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REPRODUCTIVE AND PSYCHOLOGICAL OUTCOMES OF EATING DISORDERS

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ACADEMIC DISSERTATION

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A goddess is a woman who emerges from deep within herself. She is a woman who has honestly explored her darkness and learned to celebrate her light. She is a woman who is able to fall in love with the magnificent possibilities within her. She is a woman who knows of the magic and mysterious places inside her, the sacred places that can nurture her soul and make her whole.

Rafael Espitia Perea

*To all women seeking their true nature
&
My family*

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ABSTRACT

The aim of this thesis was to study the impact of eating disorders on young women's reproductive and psychological health in both clinical and population-based settings.

Two samples of women were utilized to meet these goals. First, women treated at the eating disorder clinic of Helsinki University Central Hospital during 1995-2010 (n=2257) were compared with matched controls drawn from the Central Population Register (n=9028). Register-based measures of general reproductive outcomes, course of pregnancy and childbirth, and perinatal health outcomes were compared across these two groups in Studies I and II. Second, twins born in Finland during 1975-1979 (FinnTwin16, n=2825 women) were assessed at the age of 22-28 years by means of a mailed questionnaire that included several measures of psychological health as well as a screen for eating disorders, followed by diagnostic interviews. Studies III-V compared the twins with a history of lifetime eating disorders with their unaffected twin sisters and healthy women to evaluate recovery rates and psychological outcomes.

The probability of recovery from anorexia nervosa and bulimia nervosa in the twin sample five years after the onset of the illness was 67% and 57%, respectively. Many of the women treated for an eating disorder had experienced reproductive health problems at follow-up, but most of them had no complications in pregnancy or childbirth. In the clinical sample, an increased likelihood of remaining childless was found among women with anorexia nervosa, whereas women with bulimia nervosa were more likely to experience induced abortion, and miscarriage was common among women with binge eating disorder (BED) in comparison with the controls. Maternal anorexia nervosa and BED were related to abnormal patterns of fetal growth during pregnancy. Significantly, severe perinatal health complications were observed in women treated for anorexia nervosa or bulimia nervosa.

The psychological outcomes of anorexia nervosa and bulimia nervosa were more favorable in the twin cohort than previously reported. Recovery was slow and gradual, but most women with anorexia nervosa reached the level of their unaffected twin sisters in terms of psychological health over time. The course of bulimia nervosa was marked by a more gradual easing of symptoms. Body dissatisfaction and psychosomatic symptoms seemed to be the most persistent residua of both illnesses.

Overall, the outcome was poor for some, but favorable for most women with a history of eating disorders. Several reproductive health problems were observed among women who had received treatment, suggesting the need for enhanced monitoring of pregnancies among these women. However, in the twin cohort, most women with a history of eating disorders proceeded towards recovery, did not experience reproductive impairment, and, on measures of psychological health, resembled their unaffected twin sisters more closely over time.

TIIVISTELMÄ

Tämän tutkimuksen tarkoituksena oli selvittää syömishäiriöiden vaikutuksia nuorten naisten lisääntymisterveyteen ja psykologiseen terveyteen.

Näiden tavoitteiden saavuttamiseksi käytimme tutkimuksessa kahta aineistoa. Kliininen aineisto koostui Helsingin yliopistollisen keskussairaalan syömishäiriökllinikalla vuosina 1995-2010 hoidetuista naispotilaista (n=2257), joita verrattiin väestörekisterikeskuksesta poimittuihin kaltaistettuihin verrokkeihin (n=9028) useiden rekistereistä poimittujen yleistä lisääntymisterveyttä, raskauksien ja synnytysten kulkua ja lasten perinataaliterveyttä mittaavien muuttujien suhteen osatöissä I ja II. Väestöaineisto koostui Suomessa vuosina 1975-1979 syntyneistä kaksosista, joita tutkittiin 22-28 vuoden iässä (FinnTwin16, n=2825 naista) kyselylomakkein, jotka sisälsivät useita psykologisen terveyden mittareita sekä syömishäiriöiden seulontaan tarkoitettuja kysymyksiä. Diagnostisten haastattelutietojen perusteella vertasimme syömishäiriön sairastaneita naisia heidän terveisiin kaksossisariinsa sekä terveisiin verrokkeihin arvioidaksemme syömishäiriöiden paranemistaipumusta sekä psykologista toipumista osatöissä III-V.

Kaksosaineistosta arvioituna, viisi vuotta sairastumisen jälkeen laihuushäiriön paranemisen todennäköisyys oli 67% ja ahmimishäiriön 57%. Kliinisessä aineistossa havaittiin, että seuranta-ajan kuluessa monet syömishäiriön vuoksi hoidossa olleista naisista olivat kohdanneet lisääntymisterveyteen liittyviä ongelmia, mutta valtaosalla raskaus ja synnytys olivat sujuneet hyvin. Lapsettomuuden todennäköisyyden todettiin olevan kohonnut laihuushäiriön sairastaneilla, ahmimishäiriön sairastaneet olivat todennäköisemmin keskeyttäneet raskauden, ja ahmintahäiriöön (binge eating disorder, BED) liittyi kohonnut keskenmenon riski verrokkeihin nähden. Äidin laihuushäiriöön ja ahmintahäiriöön liittyi sikiön kasvun poikkeavuuksia raskauden aikana. Merkillepantavaa on, että laihuushäiriöön ja ahmimishäiriöön liittyi vakavia komplikaatioita syntyneiden lasten perinataaliterveyteen liittyen. Kaksosaineistosta saadut arviot laihuushäiriön ja ahmimishäiriön jälkeisestä psykologisesta toipumisesta olivat suotuisampia kuin aiempien tutkimusten antamat arviot. Toipuminen oli hidasta ja vaiheittaista, mutta valtaosa laihuushäiriön sairastaneista saavutti ajan kuluessa terveitä kaksossisariansa vastaavan psykologisen hyvinvoinnin tason. Ahmimishäiriölle ominaista oli vähittäisempi oireiden lievittyminen. Laihuushäiriön ja ahmimishäiriön oireista sitkeimpiä olivat tyytymättömyys omaan kehoon sekä psykosomaattiset oireet.

Tässä tutkimuksessa syömishäiriöstä toipuminen oli polarisoitunutta. Syömishäiriön vuoksi hoidossa olleilla naisilla havaittiin kohonnut riski useisiin lisääntymisterveyden ongelmiin, mistä johtuen voidaan suositella tehostettua raskaudenaikaista seurantaä näillä naisilla. Kaksosaineiston pohjalta toisaalta havaittiin, että monet syömishäiriön sairastaneista naisista toipuvat, eikä heillä havaittu lisääntymiseen liittyviä ongelmia. Kliinisen paranemisen jälkeen psykologinen terveys parani vähittäin vuosien kuluessa terveiden kaksosarten tasoa vastaavaksi.

LIST OF ORIGINAL PUBLICATIONS

The thesis is based on the following original articles, which are referred to in the text by Roman numerals (I-V).

- I Linna MS, Raevuori A, Haukka J, Suvisaari J, Suokas JT, Gissler M. Reproductive health outcomes in eating disorders. *Int J Eat Disord* 2013;46:826-833
- II Linna MS, Raevuori A, Haukka J, Suvisaari J, Suokas JT, Gissler M. Pregnancy, obstetric and perinatal health outcomes in eating disorders. *Am J Obstet Gynecol* (in press)
- III Linna MS, Kaprio J, Raevuori A, Sihvola E, Keski-Rahkonen A, Rissanen A. Body mass index and subjective well-being in young adults: a twin population study. *BMC Public Health* 2013;13:231.
- IV Keski-Rahkonen A, Hoek HW, Susser ES, Linna MS, Sihvola E, Raevuori A, Bulik CM, Kaprio J, Rissanen A. Epidemiology and course of anorexia nervosa in the community. *Am J Psychiatry* 2007;164:1259-65.
- V Keski-Rahkonen A, Hoek HW, Linna MS, Raevuori A, Sihvola E, Bulik CM, Rissanen A, Kaprio J. Incidence and outcomes of bulimia nervosa: a nationwide population-based study. *Psychol Med* 2009;39:823-31.

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ABBREVIATIONS

APA	American Psychiatric Association
BED	Binge Eating Disorder
BMI	Body Mass Index
CI	Confidence Interval
EDI	Eating Disorder Inventory
EDNOS	Eating disorder not otherwise specified
IQR	Interquartile range
LGA	Large for gestational age
N	Number of participants
OR	Odds Ratio
RR	Rate Ratio
SD	Standard deviation
SGA	Small for gestational age
WHO	World Health Organization

1. INTRODUCTION

“Too many of us are labouring under the tyranny of a culturally prescribed body shape; where dieting is the norm and a skinny body the goal.”

Louise Foxcroft, *Calories and Corsets*, 2011

Body shape and weight have been an issue of passionate debate in the course of history. Every culture has its own version of the ideal body shape that influences the perception we have of our own bodies and what is seen as beautiful or ugly. The ideal body has undergone major changes during the past century, from the flat-chested and slim women of the 1920s to the curvy hourglass figures of the 1950s, the skinny Twiggy in the 1960s, and the emaciated “heroin chic” models of the 1990s. Garner et al. (1980) hypothesized that the increase in the prevalence of anorexia nervosa and bulimia nervosa during the second half of the 20th century reflected the increasing idealization of thinness among women. The authors explored the changing of beauty ideals from 1959 to 1978 as reflected in Miss America contestants, Playboy magazine centerfolds, and women’s magazines. Indeed, both contestants and winners in the Miss America Pageant were increasingly thin during the time period in question. Some of the winners had a body mass index as low as 16.9 kg/m², which is categorized as underweight according to the World Health Organization (WHO), and is below the weight criterion for anorexia nervosa in DSM-IV (Rubinstein & Caballero 2000). Likewise, there was a tendency to use thinner female figures in Playboy centerfolds, and there was a shift from the womanly hourglass shape to an adolescent tubular shape (Voracek & Fisher 2002). A similar shift was observed in women’s magazines, as the number of articles on weight-loss diets doubled from 1959 to 1978 (Garner et al. 1980, Wiseman et al. 1992).

As a counterbalance, the feminist movement of the 1960s-1980s aimed at objecting the thin ideal by taking the body back to women themselves. Within this movement, women sought to acquire weight, to gain power and gravitas, and to enlarge their frame of influence as opposed to the dieting trend (Chernin 1981). More recently, fashion magazines have taken steps towards questioning the prevailing body ideal: V Magazine predicted the resurrection of the curves (2010), and in 2010 Vogue Italia launched Vcurvy, which is devoted to women with fuller figures.

Studies have shown that as many as 60 percent of adolescent girls are dissatisfied with their weight and their body shape (Field et al. 1999). Weight and shape concerns are predictive of disordered eating and eating disorders and have been linked to Westernization. Disordered eating behaviors were almost nonexistent in Fiji before the arrival of Western culture, but there was a steep upsurge when Western television broadcasts were first transmitted (Becker et al. 2002). With the prevailing exposure to both an obesogenic environment and the cultural pressure to be slim, women are currently facing an enormous challenge. This is manifested in body image problems, disordered eating, and eating disorders, all of which place a substantial burden on the female population of today. Despite the commonness of eating disorders, our understanding of their long-term consequences is still very limited. The aim of this study was to examine whether a history of eating disorders permanently marked young women's lives from the perspective of reproductive and psychological health.

2. REVIEW OF THE LITERATURE

2.1. EATING DISORDERS

The spectrum of disordered eating ranges from slightly disturbed eating and body image to clinically diagnostic eating disorders. This study focuses on eating disorders. The Diagnostic and Statistical Manual for Mental Disorders (DSM-IV; American Psychiatric Association (APA), 1994) defines a mental disorder as a clinically significant behavioral or psychological syndrome or pattern that occurs in an individual and that is associated with present distress, or disability (i.e., impairment in one or more important areas of functioning), or with a significantly increased risk of suffering death, pain, disability, or an important loss of freedom. Furthermore, DSM-IV notes that “...although this manual provides a classification of mental disorders, it must be admitted that no definition adequately specifies precise boundaries for the concept of ‘mental disorder.’ “

The recognized types of eating disorder have changed over the course of time. Given the scope of this study, the focus is on anorexia nervosa, bulimia nervosa, and binge eating disorder (BED). According to DSM-5 (APA, 2013), feeding and eating disorders also include pica, rumination disorder, avoidant/restrictive food intake disorder, other specified feeding or eating disorder (sub-threshold anorexia nervosa, bulimia nervosa, or BED, purging disorder, and night eating syndrome), and unspecified feeding or eating disorder.

2.1.1. EATING DISORDERS: A HISTORICAL PERSPECTIVE

Richard Morton wrote the first medical description of eating disorders in 1694 (Morton, 1694). The term *anorexia nervosa* was first used in 1874 by British physician Sir William Gull in reference to several adolescent female patients engaging in self-starvation that led to severe weight loss (Gull, 1874). Before this, French physician Charles Lasegue described a pattern of self-starvation, *l'anorexie hysterique* (Lasegue, 1873). There is evidence that the disorder existed long before these descriptions surfaced. Stories of self-starvation among saints of the Roman Catholic Church in the 13th to the 18th century, miraculous maids in the 18th century, and fasting girls in the 19th century have been found in historical documents.

Bulimia nervosa, in contrast, was first named and described much later, in 1979, by British psychiatrist Gerald Russell (Russell, 1979). Two independent authors had previously written in German and Spanish about a binge-purge syndrome among women of normal weight, with English translations by the original authors appearing in 1994 (Dörr-Zegers, 1994, Ziolko, 1994). Binge eating was regarded as a symptom of a multitude of somatic and mental disorders, but not as a core pathologic feature of a syndrome of its own until the 1960s (Casper, 1983). Dörr-Zegers' and Ziolko's publications mark a shift from a symptom to a syndrome approach in binge behaviors (Vandereycken, 1994). *Bulimia nervosa* was first included in the diagnostic and statistical manual of mental disorders in 1980 (DSM-III; APA, 1980).

The term BED entered the medical literature even later than *bulimia nervosa*. Anecdotal descriptions of BED exist in historical documents, but the characteristic eating behaviors were first described in a research setting in 1959 (Stunkard, 1959, Heaner & Walsh 2013). BED was included as a research diagnosis in the appendix of DSM-IV in 1994, and as an official diagnosis in DSM-5 (2013).

2.1.2. DEFINITIONS

DSM-IV and ICD-10 criteria were utilized in this study, and are therefore reviewed here. Comparison is also made to the newly launched DSM-5 criteria.

Anorexia nervosa

Anorexia nervosa is a serious mental illness characterized by substantial self-induced weight loss, dread of fatness, distortion of the body image, and widespread endocrine dysfunction. The DSM-IV criteria established by the APA (1994) and the ICD-10 criteria established by the WHO (1992) have been most widely used in recent research for the diagnosis of anorexia nervosa. DSM-IV classifies the disorder into two subtypes, the restricting type and the binge/purge type (Table 1). The DSM classification and diagnostic criteria for mental disorders were updated in 2013 (DSM-5; APA, 2013). The criteria for anorexia nervosa were broadened from DSM-IV to DSM-5, diminishing the proportion of subjects diagnosed with an eating disorder not otherwise specified (EDNOS). The weight limit in DSM-5 is "below what is minimally expected for age", and the amenorrhea criterion has been omitted. Table 1 compares the DSM-IV and ICD-10 criteria. One of the main differences is that ICD-10 does not recognize subtypes of anorexia nervosa.

Table 1. Diagnostic criteria for anorexia nervosa according to DSM-IV (APA, 1994) and ICD-10 (WHO, 1992).

DSM-IV criteria for anorexia nervosa (307.1)		ICD-10 criteria for anorexia nervosa (F50.0)	
A.	Refusal to maintain body weight at or above a minimally normal weight for age and height (e.g. less than 85% of that expected)	A.	Body weight at least -15% of that expected, or body mass index 17.5 or less.
B.	Intense fear of gaining weight or becoming fat, even though underweight	B.	Weight loss is self-induced and one or more of the following is present: self-induced vomiting/ purging; excessive exercise; use of appetite suppressants/ diuretics.
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.	C.	Patient manifests body-image distortion, dread of fatness and has a low weight threshold for her/ himself.
D.	Amenorrhea in postmenarchal women	D.	Widespread endocrine disorder involving hypothalamic-pituitary-gonadal-axis manifests in women as amenorrhoea and in men as a loss of sexual interest and potency.
	Define type	E.	Diagnostic criteria a. and b. of Bulimia Nervosa (F50.2) are not met.
Restricting type	During the current episode of anorexia nervosa, the person has not regularly engaged in binge-eating or purging behavior (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 behavior (i.e. self-induced vomiting or the misuse of laxatives, diuretics, or enemas)	-	

Bulimia nervosa

Bulimia nervosa is characterized by recurrent episodes of binge eating, recurrent inappropriate compensatory behaviors in order to prevent weight gain, and self-evaluation strongly influenced by body shape and weight. DSM-IV recognizes two subtypes in bulimia nervosa, depending on the type of purging methods used (Table 2). The purging type includes regularly self-induced vomiting or misuse of laxatives, diuretics, or enemas, whereas the non-purging type includes fasting or excessive exercise as compensatory behaviors. The frequency criterion for binge eating and inappropriate compensatory behaviors has been relaxed to at least once a week for three months in DSM-5, and bulimia nervosa is no longer specified as a purging/non-purging subtype. Table 2 compares the DSM-IV and ICD-10 criteria; in addition to not recognizing the subtypes of bulimia nervosa mentioned in DSM-IV, ICD-10 includes persistent preoccupation with eating and craving for food, and a morbid dread of fatness as diagnostic criteria.

Table 2. Diagnostic criteria for bulimia nervosa according to DSM-IV (APA, 1994) and ICD-10 (WHO, 1992).

DSM-IV criteria for bulimia nervosa (307.51)		ICD-10 criteria for bulimia nervosa (F50.2)	
A.	Recurrent episodes 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 any 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)	A.	Patient succumbs to short episodes of overeating, consuming large amounts of food (at least twice a week for 3 months).
B.	Recurrent inappropriate compensatory behavior in order to prevent weight gain, such as self-induced vomiting, misuse of laxatives, diuretics, enemas, or other medications, fasting, or excessive exercise.	B.	Patient has a persistent preoccupation with eating and craving for food.
C.	The binge eating and inappropriate compensatory behaviors both occur, on average, at least twice a week for 3 months.	C.	Patient attempts to counteract the effects of food by one or more of the following: self-induced vomiting; purging, periods of starvation; use of drugs such as appetite suppressants, thyroid preparations or diuretics.
D.	Self-evaluation is unduly influenced by body shape and weight.	D.	Psychopathology consists of morbid dread of fatness and patient sets herself/ himself a sharply defined weight threshold.
E.	The disturbance does not occur exclusively during episodes of anorexia nervosa.		
Define type			
Purging Type	During the current episode of bulimia nervosa, the person has regularly engaged in self-induced vomiting or the misuse of laxatives, diuretics, or enemas	-	
Non-purging Type	During the current episode of bulimia nervosa, the person has used other inappropriate compensatory behaviors, such as fasting or excessive exercise, but has not regularly engaged in self-induced vomiting or the misuse of laxatives, diuretics, or enemas	-	

Binge eating disorder

The occurrence of binge eating episodes in the absence of compensatory behaviors is the core feature of BED. The disorder is often seen in obese individuals, but it differs from obesity in terms of psychopathology and weight and shape concerns (Wonderlich et al. 2009). The first official diagnostic criteria were included in the recently launched DSM-5, although the DSM-IV research criteria (Table 3) have been widely used in research settings since they were published. In line with the changes in the diagnostic criteria for bulimia nervosa, the frequency criterion of binge eating episodes is relaxed in DSM-5 to at least once a week for three months. ICD-10 describes overeating associated with other psychological disturbances (F50.4), which resembles but is not equivalent to BED.

Table 3. Research criteria for binge eating disorder according to DSM-IV (APA, 1994).

DSM-IV research criteria for binge eating disorder
The patient succumbs to episodes of overeating in which large amounts of food are consumed, there is a subjective sense of loss of control, and at least three of the following symptoms are present:
-Eating much more rapidly than normal -Eating until uncomfortably full -Eating large amounts of food, even when not physically hungry -Eating alone out of embarrassment at the quantity of food being eaten -Feelings of disgust, depression, or guilt with overeating.
These behaviors must occur at least 2 times per week over the course of 6 months with no compensatory behaviors.

2.1.3. EPIDEMIOLOGY

Estimates of the prevalence and incidence of eating disorders depend on the screening method, the population in question, and the diagnostic criteria used. In terms of estimating prevalence, a two-stage screening process is currently the standard method for detecting eating disorder cases (Hoek et al. 2003, Pelaez-Fernandez et al. 2008). The first stage is to screen the studied population by means of a questionnaire, and in the second stage a diagnostic interview is administered to establish the diagnosis.

Lifetime prevalence

Estimates of the lifetime prevalence of anorexia nervosa among women vary from 0.9% to 2.2% for DSM-IV anorexia nervosa, and from 2.4% to 4.3% for broadly defined anorexia nervosa (Bulik et al. 2006, Wade et al. 2006, Hudson et al. 2007, Keski-Rahkonen et al. 2007, Preti et al. 2009). The estimated lifetime prevalence of bulimia nervosa is from 0.9% to 2.9% (Wade et al. 2006, Hudson et

al. 2007, Keski-Rahkonen et al. 2009, Preti et al. 2009), and for BED from 1.9% to 3.5% (Hudson et al. 2007, Preti et al. 2009, Swanson et al. 2011) among females representative of the general population.

Gender

All eating disorders occur more frequently in women than in men. The female-to-male ratio is estimated to range from 1:3 to 1:12 in anorexia nervosa (Hoek et al. 2003, Hudson et al. 2007, Keski-Rahkonen et al. 2007, Raevuori et al. 2009, Bulik et al. 2006, Woodside et al. 2001), from 1:3 to 1:12 in bulimia nervosa (Kinzl et al. 1998a, 1998b, Woodside et al. 2001, Currin et al. 2005), and from 1:2 to 1:6 in BED (Kinzl et al. 1998a, 1998b, Hudson et al. 2007, Preti et al. 2009).

Mortality

A meta-analysis conducted in 1998 showed that anorexia nervosa was associated with the highest mortality rates among all psychiatric disorders (Harris et al. 1998). More recent meta-analyses provide estimates of the standardized mortality ratio (SMR; the ratio of observed deaths among the study population to expected deaths in the original population) for anorexia nervosa: Arcelus et al. (2011) reported an overall SMR of 5.86 (95% CI 4.17-8.26) with a 14-year mean follow-up, and Nielsen et al. (2001) reported an SMR of 9.6 (95% CI 7.8-11.5) with a 6-12-year follow-up. In the case of bulimia nervosa, the SMR has been estimated at 1.93 (95% CI, 1.44-2.59) (Arcelus et al. 2011). Fichter et al. (2008) reported an SMR of 2.3 (95% CI 0.0–5.5), and Suokas et al. (2013) a 1.8-fold increased risk (95% CI 0.6–5.3) for premature death in BED.

2.1.4. CORRELATES

Eating disorders have profound effects on the mind and the body. Poor nutritional status, psychological stress and compensatory behaviors have the potential to deeply affect mental health, hormonal balance, and the functioning of several organ systems.

Biological correlates

Anorexia nervosa is characterized by significant weight loss. The loss of body weight includes the loss of fat tissue, muscle, organ tissue, and bone. Somatic complications include leukocytopenia, electrolyte imbalances, bradycardia, hypotension, hypothermia, and an elevated concentration of liver enzymes

(Miller et al. 2005), elevated levels of cortisol (Boyar et al. 1977), hypogonadism and a reduction in the size of the reproductive organs (Treasure et al. 1988), and lowered levels of estrogens, androgens, and luteinizing hormone pulsatility (Miller, 2011). Osteoporosis and bone fractures can occur as a consequence of the loss of bone mass (Vestergaard et al. 2002, Misra et al. 2011, Powers et al. 1999). An increase in the ventricle size of the brain accompanied by the loss of gray and white matter has been shown to occur in patients currently ill with anorexia nervosa (Dolan et al. 1988, Katzman et al. 1996).

The somatic consequences of bulimia nervosa relate mainly to compensatory behaviors, and include electrolyte imbalances, tooth decay, esophagitis, dyspepsia, esophageal rupture, swollen parotid glands, hypotension, arrhythmias, and irregular menstruation (Lasater et al. 2001, Mitchell & Crow 2006, Mehler, 2011).

BED is characterized by regular binge eating, which often leads to significant weight gain and obesity. The somatic correlates relate mainly to obesity, but there is evidence that BED may be associated with medical morbidity independently of the effects of comorbid psychopathology or comorbid obesity (Bulik & Reichborn-Kjennerud 2003). Joint pain, headaches, gastrointestinal problems, menstrual problems, shortness of breath, chest pain, and Type II diabetes have been shown to occur frequently in cases of BED (Johnson et al. 2001, Bulik & Reichborn-Kjennerud 2003).

Psychological correlates

All types of eating disorder are associated with alterations in psychological functioning. This section gives an overview of the psychological characteristics observed in individuals with anorexia nervosa, bulimia nervosa, and BED.

Body dissatisfaction, drive for thinness and preoccupation with food, weight and eating are core features of anorexia nervosa (Fairburn & Harrison 2003). Furthermore, characteristic of those affected are high levels of anxiety, perfectionism, restraint, persistence, obsessive-compulsiveness, neuroticism, harm avoidance, anhedonia, asceticism, negative emotionality, constriction of affect and emotional expressiveness, and isolation, as well as traits associated with avoidant personality disorder. Low levels of self-directedness, cooperativeness, interoceptive awareness, and novelty seeking have also been reported (Cassin & von Ranson 2005, Bardone-Cone et al. 2007, Lilenfeld et al. 2006). Some of these characteristics may represent vulnerability factors for the eating disorder, whereas others may be a direct consequence of under-nutrition, as observed in the Minnesota starvation experiment conducted in the 1940s. The aim of the Minnesota study was to explore the effects of starvation among conscientious

objectors to World War II (Keys et al. 1950). The men in question became withdrawn and depressed over the course of their starvation, and many of them showed food obsessions similar to those observed in individuals with anorexia nervosa.

The psychological characteristics of bulimia nervosa are somewhat similar to those of anorexia nervosa. Individuals with bulimia nervosa also show elevated levels of body dissatisfaction, weight and shape concerns, perfectionism, obsessive-compulsiveness, neuroticism, negative emotionality, harm avoidance, low self-directedness, and low cooperativeness, as well as traits associated with avoidant personality disorder (Cassin & von Ranson 2005, Bardone-Cone et al. 2007). In addition, they have been shown to have high levels of impulsivity, sensation seeking, and novelty seeking, and traits associated with borderline personality disorder (Cassin & von Ranson 2005).

BED is the least studied of the eating disorders addressed within the framework of this study. Psychological characteristics associated with the condition include high harm avoidance, novelty seeking, anxiety, depressive symptoms, self-criticism, over-evaluation of shape and weight, and low self-esteem and self-directedness (Telch & Stice 1998, Dunkley & Grilo 2007, Gruzca et al. 2007, Reichborn-Kjennerud et al. 2004, Peterson et al. 2010).

2.1.5. COMORBIDITY AND RISK FACTORS

Comorbidity

All types of eating disorders are associated with marked psychiatric comorbidity. A large, nationally representative, population-based study conducted by Hudson et al. (2007) showed that eating disorders were positively related to almost all of the core DSM-IV mood, anxiety, impulse-control, and substance use disorders, whereas no single class of disorders stood out as showing consistently or distinctly higher comorbidity with eating disorders. Hudson & colleagues also found that, among individuals with an eating disorder, those with bulimia nervosa were at the highest risk of a comorbid disorder (94.5% of the individuals with bulimia nervosa had at least one comorbid disorder, OR 17.6, 95% CI 4.5–68.4), followed by those with BED (78.9%, OR 4.2, 95% CI 2.2–7.9), and individuals with anorexia nervosa showed the lowest risk (56.2%, OR 1.3, 95% CI 0.6–3.1). These findings are in line with those of Swanson et al. (2011), drawn from a large, nationally representative sample of adolescents.

More specifically, several original studies and reviews have reported that

individuals with anorexia nervosa and bulimia nervosa have elevated rates of lifetime diagnoses of anxiety and depressive disorders, and obsessive-compulsive disorder (Lilenfeld et al. 1998, O'Brien et al. 2003, Kaye et al. 2004, Godart et al. 2002;2007). Furthermore, there is evidence of a link between binge/purge syndromes and substance abuse (O'Brien et al. 2003, Swanson et al. 2011). Less is known about comorbidity in BED, although research suggests an increased risk of anxiety and depressive disorders, and of substance abuse (Yanovski et al. 1993, Telch & Stice 1998, Grucza et al. 2007, Grilo et al. 2009).

Risk factors

Numerous risk factors have been described for eating disorders. Such disorders arise as a result of a complex interplay of genetic, environmental, and individual risk factors.

Interest in the biological background of eating disorders has increased recently. Biological factors contributing to the risk include genetic factors, early developmental trauma, and pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS). The role of genes has been assessed in twin studies, and estimates of heritability (i.e. the proportion of variation in the occurrence of a phenotype between individuals within a population that is due to genetic differences) in eating disorders have varied between 50 and 80 % (Klump et al. 2009). The most promising findings in candidate gene studies are related to polymorphisms in 5-HT_{2A} and BDNF genes (Scherag et al. 2010). In a similar vein, an abnormal 5-HT function has been shown after recovery, leading to the hypothesis that a trait monoamine abnormality might predispose to the development of eating disorders or to associated characteristics such as perfectionism (Kaye et al. 1999, 2001, Frank et al. 2002, Fairburn & Harrison 2003). Genome-wide association studies (GWAS) and epigenetic studies hold promise for a better understanding of the etiology and pathogenesis of eating disorders (Raevuori, 2013).

Biological processes affecting the risk of developing eating disorders later on have been identified during pregnancy and birth. There is evidence that maternal anemia, diabetes mellitus, preeclampsia, placental infarction, prematurity, being small for gestational age (SGA), neonatal cardiac problems, cephalhematoma and hyporeactivity increase the risk of eating disorders in offspring (Cnattingius et al. 1999, Favaro et al. 2006). Described in adolescents, PANDAS is a process whereby a streptococcal infection leads to the onset of anorexia nervosa through a postulated autoimmune mechanism (Vincenzi et al. 2010).

There are several other extensively recognized risk factors for the onset of eating disorders, including thin-ideal internalization, female gender, high socioeconomic status, family environment, certain personality traits such as perfectionism, high social anxiety, and high impulsivity, individual differences in biological responses to starvation, and individual differences in the reward value of starvation or eating (Stice, 2002, Striegel-Moore & Bulik 2007).

The role of culture has long been debated. Given the evidence on anorexia nervosa existing since medieval times in various geographical locations, and its relatively stable incidence over the past four decades (Robins et al. 1984, Wade et al. 1996, Hoek & van Hoeken 2003), anorexia nervosa does not appear merely to be a culture-bound syndrome (Keel & Klump 2003). Bulimic behaviors, on the other hand, seem to be more strongly related to exposure to Western culture. In a study conducted in Fiji, the prevalence of self-induced vomiting rose from zero to 11.3% among women during the three years following the arrival of television and Western culture (Becker et al. 2002). Moreover, Keel & Klump (2003) found no studies reporting the presence of bulimia nervosa in an individual with no exposure to Western ideals in their review. Incidence data suggest a significant increase in incidence between 1970 and 1990 (Hall & Hay 1991, Hoek et al. 1995, Turnbull et al. 1996, Keel & Klump 2003). Bulimia nervosa was first recognized in 1979, which may limit the data available on its existence prior to this. Keel & Klump (2003) conclude that it is a culture-bound syndrome.

2.2. RECOVERY IN EATING DISORDERS

Recovery can be defined in various ways in the context of eating disorders, ranging from ceasing to fulfill the diagnostic criteria to the full recovery of behavior, attitudes towards food and body, and somatic and psychosocial health. Recovery rates differ greatly depending on the criteria utilized for recovery, as Couturier and Lock (2006) demonstrate. Recovery is a gradual process, which is often thought to proceed from the discontinuation of binge and purge behaviors to menses and weight recovery, and further on to psychological recovery. Figure 1 illustrates this process as a function of time (Clausen, 2004). Overall, the outcome of eating disorders is most frequently assessed in four categories: global outcome, normalization of the core symptom characteristics (i.e. weight, menstruation, and eating behavior), psychiatric comorbidity, and mortality (Steinhausen, 2002). Normalization of the psychological characteristics has been addressed less frequently.

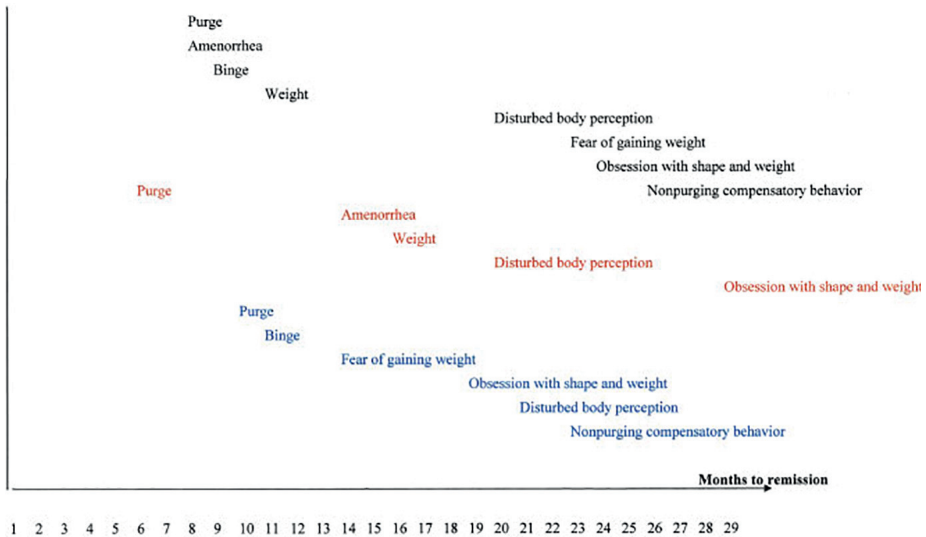


Figure 1. The time course of symptom remission. The figure is reprinted from Clausen L (2004) with the permission of the publisher. Black type indicates all eating disorders, red anorexia nervosa, and blue bulimia nervosa.

2.2.1. ASSESSMENT OF CORE SYMPTOMS

Assessment of recovery usually involves assessing the core symptoms, in other words weight recovery and the restoration of menstruation in the case of anorexia nervosa, and abstinence from binge and purge behaviors among those with bulimia nervosa and BED. The most widely used assessment methods are discussed below.

Anorexia nervosa

The Morgan-Russell Categories of General Outcome, introduced in 1975 by Morgan & Russell, is the best known instrument for defining the degree of recovery from anorexia nervosa. The original assessment schedule included physical, psychological, and social aspects of functioning in defining the outcome of the disorder. However, the more widely used abridged Morgan-Russell criteria address only two aspects of recovery, namely the restoration of weight and menstruation, yielding three categories of outcome: good, intermediate, and poor (Morgan & Hayward 1988). Strober, Freeman & Morrell (1997) further elaborated the Morgan-Russell criteria by establishing a new full recovery criterion that required the sustained absence of weight deviation, compensatory behaviors, and deviant attitudes to weight and shape (i.e., the absence of constant worry or

rumination over weight, the possibility or imminence of weight gain, or the need for vigilance over eating and weight control) for at least eight weeks (Strober et al. 1997). Garfinkel, Moldofsky & Garner (1977) developed a *Global Clinical Score* (Garfinkel's Global Clinical Score) that provides a comprehensive assessment of the overall outcome. The assessment covers the core symptoms, including the restoration of weight, menstruation and eating habits, social adjustment, and educational/vocational adjustment. In 1993, Herzog and colleagues (Herzog et al. 1993) established a *Psychiatric Status Rating Scale* for anorexia nervosa comprising a six-point rating scale ranging from full recovery to active and severe eating disorder.

Bulimia nervosa and BED

The core symptom of both bulimia nervosa and BED is the occurrence of binge behaviors. Whereas the Morgan-Russell General Outcome Criteria are widely used to assess recovery from the core symptoms of anorexia nervosa, no such uniform instrument is available for either bulimia nervosa or BED.

Olmsted et al. (2005) have shown that relapse rates in bulimia nervosa are heavily influenced by the definition of remission. Definitions vary substantially across studies, and include abstinence from bingeing and purging behaviors for at least eight weeks (Mitchell et al. 1985, Keller et al. 1992, Herzog et al. 1999), abstinence for at least four weeks (Fairburn et al. 1993, Agras et al. 2000, Halmi et al. 2002), having a maximum of one weekly binge episode for four (Maddocks et al. 1992, Olmsted et al. 1994) or two weeks (Pyle et al. 1990), and a maximum of two binge episodes per month for two months (Olmsted et al. 2005).

Keel et al. (1999) defined full remission from bulimia nervosa utilizing both behavioral and psychological criteria. Full remission in narrow terms required freedom from disordered eating behaviors for at least six months, and additionally a lack of undue influence of weight and shape on how the subject felt about or evaluated herself. The broad definition required the absence of disordered eating behaviors for at least eight weeks, with no criteria for the influence of weight and shape on self-evaluation. Cogley and Keel (2003) suggested including the remission of cognitive symptoms in a standardized definition of recovery from bulimia nervosa. The authors showed that weight and shape concerns as assessed on the EDE provide a good indicator of general outcome, clinical levels on these subscales indicating a poor outcome, and lower levels indicating a better outcome in terms of depression, anxiety, body dissatisfaction and social adjustment.

Finally, Field et al. (1997) aimed to differentiate remission from recovery based on the probability of relapse. Bulimia nervosa is an episodic disorder,

and the length of abstinence from binge and purge behaviors predicts the risk of symptom reoccurrence. The authors suggest transition from remission to recovery after an asymptomatic period of one year.

2.2.2. CLINICAL RECOVERY

Estimates of general outcome are strongly influenced by the definitions used for remission, relapse and recovery, and length of follow-up time, as well as by the population in question, and the drop-out rate. Moreover, there is a gap between hospital-based outcome studies and naturalistic follow-up studies, the latter becoming more common only recently. It is difficult to generalize across studies, and there is wide variation in the estimates of clinical recovery. Below is a summary of the state of knowledge on rates of recovery, with an emphasis on studies reporting long-term outcomes.

Clinical recovery in anorexia nervosa

Steinhausen's (2002) meta-analysis summarizes the findings of 119 studies reporting the outcome of anorexia nervosa in a clinical setting. The length of the follow-up is strongly reflected in the estimated recovery rates: with <4-year follow-up 33% of the patients could be defined as recovered, but with >10-year follow-up the proportion had increased to 73%. Overall, 47% of the surviving patients were in full recovery, the disorder had improved in 34% of the patients, whereas 21% had developed a chronic course. The findings were slightly more optimistic when the core symptoms were considered separately: weight had normalized in 60% of the patients, menstruation had normalized in 57%, and normalization of eating behavior was observed in 47%.

Pike (1998) comprehensively reviewed the literature on the long-term course of anorexia nervosa, and found that the majority of outcome studies reported a good to intermediate outcome (defined by Morgan-Russell criteria) in 50% to 70% of individuals with the disorder, whereas it became chronic in 15% to 25% of the cases. Estimates of weight and menstruation restoration varied enormously, weight restoration occurring in 25% to 80% of individuals, and normalization of menstruation in 25% to 97%.

Keel & Brown (2010) reviewed the literature on the course and outcome of eating disorders published since 2004. The length of follow-up time ranged from 2.5 to 18 years, with varying remission rates. The study with the shortest follow-up duration yielded the lowest estimate for remission (29%), whereas the highest remission rate (84%) was reported with a 16-year follow-up.

Few studies report on the long-term outcome of anorexia nervosa in the community. Wentz et al. (2009) explored the 18-year outcome of anorexia nervosa based on a community screening of cases in Sweden. They found that 54% of individuals with a history of the disorder attained full symptomatic recovery over time (full recovery defined as being free of disturbed eating and compensatory behavior and attitudes with respect to food and shape for at least six months). According to Morgan-Russell criteria, 84% had a good outcome, 10% an intermediate outcome, and 6% a poor outcome in this study. An Australian study assessed the outcome of eating disorders utilizing population-based twin data with a mean follow-up time of 14.5 years after the onset (Wade et al. 2006). The authors utilized EDE subscales in their assessment of the general outcome, as Cogley & Keel (2003) suggest, finding that 49% of those in the anorexia nervosa group were asymptomatic at follow-up, and 84% had a good outcome.

Clinical recovery in bulimia nervosa

According to Keel & Brown's (2010) review, which only included studies conducted between 2004 and 2010, the remission rates of bulimia nervosa vary considerably depending on the length of the follow-up period. The lowest rates (27-28%) were reported with one-year follow-up, and high (up to 74% remission) rates were reported in studies with a 5-20-year follow-up.

An older study (Ben-Tovim et al. 2001) assessed the five-year outcome of bulimia nervosa based on the Morgan-Russell-Hayward criteria: at follow-up, 76% of those with a history of treatment had a good outcome, and only 2% had a poor outcome. It was further found in a clinical study conducted in the US that 73% of individuals with bulimia nervosa had reached full recovery at some point at seven years, but 35% of them had relapsed (Herzog et al. 1999).

As in the case of anorexia nervosa, community-based studies on bulimia nervosa are scarce. According to one such study with a 14.5-year follow-up (Wade et al. 2006), 48% of the women with a history of bulimia nervosa were asymptomatic at follow-up, and 76% had a good outcome.

Keel et al. (2000) aimed to quantify the effects of utilizing six different definitions of recovery on recovery rates in bulimia nervosa. The authors found that depending on the criteria, 38-47% of the patients were in full recovery at 11.5 years.

Clinical recovery in BED

Very few studies to date assess recovery from BED. In their review Keel & Brown (2010) refer to four RCTs with a one-year follow-up that reported remission rates

of between 25% and 80%. A German study, in turn, reported that 67% of former BED patients were in remission 12 years later (Fichter et al. 2008). Agras et al. (2009) gave a more optimistic picture, with 82% of those with an initial diagnosis of BED being in remission at four-year follow-up.

On a community level, Wade et al. (2006) found that after a mean follow-up of 14.5 years, 69% of the women with an initial diagnosis of BED had a good outcome.

2.2.3. ASSESSMENT OF SPECIFIC OUTCOMES

One way of assessing the outcome of eating disorders is on the global level. However, several authors have addressed the need for more elaborate assessment encompassing physical, psychological, and psychosocial adjustment (Pike, 1998, Jarman & Walsh 1999). Assessment of the global outcome lacks the fine-grained qualities inherent in the study of specific outcomes, including behavioral (e.g., recovery from restrictive eating habits, excessive exercise), physical (e.g., weight, menstruation, reproductive health), psychological (e.g., overall psychological health and well-being, attitudes towards food and body, thin-ideal internalization, self-esteem, psychosomatic symptoms, symptoms of anxiety and depression, psychiatric comorbidity), and social aspects (e.g., marital status, unemployment, educational level). The aim of this thesis is to consider the impact of eating disorders on young women's lives, with a special emphasis on their reproductive and psychological health.

2.3. REPRODUCTIVE HEALTH IN EATING DISORDERS

Eating disorders have an inherently strong impact on body weight, hormonal balance, and psychological health, and thus can potentially harm reproductive functions. This section describes how reproductive health is assessed in research, the pathways through which eating disorders could affect it, and the state of knowledge on reproductive health among those with an eating disorder.

2.3.1. ASSESSMENT OF REPRODUCTIVE HEALTH

Reproductive health is a term used to describe a wide range of aspects related to the reproductive function. The reproductive period of a woman's life begins at puberty and ends at menopause. Epidemiological studies consider various

indicators of reproductive health and their relations to exposure status. The menstrual cycle, fertility, and the numbers of infertility treatments, induced abortions, miscarriages and pregnancies are frequently assessed outcomes. Furthermore, more in-depth studies explore the course of pregnancy and delivery as well as indicators of perinatal health of offspring. Many of the older studies on reproduction among women with an eating disorder relied on self-reported data, whereas the more reliable research utilizes medical records (collected specifically for the study or routinely collected for register keeping).

2.3.2. REPRODUCTION IN EATING DISORDERS: BIOLOGICAL AND PSYCHOLOGICAL BACKGROUND

Eating disorders affect a multitude of bodily processes. No organ system is left intact in states of severe starvation. At the other end of the spectrum, obesity has equally dramatic effects. Psychological well-being is reflected in the hormonal balance of the body, contributing to the physical effects of eating disorders on reproductive health. Furthermore, psychological health has independent effects on markers of reproductive health. The biology and psychology of reproductive health in eating disorders are described below.

Physiological mechanisms of nutritional status and reproduction

The female reproductive system is sensitive to changes in the energy balance of the body. This is readily comprehensible, as pregnancy and lactation require a great expenditure of energy. The control mechanisms of reproduction are linked to the mechanisms involved in appetite and nutrition (Wade & Jones 2004). In periods of under-nutrition the body prioritizes essential processes such as cell maintenance, circulation, and neural activity, and it reduces energy expenditure on less important processes such as thermoregulation and growth. The least amount of energy is directed to expendable processes such as reproduction. Energy deprivation leads to the inhibition of the reproductive function through leptin, insulin, glucose, luteinizing hormone (LH), estradiol, epinephrine, nor-epinephrine, and neuropeptide Y signaling (Sawchenko et al. 1985, Clarke & Hendry 1999, Foster & Nagatani 1999, Welt et al. 2004). The effects are seen in ovulation, the menstrual cycle and fertility. The onset and maintenance of the menstrual cycle requires attainment of a certain minimal weight for height threshold (Frisch & McArthur 1974), even though later studies have shown that there is considerable individual variation in this threshold which reflects the amount of adipose tissue needed for a healthily functioning menstrual cycle.

Furthermore, in addition to affecting ovulation, the menstrual cycle and fertility, nutritional status also has profound effects on the course and outcome of pregnancy. An association between low pre-pregnancy BMI and miscarriage has been reported (Machonochie et al. 2007). There is also evidence of a V-shaped relationship between early-pregnancy BMI and the risk of fetal and infant death, with women of normal weight showing the lowest risk (Tennant et al. 2011). There is a body of literature supporting these findings. Nutritional status is reflected in patterns of intra-uterine growth and length of gestation. A recent meta-analysis showed that pre-pregnancy underweight increased the risk of small for gestational age (SGA) and low birth weight infants, and pre-pregnancy overweight or obesity increased the risk of large for gestational age (LGA) and high birth weight infants (Yu et al. 2013). Moreover, prematurity has been linked with underweight and obesity (Sebire et al. 2001, Cnattingius et al. 2013). These factors may have long-term consequences in offspring through metabolic programming (Eriksson et al. 2001) and other mechanisms.

Hormones and the reproductive system in eating disorders

Anorexia nervosa is marked by significant weight loss, often or always (depending on the diagnostic criteria) accompanied by a widespread endocrine dysregulation. This includes dysfunction of the hypothalamic-pituitary-gonadal-axis. A lowered serum concentration of LH and the follicle-stimulating hormone (FSH), accompanied by a lowered LH pulsatility have been found among those with anorexia nervosa (Devlin et al. 1989, Miller, 2011), one consequence of which is low estrogen levels. Leptin is a hormone produced in the adipose tissue, and its concentration in serum correlates with the adipose tissue mass (Ferron et al. 1997). Low levels of leptin signal the unavailability of energy and inhibit the normal reproductive function in rodent models. Leptin may play an important role in the development of hypothalamic amenorrhea (Ahima et al. 1996, Welt et al. 1996, Miller, 2011). There is also evidence of another mechanism of hypogonadotropic amenorrhea, in which elevated levels of cortisol lead to the suppression of gonadotropin-releasing hormone secretion (Barnea & Tal 1991, Misra et al. 2004). Hormonal and functional alterations of the reproductive system are accompanied by structural changes in the reproductive organs among women with anorexia nervosa. Studies based on pelvic ultrasound examination have shown that the severe weight loss associated with the disorder leads to a reduction in the size of the uterus and ovaries, closely resembling a pre-pubertal state (Treasure et al. 1988, Key et al. 2002).

Russell (1979) identified menstrual dysfunction as a consequence of bulimia nervosa in the first description of the illness. There is a body of literature supporting these findings (Cooper & Fairburn 1983, Gwirtsman et al. 1983, Gendall et al. 2000, Crow et al. 2002). As in the case of anorexia nervosa, lowered LH concentration and pulsatility have been observed in women with bulimia nervosa. Interestingly, these abnormalities have also been observed in women of relatively normal weight (Devlin et al. 1989, Schweiger et al. 1992, Weltzin et al. 1994). A relationship between bulimia nervosa and polycystic ovaries has also been shown (McCluskey et al. 1991, Raphael et al. 1995, Jahanfar et al. 1995). This association has been attributed to certain behavioral features of bulimia nervosa, namely binge eating, independently of adiposity (McCluskey et al. 1992, Morgan et al. 2002).

The hormonal alterations seen in women with BED are a mixture of those observed in obesity and bulimia nervosa. Obesity is known to cause menstrual irregularity, amenorrhea, and infertility (Reid & van Vugt 1987, Grodstein et al. 1994). Polycystic ovary syndrome is frequently seen among obese women. The disorder involves an increased secretion of LH and resistance to insulin. The resultant hyperinsulinemia stimulates androgen secretion in the ovaries and down-regulates the secretion of sex-hormone binding globulin in the liver, leading to anovulation and dysfunction of the hypothalamus-pituitary-gonadal axis. Furthermore, an excess production of estrogen and leptin in the adipose tissue debilitates the function of the hypothalamus-pituitary-gonadal axis (Koskela-Koivisto et al. 2012).

Interestingly, the problems in menstrual function observed in women with an eating disorder are not fully attributable to alterations in body weight. Restrictive eating in the absence of significant weight loss has been shown to affect the menstrual cycle (Halmi, 1974, Kreipe et al. 1989).

Psychological background

Eating disorders are accompanied by marked levels of stress, anxiety, and depressive symptoms, all of which affect the hormonal balance of the body. For example, increased levels of cortisol have repeatedly been documented in a proportion of depressed individuals (Young et al. 2001). Prevalent among women with an eating disorder, the presence of depressive symptoms could thus further contribute to the altered hormonal status. Feeling stressed has been identified as an independent risk factor for miscarriage (Machonochie et al. 2007). Furthermore, there is evidence of a link between maternal distress and low infant birth weight and prematurity (Rondó et al. 2003).

The psychological characteristics of eating disorders potentially have independent effects on markers of reproductive health. Certain personality traits that are prevalent among women with an eating disorder, such as impulsivity and novelty seeking in bulimia nervosa, may place these individuals at risk of unwanted pregnancies and induced abortions. The social isolation associated with anorexia nervosa may alter the patterns of entering into intimate relationships and having children. Moreover, the disorder itself may delay processes related to reproduction.

2.3.3. REPRODUCTIVE HEALTH OUTCOMES IN EATING DISORDERS

Fertility

The high rate of menstrual problems among women with an eating disorder has led to speculation that they may have difficulties in conceiving. Indeed, irregular menstruation among such women has been linked with childlessness (Maxwell et al. 2010). There is also growing evidence of fertility problems among these women. Easter et al. (2011) found recently, in a large population-based study conducted in England, that women with anorexia nervosa or bulimia nervosa were more likely to have seen a doctor for lifetime fertility problems, were also more likely to take longer than six months to conceive, and were more likely to have conceived the current pregnancy following fertility treatment. These findings are in line with the results of previous studies showing a high prevalence of eating disorders (up to 20%) among women seeking treatment for infertility (Stewart et al. 1990, Freizinger et al. 2008). Moreover, according to a population-based study conducted in the Netherlands (Micali et al. 2013), women with bulimia nervosa had 2.3-fold odds of having undergone fertility treatment compared to women without psychiatric disorders. However, in most cases gonadal functioning and fertility normalize after recovery (Miller, 2011).

Irregular or absent menstruation may lead to mistaken beliefs about fertility and subsequent unwanted pregnancies. It has been found in several studies that women with anorexia nervosa or bulimia nervosa are more likely to report that their pregnancy was unplanned (Morgan et al. 1999, Bulik et al. 2010, Easter et al. 2011).

Data on the prevalence and frequency of pregnancies are inconsistent, some studies showing comparable pregnancy rates among women with anorexia nervosa or bulimia nervosa and the general population (Bulik et al. 1999, Crow et al. 2002), whereas an older study reported a reduction to one third of the

expected rate in anorexia nervosa (Brinch et al. 1988). In the latter study, conducted in Denmark, the number of children among anorexia nervosa probands who became mothers did not differ from the average number of children per woman at the time.

Prenatal period

Anorexia nervosa and bulimia nervosa have both been linked with an increased risk of miscarriage and induced abortion (Abraham, 1998, Morgan et al. 2006, Micali et al. 2007, Bulik et al. 2007, 2010). These outcomes have not previously been assessed in women with BED. However, BED is often accompanied by obesity, which has been shown to carry an elevated risk of miscarriage and of stillbirth or early neonatal death (Metwally et al. 2008, Tennant et al. 2011).

Pregnancies among women with anorexia nervosa and bulimia nervosa are more likely to be complicated by anemia and genitourinary tract infections than pregnancies among women without an eating disorder (Bansil et al. 2008, Koubaa et al. 2005). Furthermore, increased risks of higher weight gain and hyperemesis gravidarum have been shown among those with bulimia nervosa (Bulik et al. 2009, Abraham et al. 1998). Research on pregnancy among women with BED is still very limited. Studies on obesity and pregnancy show that gestational diabetes and genitourinary tract infections are common among obese pregnant women (Chu et al. 2007, Sebire et al. 2001b). Binge eating persists during pregnancy in many women with BED, which may lead to greater gestational weight gain and related complications (Bulik et al. 2007, 2009, Siega-Riz et al. 2011).

Obstetric complications

There is evidence of a link between several adverse obstetric complications and eating disorders, although some complications appear to occur less frequently among women with anorexia nervosa compared to controls. An increased risk of suspected fetal distress and slow progress of delivery have been reported in anorexia nervosa (Micali et al. 2012, Bulik et al. 2009), whereas the risk of instrumental delivery is decreased (Ekéus et al. 2006). The evidence on cesarean sections in anorexia nervosa is contradictory, some studies showing an increased (Bulik et al. 1999) and others showing a decreased risk (Bulik et al. 2009, Ekéus et al. 2006). In bulimia nervosa the evidence is based on a lower number of publications. An increased risk of cesarean section and breech presentation has been reported (Lacey & Smith 1987, Bulik et al. 2009), whereas the risk of slow progress of delivery is decreased (Bulik et al. 2009). An elevated risk of cesarean

section has been reported among those with BED (Bulik et al. 2009), as also frequently seen in obesity (Shepard et al. 1998, Sebire et al. 2001b, Ehrenberg et al. 2004).

Perinatal health of offspring

Sporadic reports of severe perinatal health consequences, such as the birth of SGA and low birth weight infants, prematurity, and high perinatal mortality among women with anorexia nervosa, emerged in the 1980s (Brinch et al. 1988, Treasure & Russell 1988). More recent population-based studies give a more optimistic view (Ekéus et al. 2006, Bulik et al. 2009, Micali et al. 2012). According to a recent meta-analysis, the offspring of women with either current or past anorexia nervosa had a lower mean birth weight compared to the offspring of control women, with a mean difference of about 200 grams (Solmi et al. 2014). Comparable infant birth weights among mothers with bulimia nervosa and healthy control women have been reported (Micali et al. 2007, 2012). SGA and LGA are clinically relevant parameters of fetal growth. Unfortunately, only a few studies exploring weight and growth among infants of mothers with an eating disorder have included these parameters. There is evidence of an increased risk of giving birth to SGA infants in the joint group of women with anorexia nervosa or bulimia nervosa (Koubaa et al. 2005), whereas Bulik et al. (2009) reported a significantly higher birth weight and higher risk of LGA in the offspring of women with BED.

The literature on prematurity in eating disorders is inconsistent, with a number of studies showing a general elevated risk of preterm birth (Bansil et al. 2008, Sollid et al. 2004), or specifically with regard to anorexia nervosa (Brinch et al. 1988, Bulik et al. 1999), bulimia nervosa (Morgan et al. 2006), and BED (Bulik et al. 2009). In contrast, Bulik et al. (2009) reported a lower risk of preterm birth in anorexia nervosa and bulimia nervosa.

Perinatal health problems have the potential to affect the later development of the child, and to increase the risk of several illnesses (Micali & Treasure 2009). Elevated risks of a number of psychiatric and somatic illnesses, such as depression, schizophrenia, anorexia nervosa, diabetes, obesity, metabolic syndrome, coronary heart disease, cerebral palsy, and visual and hearing impairments have been found among individuals with non-optimal birth characteristics (Costello et al. 2007, Nilsson et al. 2005, Cnattingius et al. 1999, Roseboom et al. 2000, Ravelli et al. 1999, Sydsjö, 2011). Only scant findings on the development of the offspring of mothers with an eating disorder exist to date. An older study showed no impairment in reaching developmental milestones between one and four years

of age (Waugh & Bulik 1999), but a recent study reported delayed neurocognitive development at the age of five among children born to mothers with a previous eating disorder (Koubaa et al. 2013).

2.4. PSYCHOLOGICAL OUTCOMES IN EATING DISORDERS

Disturbances in body image and satisfaction with one's body are among the core psychological aspects of eating disorder symptomatology (Steinhausen & Vollrath 1993). The effects also extend to mood, anxiety, self-esteem, perfectionism, life satisfaction, and general psychological well-being, all of which can be measured quantitatively using validated instruments. These symptoms and traits are severe enough in some individuals to apply a dichotomous psychiatric classification, yielding additional psychiatric diagnoses as described in the section on comorbidity.

2.4.1. PSYCHOLOGICAL HEALTH AND BODY WEIGHT

There is a substantial body of literature demonstrating a relationship between BMI and psychological health. Most studies focus on determining the effects of obesity, and thus examine linear trends in the association. There is evidence to suggest that obese individuals are more likely to be depressed and to have anxiety disorders than non-obese individuals (Scott et al. 2008, Mathers et al. 2009, de Wit et al. 2010, Luppino et al. 2010), but less is known about low BMI and psychological health. Ali & Lindsröm (2006) explored the relationship between psychological health and BMI (measured on the General Health Questionnaire, GHQ12) among 1967 young women, and found that underweight women were more likely to have poor self-reported psychological health than those of normal weight. Zhao et al. (2009) reported similar findings, underweight, overweight, and obese women showing an elevated risk of depression and anxiety. Other studies have reported positive linear associations between BMI and depression, as well as other common mental disorders in women (Bjerkset et al. 2008, McCrea et al. 2012). Whereas well-being was optimal among women of normal weight in most studies, an Australian study reported significantly lower psychological distress (measured on the Kessler 10 scale) in overweight female participants compared to those of normal weight (Goldney et al. 2009).

2.4.2. PSYCHOLOGICAL OUTCOMES

Most studies on the outcome of eating disorders have been conducted in clinical settings, and only a few are population-based with long-term follow-up. Given the scope of the present thesis, the psychological outcomes derived from treatment trials are not reported here. However, the results of some clinical studies with long follow-ups are discussed to demonstrate psychological recovery across different settings. Overall, surprisingly few outcome studies apart from treatment trials have given detailed information on psychological recovery obtained by continuously measured, validated instruments.

Population-based studies

An Australian population-based study on twins assessed the outcome of eating disorders, on average, 14 years after the onset of the illness (Wade et al. 2006). Women with anorexia nervosa continued to have stronger weight and shape concerns, lower dietary restraint, and lower current BMI relative to women without lifetime eating disorders. Women with bulimia nervosa continued to have stronger eating concerns and dietary restraint, and women with BED to have higher dietary restraint. According to a prospective cohort study conducted in Sweden, individuals with a history of anorexia nervosa remained significantly more symptomatic than controls on several measures, such as dietary restriction, concern about body weight, worry about appearance, and Eating Attitudes Test (EAT) scores in a five-year follow-up (Gillberg C et al. 1994, Gillberg IC et al. 1994, Råstam et al. 1995). Fairburn et al. (2000) studied the natural course of bulimia nervosa and BED in a community setting in England. Over a period of five years, there was significant improvement in dietary restraint, concern about shape, weight and eating (measured on the EDE) among those with bulimia nervosa and BED. Self-esteem scores (as measured on the Robson self-esteem scale) did not improve over time among women with bulimia nervosa, but did among those with BED. There was no improvement in social adjustment. No comparison group was available for this study.

Clinical studies

Women with a history of treatment for anorexia nervosa have been shown to retain characteristics such as perfectionism, cognitive restraint, and a preoccupation with symmetry and exactness even after recovery (Srinivasagam et al. 1995, Bulik et al. 2000). In a study conducted in New Zealand with a follow-up of 12 years after referral for treatment for anorexia nervosa, women with a history

of the illness had higher scores than controls on the EDI perfectionism and drive for thinness subscales, and on the Three Factor Eating Questionnaire Scale (TFEQ) cognitive restraint and hunger subscales (Sullivan et al. 1998, Bulik et al. 2000). Fichter et al. (2006) assessed the outcome of clinical anorexia nervosa with follow-up points two, six and 12 years after the end of treatment. Scores on the Symptom checklist (SCL-90), EDI and the Structured Inventory for Anorexic and Bulimic Syndromes (SIAB-EX) were assessed as a function of time and as compared to normative means from the German general population. After an initial decline in psychological pathology, an increase was observed during the first two years, followed by a steady decline during the follow-up period until 12 years. However, even at the 12-year follow-up assessment, the SCL-90 scores remained higher than the normative means. Furthermore, patients in clinical recovery demonstrated higher levels on body image and slimness ideal and general psychopathology and social integration subscales of SIAB-EX as compared to healthy controls.

Fichter & Quadflieg (1997, 2004) assessed the outcome of bulimia nervosa with two-, six-, and 12-year follow-up. They found the total EDI scores to be worse at the two-year follow-up than at discharge, but at six years, the scores had reached again the discharge level. The scores significantly improved further across all EDI subscales at the 12-year follow-up. Body image and ideal of slimness as well as bulimic behavior (as measured on the Structured Expert Interview for Anorexic and Bulimic Syndromes, SIAB-EX) were lower at the 12-year follow-up than at any of the previous time points, yet remained higher than among healthy controls. Keel et al. (1999) assessed the outcome of bulimia nervosa with a mean follow-up time of 11.5 years. The patients' scores on the Body Shape Questionnaire at follow-up were similar to the scores of a community sample of women.

Improvements in measures of depression, anxiety and obsessionality were reported in BED patients over a six-year follow-up period by a German study (Fichter et al. 1998). At the 12-year follow-up (Fichter et al. 2008), despite the significant reductions in symptoms over time, most SIAB-EX scores (such as body image and slimness ideal, general psychopathology and social integration, and sexuality) remained elevated, even in clinically recovered BED patients, as compared to healthy controls. There was improvement in all the EDI subscales over time, but no comparisons to healthy controls were made. Similar findings were observed in the SCL-90 scores.

2.5. FRAMEWORK OF THE STUDY

Eating disorders affect women mainly during their fertile years. It is well documented that such disorders may impair reproductive and psychological health. The magnitude of these effects remains unclear. Furthermore, it is not known how the outcomes differ between clinical and population-based settings. Previous studies on reproductive health outcomes have yielded conflicting findings, early small-scale clinical studies suggesting adverse outcomes, and more recent population-based studies depicting a brighter picture. These findings need replication within a large study population and with well-recorded data on outcomes. On the other hand, little is known about the natural course of eating disorders in the population, or whether these illnesses leave a scar on the psychological well-being of the sufferer later on in life. The aim of this study was to enhance understanding of reproductive and psychological outcomes of eating disorders from both the clinical and the population-based perspective. For the population-based approach, a twin study design was utilized to optimize the matching of the controls. Comparing women with an eating disorder, their unaffected twin sisters, and healthy women facilitated assessment of whether the effects were characteristic of the eating disorder itself or of the underlying psychological vulnerability, which may also be present in the twin sisters.

3. AIMS OF THE STUDY

Eating disorders are thought to be severe and relatively long-standing. However, their natural course remains poorly understood. Furthermore, little is known about the impact they have on reproductive and psychological health, and how it may differ in clinical and population-based settings.

To address these issues, the main aims of this study were:

1. To assess how eating disorders are related to general reproductive health outcomes, such as number of children, pregnancy, miscarriage, and induced abortion in women treated for an eating disorder (I)
2. To examine the risk of pregnancy and obstetric complications and adverse perinatal health outcomes in women treated for an eating disorder (II)
3. To characterize the relationship between BMI and psychological well-being in the general population and in women with lifetime eating disorders, and to assess the cross-sectional levels of general psychological well-being across the exposure groups (III)
4. To understand the time-dependent psychological and social impact of anorexia nervosa and bulimia nervosa on young women's lives (IV and V)

4. METHODS

4.1. PARTICIPANTS

4.1.1. CLINICAL SAMPLE

Female patients treated at the eating disorder clinic of Helsinki University Central Hospital during 1995-2010 were included in the sample (data available for 2257 women under 50 years of age). Given the focus on the fertile period of the women's lives, patients who were ≥ 50 years old at the beginning of the follow-up were excluded. Four matched controls were retrieved from the Central Population Register for each patient ($n=9\ 028$). Matching was done for sex, age, and geographical area. This matching was used for Study I, whereas for Study II all the controls were grouped together as unexposed women, the matching no longer being valid in this study design. General descriptive statistics are shown in Table 4, and Figure 2 gives the general outline of the study.

Table 4. General descriptive statistics of the clinical sample (used in papers I & II).

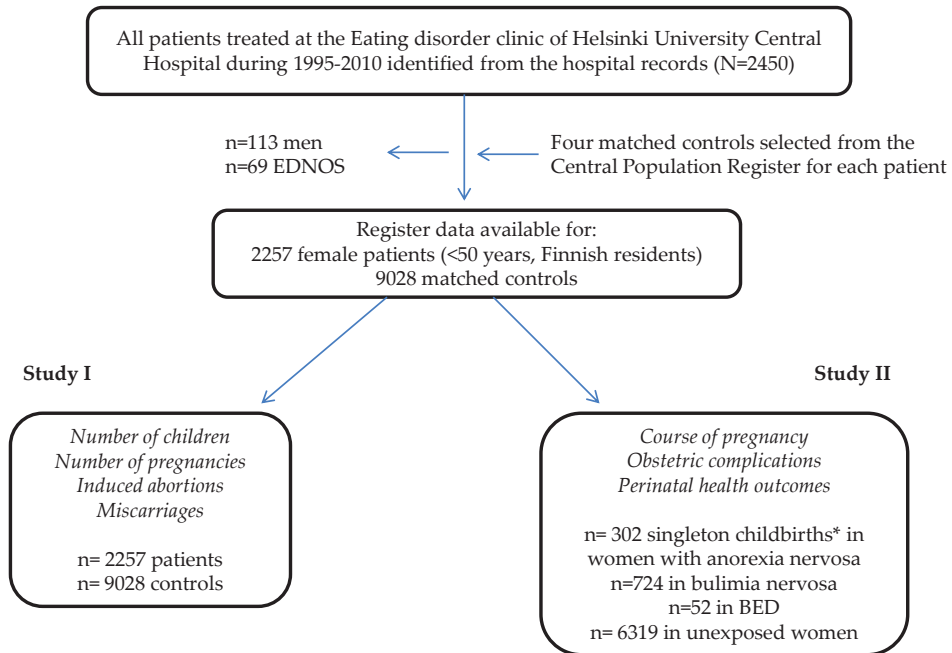
		Patients (n=2257)	Controls (n=9028)
Age at the beginning of follow-up	Years (IQR)	25.3 (20.1-28.4)	Matched
Marital status at follow-up	n (%)		
	Single	1382 (61.3%)	4734 (52.4%)
	Married	651 (28.9%)	3585 (39.7%)
	Divorced	223 (9.9%)	709 (7.9%)
Number of children at follow-up	n (%)		
	0	1395 (61.8%)	4422 (49.0%)
	1	343 (15.2%)	1594 (17.7%)
	2	332 (14.7%)	1989 (22.0%)
	≥ 3	187 (8.3%)	1023 (11.3%)

The attending physician at the eating disorder clinic set the diagnoses upon the patient's admission. ICD-10 criteria were utilized for the diagnosis of AN (F50.0, $n=502$), atypical AN (F50.1, $n=365$), BN (F50.2, $n=786$), and atypical BN (F50.3, $n=445$). Cases with a diagnosis of EDNOS ($n=69$) were not included in this study

due to the heterogeneity of this patient group and the high levels of comorbidity. DSM-IV research criteria were utilized for the diagnosis of BED (n=149). Of the patients, 19.3% had received inpatient treatment. Inpatient treatment was most common among patients with AN (45%).

The individual follow-up period of each patient and the respective controls extended from the day of admission to the clinic until the end of the follow-up period (December 31st 2010), death (n=40 patients, n=37 controls), moving abroad (n=70 patients, n=233 controls), or reaching the age of 50 years (n=107 patients, n=449 controls).

The eating disorder clinic of Helsinki University Central Hospital provides specialized assessment and treatment of adults with eating disorders for a catchment area of approximately 1.5 million people (the total Finnish population being 5.4 million in 2013). Furthermore, referrals for inpatient treatment are taken from other parts of Finland. Most treatment is provided as outpatient care, but day patient and inpatient treatments are available in severe cases.



*Childbirth defined as live or stillbirth with gestational age ≥ 22 weeks or birth weight ≥ 500 grams.

Figure 2. The flow chart of the clinical sample with the parts relevant to Studies I and II.

4.1.2. FINNTWIN16

FinnTwin16 is a nationwide longitudinal cohort study of Finnish twins and their families (Kaprio, 2006). Twins born during 1975–1979 were identified through the Population Register Centre of Finland. Data collection started between 1991 and 1995 when all live Finnish twins were mailed a baseline questionnaire around their 16th birthday. Follow-up questionnaires were sent to the twins when they were aged 17, 18.5, 22–28 years, and in their mid-thirties. The parents participated by filling in questionnaires about themselves and the twins’ childhood at baseline. Studies III-V used data from the fourth wave of questionnaires (collected on each birth cohort semi-annually from the beginning of 2000 to mid-2002). The wave 4 questionnaire was sent to all the twins in the 1975-1979 birth cohorts irrespective of previous participation, unless they had indicated that they did not wish to be contacted. The twins were asked to assess their general and mental health, various health behaviors, dieting and weight control behaviors, social relationships, well-being, and satisfaction in various domains of life. A questionnaire screen for eating disorders was also included. About 90% of the invited women participated in wave 4 (mean age 24.5 years, SD 0.9), yielding a sample of 2825 women. Table 5 contains the general descriptive statistics, and Figure 3 shows the general outline of the study.

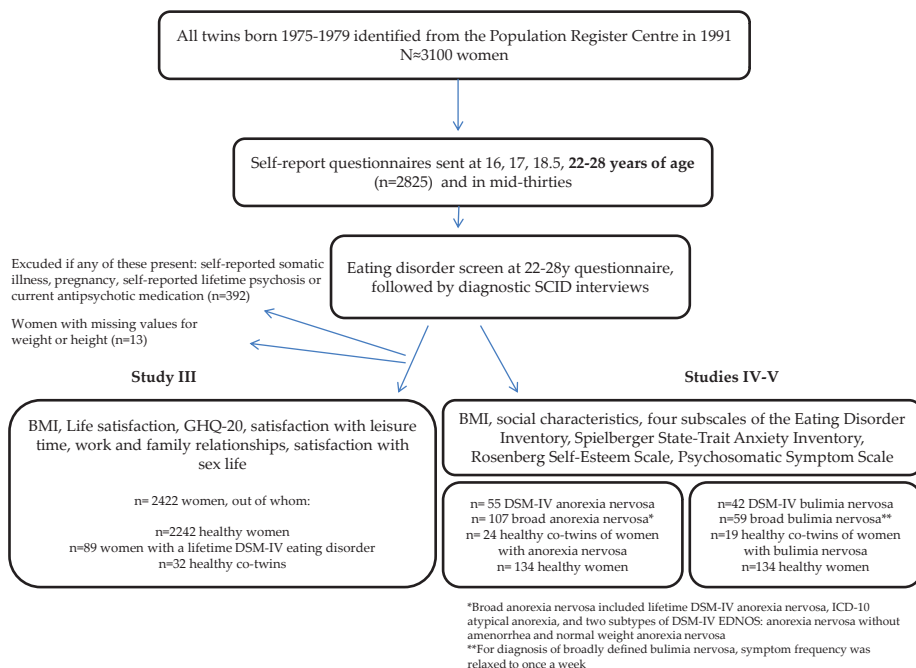


Figure 3. The flow chart of FinnTwin16 with the parts relevant to Studies III-V.

Table 5. General descriptive statistics of the female respondents to the *FinnTwin16* wave 4 questionnaire (used in Study III).

		All women	Healthy women	Women with a lifetime eating disorder	Healthy co-twins of the women with an eating disorder
N		2422	2242	89	32
Age	Years (SD)	24.5 (0.9)	24.5 (0.9)	24.3 (0.8)	24.3 (1.1)
Body mass index	mean (SD)				
Current		22.2 (3.5)	22.2 (3.5)	22.7 (3.8)	21.9 (2.4)
Minimum at current height		20.0 (2.8)	20.0 (2.7)	18.8 (3.3)	19.6 (1.8)
Subjective ideal at current height		20.8 (1.9)	20.8 (1.9)	20.6 (2.0)	20.8 (1.6)
Educational level	% (n)				
Compulsory school		4.2% (101)	4.3% (96)	3.4% (3)	2.7% (1)
Vocational secondary education		31.7% (767)	32.4% (727)	23.6% (21)	10.8% (4)
Academic secondary education		16.5% (398)	16.2% (362)	21.4% (19)	16.2% (6)
Tertiary education		47.7% (1154)	47.1% (1056)	51.7% (46)	70.3% (26)
Smoking status*	% (n)				
Non-smoker		61.5% (1430)	61.7% (1323)	66.3% (59)	54.1% (20)
Light smoker		24.9% (579)	24.6% (528)	23.6% (21)	27.0% (10)
Heavy smoker		13.6% (315)	13.7% (293)	10.1% (9)	18.9% (7)

*Non-smoker defined as a never or former smoker; a heavy smoker if 10 or more cigarettes are consumed per day, and a light smokers if less than 10 cigarettes a day, including occasional smokers

4.2. MEASURES

4.2.1. CLINICAL SAMPLE

All outcome data for the clinical sample were obtained from national registries. Four registers were used for this study, namely the Central Population Register, the Medical Birth Register, the Register on Induced Abortion, and the Hospital Discharge Register.

Reproductive health outcomes

The number of biological children was retrieved from the Central Population Register, which records the number of all live-born children. Data on childbirths were drawn from the Medical Birth Register, which keeps a record of all live and stillbirths with gestational age ≥ 22 weeks or birth weight ≥ 500 grams. The Register on Induced Abortion provided information on induced abortions. Data on miscarriages were retrieved from the Hospital Discharge Register using ICD-10 diagnosis codes from O00 to O03 to identify miscarriages and ectopic pregnancies. Data on infertility treatments are included in the Medical Birth Register. Thus, information on infertility treatments was available only for cases resulting in childbirth. The data quality has been shown to be good for the utilized registries (Gissler et al. 1995, 1996).

Pregnancy outcomes

The following pregnancy outcomes were included in the study: gestational diabetes (pathological oral glucose tolerance test), initiation of insulin treatment during pregnancy, anemia, antenatal corticosteroid treatment, eclampsia, and pregnancy related ICD-10 diagnoses of the mother (recorded since January 1st 2004). The ICD-10 diagnoses included: preeclampsia (O14), hypertension (O13, O16), slow fetal growth (O36.5, P05.0, P05.1, P05.9), fast fetal growth (O36.6), oligohydramnion (O41.0), infection of amniotic fluid (O41.1), premature rupture of membrane (O42), any placental disorder (O43, O44, O45, O73 and a separate check-box on placenta previa in the Medical Birth Register data-collection form), horror partus (O99.80), premature contractions (O47), proteinuria (O12.1), hyperemesis gravidarum (O21.0, O21.1, O21.2, O21.9), any vein complication (O22), urogenital infection (O23), hepatogestosis (O26.6), exhaustion (O26.82), symphyseolysis (O26.7), cervix insufficiency (O34.3), suspected fetal injury due to alcohol/drugs (O35.4, O35.5), and suspected fetal hypoxia (O36.3).

Obstetric outcomes

The obstetric outcomes under study included induction of labor, asphyxia, breech presentation, epidural anesthesia, use of forceps/vacuum, delivery by cesarean section, delivery by elective cesarean section, duration of the first and the second stage of labor (in minutes), and delivery related ICD-10 diagnoses (recorded since January 1st 2004). The studied diagnoses included fetal distress (O68), rupture of the perineum (O70), and maternal distress (O75.0).

Perinatal health outcomes

The following perinatal outcomes were included in the study: perinatal death (from 22 weeks of gestation), gestational age (obtained by fetal ultrasound examination at the first visit to maternity care), premature birth (<37 weeks of gestation), very premature birth (<28 weeks of gestation), birth weight (in grams), low birth weight (<2500 grams), very low birth weight (<1500 grams), small for gestational age (SGA; using cut-off points defined for the Finnish population (Pihkala et al. 1989), large for gestational age (LGA), low Apgar score at 1 minute (≤ 6), very low Apgar score at 1 minute (≤ 3), assisted ventilation, resuscitation, and neonatal monitoring.

4.2.2. FINNTWIN16

Anthropometrics

Body Mass Index (BMI, kg/m²) was calculated from self-reported height (m) and weight (kg). The correlation of measured and self-reported BMI was assessed in a subset of the cohort (n=566), yielding a correlation of 0.89 (Mustelin et al. 2009). Measurement was done a median of 650 days after the self-report. Thus, the correlation may have been lower than if the measurement and self-report had been acquired at the same time point.

Life Satisfaction

Allardt's four-item scale of life satisfaction (1973) measures levels of interest, happiness, easiness and loneliness of life. The total score ranges from four to 20, and higher scores indicate higher levels of dissatisfaction. Reliability of the scale was good in this sample (Cronbach's alpha 0.71). Life satisfaction scale has been shown to correlate strongly with Beck Depression Index (Koivumaa-Honkanen et al. 2004), and to predict the risk of suicide (Koivumaa-Honkanen et al. 2001).

General Health Questionnaire (GHQ-20)

GHQ-20 is a 20-item scale designed for screening psychological distress in community settings and non-psychiatric clinical settings (Goldberg 1972, Penninkilampi-Kerola et al. 2006). The total score ranges from 20 to 80, higher scores indicating an elevated level of psychological distress. GHQ-20 had excellent reliability in the sample (Cronbach's alpha 0.91).

Satisfaction with various life domains

Several questions assessing satisfaction with specific life domains were included in the wave 4 questionnaire. They had face value in assessing general satisfaction in life. Given the high correlation among the items satisfaction with leisure time, work, and family relationships, a composite variable was created, higher scores indicating higher levels of dissatisfaction. The Cronbach's alpha was 0.70.

Satisfaction with sex life was included in the questionnaire as a single-item question, graded on a five-point Likert-scale, higher scores indicating greater dissatisfaction.

Social characteristics

Occupation, education, parity, and marital status were used to assess the social outcomes of anorexia nervosa and bulimia nervosa.

Eating Disorder Inventory

The Eating Disorder Inventory, second revision (EDI-2) is a self-report instrument designed to assess psychological and behavioral traits related to eating disorders (Garner, 1991). Four sub-scales were studied: drive for thinness (7 items, sum score 7-42, Cronbach's alpha 0.79 in women), bulimia (7 items, sum score 7-42, Cronbach's alpha 0.54), body dissatisfaction (9 items, sum score 9-54, Cronbach's alpha 0.88), and perfectionism (6 items, sum score 6-36, Cronbach's alpha 0.85). These scales assess the essential characteristics of anorexia nervosa and bulimia nervosa.

Spielberger State-Trait Anxiety Inventory

The State-Trait Anxiety Inventory (STAI) is a commonly used measure of state and trait anxiety (Spielberger et al. 1983). The state anxiety sub-scale (sum score 20-80, Cronbach's alpha 0.93 in women) assesses current anxiety, whereas the trait anxiety sub-scale (sum score 20-80, Cronbach's alpha 0.91 in women) measures anxiety level as a personal characteristic. The STAI is used in clinical and research settings to diagnose anxiety and to distinguish it from depressive syndromes.

Rosenberg Self-Esteem Scale

The ten-item Rosenberg Self-Esteem Scale (Rosenberg, 1965) was used to assess self-esteem. Each item is measured on a four-point Likert-scale, yielding a total sum score ranging from 10 to 40. The Cronbach's alpha was 0.90 in women.

Psychosomatic Symptom Scale

The Psychosomatic Symptom Scale includes six items: stomach aches, tension and nervousness, difficulties in falling asleep or nightly awakenings, headache, lower back pain, and pain in the neck and shoulder area (Aro et al. 1987). The four response alternatives assessed the frequency of the symptoms (total sum score from 6 to 24, Cronbach's alpha 0.67 in women).

4.2.3. SCREENING FOR EATING DISORDERS IN FINNTWIN16

Questionnaire screen

The wave 4 questionnaire included a few simple questions to detect self-reported eating disorders: "Have you ever had anorexia?", "Have you ever had bulimia?", and a question on the presence of purging behaviors within the past three months. The BMI and EDI-2 were also used for screening eating disorders in the cohort. Women were considered screen positive as follows: if they answered "Yes" or "Not sure" to the questions on self-reported eating disorders; reported purging behaviors within the previous three months; reported a current BMI of <17.6 kg/m², or had an EDI-bulimia subscale score of ≥97th percentile; or reported a lifetime minimum BMI of >17.6 kg/m² combined with either an EDI-Body dissatisfaction score >70th percentile or an EDI-Drive for thinness score ≥90th percentile (Keski-Rahkonen et al. 2006).

Diagnostic interviews

Screen-positive women (n=292), their same-sex co-twins (n=130), and a random sample of 105 screen-negative female twin pairs (n=210 women) were invited to participate in diagnostic telephone interviews. Trained clinicians with experience from the eating disorder clinic of Helsinki University Central Hospital (five medical doctors and one registered nurse) conducted the interviews. The short version of the SCID-I (First et al. 2002) was administered to obtain current and lifetime DSM-IV diagnoses of anorexia nervosa, bulimia nervosa, binge eating disorder, major depression, and obsessive-compulsive disorder, and the temporal occurrence of these diagnoses. This information was also used to define "broad anorexia" and "broad bulimia", utilized in Studies IV-V. Broad anorexia nervosa included DSM-IV anorexia nervosa, ICD-10 atypical anorexia, and two subtypes of DSM-IV EDNOS: anorexia nervosa without amenorrhea and normal weight anorexia nervosa. The symptom-frequency criterion was relaxed to once a week

for defining broad bulimia nervosa. Of all the invited women, 85.2% participated in the diagnostic interviews: only 1.9% refused to be interviewed, and 12.9% could not be reached (Keski-Rahkonen et al. 2006).

Definition of clinical recovery

Clinical recovery was defined in Studies IV and V as the restoration of weight (self-reported BMI ≥ 19 kg/m²) and menstruation and the absence of bingeing and purging for at least one year prior to assessment. Assessment of recovery rates was based on recovery status five years after the onset of anorexia nervosa or bulimia nervosa and at the time of the diagnostic interview. Clinical recovery could not be assessed in the clinical sample (I-II) due to the data structure of the existing registries.

4.3. STATISTICAL METHODS

4.3.1. GENERAL DESCRIPTIVE METHODS

The relationship between independent and dependent variables was investigated using cross-tabulations, Pearson's chi-squared test of independence, and Fisher's exact test when the assumptions for chi-squared test were not met. Two-tailed t-test was used to compare the differences in means. Analysis of variance was used in the comparisons of physical and social characteristics between cases and comparison groups in Studies IV and V. Stata statistical software versions 9.2, 11.0, 12.1 and R program (Stata Corporation, College Station, TX, USA and R Development Core Team, Vienna, Austria 2011) were used for all the analyses.

4.3.2. REGRESSION MODELS

Regression models were used to investigate linear and non-linear associations between outcomes and predictors. Linear regression modeling was used for normally distributed continuous variables, logistic regression for categorical variables, multinomial logistic regression for categorical variables with more than two discrete outcomes, and Poisson regression for count data on rare events. The Poisson approach allowed the individual follow-up time to be accounted for in Study I. Zero-inflated Poisson model was used for variables with a high number of observations receiving the value zero (number of children in Study II). Associations between BMI and subjective well-being in Study III were explored

by means of a linear regression, with both a linear and a quadratic term for BMI, thus investigating primarily non-linear regression functions. If the quadratic term (BMI-squared) was non-significant, linear association was studied. A random intercept linear regression model was used to examine trends toward full psychological recovery as a function of time (Studies IV and V).

4.3.3. SURVIVAL MODELS

The Kaplan-Meier survival method was used to investigate clinical recovery rates for DSM-IV and broad anorexia nervosa and bulimia nervosa, and the log-rank test to compare the differences between the curves across the study groups.

The clustering of data was taken into account in all the analyses: the clustering of births within mothers, and the clustering of observations within twin pairs in the twin data (Williams et al. 2000). This procedure takes into account the tendency of clustered observations to be more alike than individual observations. The assumption of independence of observations present in common statistical methods would be violated without this correction when clustered data are used.

5. RESULTS

5.1. CLINICAL RECOVERY AND BODY WEIGHT

5.1.1. CLINICAL RECOVERY

The clinical recovery rates five years after the onset of illness were 67% for DSM-IV anorexia nervosa and 69% for broad anorexia nervosa (IV). The five-year recovery rates were 57% for DSM-IV bulimia nervosa and 55% for broad bulimia nervosa (V).

5.1.2. BODY WEIGHT

The mean pre-pregnancy BMI (kg/m²) in the clinical sample was 20.2 (SD 2.6) among women with broad anorexia nervosa, 23.5 (SD 4.9) among women with broad bulimia nervosa, 28.5 (SD 9.4) among women with BED, and 23.5 (SD 4.3) among unexposed women. BMI was significantly lower among women with broad anorexia nervosa relative to unexposed women ($p < 0.001$, $t(3519) = 10.1$) and higher among those with BED ($p < 0.001$, $t(3356) = -4.2$). In the clinical sample, information on body weight and height prior to pregnancy was available only for those who gave birth (Study II).

In the FinnTwin16 sample, the mean BMI reported in the 22-28-year questionnaire was similar in healthy women (22.2, SD 3.5), women with a lifetime diagnosis of DSM-IV eating disorder (22.7, SD 3.8), and their healthy twin sisters (21.9, SD 2.4) (Study III). However, there were considerable differences in weight among women with different diagnoses, current BMI being lowest among women with lifetime diagnoses of both anorexia nervosa and bulimia nervosa (20.1, SD 1.2) and highest among those with BED (26.2, SD 3.7). Women with anorexia nervosa had a mean BMI of 21.2 (SD 4.3) and those with bulimia nervosa a BMI of 23.6 (SD 4.3).

The mean BMI of women with an eating disorder in clinical recovery was compared to that of their unaffected twin sisters in Studies IV and V. There were no significant differences in weight between women with DSM-IV anorexia nervosa in clinical recovery and their twin sisters (mean BMI 21.7, SD 3.0 and

21.8, SD 2.7, respectively), or between women with DSM-IV bulimia nervosa in clinical recovery and their twin sisters (mean BMI 22.7, SD 3.2 and 23.1, SD 2.4, respectively).

5.2. GENERAL REPRODUCTIVE HEALTH OUTCOMES

5.2.1. PARITY

In the clinical sample, remaining childless was more common among patients compared to controls (OR 1.86; 95% CI 1.62–2.13, $p < .001$) (Study I). Of all patients, 61.8% had no children, whereas the corresponding percentage was 49.0% in controls. However, among those who had children, the number of offspring did not differ significantly between the two groups. The most prominent differences were observed among women with anorexia nervosa, 79.9% of them having no children at the end of the follow-up period, compared to 59.7% among controls.

No differences in parity were observed between women with lifetime broad anorexia nervosa or bulimia nervosa and their unaffected twin sisters in the FinnTwin16 sample (Studies IV-V). The findings were similar for the currently ill probands and those who were in clinical recovery.

5.2.2. PREGNANCIES

Pregnancies occurred less frequently among women who had received treatment for an eating disorder than among controls (I). The rates of having at least one pregnancy during the follow-up period and overall pregnancy rates were analyzed, the aim being to assess whether the patients differed from the controls in patterns of being pregnant at all and in the frequency of pregnancies. The rate of at least one pregnancy during the follow-up period was lower among all patient groups than among controls, yet this was statistically significant only among those with anorexia nervosa ($p < 0.001$), atypical anorexia nervosa ($p = 0.005$), and atypical bulimia nervosa ($p = 0.004$). The overall pregnancy rate was significantly lowered across all patient groups. The largest differences in rates were observed among women with anorexia nervosa, at less than half of the rate in the control group (RR 0.48, 95% CI 0.40-0.58, $p < 0.001$). Figure 4 depicts the pregnancy rates across the diagnostic groups.

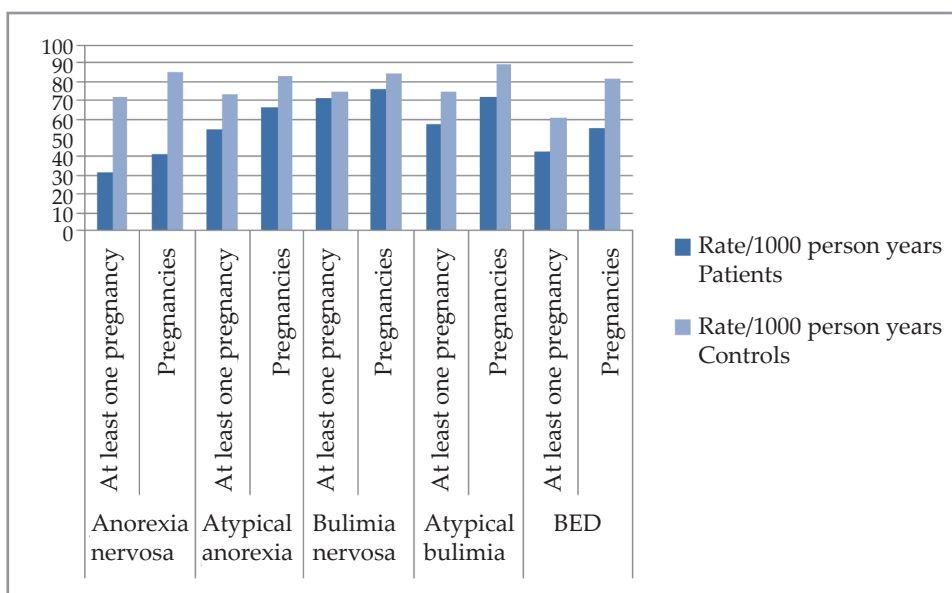


Figure 4. Pregnancy rates across the diagnostic and matched control groups (1).

5.2.3. MISCARRIAGES

Women with anorexia nervosa had a significantly lower rate of having at least one miscarriage (RR 0.62, 95% CI 0.41-0.94) and overall miscarriage rate (RR 0.62, 95% CI 0.42-0.90) compared to controls, but there were no other differences between the groups. A multinomial logistic regression model was then applied to assess the odds of miscarriage or induced abortion given that pregnancy had already begun. Contrary to the crude analyses, there was a trend towards an elevated risk of miscarriage among women with anorexia nervosa and atypical anorexia nervosa (OR 1.44, 95% CI 0.96-2.17 and OR 1.42, 0.95-2.11, respectively). The risk of miscarriage was particularly high among those with BED (OR 3.18, 95% CI 1.52-6.66): 47% of pregnancies ended with miscarriage, compared with 23% among controls. Figure 5 depicts the proportions of the three pregnancy outcomes (childbirth, induced abortion, miscarriage).

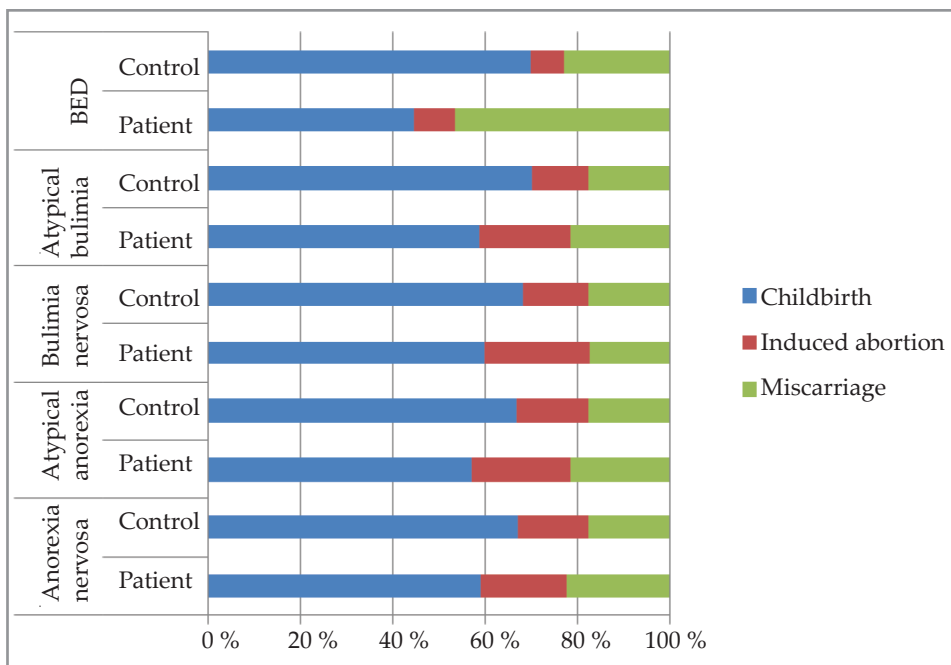


Figure 5. The proportions of pregnancy outcomes among women with an eating disorder and their matched controls (I).

5.2.4. INDUCED ABORTIONS

Reflecting the low number of pregnancies among women with anorexia nervosa, the rates of at least one induced abortion and abortions in general were lower among this patient group compared to controls (RR 0.61, 95% CI 0.39-0.96 and RR 0.57, 95% CI 0.37-0.86, respectively). Among women with bulimia nervosa, the crude rates of at least one abortion and abortions in general were elevated (RR 1.56, 95%CI 1.25-1.96, RR 1.46, 95% CI 1.19-1.79, respectively). Similarly, in the second set of analyses, the proportion of pregnancies ending with induced abortion was significantly higher among women with bulimia nervosa (OR 1.85, 95% CI 1.43-2.38) and atypical BN (OR 1.92, 95% CI 1.27-2.89) compared to controls. The risk of induced abortion was comparable among women with anorexia nervosa or BED and their controls.

5.2.5. INFERTILITY TREATMENTS

The number of infertility treatments was generally low. There was insufficient power to detect differences across the diagnostic groups, and the analysis was

restricted to joint groups of patients and controls giving birth during the follow-up period. In the control group, 4.5% of the conceptions followed infertility treatment versus 7.2% in the patient group ($\chi^2(1)=6.9$, $p=0.009$) (I).

5.3. PREGNANCY, OBSTETRIC AND PERINATAL HEALTH OUTCOMES

5.3.1. PREGNANCY OUTCOMES

Pregnancy outcomes were assessed across broadly defined patient groups (ICD-10 typical and atypical forms combined) and the joint group of unexposed women (Study II). All births at a gestational age of ≥ 22 weeks or with a birth weight ≥ 500 grams occurring during the follow-up period were included. The findings from the adjusted regression models show that the course of the pregnancies was mainly favorable among women who had previously received treatment for an eating disorder. Only a few differences were observed: those with anorexia nervosa had an elevated risk of anemia (adjusted OR 2.39, 95% CI 1.20-4.76), slow fetal growth (OR 2.59, 95% CI 1.43-4.71), and premature contractions (OR 2.31, 95% CI 1.05-5.11) compared to unexposed women; hypertension occurred frequently among women with BED (OR 13.29, 95% CI 4.03-43.81); and those with bulimia nervosa had an elevated risk of premature contractions (OR 2.20, 95% CI 1.17-4.14). Table 6 gives the detailed information.

Table 6. Pregnancy and birth outcomes among women with anorexia nervosa, bulimia nervosa, and BED: results from the logistic regression models; analyses adjusted for maternal age, parity, marital status, and smoking status; unexposed women form the reference group (OR=1).

Outcome		Anorexia nervosa	Bulimia nervosa	BED	Unexposed women
Number of singleton childbirths	N	302	724	52	6319
Anemia	N (%)	12 (3.97)	12 (1.66)	0	97 (1.54)
	OR (95% CI)	2.39 (1.20-4.76)	1.05 (0.54-2.03)		1
Hypertension*	N (%)	3 (1.4)	6 (1.22)	4 (22.22)	87 (2.24)
	OR (95% CI)	0.63 (0.20-2.00)	0.51 (0.20-1.33)	13.29 (4.03-43.81)	1
Slow fetal growth*	N (%)	14 (4.64)	22 (3.04)	0	122 (1.93)
	OR (95% CI)	2.59 (1.43-4.71)	1.53 (0.94-2.48)		1
Premature contractions*	N (%)	7 (3.26)	16 (3.25)	1 (5.56)	59 (1.52)
	OR (95% CI)	2.31 (1.05-5.11)	2.2 (1.17-4.14)	3.96 (0.51-30.95)	1
Resuscitation	N (%)	3 (0.99)	15 (2.07)	0	58 (0.92)
	OR (95% CI)	1.06 (0.33-3.37)	2.12 (1.18-3.79)		
Perinatal death	N (%)	3 (0.99)	3 (0.41)	1 (1.92)	21 (0.33)
	OR (95% CI)	4.06 (1.15-14.35)	1.78 (0.51-6.19)	9.51 (1.33-68.26)	
Small for gestational age	N (%)	13 (4.30)	23 (3.18)	0	133 (2.10)
	OR (95% CI)	2.20 (1.23-3.93)	1.51 (0.92-2.48)		
Large for gestational age	N (%)	1 (0.33)	19 (2.62)	5 (9.62)	155 (2.45)
	OR (95% CI)	0.13 (0.02-0.91)	1.1 (0.66-1.84)	4.32 (1.64-11.36)	
Premature birth	N (%)	15 (4.98)	36 (5.01)	0	259 (4.11)
	OR (95% CI)	1.28 (0.71-2.33)	1.28 (0.85-1.91)		
Very premature birth	N (%)	3 (0.99)	3 (0.42)	0	18 (0.29)
	OR (95% CI)	4.59 (1.25-16.87)	1.84 (0.51-6.62)		
Low birth weight	N (%)	19 (6.31)	30 (4.16)	0	201 (3.19)
	OR (95% CI)	2.16 (1.30-3.58)	1.37 (0.90-2.07)		
Very low birth weight	N (%)	3 (0.99)	6 (0.83)	0	34 (0.54)
	OR (95% CI)	2.14 (0.64-7.20)	1.81 (0.72-4.57)		
Low Apgar score at 1 min (<7)	N (%)	16 (5.39)	39 (5.41)	5 (9.62)	299 (4.75)
	OR (95% CI)	1.17 (0.68-2.01)	1.13 (0.79-1.60)	2.23 (0.74-6.68)	
Very low Apgar score at 1 min (<3)	N (%)	4 (1.35)	19 (2.64)	1 (1.92)	80 (1.27)
	OR (95% CI)	1.16 (0.42-3.20)	2.31 (1.34-3.98)	1.74 (0.25-12.1)	

* Information is based on ICD-10 diagnosis

5.3.2. OBSTETRIC OUTCOMES

With regard to obstetric outcomes, women who had received treatment for an eating disorder differed significantly from the unexposed women only in terms of the duration of the stages of labor (II). The first stage was shorter than expected among those with anorexia nervosa (adjusted $p=0.031$), whereas both the first and second stages were prolonged among women with BED (adjusted $p<0.001$ and $p=0.018$, respectively). Table 7 shows the absolute differences between the groups.

Table 7. Birth outcomes among women with anorexia nervosa, bulimia nervosa, and BED: results of linear regression models with maternal age, parity, marital status (single/married or cohabiting), and smoking status (yes/no) as covariates; comparisons were relative to unexposed women across all diagnostic groups.

Outcome	Anorexia nervosa (N=302 singleton births)		Bulimia nervosa (N=724)		BED (N=52)		Unexposed women (N=6319)
	Mean (SD)	p-value	Mean (SD)	p-value	Mean (SD)	p-value	Mean (SD)
Birthweight (grams)	3301 (562)	<0.001	3464 (563)	0.037	3812 (519)	<0.001	3520 (539)
Gestational age (weeks)	39.6 (2.1)	0.032	39.7 (1.9)	0.026	40.1 (1.4)	0.27	39.9 (1.8)
Duration of the first stage of labor (min)	733 (401)	0.031	849 (500)	0.79	1249 (309)	<0.001	811 (503)
Duration of the second stage of labor (min)	39 (45)	0.18	45 (58)	0.64	110 (73)	0.018	43 (55)

5.3.3. PERINATAL HEALTH OUTCOMES

Major differences were observed between patients and unexposed women in terms of the perinatal health of the offspring across all diagnostic groups (II). Overall, those with an eating disorder differed from unexposed women on various dichotomous parameters assessing growth and prematurity (Table 6). The mean infant birth weight differed significantly between patients and unexposed women: maternal anorexia nervosa and bulimia nervosa were related to lower birth weight (adjusted $p<0.001$ and $p=0.037$, respectively), whereas the offspring of mothers with BED were heavier than those of unexposed women (adjusted $p<0.001$) (Table 7). Furthermore, elevated risks of a few severe health problems were observed among the offspring of mothers with anorexia nervosa and bulimia nervosa: the risk of perinatal death was fourfold in the babies of mothers with anorexia nervosa compared to the babies of unexposed women

(adjusted OR 4.06, 95% CI 1.15-14.35), and maternal bulimia nervosa was related to elevated risks of resuscitation of the neonate (OR 2.12, 95% CI 1.18-3.79) and a very low Apgar score at one minute from birth (OR 2.31, 95% CI 1.34-3.98).

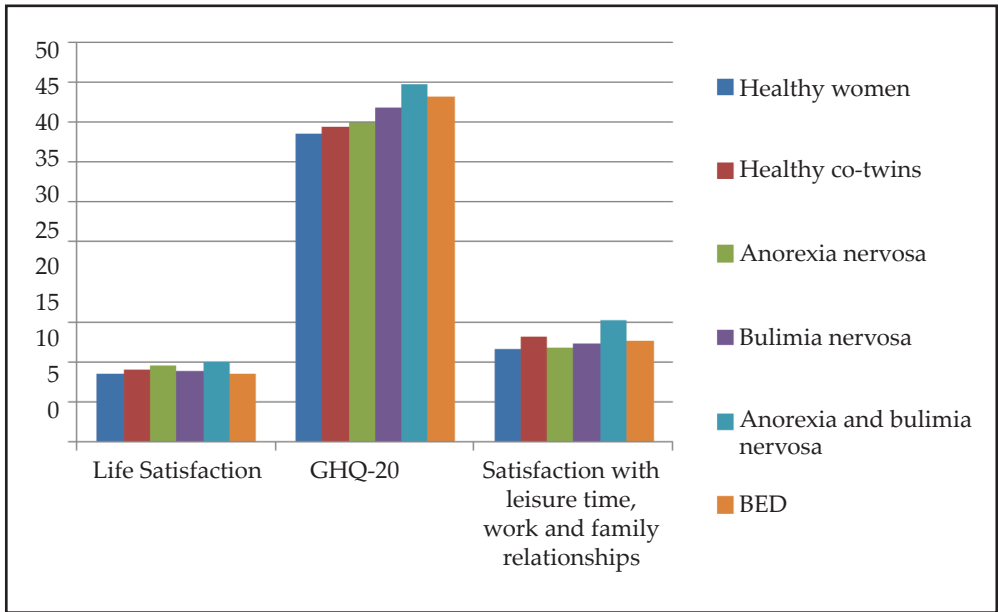
5.4. PSYCHOLOGICAL AND SOCIAL OUTCOMES

5.4.1. PSYCHOLOGICAL WELL-BEING AND BODY WEIGHT

The relationship between psychological well-being and weight in the general population was different for women and men (Study III): the relationship between various indicators and BMI was strongly U-shaped in the general population of men, but no associations were observed among women. However, three of the four indicators studied (life satisfaction, GHQ-20, and satisfaction with leisure time, work and family relationships) showed a U-shaped association with BMI among women with lifetime DSM-IV eating disorders, but not among healthy women.

5.4.2. GENERAL PSYCHOLOGICAL OUTCOMES IN EATING DISORDERS

Cross-sectional associations between eating disorders and general psychological outcomes were explored in Study III. Women with a lifetime diagnosis of DSM-IV eating disorders reported higher scores on life satisfaction ($p=0.03$), GHQ-20 ($p=0.001$), and satisfaction with leisure time, work and family relationships ($p=0.06$) compared to unaffected women, indicating lowered well-being among these women. There were no significant differences across these measures between the eating disorder probands and their unaffected twin sisters. Figure 6 depicts the distributions of the mean values of general psychological outcomes.



Higher scores in all measures indicate lower levels of well-being.

Figure 6. Distribution of the mean values of the measures of general psychological outcome across the diagnostic groups, healthy co-twins, and healthy control women (III).

5.4.3. TIME-DEPENDENT TRENDS IN PSYCHOLOGICAL OUTCOMES

Psychological outcome measures were explored during illness and recovery among women with anorexia nervosa and bulimia nervosa in Studies IV and V. A broad definition was used in bulimia nervosa due to the limited number of cases. Table 8 shows the group means and 95% confidence intervals of the psychological measures studied among probands, unaffected twin sisters, and healthy comparison women. Over time, there was major improvement on nearly all psychological outcome measures in both anorexia and bulimia nervosa, and the probands closely resembled their unaffected twin sisters after five years in clinical recovery. Body dissatisfaction and psychosomatic symptoms seemed to be the most persistent residua in both illnesses.

Table 8. Psychological outcomes: group means and their 95% confidence intervals in women currently ill with DSM-IV anorexia nervosa or broad bulimia nervosa, >5 years after recovery, and in comparison women. (Papers IV & V)

	DSM-IV anorexia nervosa			Broad bulimia nervosa			
	Currently ill (n=16)	Recovered >5 years (n=24)	Healthy co-twins (n=24)	Currently ill (n=23)	Recovered >5 years (n=16)	Healthy co-twins (n=19)	Healthy women (n=134)
Eating Disorder Inventory							
Drive for thinness	28.5 (24.8-32.3)	22.7 (19.1-26.2)	17.8 (15.6-20.0)	31.2 (28.7-33.7)	23.5 (20.0-27.0)	19.9 (17.0-22.9)	17.2 (16.0-18.5)
Body dissatisfaction	32.3 (29.0-35.6)	29.8 (25.9-33.7)	25.9 (23.3-28.4)	32.3 (29.0-35.6)	31.1 (25.3-36.9)	25.9 (21.9-29.9)	23.1 (21.3-25.0)
Bulimia	18.9 (15.1-22.8)	13.9 (12.1-15.7)	11.0 (9.5-12.4)	22.8 (20.6-25.0)	14.9 (12.6-17.3)	11.6 (9.5-13.7)	10.6 (10.1-11.1)
Perfectionism	20.9 (16.7-25.0)	15.4 (13.6-17.1)	15.3 (13.7-17.0)	20.0 (17.5-22.5)	18.3 (15.6-20.9)	18.4 (16.1-20.7)	15.0 (14.2-15.9)
State-Trait Anxiety Inventory							
Trait Anxiety	51.1 (47.6-54.7)	41.5 (38.0-45.0)	39.0 (35.9-42.1)	47.2 (43.8-50.5)	42.2 (37.5-46.9)	39.1 (35.7-42.5)	37.9 (36.7-39.2)
State Anxiety	45.5 (40.5-50.5)	34.9 (30.6-39.1)	35.9 (31.3-40.4)	42.7 (37.9-47.6)	36.5 (31.0-42.0)	35.6 (31.2-40.0)	33.2 (31.6-34.8)
Psychosomatic Symptom Scale	5.4 (4.0-6.8)	5.4 (4.1-6.6)	5.0 (4.0-6.1)	7.7 (6.2-9.1)	6.7 (5.3-8.0)	6.2 (4.6-7.7)	4.7 (4.2-5.2)
Rosenberg Self-Esteem Scale	14.6 (11.8-17.3)	22.9 (20.2-25.6)	23.1 (21.3-25.0)	18.8 (16.2-21.5)	20.8 (18.0-23.5)	22.3 (20.2-24.4)	22.5 (21.7-23.6)

Next, time-dependent trends towards psychological recovery following clinical recovery from anorexia nervosa were modeled. Probands with broadly defined anorexia nervosa were compared to their unaffected twin sisters using a random intercept linear regression model, which tests the null hypothesis that the psychological measures of probands do not reach the level of their unaffected twin sisters over time. This hypothesis was rejected on six of the eight outcome measures: drive for thinness ($z=-2.30$, $p=0.021$), bulimia ($z=-3.23$, $p<0.001$), perfectionism ($z=-3.01$, $p=0.003$), state anxiety ($z=-2.49$, $p=0.013$), trait anxiety ($z=-2.53$, $p=0.011$), and self-esteem ($z=4.02$, $p<0.0001$), meaning that women with anorexia nervosa attained recovery over time. In terms of body dissatisfaction and psychosomatic symptoms, the anorexia nervosa probands remained more symptomatic than their twin sisters.

5.4.4. COMORBIDITY

Psychiatric diagnostics was not the main focus of this study, but it was possible to determine the comorbid conditions of lifetime major depressive disorder and lifetime obsessive-compulsive disorder in the twin sample, based on the SCID-I interviews. Of the women with lifetime DSM-IV eating disorders, 41.3% also had lifetime major depressive disorder as a co-morbid condition, and 7.3% had lifetime obsessive-compulsive disorder. The relative frequencies among the eating-disorder-free co-twins of women with a lifetime eating disorder were 16.7% and 2.4% (unpublished data, Linna et al. 2013).

5.4.5. SOCIAL OUTCOMES

Women with lifetime eating disorders were compared to unaffected controls and unaffected twin sisters in terms of marital status, occupation, and education in Studies I, IV and V. In the clinical setting (Study I), being married was less common among patients compared to controls (28.8% of patients, 39.7% of controls, $p < 0.001$). This held true across all five eating disorder categories in question. In the FinnTwin16 sample, women currently ill with broad anorexia nervosa or bulimia nervosa were less likely to be married or cohabiting than their unaffected twin sisters (anorexia nervosa $p = 0.04$, bulimia nervosa $p = 0.018$), but no differences in marital status were found following clinical recovery.

In terms of unemployment rates and educational attainment, neither women currently ill with broad anorexia nervosa/bulimia nervosa nor those in recovery differed from their unaffected co-twins (Studies IV-V).

6. DISCUSSION

6.1. SUMMARY OF THE FINDINGS

Eating disorders can have lasting reproductive and psychological consequences. On the community level, no reproductive impairment was observed among women with either current or past eating disorders at the (mean) age of 24.5 years. Reproductive outcomes were also favorable for the majority of former eating disorder patients. Nevertheless, many women treated for an eating disorder experienced adverse reproductive health outcomes, such as miscarriages, remaining childless, or adverse perinatal conditions. Some adverse effects were severe enough to warrant closer monitoring of pregnancies among women with a history of eating disorders.

Beyond reproductive functioning, eating disorders have an overall impact on psychological functioning. The long-term psychological outcomes in anorexia nervosa were found to be quite favorable in the community, but symptoms of bulimia nervosa were relatively long-standing, and recovery more gradual.

The association between psychological well-being and body weight differed among women with and without a history of eating disorders. In a cross-sectional approach, women with either current or past eating disorders showed a lowered sense of well-being than controls, but no differences were observed in comparisons with their unaffected twin sisters.

Taken together, these findings indicate that the outcome of eating disorders is polarized: most women proceed towards recovery, but some continue to encounter problems with reproduction and psychological health years after the onset of the illness.

6.2. CLINICAL RECOVERY

In this study (IV), the probability of recovery from anorexia nervosa five years after onset was 67%. Comparison with other studies is complex because of the differences in follow-up time and in the definition of recovery. However, the findings are broadly comparable to the most optimistic recovery estimates

reported previously. Steinhausen's (2002) meta-analysis revealed a 33% recovery rate among women with anorexia nervosa within a 4-year follow-up, and 73% within 10 years in clinical settings. Both Steinhausen's and the present findings of an increasing recovery rate over time signal that recovery from anorexia nervosa is quite possible, but often requires several years. Comparison with other long-term population-based studies (Wentz et al. 2009, Wade et al. 2006) is not meaningful due to the widely varying definitions of recovery, namely the inclusion of psychological criteria by these two studies.

In bulimia nervosa, the probability of recovery was 57% five years after the onset (V). Thus far there has been no meta-analysis of recovery rates in bulimia nervosa. Generally, rates based on clinical data are lower than those based on samples drawn from the population. The recovery rates reported in this study are higher than those given in studies with similar follow-up times (Agras et al. 2009, Bøgh et al. 2005, Grilo et al. 2007), although studies with longer follow-up times (12 and 20 years) have reported even higher rates than those found in this study (Fichter & Quadflied 2004, Keel et al. 2010). Previous findings emphasize the recurrent (Herzog et al. 1999) and long-term nature of bulimia nervosa (Wade et al. 2006). According to Wade et al. (2006), less than half of those with an initial diagnosis of bulimia nervosa were asymptomatic even after a 14.5-year follow-up.

Recovery rates were not available for the clinical cohort examined in Studies I and II.

6.3. REPRODUCTIVE HEALTH OUTCOMES

This study showed that women with a history of eating disorders have an elevated risk of encountering adverse reproductive outcomes such as childlessness, miscarriage, and several negative fetal and perinatal health conditions (I, II). However, pregnancy and childbirth progressed without complications among the majority of these women, and no impairment in having children was observed in the population-based sample of women with lifetime eating disorders at the age of 24.5 years (IV, V). In the clinical cohort, the impairment in having children was most visible among women with anorexia nervosa, their pregnancy rates being less than half of those observed among controls. This may be attributable to various factors: infertility; continuation of restrictive eating patterns; low body weight; psychological symptoms; delay in having children as a consequence of the disorder, continuing education or focusing on career; and other underlying factors such as differing patterns of individual values or personality. It is worth noting that the low number of children among women with anorexia nervosa

was driven by a high number of those who had not had children at follow-up, as described earlier by Brinch et al. (1988). The design of the present study was not optimal for assessing infertility given that only infertility treatments leading to childbirth are recorded in the registries, which may provide a lower bound estimate. Even with this limitation, however, women with an eating disorder were more likely to have conceived with the help of infertility treatment, and no differences were found across the diagnostic categories. Two recent studies have shown that women with anorexia nervosa and those with bulimia nervosa are more likely to have fertility problems and utilize infertility treatments to conceive compared to controls (Easter et al. 2011, Micali et al. 2013). Given the devastating psychological consequences of infertility among women (Greil, 1997), these aspects need to be addressed in both research and in clinical practice.

During the prenatal period, women with anorexia nervosa and bulimia nervosa were more likely to undergo induced abortion relative to controls. These findings are in line with those reported in previous studies (Abraham, 1998, Bulik et al. 2010), and may reflect the elevated rate of unplanned pregnancies among these women (Bulik et al. 2010, Micali et al. 2013). This study provides further evidence of an elevated risk of miscarriage among women with anorexia nervosa and BED (Bulik et al. 2007). However, there was a lack of evidence to support the previously found elevated risk in bulimia nervosa (Abraham et al. 1998, Micali et al. 2007, Morgan et al. 2006), possibly reflecting the remission of symptoms. The identification of an increased likelihood of miscarriage in BED is a novel finding, the literature on reproduction among women with BED being scarce. Similar findings have been reported with regard to obesity, which often coexists with BED (Metwally et al. 2008). However, the number of miscarriages among BED patients identified in this study exceeds previous estimates derived from obesity studies, suggesting the need in future studies to determine whether the occurrence of binge behaviors independently increases the risk of miscarriage. Furthermore, estimates of the magnitude of risk may differ between clinical and population-based studies. The findings of this study are likely to represent the more severe end of the spectrum. Even so, the course of pregnancy was mostly favorable among women with an eating disorder. A few differences were observed during pregnancy across the diagnostic groups and unexposed women, namely an increased likelihood of anemia, slow fetal growth and premature contractions in anorexia nervosa and an increased risk of hypertension in BED.

With regard to childbirth, few differences were observed between the patients and the controls. However, the increased likelihood of several perinatal health complications in all patient groups requires attention. As hypothesized, the most adverse outcomes were related to patterns of growth and length of gestation,

but severe complications such as low Apgar score, resuscitation of the neonate, and perinatal death were also observed. Mothers with anorexia nervosa gave birth to infants with a lower birth weight compared to unexposed women, which is a previously well-documented finding (Solmi et al. 2014). The risks of a low birth weight, being small for gestational age, and being born prematurely observed in the infants of mothers with anorexia nervosa could be attributable to low maternal pre-pregnancy BMI, insufficient weight gain during pregnancy, insufficient intake of micronutrients, and fetal exposure to high cortisol levels (Micali et al. 2007, Sebire et al. 2001, Baker et al. 2009, Rondó et al. 2003, van der Spuy et al. 1988, McTernan et al. 2001), although the current study design did not allow more in-depth analysis of the mechanisms. In contrast, infants of mothers with BED were heavier than might have been expected, which was also reported by Bulik et al. (2009) and is likely to be attributable to higher maternal weight and gestational weight gain.

The observed increased risks of severe perinatal health complications support the findings from earlier clinical studies. Recent population-based studies have not, however, provided evidence of an increased likelihood of such severe complications in eating disorders, thereby demonstrating divergent outcomes in population-based and clinical studies. The risk of perinatal death identified in this study was four-fold among infants of women with anorexia nervosa. A previous study reported a six-fold risk (Brinch et al. 1988), but most studies on reproductive outcomes have not assessed perinatal death, or had insufficient power to detect differences. Maternal underweight has not been linked with an excess risk of stillbirth (Stephansson et al. 2001, Kristensen et al. 2005, Tennant et al. 2011), which suggests the need for more detailed analyses in large samples to replicate or refute the findings of this study, and give further insight into the mechanisms. A novel finding of this study is the two-fold risk of resuscitation of the infants of mothers with bulimia nervosa. An increased likelihood of very low Apgar score at one minute from birth was also found among their offspring. The latter finding parallels the findings of a clinical study conducted by Stewart et al. (1987), but more recent population-based studies have observed comparable Apgar scores in infants of bulimia nervosa probands and in those of unexposed women (Bulik et al. 2009, Micali et al. 2012). The underlying mechanisms need to be explored in future studies. Binge and purge episodes leading to rapid shifts in blood glucose and insulin levels, and subsequent effects on fetal growth patterns could act as mediators. However, these findings should be interpreted with caution, and replication is required to see whether the phenomenon recurs in other samples.

Overall, the course of pregnancy and birth potentially affects the later life of offspring through a number of mechanisms, such as epigenetic modifications and metabolic programming. Birth complications have been described in the etiology of eating disorders (Cnattingius et al. 1999, Favaro et al. 2006), and maternal stress during pregnancy has been linked with childhood fearfulness, hyperactivity, inattention, conduct problems and cognitive development in the offspring (Bergman et al. 2007, O'Connor et al. 2002). More recently, pre-pregnancy maternal eating disorders have been linked to impaired neurocognitive development in the offspring at the age of five years (Koubaa et al. 2013). Thus, it is warranted to study further the health and psychological development of children born to mothers with eating disorders.

6.4. PSYCHOLOGICAL OUTCOMES

Body weight and psychological well-being

No relationship between psychological well-being and body weight was observed in the general population of women or in healthy women as investigated in this study (III). However, a strong U-shaped relationship was found among those with a history of eating disorders and among their healthy twin sisters. Most studies have thus far focused on the effects of obesity on psychological well-being, and little is known about psychological well-being among underweight women. Elevated levels of self-reported poor psychological health, depression and anxiety have been reported among underweight women (Ali et al. 2006, Zhao et al. 2009), but it remains to be determined to what extent eating disorders explain the impaired well-being found in these studies. These findings suggest that susceptibility to eating disorders plays an important role in the relationship between body weight and psychological well-being: in other words, factors other than body weight explain individual differences in psychological well-being among women with no susceptibility to eating disorders, whereas it is, to a large degree, determined by body weight among women with a vulnerability in this regard, or these women may more readily react by either losing or gaining weight when exposed to stress. However, these findings are preliminary and based on cross-sectional analysis, and should therefore be interpreted with caution.

Psychological outcomes in eating disorders

Reviewing the literature on psychological outcomes of eating disorders is complex due to the methodological heterogeneity, including instruments, study populations, duration of follow-up, and definitions of recovery. Overall, the women with a history of eating disorders investigated in this study reported higher scores on life satisfaction, GHQ-20, and satisfaction with leisure time, work and family relationships compared to healthy women, implying generally impaired psychological well-being among these women (III). However, the differences between these women and their unaffected twin sisters were small. This may indicate that the impairment seen among women with a history of eating disorders is not simply a consequence of the eating disorder, but reflects underlying psychological vulnerability. Previous population-based long-term outcome studies have tended to focus on assessing eating-disorder-specific psychological outcomes (Wade et al. 2006, Gillberg et al. 1994, Råstam et al. 1995, Fairburn et al. 2000), and thus there is still very limited research in non-clinical settings on general psychological well-being among women with a history of eating disorders. Fichter et al. (2006) assessed general psychopathology on the SCL-90 in a clinical sample of women treated for anorexia nervosa, and found elevated SCL-90 scores as compared to normative population means, even in the 12-year assessment.

Assessment of psychological outcomes of anorexia nervosa and bulimia nervosa indicated major improvement across almost all of the measures over the course of recovery (IV, V). Body dissatisfaction and psychosomatic symptoms were the most persistent residua of both illnesses. This finding is in line with previous literature reporting persistent high levels of weight and shape concerns in both population-based (Wade et al. 2006, Gillberg et al. 1994, Råstam et al. 1995) and clinical settings (Fichter et al. 2006), even after clinical recovery. Clausen (2004) illustrated this phenomenon, as shown above in Figure 1. Definitions of clinical recovery typically include criteria for weight, menstruation and behavior, which normalize much earlier than the cognitive and emotional aspects of eating disorders. Psychological recovery is a slow and gradual process, and estimates of the degree of residual symptoms depend on various methodological factors. A random intercept regression model was utilized to assess recovery trends, in other words whether the women in clinical recovery from anorexia nervosa would, over time, reach the level of their unaffected twin sisters across measures of state and trait anxiety, self-esteem, and eating disorder specific pathology (as measured by the EDI). The unaffected twin sisters were regarded as the as-closely-as-

possible matched controls in order to untangle the eating disorder specific effects. According to the model estimates, the anorexia nervosa probands would reach the level of their twin sisters on most measures, but only after some 5-15 years from attaining clinical recovery. Previous studies also report an improvement in measures of general and eating disorder specific psychopathology several years after the illness, namely between the time points of six and 12 years from the end of treatment for both anorexia nervosa and bulimia nervosa (Fichter et al. 2006, Fichter & Quadflieg 1997, 2004).

Impairment in the psychological health of individuals with a history of eating disorders has been observed in most of these studies, even in those with a long follow-up time. The fact that the outcome of eating disorders differs across population-based and clinical settings may explain these findings to some extent. Moreover, whereas most women attain clinical recovery and proceed towards full or nearly full psychological recovery thereafter, a minority develops a chronic disorder with marked somatic, psychological, and social impairment. Prospective studies are needed to determine whether impaired psychological health is a direct consequence of the illness, or whether it precedes the onset.

6.5. METHODOLOGICAL CONSIDERATIONS

Strengths

The strengths of this study include the utilization of two unique data sets. Clinical and population-based data provide diverse perspectives on the outcome of eating disorders across different settings. The sample in the clinical cohort was large, providing generalizability of the findings on clinical populations. The wide range of different outcome measures recorded in the registries facilitated the comprehensive analysis of pregnancy and birth outcomes in eating disorders. Moreover, good validity can be assumed given the use of national, representative health registries with excellent coverage and well documented agreement between register data and hospital records. Data on BED, which has been diagnosed at the eating disorder clinic since the research criteria were first issued in 1994, are extensive.

Twin studies offer an excellent opportunity to extract nationally representative population-based samples with high response rates. The use of unaffected twin sisters as controls for the eating disorder probands gave a deeper understanding of psychological health in eating disorders. Given the implementation of the

twin study design, it was possible to give an overview of the effects of the eating disorder and of the underlying familial psychological vulnerability, present also in the twin sisters.

Limitations

The limitations of the clinical cohort include the inability to distinguish between active eating disorders and those in recovery. The sample may represent the more severe end of the eating disorder spectrum in comparison with population-based samples. Studies I and II were limited to the variables recorded in the health registries, and thus many potential mechanisms of causation, such as gestational weight gain, could not be assessed. The attending physician at the eating disorder clinic gave the initial diagnosis, whereas structured or semi-structured diagnostic interviews would have added to the accuracy. Moreover, intake diagnoses were utilized, therefore diagnostic cross-over or comorbidity could not be accounted for. Despite the fact that the sample was the largest one to date to study reproductive outcomes of eating disorders, some of the adverse birth outcomes were still so rare that the findings need to be confirmed in future studies. The lack of power was most visible among the BED diagnostic group.

The twin sample is comparably large in terms of studying phenomena in the general population, but the number of cases within each diagnostic group was limited. The statistical power may not be sufficient to detect differences, especially when the diagnostic groups were split into the currently ill and the recovered, and comparisons were made with unaffected twin sisters. Furthermore, it is likely that not all eating disorder cases were identified through the screening process. Given the young age of the twin sample, a limited number of cases had been longer than five years in recovery, thus impairing the ability to assess the long-term psychological outcome of anorexia nervosa and bulimia nervosa. The twins were also relatively young at the time of the study, impairing the estimates of reproduction given in studies IV and V.

The extent to which twins are representative of the general population has been the subject of debate. However, it has been shown that adolescent and adult twins do not differ from the general population in terms of BMI, psychiatric morbidity and overall mortality (Rissanen et al. 1988, Chitkara et al. 1988, Christensen et al. 1995, Kendler et al. 1995, Kaprio et al. 2013).

6.6. CONCLUSIONS AND IMPLICATIONS

The present study depicts a polarized outcome of eating disorders. The severe nature of eating disorders is reflected as problems in reproductive health. However, the estimates related to both recovery and psychological health turned out to be more optimistic than previously thought. Nevertheless, psychological recovery from eating disorders remains a slow and gradual process, and may take several years after the normalization of weight, menstruation, and eating behavior.

Existing studies vary in terms of design, study populations, instruments, and length of follow-up, all of which contribute to making it difficult to gather collective evidence and to get a comprehensive understanding of the outcome of eating disorders. Future research would benefit from more unified assessment of these outcomes, which would make comparisons between studies more meaningful. Moreover, given that most studies have assessed psychopathology specific to eating disorders, more research is needed on other aspects of psychological well-being, such as general well-being, life satisfaction, self-esteem, and self-acceptance. Qualitative research on outcomes involving the subjective evaluation of recovery is scarce, but could potentially enhance understanding of the recovery process. In terms of reproductive outcomes, more attention should be paid to studying individuals with BED, and the health and development of the offspring of mothers with an eating disorder.

The findings of this study underline the importance of reproductive health counseling for women with either current or past eating disorders. Close monitoring of pregnant women with such a history is recommended in order to optimize fetal outcomes. An important message to clinicians, family members and women suffering from an eating disorder is that, with time and patience, recovery is possible.

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