini et al., 2009), because separation of the training and test sets was not possible. In this method the learning algorithm is trained multiple times using all but one of the training set data points. The NBC tries to predict which data point is left out by using all the other training examples.

The logarithmic loss function (log score) is a way of presenting losses from actual outcomes in prediction tasks: the log score is a measure of the prediction distribution (the closer to zero, the better). The log score reaches a minimum only when true probabilities are predicted, thus being a strictly proper scoring rule. The log score also penalizes the inability to produce faithful probabilities. Due to the lack of a test set, the specificity, sensitivity, predictive values and area under the ROC curve were not relevant for calculation.

4.7 Ethical aspects

All patients received routine treatment and, besides being asked to complete the questionnaires and to give written informed consent, were not approached in any other way. The study protocol was approved by the Ethics Committee of the Helsinki and Uusimaa Hospital District.

4.8 Personal involvement

The author had the main responsibility for analysing the data. She participated in the design of the study and the writing of the manuscripts. She served as the first and corresponding author of all four publications of the study.
5 RESULTS

5.1 Cost-utility in bulimia nervosa (Study I)

5.1.1 Clinical outcomes

All the BN patients (n= 72) were female, their mean age was 25 years (SD 6.0) and the average duration of illness was 8 years (SD 6.3). The mean EDI score was 80 (SD 28) and mean BMI was 22.0 kg/m² (SD 3.9) (Table 6). The patients suffering from BN had a global, severely impaired HRQoL compared to the age-standardized general population (0.80 vs. 0.96) (Fig. 1) at baseline. Those who only returned the baseline questionnaire did not differ significantly regarding HRQoL, age or treatment costs from those who also returned the 6-month questionnaire.

After 6 months from the start of the treatment, there was a statistically significant and clinically important improvement in the mean HRQoL score of the BN patients (0.85, p < 0.001) (Study I, Table 1, Figure 2), although it still remained significantly worse (p < 0.001) than that of the general population (Study I, Table 1). A significant improvement occurred in seven dimensions of 15D, and there was a significant decrease in the EDI score (p < 0.001), indicating an improvement in the psychological characteristics of bulimia. The BMI did not significantly change (p = 0.1).
Figure 6. The 15D profiles of bulimia nervosa patients (n = 72) at baseline and after 6 months of treatment, as well as those of the age- and gender-matched general population (n = 1482) (* denotes a statistically significant improvement from baseline at the p < 0.05 level, ** at the p < 0.01 level and *** at the p < 0.001 level).

5.1.2 Costs

The mean cost of providing treatment during the 6-month follow-up was €3,972 ± 5,518. The mean distribution of costs is presented in Study I, Table 2.

5.1.3 Cost-utility and sensitivity analysis in bulimia nervosa.

The mean number of QALYs gained ranged from to 2.729 (best-case analysis) to 0.241 (base-case analysis), and the mean undiscounted cost per QALY gained ranged from €1,455 (best-case
analysis) to €16,481 (base-case analysis) (Study I, Table 3). The corresponding discounted (5%) figures ranged from €4,428 to €19,663 per to QALY gained, respectively.

5.2 Cost-utility in anorexia nervosa (Study II)

5.2.1 Clinical outcomes

All patients were female (n = 39). At baseline, the mean age was 22 years (SD 5.0), mean 15D score 0.792 (SD 0.12), mean BMI 16.5 kg/m² (SD 2.4) and mean EDI score 73 (SD 27) (Table 6). Those who returned only the baseline questionnaire did not differ significantly regarding HRQoL, age or treatment costs from those who also returned the 2-year questionnaire. Compared with the mean 15D score of the age-matched general female population, AN patients had a global, severe deterioration in their HRQoL at baseline (mean 15D score 0.963 vs. 0.792) (Study II, Figure 1). After 2 years from the start of the treatment, there was a significant improvement in 8 of the 15 dimensions, and the improvement in the mean 15D score (0.855 at two years) was statistically significant and clinically important (MID > 0.03) (p < 0.001) (Figure 3). The BMI increased in a statistically significant manner from 16.6 to 18.4 kg/m² (p < 0.001) after 2 years from the start of treatment. There was also a significant improvement in the EDI score (p < 0.001), indicating an improvement in the psychological characteristics of AN. Although the HRQoL of AN patients had improved during the follow-up, after two years from the start of the treatment the HRQoL still remained significantly worse in AN patients (p < 0.001) than in the age-matched general population (Study II, Figure 1).
Figure 7. The 15D profile of anorexia nervosa patients (n = 39) at baseline and after two years of treatment, as well as in the age- and gender-matched general population (n = 1482) (* denotes a significant improvement from baseline at the p < 0.05 level; ** at the p < 0.01 level, and *** at the p < 0.001 level).

5.2.2 Costs

The mean cost of providing specialist treatment during the two-year follow-up was €20 621 (SD 23 167).

5.2.3 Cost-utility and sensitivity analysis in anorexia nervosa

The mean number of QALYs gained is presented in Study II, Table 1. In the best-case sensitivity analysis, the cost per QALY gained was €5296. Using discounted (3%) values for QALYs, the cost per QALY gained increased to €11 559. In the base-case analysis, the mean cost per QALY gained was €64 440. Using discounted (3%) values for QALYs, the cost per QALY gained increased to €71 600.
5.3 Bayesian prediction of the treatment outcome in anorexia nervosa (Study III)

The baseline characteristics of anorexia nervosa patients are presented in Table 6. The results of four outcome variables are presented in Study III, Table 1. The sum variable was correlated with the EDI variable (Pearson correlation coefficient 0.74) and the BMI variable (Pearson correlation coefficient 0.48). No other correlation was statistically significant.

In NBC analysis, the sum of the outcome variables and EDI could not be predicted from this data set. A simple model with three predictor variables was found for HRQoL. A lower HRQoL after two years of treatment was predicted by a lower score in the vitality dimension at baseline (15D), more strongly controlled eating from the questionnaire designed for this study and a poor self-reported baseline health status.

For the BMI outcome variable, a model with two predictor variables was found. A lower baseline BMI and lower score in the 15D eating dimension (indicating further need for help with eating) predicted in the two-year follow-up a BMI value of less than 19 kg/m². These models are presented in Study III, Figures 1 and 2.

A fixation table of the model predicting the outcome variable QoL is presented in Study III, Table 3. The model was fixed to different values to demonstrate the effect of fixation on the target variable. A corresponding fixation table for the target variable BMI is presented in Study III, Table 4.
Figure 8. A naïve Bayesian classifier (NBC) model for predicting the outcome variable HRQoL.

Figure 9. A naïve Bayesian classifier (NBC) model for predicting of outcome variable BMI.
5.4 Long-term health-related quality of life in eating disorders (Study IV)

5.4.1 Clinical outcomes

5.4.1.1 Anorexia nervosa

Anorexia nervosa (n = 47) patient characteristics (with SDs) are presented in Table 7. The values are means (and SD) or percentages. (AN = anorexia nervosa, HRQoL = health-related quality of life, EDI = Eating Disorder Inventory, BMI = body mass index)

Table 7. Baseline characteristics of the anorexia nervosa patients. Values are means (and SD) or percentages. (HRQoL = health-related quality of life, EDI = Eating Disorder Inventory, BMI = body mass index).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Anorexia Nervosa (n=47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age, years (SD) (Age range)</td>
<td>23(7.8) (17-64)</td>
</tr>
<tr>
<td>Female %</td>
<td>100</td>
</tr>
<tr>
<td>HRQoL-score</td>
<td>0.807 (0.123)</td>
</tr>
<tr>
<td>EDI–score</td>
<td>74 (29)</td>
</tr>
<tr>
<td>BMI kg/m²</td>
<td>16.4 (2.1)</td>
</tr>
</tbody>
</table>

Compared with the mean 15D score of the age-matched general female population, AN patients had a global, severe deterioration in their HRQoL. During the follow-up there was a significant improvement in seven dimensions and in the mean 15D score (Figure 3). There was also a significant improvement in the EDI and BMI (Table 2). Although improvement occurred in
the HRQoL, it still remained severely impaired compared to the general population (0.893 vs. 0.935, p < 0.001). The average BMI of AN patients reached a normal level (20.1), since the cut-off for being underweight is normally considered as BMI > 18.5 (http://apps.who.int/bmi/index.jsp?introPage=intro_3.html).

**Table 8.** Baseline characteristics and follow-up outcomes in anorexia nervosa. Values are means (and SD) or percentages. (HRQoL = health-related quality of life, EDI = Eating Disorder Inventory, BMI = body mass index).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Anorexia nervosa (n = 47)</th>
<th>Significance of change compared to baseline (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRQoL at baseline</td>
<td>0.807 (0.123)</td>
<td></td>
</tr>
<tr>
<td>HRQoL at 8 years</td>
<td>0.893 (0.079)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>EDI at baseline</td>
<td>74 (29)</td>
<td></td>
</tr>
<tr>
<td>EDI at 8 years</td>
<td>44(28)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>BMI at baseline</td>
<td>16.4(2.1)</td>
<td></td>
</tr>
<tr>
<td>BMI at 8 years</td>
<td>20.1 (2.8)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
Figure 10. The 15D profiles of anorexia nervosa (AN) patients (n = 47) at baseline and after approximately 8 years of treatment, as well as in the age- and gender-matched general population at baseline and after 8 years (n = 2342) (* denotes a significant improvement from baseline at the p < 0.05 level; ** at the p < 0.01 level, and *** at the p < 0.001 level).

5.4.1.2 Bulimia nervosa

The baseline patient characteristics of the BN patients are presented in Table 9.
**Table 9.** Baseline characteristics of the bulimia nervosa patients. Values are means (and SD) or percentages. (HRQoL = health-related quality of life, EDI = Eating Disorder Inventory, BMI = body mass index).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Bulimia Nervosa (n=54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age, years(SD)</td>
<td>25.7(6.0)</td>
</tr>
<tr>
<td>(Age range)</td>
<td>(17-45)</td>
</tr>
<tr>
<td>Female %</td>
<td>100</td>
</tr>
<tr>
<td>HRQoL-score</td>
<td>0.818 (0.088)</td>
</tr>
<tr>
<td>EDI-score</td>
<td>82 (32)</td>
</tr>
<tr>
<td>BMI kg/m2</td>
<td>21(7.3)</td>
</tr>
</tbody>
</table>

The HRQoL of BN patients was significantly diminished compared to the age-matched general female population. There was a statistically significant improvement in the mean score and nine subscales of 15D during the follow-up (Figure 4). The EDI score improved significantly, but there was no change in BMI during the follow-up. In BN, the HRQoL also remained severely impaired compared to the general population (0.885 vs. 0.938, p < 0.001) (Table 10).
Table 10. Baseline characteristics and follow-up outcomes in bulimia nervosa. Values are means (and SD) or percentages. (HRQoL = health-related quality of life, EDI = Eating Disorder Inventory, BMI = body mass index).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Bulimia Nervosa (n=54)</th>
<th>Significance of change compared to baseline (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRQoL at baseline</td>
<td>0.818 (0.088)</td>
<td></td>
</tr>
<tr>
<td>HRQoL at 8 years</td>
<td>0.885 (0.093)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>EDI at baseline</td>
<td>82 (32)</td>
<td></td>
</tr>
<tr>
<td>EDI at 8 years</td>
<td>44 (32)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>BMI at baseline</td>
<td>21 (7,3)</td>
<td></td>
</tr>
<tr>
<td>BMI at 8 years</td>
<td>23 (5,3)</td>
<td>NS</td>
</tr>
</tbody>
</table>
Figure 11. The 15D profiles of bulimia nervosa (BN) patients (n = 54) at baseline and after approximately 8 years of treatment, as well as in the age- and gender-matched general population at baseline and after 8 years (n = 1215) (* denotes a significant improvement from baseline at the p < 0.05 level; ** at the p < 0.01 level and *** at the p < 0.001 level).
6 DISCUSSION

6.1 Main findings

In this naturalistic follow-up study of eating disorder patients, it was found that the HRQoL of female AN and BN patients is poor when entering treatment at the Eating Disorder Unit compared to the normal population. During the follow-up, the HRQoL of AN and BN patients improved significantly, but after 8 years it was still less than in the general population. However, at 8 years, the average BMI was normal and EDI scores indicated improvement in the psychological characteristics of EDs, but the HRQoL was still low. Prognostic factors concerning the HRQoL in AN were found to be a lower score in the vitality dimension at baseline (15D), more strongly controlled eating from the questionnaire designed for this study and a poor self-reported baseline health status.

Cost-effectiveness in terms of cost per QALY was measured in young women suffering from AN or BN. The cost per QALY in BN was less than the commonly cited guidelines recommend. In AN, the cost per QALY was in the same range as that of other cost per QALYs in somatic conditions treated at our hospital (e.g. hip arthroplasty, cataract surgery). The conclusions of our study can only be generalized to female AN and BN sufferers, since the participants of the study were all female. This is, however, usually the case in eating disorder studies.

6.2 Results in relation to previous studies

6.2.1 Cost-utility of bulimia nervosa and anorexia nervosa (Studies I and II)

6.2.1.1 HRQoL

In both BN and AN, the baseline HRQoL was worse than in the normal population, and a significant improvement in HRQoL was seen during the follow-up. However, the HRQoL of BN and AN remained compromised compared to the normal population. These findings are in line with previous studies, which have reported a global deterioration in the HRQoL of eating disorder patients (Padierna et al., 2000, 2002; Jenkins et al., 2011; Winkler et al., 2014; Abbate-
Daga et al., 2014) and a significant improvement in HRQoL after treatment (Padierna et al., 2002). Padierna (2000) investigated eating disorder outpatients (n = 197) as one group and found that the patients with eating disorders were more dysfunctional in all areas measured with the SF-36 compared with the general population. In a follow-up study of HRQoL, Padierna and colleagues measured HRQoL after 2 years from the start of treatment and found an improvement, but the HRQoL was still lower than in the general population.

In BN, the 15D score after treatment was 0.85, which is in the same range as in AN (0.86). This is in line with a recent meta-analysis finding no differences between diagnostic groups (Winkler et al., 2014). The profiles of the 15D dimensions in AN and BN were different. An AN-specific improvement was seen in the dimensions eating, usual activities and mental health. To our knowledge, no previous studies have measured the HRQoL of ED patients using the 15D. Thus, we are unable to compare our results to previous HRQoL ED studies using the 15D. However, compared to other psychiatric conditions, the HRQoL of AN (0.79) and BN (0.80) patients before treatment was higher than that seen in patients entering secondary care psychiatric treatment because of depression (0.698) (Suominen et al., 2011). Compared to the mean baseline HRQoL of patients entering secondary care treatment for a variety of somatic conditions, it was, however, much worse (Suominen et al., 2011).

The baseline HRQoL of BN and AN patients was in the same range as seen in much older patients suffering from chronic conditions such as stroke, macular degeneration or coronary heart disease in a population-based study using the 15D (Saarni et al., 2006). In a study by Keilen et al. (1994), it was also found in a group of women referred to a tertiary ED service that those with EDs reported a lower QoL than physically impaired (angina, cystic fibrosis) patients. Compared to other psychiatric conditions, AN and BN patients at baseline in our study had an even worse HRQoL than older (45–49 years) patients suffering from depression (0.84), alcohol dependence (0.89) or panic disorder (0.86) (Saarni et al., 2007). The HRQoL of BN and AN patients was in the same range as that of people suffering from anxiety disorders (0.832), agoraphobia (0.781), generalized anxiety disorder (GAD) (0.783) or dysthymia (0.766) (Saarni et al., 2007).

The mean improvement in the 15D score seen in eating disorder patients (0.063) was somewhat greater than that seen as a consequence of treatment for depression (0.051) or back surgery (0.047), and more than threefold greater than in patients who had undergone a hysterectomy (0.020) or cataract surgery (0.008) (Suominen et al., 2011).
6.2.1.2 Costs and cost-utility

In our study, the average cost of the treatment in BN was €3972 (SD 5518) and in AN €20 621 (SD 23 167), and the cost per QALY in AN was also higher than in BN. Other studies have demonstrated that the treatment of AN is most costly due to the fact that AN patients are often hospitalized. In a systematic review (Agh et al., 2016), the annual healthcare costs for AN varied considerably from €2900 to €55 270 and in BN from €888 to €18,823. The cost estimates varied considerably. However, several differences in the design and analysis of the costs in the studies reduce the comparability of the cost data.

Compared to some other interventions so far studied in our project, the cost per QALY in BN in the best-case scenario (ca. €4428 discounted at 5%) was in the same range as that of lumbar spine surgery (€3700) (Räsänen et al., 2007) or cataract surgery in the best case (€7967 for patients whose both eyes were operated) (Räsänen et al., 2006b), and only approximately one-third of that observed for total hip arthroplasty (€12 340) (Räsänen et al., 2007) (5% discount rate). In AN, the cost per QALY in the best-case scenario (€11 559 discounted at 3%) was less than that observed for primary total knee arthroplasty (€18 890, 3% discount rate) (Räsänen et al., 2007), and in the same range as cataract surgery (€11 609, 3% discount rate) (Räsänen et al., 2006b) or total hip arthroplasty (€9906, 3% discount rate) (Räsänen et al., 2007). Although the economic burden and health service use in eating disorders is usually considered substantial (Mitchell et al., 2009), in our study the cost per QALY in BN and AN treatment was in the same range as in other conditions treated in our hospital district.

It is difficult to compare our results with other psychiatric interventions, because so few studies have reported the cost per QALY in psychiatry. To our knowledge, there have been no previous studies measuring the cost per QALY of treatment in EDs studied in a naturalistic setting. However, it is noteworthy that the commonly cited guidelines recommend the adoption of interventions that cost less than $20 000 to $100 000 per QALY (approximately €16 400 to €82 000) (Laupacis et al., 1992; Hirth et al., 2000; Neuman, 2005). The cost per QALY in BN was less than the guidelines recommend, and in AN the cost per QALY was in the range the commonly cited guidelines recommend for the adoption of health care interventions. This indicates that the treatment of AN and BN is cost-effective in terms of cost per QALY.
6.2.2 Prognostic factors in anorexia nervosa (Study III)

To our knowledge, the literature includes no studies using HRQoL instruments for assessing prognostic factors in EDs. In our study, we found that a low eating dimension score in the 15D was associated with not reaching a BMI of at least 19 kg/m² during the two-year follow-up. A lower score in the 15D dimension vitality at baseline was associated with an impaired mean 15D score (less than 0.85). We also found out that high eating control at baseline was associated with a low HRQoL score two years after the start of treatment.

AN is often associated with several health problems (Goldbloom and Kennedy, 1995, Westmoreland et al. 2016). In our study, we found that a poor self-reported health status at baseline was associated with an impaired follow-up HRQoL. However, we could not distinguish whether poor general health is a consequence of AN or precedes the onset of AN. The results regarding BMI in our study are partially consistent with previous studies. A low baseline BMI was a risk factor for not reaching a BMI level of at least 19 kg/m² during a follow-up of two years, which is in line with previous studies (Steinhausen 2008; Castro-Fornieles et al., 2007).

Against our assumptions, the improvement in BMI did not correlate with an improvement in HRQoL during the follow-up. This raises the question of what really indicates an improvement in AN. It has been suggested in the literature (Jenkins et al., 2011) that people suffering from AN can sometimes view aspects of the disorder as a positive part of themselves. This egosyntonicity may cause denial of their problems regarding AN and their seriousness. It might also be that in those with limited insight, a self-reported QoL may fail to capture the degree of impairment. In a study by Doll and colleagues (2005), for example, AN patients reported better QoL, but they still had a higher rates of suicidal thoughts and parasuicidal actions than subjects with other diagnoses. However, in a study by Bamford and Sly (2010), lower BMI predicted lower EDQoL in a sample of adults suffering from ED. In the literature, there are studies demonstrating that QoL worsens as BMI departs from the normal range (Abraham et al., 2006; Adair et al., 2007).

6.2.3 Long-term quality of life in eating disorders (Study IV)

The aim of our study was to measure for the first time the long-term development of health-related quality of life in AN and BN. According to our studies, the HRQoL appears to improve in AN the longer the patients are followed. The HRQoL of AN patients was 0.855 after 2 years of
follow-up. There was a clinically important (>0.03) improvement in HRQoL in AN from 2 years to 8 years (0.855 vs. 0.893). In BN, the HRQoL was 0.85 after 6 months from the start of the treatment, and it improved clinically importantly to 0.885 during the 8-year follow-up. However, the HRQoL was still severely impaired in both AN and BN compared to the normal population (0.94). Both AN and BN severely affected the QoL for a long period of time.

In our study, the HRQoL of both AN and BN patients 8 years after the start of the treatment was still significantly lower than in the normal population. This raises the question of what recovery in eating disorders means. Although the average BMI in AN had reached a normal level and the EDI score had significantly improved, the HRQoL was still impaired. De la Rie and colleagues (2005) also suggested in their study that symptom remission in EDs alone is not a sufficient condition for improvement in the quality of life.

6.3 Strengths and limitations

6.3.1 Strengths

6.3.1.1 Subjects

The study participants were "real-life patients" entering the outpatient or inpatient Eating Disorder Unit. Because of the naturalistic setting of the study, we did not want to exclude any patients. This gave us the possibility to gain more information on the everyday-life effectiveness and cost-utility of the routine treatment. The patients could have had a long history of eating disorders, many comorbidities and prior treatment elsewhere. The representativeness of the present study group was tested in terms of age, HRQoL, BMI and EDI, and they did not differ from the individuals who did not respond to the follow-up.

6.3.1.2 Study design

The strengths of this study are the long follow-up (8 years) and the inclusion of actual patients, who received treatment according the normal hospital routine. This gave us a possibility to gain more information on the actual treatment and its effectiveness.
6.3.1.3  Cost-utility and cost per QALY

The topic of Studies I and II was new. A strength of this study is that, to our knowledge, we were the first to measure the cost-effectiveness of routine treatment for eating disorders in terms of quality-adjusted life years. This is also the recommendation stated in the literature (Pirragilia et al., 2004). Furthermore, the costs of the treatment were actual costs obtained from our patient administration system and not cost estimates.

6.3.2  Limitations

6.3.2.1  Subjects

A shortcoming of this study is the limited number of patients, since only approximately half of the patients responded to the follow-up, and there was data missing. However, the patients were approached before the treatment even started and many of the patients may have decided not to begin the treatment, since ED patients are usually very ambivalent about receiving treatment, and dropout rates from inpatient treatment for eating disorders are very high (Pham-Scottez et al., 2012). The number of BED and EDNOS patients was also too limited to include in the analysis. In addition, the study group only consisted of female participants, so the conclusions can only be generalized to female samples, but this is usually the case in eating disorder studies (Jenkins et al., 2011).

A further drawback in this study is that the subjects were not representative of all individuals with anorexia nervosa and bulimia nervosa, as they were drawn from a group of patients entering treatment in a special-level tertiary Eating Disorder Unit.

6.3.2.2  Study design

The lack of measurement of psychiatric comorbidities is a major limitation, since depression or anxiety can affect the QoL (Gonzalez-Pinto et al., 2004), and this may be a confounding factor. The lack of measurement of the socioeconomic status of the family is also a limitation, since
higher parental education has independently predicted a higher rate of EDs in females (Ahren et al., 2013). We only measured the HRQoL with a generic instrument (15D), although in the literature it is suggested that generic QoL instruments may not be sufficiently sensitive to record the unique features that might be important for each disorder. ED-specific measures are better able to precisely measure QoL in ED samples (Engel et al., 2009). However, at the start of the study, no ED-specific measures were available to use. One shortcoming is the lack of a control group, since our results were compared to the age-adjusted general population.

6.3.2.3 Diagnostic interview and self-reported scales

The diagnosis was made by psychiatric resident or consultant after meeting with the patient. The lack of a structured diagnostic interview can be seen as a limitation. Other baseline data were gathered by using self-reported scales, which may possess reliability and validity problems. Although ED patients normally self-report their weight very accurately (McGabe et al., 2001), this can still cause major uncertainties. Finally, an extreme lack of insight in some ED patients may result in problems in self-reporting HRQoL (Jenkins et al., 2011; Engel et al., 2009).

6.3.2.4 Cost-utility and cost per QALY

A shortcoming of this study is that our cost data covered only the costs of specialized medical care. This may introduce some bias, as general health care utilization by eating disorder patients is high (Simon et al., 2005; Mitchell et al., 2009). We did not include indirect costs (losses of productivity: sickness absence, reduced productivity, premature death), which are major costs when concerning EDs.

One limitation is that the QALY calculations were based on the assumption that the improvement in HRQoL is long-lasting, although the course of eating disorders can be recurrent and patients may need treatment again. However, this kind type of calculation of QALYs is the approach typically used. Furthermore, knowledge of the long-term development of HRQoL is scarce, and the prognosis of patients not receiving any treatment is unclear. We made two
assumptions based on the literature and our clinical expertise, but the calculations of best-case and base-case analyses are only models and not actual costs.

7 CONCLUSIONS AND FUTURE PERSPECTIVES

7.1 Summary of main conclusions

Eating disorders are serious mental disorders affecting young people, and especially women. They have a major effect on the HRQoL of ED patients for a long period of time. The literature suggest that in people with subclinical pathology, QoL may still be negatively affected (Doll et al., 2005). According to our report, full recovery in terms of the health-related quality of life was not achieved even after 8 years after the start of the treatment. It should be recognised that after symptom remission, former patients can still suffer from diminished HRQoL, and a follow-up of the quality of life should be considered. Cost-effectiveness in terms of cost per QALY was measured in BN and AN. The cost per QALY in BN was less than the commonly cited recommend guidelines. In AN, the cost per QALY was in the same range as that of other cost per QALYs in somatic conditions treated at our hospital. However, all the participants were female, so the conclusions can only be generalized to female samples, although this is usually the case in eating disorder studies.

AN and BN are very serious conditions with high morbidity and a long-lasting impact on the HRQoL, even after symptom remission. In conclusion, the treatment of AN and BN is cost-effective and worthwhile.

7.2 Other conclusions

Our findings emphasize the importance of measuring the everyday-life effectiveness of routine treatment interventions. The patient perspective using the HRQoL instrument can provide us valuable information on the well-being of the patient when taking into consideration the long-
lasting impact of the disorder on HRQoL. Implementation of the routine measurement of HRQoL in the treatment of EDs should be considered. The everyday-life effectiveness of different treatment options should be studied, for instance in day patient vs. inpatient treatment or different psychological treatment options.

7.3 Clinical implications

It is important to know how and which patients with AN will respond to treatment. For example, those with a good prognosis may respond to less intensive treatment, while those with a worse prognosis may need more intensive treatment, e.g. inpatient treatment. We also need more information on how to improve or target the treatment at those patients not responding to first-line treatments. Knowledge of outcome factors may suggest how to do this (NICE Guidelines 2004). According to our study, we should put extra effort into the treatment of those AN patients who at baseline control their eating very strongly, have an extremely low BMI and report diminished vitality. We could have an impact on the prognosis of these patients by focusing on these clinical phenomena. This, however, should be examined in a future intervention study.

7.4 Implications for further research

Studies on the everyday-life effectiveness of treatment options should continue, since the results of randomized controlled trials (RCT) do not possibly reflect the situation of "real-life patients". A patient perspective should be included, e.g. by measuring the HRQoL using a generic and eating disorder a specific instrument. The follow-up should be long enough, since EDs are long-lasting and patients may have relapses. Cost-analysis should be incorporated into new studies, also measuring indirect costs. One should try to take into account the morbidity in eating disorders and the relapse rate, and thus create a model to estimate the actual cost per QALY. Comorbidities including depression and also the socio-economical status (SES) should be taken
into account in further studies on eating disorders and the health-related quality of life. More information on the cost per QALY in the treatment of EDNOS and BED is needed.
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