Eating Disorders - Aspects of Treatment and Outcome

AGNETA ROSLING
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Abstract

Eating disorders (ED) usually develop during adolescence, and intervention to stop further weight loss is believed to improve outcome and long-term prognosis. Adolescents with ED who do not receive effective treatment risk poor outcome and even untimely death as adults.

The first aim of this thesis was to investigate long-term mortality and causes of death in a series of female adults with chronic ED. The second aim was to study the one-year outcome of an unselected series of adolescent girls with anorexia nervosa (AN) and “other restrictive eating disorders” who had been treated within a specialist ED out-patient service focused on nutritional rehabilitation based on family therapy and without planned hospitalization. The third aim was to investigate the possible metabolic and hormonal side effects of olanzapine when used as an adjunct to facilitate nutritional rehabilitation. The fourth aim was to investigate the relationship between polyunsaturated fatty acid (PUFA) status and depression.

In adult women with chronic ED, a very low body mass index and psychiatric co-morbidity confer a substantially increased risk of premature death.

A treatment programme for adolescent ED with rapid access to assessment and prompt start of treatment with initial emphasis on nutritional rehabilitation proved efficient. The outcome was encouraging, as 43% of all patients with ED and 19% of those with AN did not have an ED at one-year follow-up. Of the remaining patients the vast majority had gained weight and regained menstruation, and were back in school on a full-time basis. Olanzapine was used to reduce anxiety, excessive exercise and rumination over weight and shape. Side effects were similar to those observed in normal-weight individuals, and do not preclude its use in underweight adolescents with ED. Low ω3 PUFA were associated with depression. The ω3 PUFA status improved during nutritional rehabilitation with ordinary foods and without supplementation.

The investigations indicate that adolescent ED can be successfully treated in an out-/day-patient setting. An essential feature of the service is rapid handling and weight gain. Further weight loss can be avoided, and chronic disease hopefully prevented.

Keywords: Anorexia Nervosa, Eating Disorders, Mortality, Standard Mortality Ratio, Adolescent, Family-Based Treatment, Out-patient, Olanzapine, Omega-3

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To whom it may concern
List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.


II Rosling, A., Salonen Ros, H., Swenne, I. Favourable one-year outcome of anorexia nervosa and other restrictive eating disorders in adolescent girls following family-based treatment in an out-/day-patient setting. Manuscript


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### Abbreviations

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<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ADHD</td>
<td>Attention Deficit Hyperactivity Disorder</td>
</tr>
<tr>
<td>AFT</td>
<td>Adolescent Focused Therapy</td>
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<tr>
<td>AMI</td>
<td>Adaptations of Motivational Interviewing</td>
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<tr>
<td>AN</td>
<td>Anorexia nervosa</td>
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<tr>
<td>APA</td>
<td>American Psychiatric Association</td>
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<tr>
<td>BN</td>
<td>Bulimia nervosa</td>
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<tr>
<td>BMI</td>
<td>Body Mass Index</td>
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<td>BMI-SDS</td>
<td>Body Mass Index-Standard Deviation Score</td>
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<tr>
<td>CAMHS</td>
<td>Child and Adolescent Mental Health Service</td>
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<td>CAP</td>
<td>Child and Adolescent Psychiatry</td>
</tr>
<tr>
<td>CBT</td>
<td>Cognitive Behavioural Therapy</td>
</tr>
<tr>
<td>CFT</td>
<td>Conjoint Family Therapy</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>COPE</td>
<td>The Community Parent Education Program</td>
</tr>
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<td>DHA</td>
<td>Docosahexanoic Acid</td>
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<tr>
<td>DSM-III-R</td>
<td>Diagnostic and Statistical Manual-3rd edition-revised</td>
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<tr>
<td>DSM-IV</td>
<td>Diagnostic and Statistical Manual-4th edition</td>
</tr>
<tr>
<td>ED</td>
<td>Eating Disorder</td>
</tr>
<tr>
<td>EDI-C</td>
<td>Eating Disorder Inventory-Children’s version</td>
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<tr>
<td>EDNOS</td>
<td>Eating Disorder Not Otherwise Specified</td>
</tr>
<tr>
<td>EDNOSb</td>
<td>Eating Disorder Not Otherwise Specified with Bulimic behaviour</td>
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<tr>
<td>EDNOSr</td>
<td>Eating Disorder Not Otherwise Specified with restrictive behaviour</td>
</tr>
<tr>
<td>EDU</td>
<td>Eating Disorder Unit</td>
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<tr>
<td>EPA</td>
<td>Eicosapentanoic Acid</td>
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<tr>
<td>FA</td>
<td>Fatty Acid</td>
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<td>FBT</td>
<td>Family-Based Therapy</td>
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<td>FT</td>
<td>Family Therapy</td>
</tr>
<tr>
<td>ICD-8</td>
<td>International Classification of Diseases 8th edition</td>
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<td>ICD-9</td>
<td>International Classification of Diseases 9th edition</td>
</tr>
<tr>
<td>ICD-10</td>
<td>International Classification of Diseases 10th edition</td>
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<tr>
<td>IHME</td>
<td>Institute for Health Metrics and Evaluation</td>
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<td>Acronym</td>
<td>Description</td>
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<tr>
<td>MADRS-S</td>
<td>Montgomery-Åsberg Depression Rating Scale-Self report</td>
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<td>MI</td>
<td>Motivational Interview</td>
</tr>
<tr>
<td>MROAS</td>
<td>Morgan Russell Outcome Assessment Schedule</td>
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<tr>
<td>NICE</td>
<td>National Institute for Health and Clinical Excellence</td>
</tr>
<tr>
<td>OCD</td>
<td>Obsessive Compulsive Disorder</td>
</tr>
<tr>
<td>PUFA</td>
<td>Polyunsaturated Fatty Acid</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised Controlled Trial</td>
</tr>
<tr>
<td>TSH</td>
<td>Thyroid Stimulating Hormone</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
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<td>SFT</td>
<td>Separated Family Therapy</td>
</tr>
<tr>
<td>SMR</td>
<td>Standardized Mortality Ratio</td>
</tr>
<tr>
<td>SSRI</td>
<td>Selective Serotonin Reuptake Inhibitors</td>
</tr>
<tr>
<td>UUH</td>
<td>Uppsala University Hospital</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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</table>
Introduction

In August 1868 Sir William Withey Gull, M.D., physician in London described in The Lancet “a peculiar form of disease occurring mostly in young women between 16 and 23 years of age, characterised by extreme emaciation”, and he named the disorder, anorexia nervosa or anorexia hysterica. The main features were: starvation, amenorrhea and an almost complete anorexia for “animal food”, but also certain days with voracious appetite. Some patients had difficulty sleeping but did not complain of pain, and were restless and active. William Gull wrote: “it seemed hardly possible that a body so wasted could undergo the exercise which seemed agreeable”. There was some peevishness of temper, and a feeling of jealousy. No somatic disorder could be identified to explain the course. His treatment recommendations were to supply the patient with a nourishing diet “at intervals varying inversely with the exhaustion and emaciation”, to serve “a dessert-spoonful of Brandy every two or three hours” along with the meals, and that “the inclination of the patient must be in no way consulted”. He also recommended warm clothing and that the restless activity be controlled, “but this is often difficult”. He noted “that these wilful patients often are allowed to drift their way into a state of extreme exhaustion, when it may have been prevented by placing them under different moral conditions”. As regards prognosis, he wrote “none of the cases are hopeless whilst life exists”, and for the most part prognosis may be considered favourable. He noted that some cases did have a fatal outcome, but that a majority were cured within some years, the description was first published in The Transactions of the Clinical Society of London (Gull, 1873).

Today, anorexia nervosa (AN), bulimia nervosa (BN), and eating disorder not otherwise specified (EDNOS) are the categories of eating disorders (ED) defined in the Diagnostic and Statistical Manual (DSM-IV) published by the American Psychiatric Association (APA) (1994) as well as in the International Classification of Disorders (ICD-10), published by the World Health Organization (1994). Eating disorders have in common an excessive preoccupation and dissatisfaction with one’s body weight or shape, and can have serious physical and psychological consequences. There are ambiguous findings concerning the prognosis of AN with adolescent onset. In some studies it holds a better prognosis than later onset AN, but there are also reports suggesting that premenarcheal onset confers a risk for poor outcome (Bryant-Waugh, Knibbs, Fosson, Kaminski, & Lask, 1988; Steinhausen, 2002).
Unfortunately, after 150 years AN still has the second highest mortality rate of all mental illnesses, surpassed only by substance abuse disorders (Harris & Barraclough, 1998). There is also a heavy burden of co-morbidity, especially with anxiety and depressive disorders (O'Brien & Vincent, 2003). There is no specific treatment for AN, except for the consensus that nutritional rehabilitation is needed. For young persons with AN, the best evidence is for nutritional rehabilitation combined with family-based therapy (FBT) (Lock, 2010). For BN, there is evidence supporting cognitive behavioural therapy (CBT) (National Institute for Clinical Excellence (NICE), 2004) as an effective treatment that could possibly also be applied to EDNOS (Fairburn, Cooper, & Shafran, 2003).

For emaciated patients, hospitalization is still recommended in the American Psychiatric Association’s guidelines for eating disorders (American Psychiatric Association, 2006), but there is no evidence of a better outcome following hospitalization compared to outpatient treatment in specialist units (Gowers, Weetman, Shore, Hossain, & Elvins, 2000). Patients with AN often demonstrate a restrictive and selective eating behaviour, and especially their fear of fat can cause specific nutritional deficits. In nutritional rehabilitation, supplementation with specific nutrients has been proposed, but the most successful treatment is probably a normalization of eating habits and a normalized energy intake. There is some evidence supporting treating the core symptoms of AN with second-generation antipsychotics, otherwise there is no specific pharmacological treatment for an ED, although symptoms of co-morbidity can be alleviated through medication.

There is a sad truth that 17 - 35% of patients with AN become chronically ill, with longstanding restrictive or binge-purge eating behaviours together with co-morbid psychiatric diseases, all adding up to poor quality of life (Steinhausen, 2002; Walsh, 2013). The recently published Global Burden of Disease 2010 shows that eating disorders, in women aged 15-19 years in West Europe, rank as number eleven in the burden of disease (IHME 2012).

Definitions of eating disorder diagnoses

During the 20th century the ED diagnosis was modified in accordance with the International Classifications of Disorders (ICD) by the World Health Organization (1994) and also in the Diagnostic and Statistical Manual (DSM), edited by the American Psychiatric Association (APA, 1994). There have been several attempts to synchronize the texts of the different versions of the manuals to clarify criteria. DSM-IV criteria are now widely in use, but will be substituted during 2013 by DSM-V. Interestingly, the restlessness and excessive exercising seen in many patients with AN, and already described by William Gull (Gull, 1873), is included in the description of
symptoms in ICD-10, but not highlighted among the DSM-IV (Table 1) and DSM-V criteria for AN.

Table 1. DSM-IV criteria for anorexia nervosa

A Refusal to maintain body weight at or above a minimally normal weight for age and height (e.g., weight loss leading to maintenance of body weight less than 85% of that expected; or failure to make expected weight gain during period of growth, leading to body weight less than 85% of that expected).
B Intense fear of gaining weight or becoming fat, even though underweight.
C Disturbance in the way in which one’s body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or denial of the seriousness of the current low body weight.
D In postmenarcheal females, amenorrhea i.e., the absence of at least three consecutive menstrual cycles. (A woman is considered to have amenorrhea if her periods occur only following hormone, e.g., estrogen administration.)

Specify type:
- **Restrictive type**: during the current episode of anorexia nervosa, the person has not regularly engaged in binge-eating or purging behaviour (i.e., self-induced vomiting or the misuse of laxatives, diuretics or enemas).
- **Binge-Eating/ Purging type**: during the current episode of anorexia nervosa, the person has regularly engaged in binge-eating or purging behaviour (i.e., self-induced vomiting or the misuse of laxatives, diuretics or enemas).

During the period 1969-1986, ED was classified in ICD-8 as “Perturbationes appetitus” or “anorexia nervosa”, both coded as 306.5. From 1987 to 1995, diagnoses were based on ICD-9 with ED classified as “anorexia nervosa” (307B) or other unspecified eating problems (307F). ICD-10 came into use in 1993 and has since undergone yearly revisions, whereby ICD-10-SE is the latest Swedish version from 2011. The corresponding DSM manual went through an important change when DSM-III was revised. Weight loss of 25% was changed to a weight 15% below the expected weight for height and age, and amenorrhea for three months became a necessary criterion for the diagnosis of AN. Recently DSM-IV was revised, and the need for amenorrhea as a criterion for AN has been eliminated in DSM-V (APA, 2013). The argument is that amenorrhea could be seen as a result of the weight loss and is thus not an independent criterion. Arguments to retain the amenorrhea criterion have been the assertion that it is a sign of severe hormonal disturbances with impact on somatic health, for example bone mineralization, and possibly also on the central nervous function. All types of eating disorders have in common an over-evaluation of...
weight and shape. There is often co-morbid psychopathology, including high levels of anxiety (Kaye, Bulik, Thornton, Barbarich, & Masters, 2004; Swinbourn et al., 2012; Swinbourne & Touzy, 2007) and depression, low self-esteem and interpersonal difficulties, as well as alcohol or drug abuse disorders (O’Brien & Vincent, 2003).

AN is characterized by a restrictive eating pattern, often in combination with excessive exercising, which results in weight loss, amenorrhea and a distorted perception of one’s body weight and shape, DSM-IV (American Psychiatric Association, 1994).

BN (Table2) is characterized by binge eating and compensatory behaviours to avoid weight gain, including vomiting, laxative abuse and excessive exercise. Psychiatric co-morbidity, such as personality disorders and substance abuse disorders, is more often seen in patients with BN compared to AN (O’Brien & Vincent, 2003).

<table>
<thead>
<tr>
<th>Table 2. DSM IV Criteria for bulimia nervosa</th>
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<tr>
<td>A Recurrent episode of binge eating. An episode of binge eating is characterized by both of the following: (1) eating, in a discrete period of time (e.g., within 2-hour period), an amount of food that is definitely larger than most people would eat during a similar period of time and under similar circumstances (2) a sense of lack of control over eating during the episode (e.g., a feeling that one cannot stop eating or control what or how much one is eating).</td>
</tr>
<tr>
<td>B Recurrent inappropriate compensatory behaviours in order to prevent weight gain, such as vomiting; misuse of laxatives, diuretics, enemas or other medications; fasting or excessive exercise.</td>
</tr>
<tr>
<td>C The binge eating and inappropriate compensatory behaviours both occur, on average, at least twice a week for 3 months.</td>
</tr>
<tr>
<td>D Self-evaluation is unduly influenced by body shape and weight.</td>
</tr>
<tr>
<td>E The episode does not occur exclusively during episodes of anorexia nervosa.</td>
</tr>
</tbody>
</table>

Specify type:
- **Purging type:** during current period of bulimia nervosa, the person has regularly engaged in self-induced vomiting or the misuse of laxatives, diuretics or enemas.
- **Nonpurging type:** during the current episode of bulimia nervosa, the person has used inappropriate compensatory behaviours, such as fasting or excessive exercise, but has not regularly engaged in self-induced vomiting or the misuse of laxatives, diuretics or enemas.
There are also mixed states of AN/BN, with both restrictive and binge eating behaviours combined with compensatory practices to avoid weight gain. The majority of patients with an ED are diagnosed with an EDNOS (Fairburn & Bohn, 2005). Symptoms are those of AN or BN but less severe; i.e. the degree of weight loss, the presence of menstruation or the frequency of binging do not fulfil the criteria for AN or BN (Table 3).

<table>
<thead>
<tr>
<th>Table 3. DSM-IV Criteria for EDNOS</th>
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<tbody>
<tr>
<td>Includes disorders of eating that do not meet criteria for any specific eating disorder. Examples include</td>
</tr>
<tr>
<td>A For females, all of the criteria for anorexia nervosa are met except that the individual has regular menses.</td>
</tr>
<tr>
<td>B All of the criteria for anorexia nervosa are met except that, despite significant weight loss, the individual’s current weight is in the normal range.</td>
</tr>
<tr>
<td>C All of the criteria for bulimia nervosa are met except that the binge eating and inappropriate compensatory mechanisms occur at a frequency of less than twice a week or for duration of less than 3 months.</td>
</tr>
<tr>
<td>D The regular use of inappropriate compensatory behaviour by an individual of normal body weight after eating small amounts of food (e.g., self-induced vomiting after the consumption of two cookies).</td>
</tr>
<tr>
<td>E Repeatedly chewing and spitting out, but not swallowing, large amounts of food.</td>
</tr>
<tr>
<td>F Binge-eating disorder: recurrent episodes of binge eating in the absence of the regular use of inappropriate compensatory behaviours characteristic of bulimia nervosa.</td>
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</table>

Despite the widespread use of DSM-IV and ICD-10, the criteria proposed for ED are not exhaustive (Treasure, Claudino, & Zucker, 2010). In DSM-IV the weight criterion for AN is a body weight of less than 85% of what is considered normal for sex, age and height. In North America the percentage of ideal body weight or expected body weight is usually computed using the Metropolitan Life Insurance tables defined in a standard population (Metropolitan, 1983). For children and adolescents, paediatric growth charts are used. In a recent analysis the question “Eighty-five percent of what?” was raised (Thomas, Roberto, & Brownell, 2009). The study reviewed 99 articles on the weight criterion for AN and ten different methods for calculating the 85% level were found, with a possible weight range of 6.8 kg between the different weight cut-offs used in 20-year-old females. The cut-off weight for AN thus varies greatly between studies (Thomas et al., 2009). An alternative and stricter guideline is proposed in the ICD-10 diagnostic criteria for research (WHO, 1993): in adults, the body mass index (BMI) is equal to or below 17.5 kg/m². However, the BMI criteria are not defined for children or adolescents, and there is a need to
include age and stature in the calculation (Cole, Flegal, Nicholls, & Jackson, 2013; Lindgren, Strandell, Cole, Healy, & Tanner, 1995).

There are two methods for calculating leanness in children. One is to calculate weight as a percentage of ideal or expected body weight for height and age, and the other is to calculate standard deviation scores (SDS) for BMI. Both methods are used in clinical work, but for the comparison of groups of patients in research, BMI standard deviation scores (BMI SDS) are more appropriate (Lindgren et al., 1995). In 1983 the WHO formally recognized the classification by the US National Center for Health Statistics (NCHS) as the international reference for anthropometry in children, and has used it since to classify children as underweight, wasting or stunting based on a cut-off of -2.0 SDS. This definition of thinness in children and adolescents was determined in an international survey based on the median weight and mean height in six standard populations on different continents (Cole, Flegal, Nicholls, & Jackson, 2007). The choice of growth standard and method of calculation is rarely stated in investigations of children with ED. Furthermore, the DSM criteria give no guidance as to what constitutes a “normal weight” during recovery.

The intense fear of gaining weight and the dissatisfaction with one’s body may not be verbally expressed by children or adolescents, although parents may have observed behaviours and rituals such as body checking, the measuring of parts of the body or the persistent use of a mirror to check for areas perceived as “fat”, suggesting such ideation. Whether parents’ reports are sufficient for diagnosis is not evident in the DSM-IV criteria (Uher & Rutter, 2012). Finally, criteria are not specified regarding the minimal level at which these disturbed ideas must be present to qualify for a diagnosis of an EDNOS, or when to judge that someone is “free” from this “undue influence of body weight and shape on the self evaluation” (Couturier, & Lock, 2006a; Couturier, & Lock, 2006b).

Amenorrhea for three months is a criterion for AN, in women after menarche, introduced in 1994 (DSM-IV). However, there are few psychological differences between patients with and without amenorrhea, and they differ significantly only in the lowest BMI ever attained (Attia & Roberto, 2009; Roberto, Steinglass, Mayer, Attia, & Walsh, 2008). This is a problem, since some individuals retain menstruation at a very low weight and thus do not qualify for a diagnosis of AN. Moreover, in the diagnostic process the handling of the menstrual criterion in boys, premenarcheal girls and women on hormonal contraceptives has not been defined in DSM-IV. Thus the criterion has been removed in DSM-V (APA, 2013).

Aetiology

There is no unequivocal explanation as to why individuals become ill with an ED. The descriptive name of anorexia nervosa (AN) is misleading, as it
means the loss or absence of appetite of a nervous origin. The affected individuals rather exercise a deliberate suppression of appetite and hunger due to their unceasing pursuit of thinness. The suggested causes of AN have changed over time. There have been religious interpretations of the holiness of hermits and saints who could live on what God provided, for want of worldly nutrition (Vandereycken & van Deth, 1996). The symptoms and signs of AN were vividly described already in 1868 by William Gull in London, whose description in most aspects matches that of the 21st-century adolescent with AN (Gull, 1873). In Paris, Lasegue (1873) (Vandereycken & van Deth, 1996) early on emphasized the role of the family in the aetiology of ED. Early in the 20th century, explanations of the aetiology of AN and other types of ED rested on somatic causes. Later, psychogenic aetiologies such as a fear of maturity or the pivotal role of the family were in focus. In the family system theories previously used in treatment, the ED patient was seen as the carrier of symptoms in a dysfunctional family system (Minuchin et al., 1975). In recent decades there has been a shift of the view of the family from being the cause of the problem to constituting an important resource to assist in the behavioural change needed during treatment (Russell, Szmukler, Dare, & Eisler, 1987).

Epidemiological studies have identified that risk factors for ED are prenatal factors (Cnattingius, Hultman, Dahl, & Sparén, 1999), early childhood factors and a wide range of genetic factors (Schmidt, 2003; Treasure et al., 2010).

Personality traits such as perfectionism have been investigated, but results are not conclusive as these traits are shared between different types of ED, anxiety and depressive disorders. In a review by Egan (Egan, Wade, & Shafran, 2011) the evidence for perfectionism being a transdiagnostic process was discussed. In treatment of perfectionism, symptoms of ED, anxiety and depressive disorders were found to be significantly reduced, despite there not being any focus on the symptoms of these disorders in the treatment.

Psychosocial risk factors for AN include parental psychiatric disorders, foster care and international adoption (Lindeberg & Hjelm, 2003; Steiner et al., 2003). This plethora of changing theories and the wide range of risk factors indicate that the aetiology of ED may be multi-factorial and is still not understood.

Irrespective of background, risk factors and triggering events such as active dieting, an imbalance between food intake and training, ideas of what an ideal woman is, or whether the illness started with gastro-enteritis with vomiting or during a depression with reduced appetite, the symptoms become self-perpetuating. The behaviours of affected patients then appear similar, regardless of how the weight loss started. The question as to why some individuals develop an ED, especially AN, is not yet understood.
Epidemiology

Epidemiological studies are performed to provide information about the occurrence of new cases and the prevalence of disorders over time. ED are relatively rare disorders in the general population, but are more common among adolescent girls. Patients tend to deny their illness and avoid seeking professional help, which makes case detection difficult. Community studies are costly, as they involve screening many individuals to detect few cases. Most epidemiological studies therefore use clinical psychiatric registers or medical records from hospitals or out-patient clinics in a defined area to estimate the prevalence and incidence of ED.

Prevalence of anorexia nervosa

The prevalence of AN is an estimation of the number of persons who have the disorder at a defined time point (“point-prevalence”). It can also be an estimation of cumulative prevalence up to a specific age, for example all persons who have had a disorder or still have it at a specific age and year (Preti, 2009).

The average point prevalence rates for AN and BN among “young females” are estimated at 0.3 and 1%, respectively (Hoek, 2006). In young females (11-35 years old) the point prevalence of AN is estimated to be around 0.3% for strictly defined AN and about a tenth of this, or less, in males (Hoek & van Hoeken, 2003). A severe problem with this estimate is that “a young female” between 11 and 35 years of age includes “a range of age groups” with a wide variation in both incidence and prevalence. About one in 250 females and one in 2,000 males are reported as having AN during adolescence or as a young adult, and about five times as many will have BN (National Institute for Clinical Excellence (NICE), 2004).

Incidence of anorexia nervosa

The incidence is the number of new cases of a disorder occurring in a defined population during a defined time period, often calculated as new cases per 100,000 inhabitants in specified age groups.

Onset of an ED almost always occurs before the age of 25, with a preponderance of cases and a steep increase of incidence between ten and 20 years of age (Preti, 2009). According to Hoek, there has been an overall stable incidence of AN in recent decades, with the exception of the high risk group of 15-19 year old girls, which has seen a slowly increasing incidence of AN (Hoek, 2006). In another Dutch study, van Son et al. used a primary-care-based design, to avoid dependence on psychiatric or hospital records. They found a significant rise in incidence rate from 56 per 100,000 per year 1985 - 1989, to 109 per 100,000 per year 1995-1999, in girls 15-19 years old (van Son et al., 2006).
It is unclear whether this rising incidence in adolescent girls is due to earlier detection of AN, earlier onset of the disorder or a true increase in the incidence of the disorder among adolescents (Smink, 2012). The very long time incidence study “50-Year Trends” at the Mayo Clinic also indicated an incidence peak in the ages between 15 and 19 years (Lucas, Beard, O'Fallon, & Kurland, 1991). The yearly incidence of AN in adolescent girls has been reported from a number of other studies. The incidence ranges from eight (Hoek, 2006) to 270 (Keski-Rahkonen et al., 2007; Smink, 2012). Altogether this may not represent a true variation in incidence between populations or between countries but may rather be the result of different study designs.

The considerable variation in reported incidence of AN may be mainly due to methodological problems confounding results. First, the application of the diagnostic criteria for AN vary and are rarely explicitly defined. Second, the stratification of incidence by age varies and age spans may be poorly defined and even be given as unclearly as “young women”. Third, and possibly most important, case detection may be incomplete or biased due to unclear definition of the study population. Population-based studies are few, and register studies have the limitation that only patients who have been seen in the health care system are included. As younger girls may be brought to a consultation by their parents while young women may avoid health care, the case detection may be more complete in teenagers and hence the reported incidence higher.

Incidence of bulimia nervosa

The incidence of BN has been estimated to be 41 per 100,000 in the adolescent population (15-19 year olds), and has not increased in recent decades. The incidence among 20-24 year olds is estimated to be 43 per 100,000 (van Son et al., 2006). BN is seen less commonly in child and adolescent psychiatry (CAP), but is more common in adult psychiatry. This could be due to the course of the illness with a maintenance of normal weight, which makes it possible to conceal the disease, and possibly also because the condition usually develops at a slightly older age compared to restrictive ED. Bulimia nervosa sometimes arises by “cross-over” from a pre-existing restrictive ED. As many as 30% of patients with AN may develop BN with binge eating and purging (Fairburn & Harrison, 2003; National Institute for Clinical Excellence (NICE), 2004).

Incidence of eating disorder not otherwise specified

EDNOS has an unclear demarcation towards AN and BN, and includes ED with similarities with both AN and BN but that do not fulfil the criteria for either diagnosis. These “sub threshold” or “partial” syndromes are more common than AN and BN (Fairburn & Bohn, 2005; Hoek & van Hoeken,
Useful incidence and prevalence data is virtually impossible to obtain for the EDNOS group, as the demarcation against normality, concerning both disordered weight and eating ideation, is not defined (Hoek & van Hoeken, 2003).

Mortality rates

Disease specific mortality rates can be expressed in two ways. The most common is crude mortality, which only gives the percentage of persons in a defined population who have died during a follow-up period. The other, and better, one is the standardized mortality ratio (SMR), which gives the observed number of deaths among patients divided by the expected number of deaths in the patient group. The expected number of deaths is based on data from the whole population and can take into account, for example, the gender and age of the patient group, the time period of study and the location in the country.

AN is reported to be the psychiatric disorder with the second highest mortality rate, surpassed only by substance abuse disorders (Harris & Barraclough, 1998). The mortality rate for AN appears to be higher for people with lower weight for their height and age during their illness, and those presenting between 20 and 29 years of age (National Institute for Clinical Excellence (NICE), 2004). In Sweden there has been a dramatic decrease in mortality rates in recent decades, with the most recent lethal case due to AN in a person under 19 years of age being recorded in 1991 (Personal communication, National Board of Health and Welfare, The Swedish Cause-of-Death Register December 2012).

Following a national meeting in 1993 at the National Board of Health and Welfare, the need for specialized services for ED treatment was recognized, and a countrywide development of treatment facilities was started. The subsequent absence of fatal cases of adolescent ED could in part be explained by the generation of an increased awareness of ED, both among health care providers and in the general Swedish population, after the 1993 meeting (Medicinska forskningsrådet (MFR) & Hälso och sjukvårdenst utvecklingsinstitut (Spri), 1993).

There is still excess mortality in adults with ED. In relatively recent Swedish studies of AN mortality, SMR in adults has been estimated at between 6 and 18 (Norring & Sohlberg, 1993; Papadopoulos, Ekbom, Brandt, & Ekselius, 2009). In studies specifying cause of death, about one third of patients have died from the consequences of starvation, one in five had committed suicide, the rest have died from either alcohol-related disorders or other causes (Arcelus, Mitchell, Wales, & Nielsen, 2011; Franco et al., 2013; Hoek, 2006).
Prognosis of anorexia nervosa

A summary of 68 treatment studies published before 1989, with a duration of follow-up between one and 33 years, found that about 45% of AN patients had recovered completely, 20% had developed a chronic eating disorder and 5% had died (Steinhausen, 1997, 2002). In another follow-up, 21 years after treatment, 51% had recovered, 10% were chronically ill and 15% had died. Age at onset, duration of in-patient care, co-morbidity and social problems have been identified as important prognostic factors (Lowe et al., 2001). In a Swedish register follow-up seven to 14 years after in-patient treatment, more than 20% of former patients with AN relied on financial support from society for their main income. Hospital admissions and persistent psychiatric problems were more frequent and childbearing less common compared to the general population (Hjern, Lindberg, & Lindblad, 2006).

Although the prognosis is known to be somewhat better for patients with early onset AN, before 17 years of age, the psychosocial outcome was found to be poor in over 25% of patients at age 35 (Wentz, Gillberg, Anckarsater, Gillberg, & Råstam, 2009). The natural course of apparently “mild”, early-onset cases of anorexia nervosa can be protracted (Treasure & Russell, 2011) the authors concluded. “Treatment for anorexia nervosa is more likely to be successful if the illness is recognized early – before weight loss becomes severe and protracted” (Treasure & Russell, 2011). Four important prognostic factors that emerge from a number of outcome studies are BMI at presentation, duration of the ED, co-morbidity and family factors. Both BMI at presentation and duration of the ED are not solely features of the disorder itself, but are highly influenced by the access to health care services with experience of specialized ED treatment and, last but not least, the promptness of initiating treatment.

Psychiatric co-morbidity

Co-morbidity is very common among ED patients, and depression is seen in more than 60% in some studies (Treasure et al., 2010). Anxiety disorders, with onset early in life, are not uncommon (25%) in patients with AN and are often diagnosed together with depression (Jacobi, Wittchen, & Holting, 2004). Both anxiety and depressive disorders often have a lifelong course, with better and worse periods, and are reported both before and after the onset of ED. In a follow-up study after 21 years, 18% of former ED patients still met the criteria for a depressive disorder, 16% had anxiety disorders, 11% had substance misuse disorder and 6% had personality disorders (Lowe et al., 2001). According to WHO, depression, suicide and anxiety are the leading causes of disease in young women in middle- and high-income countries (IHME, 2012). In recent years, the lifetime rates of major depression have increased and the age of onset has decreased (Bohman et al.,
The one-year prevalence of major depression in high school students in Uppsala, Sweden, was during the 1990s found to be 5.8% (boys 2.3%; girls 9.2%), and the lifetime prevalence for the same group was 11.4% (Olsson & von Knorring, 1999).

Depression and anxiety disorders are frequently seen in individuals with weight loss for reasons other than ED (Schiele, 1948). However, in patients with ED correlations are usually not found between BMI and psychometric scores indicating depression. The relationship between mood disorders and ED is still not fully understood (Godart, Perdereau, Rein, Berthoz, & Wallier, 2007).

Autistic spectrum and attention-deficit hyperactivity disorder (ADHD) have been reported in about a fifth of patients with AN (Mattar, Huas, & Godart, 2012; Wentz et al., 2005). Patients with BN and binge eating disorder more often have affective disorders and problems with alcohol or substance misuse (Olsson & von Knorring, 1999; Treasure et al., 2010).

Although mental disorders are not uncommon in the general population (Olsson & von Knorring, 1999), the burden of psychiatric disease is higher in both current and former ED patients (Godart et al., 2007; Godart, Flament, & Perdereau, 2002; Holtkamp, Muller, Heussen, Remschmidt, & Herpetz-Dahlmann, 2005; Wentz, 1999; Wentz, Gillberg, Gillberg, & Råstam, 2001).

Long-term physiological effects of eating disorders

The physical consequences of ED, such as stunted growth, osteoporosis (Konstantynowicz, Kadziela-Olech, & Kaczmarski, 2005), enamel erosions and dyslipidemia with possible premature arteriosclerosis, are well known. However, the long-term consequences on the immature brain have hitherto been little discussed. Most studies indicate that cerebral function is improved with recovery from AN but there are mixed findings concerning neurocognitive functioning, whether abnormalities are caused by the endophenotype or are a consequence of starvation (Hay, 2011). AN often develops at a time when the brain is particularly vulnerable because it is undergoing structural and functional changes. The brain shrinks during starvation, while the white matter is known to be rebuilt during weight gain, less is known about the capacity for rehabilitation of grey matter (Treasure & Russell, 2011).
The interface between nutrition and psychiatry

The connections between nutritional state and mental functioning were studied in the semi-starvation experiments at the University of Minnesota in 1944-45. The aim of that study was to investigate the effectiveness of various diets for recovery from prolonged inanition, a question that had been actualized among prisoners of war during World War II (Franklin, Schiele, Brozek, & Kays, 1948; Keys, 1948; Schiele, 1948)

The Minnesota experiment

At a Laboratory of Physiological Hygiene, 36 healthy men were selected to participate in a study (Schiele, 1948). They were recruited among conscientious objectors who prior to the experiment had participated in various projects of national importance under a programme initiated by the Civilian Public Service (C.P.S). They were somatically and psychologically fit to have good opportunities to manage the six-month semi-starvation period preceding the nutritional rehabilitation. The starvation period included two meals a day with normal vitamin content but low energy level. The men lost an average of 24% of their body weight and experienced a gradual wasting of muscle and subcutaneous adipose tissue. After 12 weeks oedema became common around the knees and ankles and in the face. The physical ability to laugh, sneeze and blush was reduced or absent in the later stages of the starvation. Muscle cramps were common, paresthetic and hyperesthetic sensations were observed in some subjects, and feeling cold was common. Vertigo and giddiness, were felt by all subjects in the first month, and by some for the whole period. Most of the physical symptoms were similar to those observed in AN. Attitudes towards physical activities were ambivalent, with some exercising to earn extra rations, but most became inactive and voluntary energy loss was reduced. Another difference compared to AN was the attitude towards food. In some respects the men resembled patients with BN, eagerly trying to get as much as possible to eat and drinking huge quantities of tea and coffee, using too much salt and spices, or using chewing gum in enormous quantities, all which had to be restricted later in the study.

All participants underwent personality alterations described as “psychoneurotic”. They became more irritable and less social, and had periods of depressive mood and anxiety. Many complained of having difficulty sleeping, felt they had intellectual and concentration problems, and lost interest in academic studies. Some started collecting recipes, discussing menus or reading cookbooks. Four subjects could not complete the study due to mental problems and/or self-harming practices. During the three months of nutritional rehabilitation, the study group was divided into subgroups that got diets at different energy levels. The rehabilitation of both mental and somatic symptoms was related to level of energy supplied. It is worth noting
that, although their weight was normalized, the men needed a prolonged rehabilitation period to regain physical strength at a level similar to that before starvation. After the study some of the men were trapped in overeating/binge eating, and gained weight above their initial level. Psychiatric symptoms, and how they disappear with weight gain, resemble many symptoms observed in patients with ED and weight loss (Schiele, 1948).

Patients with restrictive eating disorders and weight loss

At presentation in a patient with restrictive ED, low weight and ongoing weight loss, cognitive function is impaired (Hatch et al., 2010) and symptoms of depression, anxiety and obsessive-compulsive behaviours may be observed (Holtkamp et al., 2005). Clinical experience suggests that this is related to starvation, since re-feeding in most cases alleviates the symptoms (Meehan, Loeb, Roberto, & Attia, 2006). However, these symptoms are only rarely correlated with simple anthropometric measures such as weight or BMI (Minasaka, Yoshiuchi, & Yamanaka, 2003). This would suggest that the effects of starvation on psychological symptoms are mediated by further mechanisms.

One possibility would be that the energy deficiency per se influences the central nervous function, as suggested in the Minnesota Experiment (Schiele, 1948). Another possibility is that the effects are mediated by endocrine alterations secondary to starvation that influence both mood and restlessness. It has been hypothesised that the restlessness could be seen as a gene/environmental interaction that reflects the reactivation of evolutionary conserved genes regulating foraging behaviour, which have been important during food scarcity (Casper, 2006). There are data that suggest that thyroid hormones in part mediate the effects of starvation on mood (Swenne & Rosling, 2010). It is also possible that the low concentrations of circulating oestrogen during starvation, in addition to effects on the hypothalamus, ovulation and reproductive behaviour also may alter other central nervous functions such as emotions and affective state (McEvan, 1999). A third possibility is that starvation and changes in eating habits cause deficiencies in specific nutrients, which in turn could influence the symptoms. Zinc (Zn) supplementation has been suggested as an adjunct in treatment, since Zn deficiency seems to cause ED-like symptoms. The role of Zn supplementation remains controversial, as results from three different RCTs are not conclusive (Flament, Bissada, & Spettigue, 2012). There are suggestions that vitamin D supplementation may improve symptoms of mild depression, “but it is still too early to conclude that vitamin D status is related to the occurrence of depression” (Bertone-Johnson, 2009).

Polyunsaturated fatty acids (PUFA) have been suggested as putative mediators of the co-morbidity in starvation. PUFA of the ω3 series have been implicated as etiological factors in mood disorders (Lin, Huang, & Su,
2010; Ross, Seguin, & Sieswerda, 2007). There are several putative mechanisms for explaining how \( \omega-3 \)-PUFA relate to mood: they influence serotonergic transmission in the CNS, modulate inflammatory response in the CNS and help maintain membrane integrity and function, all of which can be related to mood (Alessandri et al., 2004; Horrocks & Farooqui, 2004; Ross et al., 2007). Adolescents with ED do not only restrict food in quantity but also tend to avoid fat and have an inclination towards vegetarian-style diets, all of which would lower the intake of PUFA (Misra et al., 2006). In a previous report (Swenne, Rosling, Tengblad, & Vessby, 2011) a fatty acid profile indicating a low-energy, low-fat diet was demonstrated in adolescent girls with ED. It has not been investigated how this relates to mood, and whether these patients would benefit from supplementation with PUFA during rehabilitation. The concept of a deficiency of specific nutrients as mediators of psychiatric symptoms is of special interest, since supplementation during rehabilitation would offer a complement in treatment.

**Treatment**

There is no clear evidence base for any specific treatment for AN or EDNOS (National Institute for Clinical Excellence (NICE), 2004). Nevertheless, it appears crucial, and is a recommendation based on clinical experience, that for a prompt and efficient weight restoration the first step be taken without delay (Treasure et al., 2010). Family therapy is suggested for young patients, as there is a growing body of evidence of its effects on both weight and psychosocial functioning (Lock, 2010). Evidence supporting CBT for AN has not been documented (McIntosh, Jordan, & Luty, 2006; McIntosh, Jordan, & Carter, 2005).

For BN, there is good support for the use of CBT, but most studies are performed on adults (Crow, Mussell, Peterson, Knopke, & Mitchell, 1999; Gowers, 2008) and evidence concerning efficacy in adolescents is limited.

Research findings on outcome of the treatment of EDNOS are limited. Current recommendations are based on clinical experience and are in line with those for AN or BN treatment, depending on the subtype of EDNOS. One of the first studies on EDNOS treatment is “Transdiagnostic Cognitive-Behavioural Therapy for Patients With Eating Disorders: A Two-Site Trial With 60-Week Follow-Up” (Fairburn et al., 2009). That study was performed in patients over 18 years of age, but is among the first studies to demonstrate the efficacy of a manual-based treatment for EDNOS” (Crow et al., 1999). As the patients with EDNOS comprise 50-80% of the adolescent ED patients, an important task is to develop an efficient treatment for these patients. Hopefully, studies in younger individuals will follow.
Nutritional rehabilitation

The APA (American Psychiatric Association, 2006), The Royal College of Psychiatrists and the National Institute for Clinical Excellence (National Institute for Clinical Excellence (NICE), 2004) have all published guidelines with recommendations for the management of children and adolescents with ED. There is consensus concerning the importance of a prompt weight stabilization followed by weight gain as the first measure in the treatment of restrictive ED. A weight gain of about 0.5-1.0 kg per week is possible to attain both during in-patient (Royal College of Psychiatrists, 2004) and out-patient treatment. The guidelines underline the importance of utilizing the least invasive method possible. If children have to be hospitalized, this should be done within a paediatric service (Gowers, 2008).

Our experience is that feeding by naso-gastric-tube must be regarded as only a last-resort measure as nearly all children can accept eating ordinary food following knowledgeable and firm information about what is needed to regain normal weight. Most patients prefer eating in a day-care setting rather than being hospitalized.

A crucial point in handling eating and weight restoration is to have a good and comprehensible rationale for the aspects of treatment that is “not negotiable”. Once the patients are informed about the routines for meals and the meal schedule, and have had the opportunity to give their opinion a simple rule could be “never to accept negotiation about what is to be eaten” (Geller & Srikameswaran, 2006).

When weight loss has been stopped, the first steps towards weight gain must be taken. The food intake has to be adjusted to ensure that weight gain and growth reach the normal trajectories of the individual (Gowers, 2008). If the onset of AN occurs before growth is completed, treatment needs to address both the physical and psychological sides of puberty (Gowers & Bryant-Waugh, 2004).

Care must be taken to avoid re-feeding syndrome, by the regular monitoring of heart rate, orthostatic vital signs and serum electrolytes, but it is important to note that re-feeding syndrome is more common with parenteral than enteral re-feeding (Mariella, 2004; Mehler, Winkelman, Andersen, & Gaudiani, 2010).

Psychological and psychosocial treatment

In terms of user satisfaction, the opportunity to talk and be understood seems to be more important than the type of psychotherapy or service setting (National Institute for Clinical Excellence (NICE), 2004). The evidence base for psychosocial treatments for ED in children and adolescents is limited. Family-based therapy (FBT) represents the most promising method for
future treatment studies, based on the efficacy experienced to date in the treatment of adolescent patients with AN (Keel & Haedt, 2008).

Motivational interview
Motivational interviewing (MI) has been found to be a useful method in the treatment of ED for enhancing the willingness to fulfil treatment. NICE states that motivational enhancement should be offered to people with AN (Gowers 2004). Patients with AN and EDNOS are often poorly motivated to change, and it has been asserted that they might benefit from Adaptations of Motivational Interviewing (AMI) just as alcohol addicts were motivated to change their behaviours (Prochaska, DiClemente, & Norcross, 1992). Most patients with AN do not approve of the idea of combating their low weight to attain health. Seemingly inconsistently, they argue that they want to achieve health and return to an age-appropriate lifestyle without changing their eating habits. It is important to explore their “autonomous and intrinsic motivation” (Nordbø et al., 2008). In this situation, parents have an important role to play by having motivational discussions with their child.

A recent study suggested that, “the current evidence base does not support the widespread dissemination of motivation-enhancing interventions in eating disorders. With the exception of binge eating, there is almost no evidence supporting the use of AMI in eating disorders” (Knowles, Anokhina, & Serpell, 2013). Probably, new discussion will follow.

Psycho-education
Psycho-education may form an important part of treatment for both patients and family members, as the close connections between under-nutrition, low weight, anxiety, depressive symptoms, problems sleeping and hormonal disturbances are not obvious to everyone. Psycho-education can preferably be performed with groups of parents, with a combination of a short lecture and possibilities for them to discuss matters (Holtkamp et al., 2005). Experiences of group activities for families with children affected by psychiatric difficulties are positive in child and adolescent psychiatry (CAP). The Community Parent Education Program (COPE), developed in Canada (Cunningham, 1998) has been an inspiration in our psycho-education for parents.

Family-based treatment
The parents could be seen as the most important treatment resource, as a part of the team, fulfilling the treatment intentions outside the clinic. FBT, in combination with programmes for weight restoration, is the treatment successively gaining more support in research especially for adolescents with AN. “When the ED is of a shorter duration than three years, FBT has
favourable results at five-year follow-up” (Treasure & Russell, 2011). If the illness has a duration of longer than three years at start of FBT, the results are not as promising. Family Therapy (FT) can be performed in different settings. In conjoint FT (CFT), the parents and child together meet with the family therapist. However, when the expressed emotions in the family are high, the therapist will see the parents and the child at separate FT sessions (SFT)(Eisler & Dare, 2000; Eisler, Simic, & Dare, 2007).

Sessions can be given a psycho-educational form, “parental counselling”, or be designed as treatment of the whole family system (S. Gowers & Bryant-Waugh, 2004). In many families, siblings may be included in the FT to allow them to express their fears and to dispel any false ideas they may have about the nature of the ED. FBT, also known as the “Maudsley Family Therapy” (Couturier, Kimber, & Szatmari, 2013) is now recommended by the APA (American Psychiatric Association, 2006). In many studies, FT is the step to be taken when weight restoration is well established, but it can also be practiced together with weight restoration in an out-patient setting.

In a randomized controlled trial (RCT)(Lock, Le Grange, Agras, et al., 2010), FBT was compared with adolescent-focused individual therapy (AFT) in a group of 121 adolescents with a mean duration of illness of 11.3 months. Assessment was made at the end of one year of treatment, and at follow-ups at six and 12 months post-treatment. Both FBT and AFT led to marked improvements, and had similar rates of full remission at the end of treatment. However, at the follow-ups six and 12 months after treatment, FBT was superior to AFT in maintaining full remission. This lends substantial support to the Maudsley model in that FT produces a better long-term outcome in young patients with a short duration of illness (Treasure & Russell, 2011).

**Individual psychotherapy**

The weight of evidence does not favour individual psychotherapy for adolescents with ED (Eisler, 2011). However, from the adolescent perspective, it could be important to have a therapist “of their own” whom they can visit without their parents. This can be used for psychological support and social training, individually or in a group. Treatment for depression and other conditions that are co-morbid with CBT as well as relapse prevention (National Institute for Clinical Excellence (NICE), 2004), could be performed in an individual setting when weight and eating have been normalized in the final steps of treatment.

Perfectionism is an upcoming focus for CBT in ED, as it can be considered a transdiagnostic process that contributes to not only the development of the ED and the maintenance of symptoms but also co-morbidity (Fairburn et al., 2003). Suggestions of the efficacy of targeting perfectionism across disorders have been presented (Egan et al., 2011). The argument for addressing perfectionism is based on the fact that it is elevated
in anxiety disorders, obsessive-compulsive disorder (OCD), depression and eating disorders. When perfectionism is present and targeted in CBT, effects on the co-morbid disorders are also seen.

Psycho-pharmacological treatment

There is no support for first-line pharmacological treatment with SSRI for weight gain or relapse prevention in AN, either in the Cochrane meta-analysis of SSRI treatment or in the treatment recommendations by APA (2006) or NICE (2004). There is a recommendation from APA (2006) for second-generation antipsychotics which, based on individual considerations, could be tried in AN with severe resistance to weight gain. Although there is no evidence of a specific pharmacological treatment for ED, the frequently seen co-morbid conditions can often be treated with medication (Gowers, 2008).

It is important to remember the different pharmacodynamics and pharmacokinetics of children compared to adults. In general, children and adolescents have a more rapid liver metabolism and more efficient clearance of drugs by the kidney. As a consequence, they require higher doses of drugs per kg of body weight to attain appropriate circulating concentrations and therapeutic effects. However, in severely underweight children and adolescents, great caution must be exercised during pharmacological treatment (Cawthron, 2001; Lindström, 2013).

The atypical antipsychotic drugs

Interest has been renewed in antipsychotic drugs for the treatment of AN. Use of the traditional antipsychotics is not recommended, as side effects are too common. However, the atypical antipsychotic drugs that target dopaminergic dysregulation can reduce distorted cognitions, anxiety, an excessive urge to exercise and the rumination of disturbed eating ideations in AN (Mondraty, Birmingham, Touyz, & V., 2005). There is a small number of RCT as well as case reports in children and adolescents with atypical antipsychotics that demonstrate effects, similar to those in adults, on the core symptoms of AN. For hospitalized patients with AN, olanzapine has been shown to have an adjunctive effect in treatment by increasing weight gain and compliance to treatment (Bissada, Tasca, Barber, & Bradwejn, 2008; Flament et al., 2012). For quetiapine (Mehler-Wex, Romanos, Kirchheiner, & Schulze, 2008), risperidon (Hagman et al., 2011), and aripiprazole (Trunko, 2011), there are case reports indicating similar or no effects. Considering that these potent drugs are used in physically fragile patients, it is surprising that potential side effects have not been systematically studied.
Antidepressants
Among the selective serotonin re-uptake inhibitors (SSRI), fluoxetine is the only drug approved in UK, US and Sweden for the treatment of depression in children (Claudino, 2007; Swedish Medical Products Agency, 2005). In Sweden, sertraline is also approved for the treatment of anxiety and OCD in children under 18. There have been several RCTs, with different SSRI as well as other antidepressants, on the possible effects on weight gain, eating disorder symptoms and relapse prevention in ED. The results are contradictory, as in about half of the trials fluoxetine has been suggested to prevent relapse in weight-restored AN patients but is without effect in other studies (Flament et al., 2012). SSRI have promising effects in some RCTs for the treatment of the binge-purging symptoms of BN (Flament et al., 2012). In low weight AN, however, there is no evidence of an effect on weight gain or depression when used during in-patient treatment. The overall conclusion is that weight restoration is the effective part of treatment. Most authors favour the use of SSRI only after weight restoration, while others find it appropriate to consider it in patients with worsening depressive symptoms, severe anxiety or OCD, earlier in the course of treatment (Gowers & Bryant-Waugh, 2004).

Tranquillisers
Although no controlled studies have been conducted on the matter, antihistamines are often used symptomatically to reduce high levels of anxiety and sleeping problems. Benzodiazepines are sometimes used, but the risk of addiction must always be considered, especially in the treatment of adolescents (National Institute for Clinical Excellence (NICE), 2004).

Service issues
Irrespective of the type of treatment, its accessibility and setting may influence outcome.

In-patient treatment
During the last decades of the 20th century, the view that the weight rehabilitation of patients with restrictive ED should be performed on an in-patient basis was seldom challenged. Most treatment programmes, historically and internationally, have had a firm base in in-patient treatment for extended periods. The most recent recommendations from APA (American Psychiatric Association, 2006) also recommend weight rehabilitation during hospitalization, although it has been found to be no more effective than out-patient/day-patient treatment (Meads, 2001). This treatment tradition is probably maintained by a combination of the view that in-patient treatment is more “advanced and efficient” than out-patient
treatment, together with rigid requirements from the insurance systems that finance health care in many countries.

Patients treated in an in-patient programme weigh less on average, but do not differ in psychopathology compared to those treated as out-patients (Meads, 2001). More out-patient treatment with shorter periods of hospitalization is therefore a possibility pointed out in recent studies. “The in-patient facilities may be reserved for those most physically ill or with dire social circumstances” (Meads, 2001).

**Day-care or day hospital**

The first day hospital for psychiatric patients was founded in 1937, and the first description of its use in the treatment of ED patients was in 1989. A day hospital is often defined as a facility that provides treatment services for patients who would otherwise receive in-patient care. Day hospitals also function as a transition from in-patient to out-patient care (Goldstein et al., 2011; Zipfel et al., 2002). They could also be used to provide reinforced out-patient service, including three to seven full- or half-days per week, when weekly visits are insufficient. Day hospitalization programmes are increasingly being developed worldwide. The treatment often relies on group therapy and the use of a multidisciplinary team. As day-care constitutes a less expensive treatment compared to hospitalization it is likely to be available to a larger number of patients, which is an additional benefit of day programmes compared to in-patient care (Gowers et al., 2007; Gowers et al., 2000; Meads, 2001).

**Specialized out-patient treatment**

A recent study from London shows that specialized out-patient care reduces the need for hospitalization (Byford, Barrett, & Roberts, 2007; House et al., 2012). When specialist out-patient services are available more cases of ED/AN are identified, compared to areas without specialized units. Patients also adhere better to specialist out-patient treatment compared to “out-patient treatment as usual” in CAP. The author concluded “Developing specialist out-patient services with direct access from primary care is likely to lead to improvements in treatment and reduce overall costs” (House et al., 2012).

**Lower costs and therapeutic advantages**

Day-care and/or out-patient treatment is often advocated because of the lower costs. Out-patient treatment costs are approximately 1/10 of those of in-patient treatment (Meads, 2001). Considering the economic standpoint, more patients would have access to treatment, at the same cost, if specialist out-patient treatment were more developed (Byford et al., 2007; National Institute for Clinical Excellence (NICE), 2004).

There is also the therapeutic advantage of patients not being completely removed from their home environment (Gowers et al., 2000).
Treatment is not fully taken over by professional staff, but remains the responsibility of the families. When patients acquire new eating behaviours, they are continuously practiced in “everyday life”, which is where they should be adopted for the future (Gowers, 2008).

Accessibility

Early recognition of a suspected ED by, for example, the nurses in the school health system or the parents themselves, and an easily accessible first consultation, are important for avoiding unnecessary treatment delay. A short chain of referral to a specialist ED service minimizes weight loss and the duration of untreated disease, which in turn favours a good outcome (National Institute for Clinical Excellence (NICE), 2004; Treasure & Russell, 2011). It is notable that the transition in the health care system from in-patient treatment to out-patient services and towards easily accessible specialized units is largely driven by, and discussed in terms of, cost-effectiveness. This transition, however, also holds therapeutic advantages that themselves motivate the change in treatment (Byford et al., 2007; House et al., 2012).

Treatment studies and challenges

RCTs are considered to be the gold standard that all clinical treatment researchers should strive to perform. However, there are many challenges with RCT studies on ED, especially in children and adolescents. ED are complex disorders with a relatively low incidence in the general population and a mixture of physical, psychological, social, genetic and behavioural features (Schmidt, 2003). Furthermore, both aetiology and maintaining factors are unknown, and the criteria for diagnosis and recovery are not well defined (Couturier & Lock, 2006a, 2006b). The risks of a chronic course of the disorders and premature death are substantial (Steinhausen, 2002). Finally, “there is a principal problem with the low attrition rate in studies, as many ED patients do not accept the treatment arm they have been randomized to follow” (Gowers et al., 2007). As a consequence of all these factors, it is considerably difficult to perform RCTs in ED. Only a small number of well-designed RCTs on the treatment of AN in adolescents have been accomplished (Lock, 2011; Stiles-Shields, Goldschmidt, Lock, & D., 2013).

What can be learnt from two recent large RCTs?

RCT- Manchester, NW, UK (2007)
A study on the “Clinical effectiveness of treatment for AN in adolescents” (Gowers et al., 2007) was performed in the north-west of England. In a population of 7.2 million, the local child and adolescent mental health
services identified 347 probable cases of adolescent AN, between 2000 and 2003. Of these, 103 did not fulfil AN criteria, 77 refused to participate in randomization or follow-up. Randomization was performed on 167, either to general CAP “treatment as usual” (n=53), “specialist out-patient treatment” (n=55) or “in-patient treatment” (n=57), but only 38, 41 and 28 from each group, respectively, participated in the treatment arm to which they were randomized. However, the follow-up was nearly complete, also among those who had not participated in their planned treatment. In each group there was considerable improvement during the first year and further progress during the second year. Two years after start of treatment, full recovery had been obtained in 33%, while 27% still had AN at this time. Contrary to the research hypotheses, there were no better results in hospitalized patients compared to out-patients and neither was there a difference between the two arms of out-patient treatment.

**RCT- Stanford /Chicago, USA (2010)**

An often cited study, “RCT comparing family based treatment (FBT) with adolescent focused therapy (AFT) for adolescents with AN” (Lock, Le Grange, & Agras 2010), was performed by researchers at the Universities of Stanford and Chicago. Participants were recruited for 2.5 years by advertising to clinicians and organizations treating patients with ED. A total of 331 patients were identified and screened through telephone calls, followed by an interview of 175 patients, of whom 121 were randomized to either AFT (n=60) or FBT (n=61). Finally, 59 and 57 patients, respectively, received the interventions.

Altogether 33% of the patients were hospitalized “during the course of out-patient therapy”. In three cases hospitalization was due to suicidal ideations, and in 38 cases it was for medical stabilization, 53% in the AFT group and 15% in the FBT group, for a mean of 17 to 32 days, respectively.

The outcome at end of treatment did not differ between groups. At follow-up 6 and 12 months after treatment FBT was superior to AFT. A considerable group of patients had a poor outcome at six months (22%) and at one year (27%). In a brief report, published online, the problems with differences between patients recruited especially for RCTs compared to other treatment-seeking patients were discussed, and the results suggested that there was no difference between the groups concerning ED problems (Stiles-Shields et al., 2013). What was not discussed were the problems with high attrition rates and how representative these patients were compared to the huge background populations from which they were recruited.

The two RCTs have a common problem of selection bias. The number of incident cases in the catchment area is unknown, and there is a high attrition rate throughout the recruitment procedure and during treatment. If the aim is to study the efficacy of out-patient treatment, it is disconcerting that a large number of patients had to be hospitalized. Overall, the results are not
encouraging as many patients still have AN both at end of treatment and at follow-up. It is impossible, however, to determine whether this might be due to selection of the sickest patients during recruitment.

There are thus considerable difficulties with RCTs of AN treatment. Other study designs could be used to follow treatment effects and the course of disease. If it were possible to perform a naturalistic, descriptive study of the course of treatment of virtually all patients in a catchment area, another type of information would be obtained. Findings would not be biased by selection, and if treatment were uniform, the course of disease, outcome of treatment and service organization could be evaluated.
AIMS OF THE PRESENT THESIS

The overall aim of this thesis was to investigate the causes of death in adults with longstanding anorexia nervosa (AN) and bulimia nervosa (BN) as well as to study the outcome and aspects of treatment in an unselected cohort of adolescents with AN and restrictive eating disorders not otherwise specified with features of AN (EDNOSr).

The specific aims were to:

- investigate the long-term mortality, standardized mortality ratio (SMR) and causes of death in a series of chronically ill adult patients with AN and BN.

- study whether the outcome after one year, in an unselected cohort of adolescents with AN and EDNOSr in a specialist out-patient setting, could yield a good outcome without planned hospitalizations.

- investigate the possible metabolic and hormonal side effects of olanzapine when used to facilitate nutritional rehabilitation in adolescent AN and EDNOSr.

- investigate the relationship between polyunsaturated fatty acid (PUFA) status and depression in adolescents with ED, and

- investigate whether ω3 PUFA status is improved during the weight rehabilitation of adolescent girls with AN and EDNOS, without supplementation.
Methods

This thesis is based on two different groups of patients. Paper I is a retrospective follow-up of former adult patients with chronic ED, treated in a 12-week in-patient programme at Uppsala University Hospital (UUH). Papers II-V are prospective studies based on a population of adolescent patients with ED, treated as out-patients at the Eating Disorder Unit (EDU) of the Department of Child and Adolescent Psychiatry (CAP) at UUH.

Paper I

From 1974 to September 1993 UUH provided one of two Swedish in-patient treatment programmes at a tertiary level for severe and chronically ill patients with ED. During the period of nearly 21 years a total of 220 patients had been admitted, of whom 16 men were excluded from this study. When the diagnoses of the 204 female patients were revised and reclassified according to DSM-IV, three who did not meet the criteria of an ED were excluded. Of the remaining 201 patients who were included in the follow-up study, 111 had been referred from different parts of Sweden and 90 were from the local catchment area. Co-morbidity and recorded suicide attempts were obtained through a review of the clinical records at UUH. Survival on 31 December 2000 was verified for 176 patients in the computerized Swedish Civil Registration. Two had emigrated and were identified as survivors in the corresponding registers in Denmark and Norway. Using the computerized Swedish Civil Registration, the 23 remaining patients were confirmed to be deceased, and their death certificates with causes of death were obtained. Standardized mortality ratios (SMR) were calculated and subdivided into groups based on lowest BMI, after age 18.

Statistics

SMR were calculated as the observed number of deaths among the patients divided by the expected number of deaths. Corresponding 95% confidence intervals (CI) were calculated under the assumption that the observed number of cases followed a Poisson distribution. The expected number of deaths was estimated by multiplying the person-years of follow-up by the mortality rate in the general Swedish female population, stratified by
calendar time period (5 years) and age class (5 years). Person-years were calculated from the date of first admission to UUH with an ED diagnosis during the period from 1 January 1974 to 30 September 1993 and to the end of follow-up on 31 December 2000, or to death before this date if applicable. SMR for all causes of death and suicide were stratified by years following first admission to the psychiatric clinic in UUH (0–2, 2–10, 10+), as well as self-reported onset before or after 17 years of age, local or national patients and BMI level (<10.5, 10.5–11.5, 11.5–13.5, 13.5–15.5, 15.5–17.5, >17.5). Pearson Chi-square, or Fisher’s exact test when applicable, was used to test the difference between proportions, while t-test and one-way ANOVA were used to test differences of means.

Ethics
The protocol was approved by the ethics committee of the Faculty of Medicine, Uppsala University.

Papers II-V
Patients and assessment
Since 2003, the Eating Disorder Unit (EDU) at the Department of Child and Adolescent Psychiatry (CAP) at Uppsala University Hospital (UUH) has followed a manual-based out-patient/day-patient programme without planned hospitalization during weight restoration for adolescents with ED and weight loss. An important structural feature of the programme is to give rapid access to treatment and to perform a medical assessment prior to the start of treatment to exclude other causes of weight loss and evaluate medical risk. Weight restoration is based on eating ordinary foods with meals three times a day and snacks three times. Initially, at the EDU the meals are eaten one by one together with a nurse. At home all meals are eaten with support from the parents. In most cases, 10-15 weeks are needed for weight restoration in patients with AN, who may have lost around 10 kg during the course of the disorder. With rapid and efficient handling and knowledgeable information, parents and – in most cases – patients feel safe and confident in accepting the proposed treatment.

The treatment programme consists of four steps, similar in day-care and out-patient treatment. The first step has a single focus on stopping the ongoing weight loss. Patients temporarily leave school and have all meals at home with their parents or at the EDU. Three times a day, after breakfast, lunch and dinner they have to rest on their bed for one hour. They are encouraged to try to sleep, and not to read or listen to music. The second step ensues when eating has been normalized and routines of everyday life are re-established. It aims at restoring weight at a rate of 0.5-1 kg/week. The third step consists of a gradual reintroduction into school without disturbing the
re-established meal routines. The fourth and final step is started only when eating, attending school and daily routines are reliably maintained. CBT with a “transdiagnostic” approach for emotional self-regulation and relapse prevention is introduced, and CBT for co-morbid disease such as depression and anxiety is considered. The four steps of the treatment programme do not have fixed durations but are instead goal-oriented. Progression to the next step can only take place when the aims of the current one have been fulfilled. Treatment is offered as long as lingering features of the ED are present. It is notable that the normalization of eating and weight gain are strongly emphasized during the first steps, and that treatment of the other aspects of the ED ensues only when eating has been normalized and weight gain is well under way.

The initial assessment followed a structured protocol and included a somatic examination and demographic, medical and psychiatric background information. Growth curves from the school health services were obtained to evaluate pre-morbid growth and weight development. The Eating Disorder Inventory-Children’s version (EDI-C) (Garner, 1991; Edlund 1999) and the Montgomery-Åsberg Depression Rating Scale – Self Report (MADRS-S) (Svanborg & Åsberg, 1994) were administered, and more than 90% filled the forms out. ED diagnoses were based on DSM-IV criteria (APA 1994). The weight criterion for AN, in adults is a BMI below 17.5 kg/m². This corresponds to a BMI SDS below −2.00 (Lindgren et al., 1995), which is used in this study as the weight criterion for AN. In young individuals, eating disorder symptoms may not be verbally expressed. Meal-related and other behaviours may nevertheless indicate a wish to avoid food and preoccupation and/or dissatisfaction with one’s shape and weight. Care is therefore taken to assess both symptoms verbalized by the patients and observed behaviours reported by the parents (Becker 2009; Bravender 2010, Russell 2012). BN, together with sub-threshold BN (with lower frequency of binging), was classified as BN. Analyses were thus performed with the three diagnostic groups AN, BN and EDNOS in Studies IV and V, but only with AN and “restrictive EDNOS”, here named EDNOSr, in Studies II and III. Depression was diagnosed according to DSM-IV criteria (APA 1994) for a “depressive episode”, except that criterion D, “symptoms are not due to the direct physiological effects of a general medical condition” (in this case starvation), was not applied.

Ethics
The protocol was approved by the ethics committee of the Faculty of Medicine, Uppsala University.
Paper II

During the study period 1 Jan 2004 to 31 Dec 2006, 183 adolescent girls from the county of Uppsala were, following assessment, offered treatment for their ED, either in day-care or as out-patients at the EDU. Ten boys were excluded from the study. The present investigation is a follow-up of the 168 patients diagnosed with AN or EDNOSr (Figure 1).

Figure 1. Flow chart for the 207 assessed adolescent girls.

One year after presentation, all were contacted for a follow-up interview, 27 (16%) were lost to follow-up and 141 (84%) agreed to participate. Of them, 132 (79%) took part in a face-to-face interview performed by a nurse/therapist. Nine (6%) patients were followed up either by the nurse/therapist in a telephone interview (n=3), supplemented by a review of the clinical records performed by the paediatrician and six (4%) were followed-up solely by a review of the clinical records. In these cases weight and height from a recent visit were used for BMI-SDS calculation. Data on treatment given, weight and menstrual status, ongoing treatment and school attendance were compiled by the nurse. The self-report instruments EDI-C and MADRS-S used at initial assessment were repeated and filled out by 115 (82%) and 118 (84%) respectively. Outcome was further assessed using the Morgan-Russell Outcome Assessment Schedule (MROAS) for 124 (88%). ED diagnoses and co-morbid conditions were finalised by the nurse in consultation with the paediatrician.
Statistics
Values are reported as means ± SD. Student’s t-test and Chi-square test were used for comparisons of continuous and categorical variables, respectively. p<0.01 was taken to indicate a significant difference. Predictions of outcome were calculated using a logistic regression analysis for three outcome criteria: 1) freedom from ED, 2) “good outcome” according to MROAS, and 3) ability to attend school on a full-time basis.

Paper III
Over the past decades the second generation of antipsychotics, usually olanzapine, has been introduced as an adjunct to weight rehabilitation and psychotherapy, in severe cases of AN and EDNOSr. The side effect profile for olanzapine in undernourished patients was studied. During the five-year period 2004–2008, 47 adolescents (32 with AN and 15 with EDNOS) were treated with olanzapine at the EDU (35 in day-care and 12 out-patients). Basal characterization of the patients was available from the first assessment. Weight and menstrual status were followed up during treatment. In order to screen for side effects blood sampling was performed before, during and three months after medication with olanzapine. Analyses included blood-cell count, liver enzymes, serum lipids, thyroid-stimulating hormone (TSH), prolactin, blood glucose, serum insulin and glycated haemoglobin (HbA1c), all performed as routine analyses at the Department of Clinical Chemistry at UUH.

Statistics
Values are given as means ± SD. Differences in laboratory parameters during treatment were analysed using a one-sided analysis of variance. The relationship between laboratory parameters and weight, menstrual status, olanzapine dose, and concomitant medication with SSRI was analysed using analysis of variance.

Paper IV
Clinical observations indicate that starvation in eating disorders (ED) augments anxiety and depression. Deficiency of PUFA of the ω3 series has been implicated in the aetiology of mood disorders (Lin et al., 2010; Ross et al., 2007). The dietary intake of ω3 PUFA is likely to be reduced in ED (Misra et al., 2006), and the FA profile is altered by starvation (Swenne et al., 2011). During the period 2004-June 2008, 325 adolescent patients with ED were assessed. Nineteen patients with other diseases that could influence
FA profiles were excluded. Blood samples from 217 out of the remaining 306 patients (209 girls, 8 boys) with AN (35), BN (7) and EDNOS (175) were available for analysis of FA in erythrocyte membranes. Basal characterization of the patients was available from the initial assessment. Depression diagnosis was by DSM-IV (American Psychiatric Association, 1994) criteria based on a clinical interview supplemented by the self report instrument MADRS-S. Analyses of fatty acids (FA) were performed in a laboratory specialized in such analyses (Swenne et al., 2011). Fatty acids were expressed as proportions of the fatty acid content of erythrocyte membranes. Desaturase activities were estimated as product/precursor ratios of FA (Warensjöö, 2007).

Statistics
Values are means ± SD. In the analyses of fatty acid proportions, p<0.01 was taken to indicate a significant difference. Predictors of depression were analysed using logistic regression analysis.

Paper V
Considering that alterations of FA profiles are associated with depression, changes in the FA profile following weight rehabilitation were studied. Of the 325 patients assessed during the period 2004-June 2008 (Paper IV), 40 were admitted to day-care. Of these, 24 girls (17 AN and 7 EDNOS; 12 with depression) were available for the one-year follow-up (age 15.4±1.8 years) interview and a second blood sample for analyses of FA. None of these patients had a co-morbid somatic disease, and none were on supplementary PUFA. Thirty-nine healthy teenage girls (age 15.5±1.0) who were not on any medication or hormonal contraception, and who were not involved in weight-loss practices, were recruited as controls. FA were analysed as above (Paper IV).

Statistics
Values are means ± SD. Student’s t-test was used for comparison of groups. In the comparison of proportions of fatty acids, p<0.01 was taken to indicate a significant difference.
Results

Paper I
The 201 former patients had been followed up for a mean of 14.3 years, and 23 had died (Figure 2). The overall standardized mortality ratio (SMR) was 10.0. The SMR for patients with AN was 11.7 (95% CI: 7.2–17.8) and for those with BN 4.0 (95% CI: 0.5–14.5). Within the first two years following the index admission, SMR for all causes of death was 38.9 and for suicide as high as 100.6. Patients with self-reported ED symptoms before 17 years of age had an overall SMR of 7.1 (95% CI: 2.6–15.5) and those with later onset an overall SMR of 10.7 (95% CI: 6.0–17.6). Thirteen per cent had been in contact with CAP before the age of 18, but only one had an ED diagnosed at that time.

Figure 2. Distribution of the 201 patients according to lowest BMI. Live patients in red and deceased shown by cause of death.
The causes of death could be categorized into three groups: a) direct consequences of starvation (n=6), b) suicide (n=9) and c) other causes (n=8) (Figure 2). The SMR was above 44 for those with lowest BMI ever <10.5 kg/m², 27 for those with the lowest BMI range 10.5–11.5 kg/m² and 7 for lowest BMI >11.5 kg/m².

Paper II

Of the 189 adolescents girls initially assessed, six did not fulfil criteria for an ED diagnosis. Fifteen girls with BN or EDNOS with features of BN were excluded from the study. Of the remaining 168, 31 fulfilled criteria for an AN and 137 for EDNOS with the restrictive features of AN (EDNOSr). Of the 168 patients included in the study, 27 (16%) were lost to follow-up (AN=2, EDNOS=25).

The annual incidence of AN in girls 10.0-17.99 years old in Uppsala county during the years 2004-2006 was calculated. The age and time span comprises 48,825 person years of observation time, and the 31 patients with AN correspond to an annual incidence of 63/100,000.

<table>
<thead>
<tr>
<th>Age in years</th>
<th>Person years</th>
<th>AN cases</th>
<th>Annual incidence</th>
</tr>
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<td>10 -11</td>
<td>11,311</td>
<td>2</td>
<td>18</td>
</tr>
<tr>
<td>12 -13</td>
<td>12,487</td>
<td>7</td>
<td>56</td>
</tr>
<tr>
<td>14 -15</td>
<td>12,869</td>
<td>9</td>
<td>70</td>
</tr>
<tr>
<td>16 -17</td>
<td>12,158</td>
<td>13</td>
<td>107</td>
</tr>
<tr>
<td>All 10 -17</td>
<td>48,825</td>
<td>31</td>
<td>63</td>
</tr>
</tbody>
</table>

At presentation, there was no age difference between patients with AN and EDNOSr. The duration of ED symptoms before presentation was 9 ± 7 months for the AN patients and 12 ± 10 months for the EDNOSr patients. The BMI SDS at presentation was -2.73 ± 0.68 (range -4.3 to -2.0) for the AN patients and -0.70 ± 0.88 (range -2.5 to 1.3) for the EDNOSr patients.

The acceptance of treatment among AN patients was high. Only two (6%) patients/families with AN did not accept the EDU treatment, had other psychiatric contacts and were lost to follow-up. Among the EDNOSr patients, only seven (6%) discontinued treatment against advice before one-year follow-up.

Of 29 patients with AN, 14 (48%) had been treated as day-patients for some part of the year and 15 (52%) entirely on an out-patient basis. Two (7%) had been admitted to a paediatric ward, of whom one had been fed via
a naso-gastric tube for seven days and the other had received a blood transfusion. One patient with AN had been admitted to a CAP ward for 57 days due to suicidal ideation.

At one-year follow-up, six (21%) of the patients with AN at assessment did not fulfil criteria for an ED, 22 (76%) fulfilled criteria for EDNOSr and one (3%) had persisting AN. Irrespective of diagnostic outcome, all former AN patients had gained weight, with a mean weight gain of 10.9 ± 3.9 kg (range 2.3-20.1kg). Menstrual status had improved during the year. Fifteen (52%) had regained menstruation and one was on hormonal contraceptives, while seven (24%) still had secondary amenorrhea and seven (24%) had not reached menarche. There had been no deaths.

Of the patients with EDNOSr at assessment, 16 (14%) had been day-patients and 88 (79%) out-patients. Two had been admitted to a paediatric ward for between three and 14 days, one for cardiac observation and the other for naso-gastric tube-feeding. Three had been admitted to a CAP ward for between two and four weeks. At follow-up, 54 (39%) patients with EDNOSr at assessment did not fulfil criteria for an ED. Only six of 141 followed-up patients had a BMI SDS < -2.0, four with AN and two with EDNOSr; a total of 14 (13%) patients had lost weight during the year. Among EDNOSr patients, the mean weight change was 5.2 ± 5.6 kg.

Sixty-four (57%) of the 112 patients with EDNOSr at assessment were menstruating at follow-up, 30 (27%) were on hormonal contraceptives, one was pregnant, eight (7%) had secondary amenorrhea and eight (7%) had not reached menarche.

Of the patients with AN at assessment, 93% were back in school on a full-time basis. In the EDNOSr group 85% were back in school, full-time. Reasons for not attending school (5/141) were the ED in three cases and other psychiatric disorders in two cases. The remaining patients attended part-time studies.

When trying to predict the outcome measure “no ED or ED” (DSM-IV) at follow-up, a large number of anthropometric, psychometric and diagnostic outcome predictors were studied. They differed only in that BMI SDS at presentation was lower in those with an ED at follow-up (p<0.01). The self-report measures, EDI-C “body dissatisfaction- ineffectiveness-asceticism and social insecurity“ were higher in those who had an ED at follow-up (p<0.05). High BMI SDS at presentation predicted “no ED at follow-up” as measured by odds ratio (OR) 2.12; 95% confidence interval (CI) 1.06-4.23 (p=0.033). The psychometric measures did not improve prediction.

“Good somatic outcome”, is defined by the MROAS as weight within 15% of expected and having menstruation (irregular or regular). Patients with good somatic outcome were older at the start of ED symptoms (p<0.01), older at presentation (p<0.01), and more often had retained menstruation (p<0.001). They did not, however, differ in psychometric
measures. Good somatic outcome according to MROAS could not be predicted in a logistic regression analysis.

“Attending school on a full-time basis or not” was analysed as an alternative outcome measure. Psychiatric comorbidity was a weak predictor for not attending school as evidenced by an OR 3.09, CI 1.02-9.35 (p=0.046). Neither anthropometric, nor psychometric measures improved prediction.

Paper III

In 47 patients with AN or EDNOSr medication with olanzapine was introduced when weight was as low as 44.1 ± 8.5 kg and BMI SDS -1.95 ± 1.32. The duration of olanzapine treatment was on average less than a year, and the typical dose was 5 mg, taken in the evening (range 1.25 mg-10 mg). During treatment and follow-up, there was an average weight gain of 9.1 ± 5.0 kg. The medication was generally well tolerated. At the low weight before start of medication there were abnormal laboratory findings of glucose, insulin and lipid profiles, which were normalized with weight gain and resumption of menstruation but were unrelated to medication. Temporary increases in TSH and prolactin could be related to olanzapine medication and co-medication with SSRI. Three months after discontinuance of medication, there were no persisting biochemical or hormonal side effects. In three patients olanzapine medication was discontinued because of galactorrhoea, seizures and increased liver enzyme activity, respectively. In three patients the laboratory screening revealed an autoimmune thyreoditis needing thyroxine replacement.

Paper IV

Of the 217 patients with ED, 104 had a MADRS-S score >18 and 84 (39%) had a clinically diagnosed co-morbid depression. Depression was overrepresented in those with BN (6/7) but was evenly distributed in the other diagnostic groups. Patients with depression did not differ from those without depression in terms of age, BMI, weight loss or duration of disease. In their FA profile, depressed adolescents had lower proportions of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), the end products of the ω3 PUFA series, resulting in higher ratios between ω6 and ω3 FA. The relationships between depression, PUFA and BMI SDS were further analysed in a logistic regression analysis. The ratios of total ω6/ω3 FA and arachidonic acid/DHA predicted depression, but BMI SDS did not contribute to prediction. Correction for the magnitude and duration of weight loss did not alter the prediction.
Paper V

At presentation, the 24 girls had a documented weight loss of approximately 10 kg. Twelve were diagnosed with depression. At one-year follow-up, the weight loss had been recovered and weight was close to normal, as evidenced by weight SDS and BMI SDS close to zero. At follow-up none had AN. Five girls no longer fulfilled criteria for an ED, 19 had EDNOS, and, 8 of the EDNOS patients still had amenorrhea. Two had a persisting depression.

The fatty acid (FA) composition in erythrocyte membranes differed from controls at first assessment, indicating a negative energy balance and low fat intake. The proportions of most saturated and monosaturated FA were increased. The proportion of the essential FA 18:2\(\omega 6\), but not of 18:3\(\omega 3\), was decreased. The product of the first step of desaturation and elongation of the \(\omega 6\) series, 20:3\(\omega 6\), was lower in participants with ED. The product of further desaturation and elongation, arachidonic acid (AA;20:4\(\omega 6\)), did not differ from controls. FA metabolism was deranged, as evidenced in altered desaturase activities. At presentation, depressed patients had lower proportions of EPA and DHA, resulting in higher ratios between \(\omega 6\) and \(\omega 3\) PUFA. In this respect they were similar to the cohort previously studied (IV). Following weight recovery, most of the alterations observed at presentation had been normalized. The proportions of long-chain \(\omega 3\) PUFA increased above those seen at presentation and in controls. At follow-up, patients with and without depression did not differ in \(\omega 3\) PUFA status.
Discussion

Paper I

A follow-up study of mortality in AN and BN, adult patients.
The present study confirms previous reports of substantially increased mortality in adult patients with a chronic course of AN (Keel et al., 2003). The novel observation is that the very high mortality is limited to those who have experienced a very low BMI at some point during the course of disease, have substance abuse and/or have a history of suicide attempts. It is notable that the causes of death in the lowest BMI range are not limited to the direct effects of starvation. A very low BMI at some time during the course of disease thus appears to confer a generally increased risk of premature death.

Based on these observations, a risk stratification of chronic AN is proposed. BMI refers to the lowest BMI registered during the course of AN.

Risk Stage I is the least severe and Risk Stage III the most dangerous in terms of mortality risk.

• Risk Stage I: BMI 11.5–17.5 without co-morbidity
• Risk Stage II: BMI 11.5–17.5 with somatic co-morbidity such as epilepsy or insulin-dependent diabetes or psychiatric co-morbidity such as substance abuse or previous suicide attempts
• Risk Stage III: BMI <11.5 irrespective of co-morbidity

Such a distinct staging could help generate a base for directing patients to the right level of care, with most attention to the patients with the greatest needs and with focus on the vital risks. Further treatment studies are needed and should use disability measures in addition to mortality as end points.

The findings underscore that BMI is an important predictor of long-term survival. If it were possible to avoid the development of chronic disease with very low BMI, the risk for premature death could probably be reduced. These findings focus on the development of services and effective treatments that could be used early in the course of disease with a hope for cure and the avoidance of a chronic course.
Paper II

One-year outcome of anorexia nervosa and restrictive eating disorders in adolescent girls.

This study is a prospective study of the one-year outcome of an entire three year cohort of adolescents with AN or “restrictive EDNOS” originating from the population in a defined catchment area. With few exceptions, patients had not been treated for their ED before assessment and the duration of ED symptoms was short, only about nine months for patients with AN. The treatment followed a goal-oriented manual with distinct steps but with individualisation concerning intensity. The patients with the most severe weight-loss and most difficulties starting the nutritional rehabilitation were offered day-care (5 days a week) others were offered out-patient treatment with a lower intensity. Assessment, treatment and follow-up were uniform for patients with AN and EDNOSr, and followed the same principles in day- and out-patient treatment. All treatment was performed at a specialized EDU. The treatment programme is similar to the APA recommendations (American Psychiatric Association, 2006) with one important exception, the avoidance of planned hospitalization during weight rehabilitation.

Treatment results are encouraging, in that only one patient (3%) with AN at assessment also had AN at one-year follow-up. Compared to the RCT performed by Gowers, the in-patient treatment arm had 46% poor-outcome, the specialist out-patient arm had 44% and general CAP had 24% after one year (Gowers et al., 2007). In an RCT by Lock, the adolescent focus therapy (AFT) treatment arm, was compared to the family based therapy (FBT) and the FBT had better results compared to AFT. However, in the FBT treatment arm, patients with “no remission” were 10%, 16% and 22% at end of treatment, after 6 months and after one year respectively (Lock, Le Grange, & Agras 2010).

Furthermore, in the one-year follow-up, our results are promising, in that 90% of all patients had gained weight, irrespective of diagnostic outcome at one year. Only six (4%) of the 141 patients had BMI-SDS <-2.0 at follow-up, two of the six had lost weight after the age of 18, when continued treatment in an adult psychiatry service was recommended. A total of 80% had a normalized menstrual status. Of those still experiencing amenorrhea, 15 (11%) had not yet reached menarche and most of them were at an age when it was not necessarily expected. Another important feature of the service was that, once assessment had been performed and the treatment suggested started the attrition rate was very low.

The incidence of AN was estimated at 63/100,000 for adolescents 10-17.9 years old in the county during the study period. This is in the range observed in other studies based on treatment-seeking patients (Lucas et al., 1991) but lower than in epidemiological studies with active screening of a population prior to assessment for confirmation of diagnosis (Råstam,
Gilberg, & Garton, 1989). In the cross sectional epidemiological study in Gothenburg, all 2136 girls born 1970 were screened for AN, at the age of 14.5-15.5 years. An “accumulated prevalence” of 15 cases were classified as AN “full syndrome”. Out of these 15 girls, five, seven and three girls had an onset at 13, 14 and 15 years of age, respectively (Råstam, Gillberg, & Garton, 1989). In a follow-up study five additional cases of AN from the same birth cohort were identified with onset before 18 years of age (Råstam, 1992). The incidence based on these 20 cases in 2136 x 5=10,680 person years is 187/100,000 in the ages 13-17.9 years. This is almost three times more than what we found in the corresponding age-groups and may suggest that we have missed two out of three patients with AN in our catchment area. However the weight criterion used for the AN diagnosis in the Gothenburg study is most probably higher than ours. It appears as though a weight loss of 15%, was sufficient for AN diagnoses in the Gothenburg study, irrespective of whether the weight loss has caused under-weight or not. The lowest mean (±SD) BMI was 16.5 (±2.7) kg/m² in the adolescents with AN. The median age in this group was 14 years (Råstam, 1992). However, the BMI cut-off for AN of 17.5 kg/ m² at age 18 corresponds to a BMI of 15.5 at age 14. More than half of those diagnosed as AN in the Gothenburg study would not have been diagnosed as AN in our study as we used BMI-SDS scores. We are convinced that we missed few, if any, patients with AN from our catchment area. The reason for this assumption is also the organisational and financial structure of health services in Sweden. Treatment for children and adolescents is free of charge for the family and fully financed by taxes paid in their residential county. Treatment of AN patients from the catchment area, at private units or other specialized public health services elsewhere in Sweden would have generated a request for reimbursement to the CAP. Private health insurances or out-of pocket payment for the specialized care of adolescents is extremely rare in Sweden. Since the CAP service is responsible for the health care offered to the population of the catchment area, we would thus have learned about all AN patients treated outside our EDU. One such case did occur during 2004-2006 and this was one of the two patients with AN who were lost to follow-up, but were included in the incidence calculation.

We can think of four reasons for the higher AN incidence reported from epidemiological screenings. One is that active screening may identify a few cases of AN which spontaneously improve without care. The second, and more important, is differences in cut-offs and age groups included. The third, and difficult to verify, is that AN incidence in adolescent girls may vary considerably over time and place, even within the same country. The fourth is when treatment is easily accessible without delay, the patients are less underweight, although they are on a weight loosing course, they have not lost weight to a level corresponding to AN at assessment. The big difference in incidence between the Gothenburg study and ours is most
probably mainly due to the second reason, difference in weight cut-off. Most of the remaining difference is probably due to the fourth reason, assessment and treatment with minimal delay. It is noteworthy that it was the results from the Gothenburg study (Gillberg, Råstam, & Gillberg, 1994) two decades ago that motivated us to provide swift assessment and treatment.

The present one-year outcome of the entire three-year cohort, and the very limited use of in-patient care, would therefore not be due to a selection bias with the severe cases being treated elsewhere.

The weight criterion for AN, in growing adolescents is not clearly defined in DSM-IV, and most studies do not explicitly describe how it is handled (Thomas et al., 2009). The choice of BMI SDS < -2.0 as the weight criterion is probably stricter compared to several other studies (Cole et al., 2013; Lindgren et al., 1995). The application of the adult ICD-10, criterion for research (WHO, 1993) BMI < 17.5 kg/m² would, even in late adolescence, include a larger number and less emaciated patients in the AN group. The present encouraging outcome of AN would therefore not be due to a selection bias with a lenient weight criterion that includes less severe ED in the AN group.

The extensive acceptance of suggested treatment, the adherence to treatment throughout the first year and the low losses in the follow-up support the view that outcome is representative of the initial cohort.

It is an important notion in that the diagnostic classification of AN and EDNOSr and state of the patient at assessment are not only dependent on the natural course of disease but can also be influenced by the service organization. The majority of patients were on a weight-losing course at first assessment. Weight loss can be reduced if the suspicion of an ED is raised early, at home or in school, and if access to adequate care is rapid and uncomplicated (Treasure & Russell, 2011). This has been achieved here through close contact between the school health care and the EDU, and also through the possibility for parents to directly contact the EDU. This “fast track” is of importance in light of the present observation that weight at assessment influences outcome at one-year follow-up. This finding confirms previous observations that low weight/BMI is an important predictor of poor long-term outcome (Steinhausen, 2002; Treasure & Russell, 2011) (Paper I). In outcome studies, long duration of disease is often another predictor of poor outcome (Steinhausen, 2009; Steinhausen, 2002). In the RCT by Gowers the mean length of illness was 13 months, and in the RCT by Lock the mean duration of illness was 11.3 ± 8.6 months. In our study, the patients with AN had a mean duration of ED symptoms, according to patients’ and parents’ recall, of 9.1 ± 7.3 months (range <1-32 months). As average duration was short in this study and of limited variation, the duration of illness could not be used for the prediction of outcome. However, the awareness of ED symptoms among parents and the school-nurses may have
contributed to the effective chain of referral that may have prevented the occurrence of longstanding disease with less favourable outcome.

The ED service is made accessible to minimize patient’s delay. Doctor’s delay is virtually non-existent, with no waiting list and immediate assessment within 19 ±12 days (range 2-46 days). Patients may nevertheless have experienced substantial weight loss and present with considerable symptoms and signs of starvation (Swenne & Engström, 2005). A first focus on normalization of eating and weight gain, combined with intensive support for the parents, immediately sets most patients off on a weight-gaining course. A difficulty may be that the egosyntonic value of the ED symptoms makes patients unwilling to undertake treatment focusing on changing eating habits and encouraging weight gain. This is addressed by offering only one treatment option and supporting the parents in adhering to it. This notion may be a problem in RCTs when patients/families must be informed about the different treatment arms. An overall ambivalence to treatment may arise when it is apparent that different options are available. Such an effect may contribute to the limited adherence to allocated treatment arms, even in well-designed RCT of AN treatment (Gowers et al., 2007). This is not to say that treatment is only about eating and that it is concluded when full nutritional rehabilitation has been achieved. The important message to get across is that psychological issues, especially those outside the core symptoms of ED, are addressed only when eating has been normalized and weight gain is well under way.

In many outcome studies, two further predictors of outcome are co-morbidity and family function (Steinhausen, 2002). Psychiatric co-morbidity is often reported in cases with less favourable outcome. The influence of co-morbid psychiatric disease did not predict a worse outcome concerning core symptoms of ED in this study. However, co-morbid psychiatric disease may influence the quality of life and be difficult to handle during the final stages of ED treatment, when responsibilities are transferred from the parents to the patient. Another factor often reported as influencing nutritional rehabilitation and weight gain is family function. However, family function has not been included in the present evaluation of treatment and outcome. In view of the emphasis on parental support to the child/patient in the treatment programme, it is evident that parents must get the support required to enable them to help their child. Further studies are needed to evaluate how actual and perceived parental support influences outcome (Nilsson, Engström, & Hägglöf, 2012). AN is often reported to be a disease with a protracted course, and there are reports of as much as a 24% persistence of AN after 10 to 15 years (Keel, Mitchell, Miller, Davis, & Crow, 1999; National Institute for Clinical Excellence (NICE), 2004; Strober, Freeman, & Morrell, 1997). The extent to which such discouraging reports represent the natural course of disease and/or treatment failures is unclear. The present results give a far more optimistic view, showing that early, decisive intervention may even
from a short-term perspective be curative, and when not, may nevertheless create a platform for further treatment. The importance of early intervention in reducing the risk of chronic development was recently underscored by Treasure (Treasure & Russell, 2011), who especially emphasizes the risk of permanent damage by starvation to the developing brain. Preventing such damage may indeed be the key to preventing a chronic course and the tragic outcome of chronic AN, with poor quality of life.
Paper III

Olanzapine as adjunct treatment in adolescent girls with AN and restrictive eating disorders.

Second-generation antipsychotics have not been demonstrated to be effective in the treatment of AN when outcome is evaluated in terms of weight gain or speed of weight gain (Balestrieri, Oriani, Simoncini, & Bellantuono, 2013). There is therefore no general recommendation for their use in AN treatment. Clinical experience does, however, suggest that these drugs may be helpful in reducing anxiety, insomnia and rumination over weight and shape. Even if final outcome is not improved, the road to recovery may be less painstaking and adherence to treatment better. The efficacy of olanzapine was not studied here. The perceived positive effects of the drug may, however, widen its use as an adjunct to nutritional rehabilitation. It is then disconcerting that possible side effects have not been thoroughly investigated. Considering that the patients are physically deteriorated, caution must be exercised when introducing drugs. Moreover, biochemical data must be interpreted in light of the fact that many changes are related to starvation (Swenne, 2004).

The present investigation indicates that olanzapine is well tolerated and that no previously unknown side effects were encountered. It was possible to discern the effects of starvation from those of olanzapine. Thus, alterations of glucose and lipid metabolism were related to weight (loss) and were normalized by weight gain and return of menstruation. On the other hand, effects on prolactin and thyroid function were related to the drug and did not persist when the patients were no longer on olanzapine.

Medication with olanzapine for a period of up to a year is thus not associated with persisting side effects. However, adverse events may occur that make it necessary to discontinue medication. Vigilance for side effects and routines for repeated blood sampling and biochemical analyses must therefore be recommended (Lindström, 2013).
Omega-3 polyunsaturated fatty acids are associated with depression, and omega-3 essential fatty acid status is improved during nutritional rehabilitation.

There is experimental evidence and some studies in humans that indicate that the FA composition of erythrocyte membranes reflects that of brain tissue (Carver, Benford, Han, & Cantor, 2001; Connor, Neuringer, & Lin, 1990; McNamara et al., 2007; Ward et al., 1998). Considering that ω3 PUFA status is associated with depression, it is conceivable that the low energy and low fat diet of adolescents with ED would deplete ω3 PUFA proportions and predispose for depression. There are putative explanations of how ω3 PUFA could influence mood (Lin et al., 2010). In a previous study, it appeared that erythrocyte ω3 PUFA status was not altered in adolescents with ED and weight loss despite other changes in FA composition, which indicated low fat intake and negative energy balance (Swenne et al., 2011). However, within the group of adolescents with ED, low ω3 PUFA proportions and high ratios of ω6/ω3 PUFA presently predicted depression. This relationship was unique to ω3 PUFA, as other FA did not differ between depressed and non-depressed patients. The observed changes to ω3 PUFA proportions were not related to BMI or weight changes, or to the activity of desaturases, the enzymes that metabolize PUFA. Altogether, this would suggest that the differences in ω3 PUFA status are of dietary origin.

A possible causal relationship between ω3 PUFA status and depression remains to be established. The association between self-reported symptoms of depression and the ω6/ω3 PUFA ratio is highly significant, but the effect size is small, indicating that other additional factors are needed to explain depression/depressive symptoms (Alessandri et al., 2004; Horrocks & Farooqui, 2004).

The changes in ω3 PUFA status and metabolism, and the presently demonstrated relationship with depression, make it tempting to suggest supplementation with PUFA during nutritional rehabilitation as an adjunct to treating co-morbid depression (Appleton, Rogers, & Ness, 2008) and possibly the ED itself (Ayton, Azaz, & Horrobin, 2004). It is not surprising that that FA changes related to low fat/low energy intake are normalized when nutritional intake is improved. It was more of an unexpected finding that the proportions of long-chain ω3 PUFA increased significantly above what was observed in both healthy adolescents and the patients before treatment. There are, however, parallel observations (in cystic fibrosis patients) of improved ω3 PUFA status when energy intake is improved (Parsons, O’Loughlin, Forbes, Cooper, & Gall, 1988). This could possibly be
explained by an increased intake of ω3 FA, less oxidation of them when energy balance is positive, and efficient synthesis of long-chain ω3 PUFA when desaturases are not inhibited by starvation. However, the improved ω3 PUFA status does not preclude the persistence of depression, again indicating that there are also other factors that cause and maintain depressive symptoms.

The findings suggest that supplementation with ω3 PUFA during nutritional rehabilitation is not necessary, since there is improvement in ω3 PUFA status simply from the normalization of food intake and weight. It is notable, however, that the duration of the ED in the patients investigated was of limited duration. In adult patients with longstanding ED, there may be further depletion of ω3 PUFA (Caspar-Bauguil et al., 2012). It is possible that such patients would benefit from supplementation.
Conclusions

The overall results point to the importance of early identification and weight rehabilitation of AN and restrictive eating disorders in children and adolescents especially as this may reduce the risk of developing chronic disease.

- In adult patients with chronic AN, there is excess mortality. Premature death is related to extremely low body mass index at some point during the course of disease, and to psychiatric co-morbidity such as alcohol abuse and suicide attempts.

- Out-patient treatment, without planned hospitalization, is possible for adolescents with AN and other restrictive ED. The outcome is promising, as a substantial proportion are free of disease at follow-up after one year, and the vast majority have improved. Preventing weight loss and rapidly starting nutritional rehabilitation are essential features of treatment.

- The antipsychotic drug olanzapine can be used to reduce the urge to exercise, anxiety and rumination over weight, and shape in patients with ED. The drug is well tolerated, and side effects in low-weight adolescents are the same as those observed in normal-weight adults. Vigilance and screening routines for metabolic and hormonal changes are nevertheless necessary.

- In patients with ED and weight loss, the fatty acid profile in erythrocyte membranes indicates a low fat intake and negative energy balance. There is an association between low ω3 PUFA and depression but ω3 PUFA status improves during nutritional rehabilitation without ω3 PUFA supplementation.
Sammanfattning på svenska

Bakgrund och frågeställning


Metod

Resultat
Dödligheten var nästan 12 gånger högre bland vuxna kvinnor som sjukhusvårdats p.g.a. anorexia nervosa, jämfört med kvinnor i motsvarande åldersgrupper i den svenska befolkningen. Bland dem som haft extremt låga vikter återfinns den högsta dödligheten. Förutom dödsfall som är direkt relaterad till svälten, är risken att dö i självmord och alkoholrelaterade sjukdomar kraftigt förhöjd. Bland dem som vårdats för bulimia nervosa var dödligheten inte förhöjd.

Det viktigaste fyndet är att av ungdomar med anorexia nervosa är 20% botade, 77% har en lindrigare form av åtstörning och bara 3% har kvar anorexia nervosa efter ett års behandling. Nästan alla klarade av heltid i skolan. Dessa resultat var möjliga att uppnå utan planerad slutenvård och tack vare föräldramans aktiva deltagande i barnets behandling. Neuroleptika-medicinering med olanzapine uppvisade inte några oväntade bieffekter, trots att ungdomarna hade ett dåligt allmäntillstånd och var yngre än den rekommenderade åldern för denna behandling när medicineringen påbörjades. Innehållet av fleromättade fettsyror i de röda-blodkropparnas cellväggar påverkades av viktnedgången och kunde relateras till förekomsten av depression. De fleromättade fettsyrorna normaliserades dock under viktuppgång utan tillägg i kosten. Sådan tilläggsbehandling förefaller därför inte nödvändig för unga patienter som varit sjuka relativt kort tid.

Slutsats
Tidig upptäckt och snabbt insatt behandling för att undvika utveckling av kroniska åtstörningar är av största vikt för barn och ungdomar med åtstörning och viktnedgång. Behandlingsstarten med normalisering av ätandet kan genomföras i öppenvård och viktökningen kan med föräldramans stöd uppgå till 0,5-1 kg/vecka. Detta kan genomföras med vanlig mat och en fast måltidsordning med tre huvudmål och tre mellanmål per dag. I vissa fall behövs energi drycker som tillskott under en period. All träning måste upphöra under behandlingen och skolarbetet bör vänta tillsvikten är påtagligt förbättrad och måltiderna fungerar på ett normalt sätt. Först när dessa aspekter av behandlingen genomförts kan ansvaret för måltiderna börja återföras till ungdomarna. Behandling som syftar till att förebygga återfall med viktnedgång och att hantera andra psykologiska problem kan påbörjas när ätandet fungerar och vikten blivit stabil på en nivå som är normal för längd och ålder.
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Thank you, everybody!


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