

# **Adolescent-onset anorexia nervosa**

## **in the acute stage and after 30 years**

Sandra Rydberg Dobrescu

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UNIVERSITY OF GOTHENBURG

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To Victor, Astrid and Wilhelm



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### ABSTRACT

Anorexia nervosa (AN) is a severe eating disorder (ED) that predominantly affects females in early adolescence. The **overarching aim** of this thesis has been to examine individuals with adolescent-onset AN in the acute stage, with regard to the neuropsychological profile, and 30 years after the onset of AN regarding overall outcome. **Study I-III** were based on a group of 51 individuals with adolescent-onset AN recruited by community screening and followed prospectively since the mid 1980's (AN group) together with a healthy age-, gender-, and school-matched comparison group (COMP group). In **Study I**, 30-years after the onset of AN, at mean age 44, ED symptoms, psychiatric morbidity, global functioning and quality of life were examined. In **Study II**, the perinatal status, mental and physical health of the offspring born to the females in the AN group were explored and compared with health outcomes of the children in the COMP group. In **Study III**, health care utilisation, social assistance, sick leave and disability pension were examined. Data were collected from Swedish national registers. **Study IV** was based on 20 adolescent females with acute AN, their parents and 28 healthy comparison cases. The cognitive profile was explored, using neuropsychological tests, and its associations with autism spectrum disorder (ASD) and ADHD were investigated. **Results** showed that at 30-year follow-up no individuals were deceased, 64% showed full ED symptom recovery, 19% had an ED and 38% had other psychiatric disorders in the AN group. Later age at onset of AN and premorbid perfectionism predicted a good outcome. Birth weight, length, head circumference and ponderal index were significantly reduced in the children of mothers in the AN group. Few differences in childhood psychiatric health were found across the two groups of offspring. However, parental interviews

showed an overrepresentation of current psychiatric diagnoses in the children of mothers in the AN group. Endocrinological, immune and metabolic disorders were more common in the offspring in the AN group. The healthcare utilisation was increased in the AN group and 22% had received disability pension. In Study IV, neuropsychological tasks revealed a more detail-oriented processing style in weight-restored adolescents with AN. A possible link between neuropsychological deficits and traits of ASD and ADHD could not be confirmed.

**In summary**, three decades after adolescent-onset AN, the outcome was favorable for the majority of the AN cases. However, one in five had an ED, a minority depended on society for their income and the offspring exhibited some unfavorable health outcomes. More efforts need to be directed towards preventing AN from developing into a protracted course with consequences on both an individual and health economic level. With the goal of potentially reducing negative perinatal outcomes in the offspring of women with current or previous EDs, we suggest that screening procedures for EDs are implemented in maternal care. Previous theories of an endophenotype in AN, characterized by a tendency to focus on details rather than perceiving the whole, were supported in this thesis and have implications for treatment strategies that address this cognitive style.

**Keywords:** anorexia nervosa, population-based, prospective, long-term follow-up, outcome, comorbidity, offspring, burden of disease, neuropsychology, autism, ADHD

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# SAMMANFATTNING PÅ SVENSKA

Anorexia nervosa (AN) är en allvarlig ätstörning som främst drabbar kvinnor i ungdomsåren. Avhandlingens övergripande syfte var att undersöka individer med AN som debuterat i tonåren, i det akuta skedet, avseende neuropsykologisk profil, samt 30 år efter insjuknande avseende långtidsutfall. **Studie I-III** var baserade på 51 individer som insjuknade i AN under tonåren (AN gruppen) och ingick i en delvis populationsbaserad, prospektiv långtidsuppföljning som initierades i Göteborg under 1980-talet. En frisk kontrollgrupp matchad för ålder, kön och skola (COMP gruppen), har följts parallellt. I **Studie I**, 30 år efter insjuknande i AN, vid 44 års ålder, undersöktes individerna avseende ätstörningar och psykiatrisk samsjuklighet, global funktion och livskvalitet. I **Studie II** undersöktes deltagarnas egna barn avseende den perinatale-, psykiska- och fysiska hälsan och jämfördes med barnen födda till kvinnorna i COMP gruppen. I **Studie III** undersöktes olika hälsoekonomiska utfall baserat på data från svenska nationella register. I **Studie IV** deltog 20 ungdomar som var i det akuta sjukdomsskedet av AN, deras föräldrar och 28 friska kontroller. Neuropsykologiska tester administrerades för att undersöka den kognitiva profilen och dess samband med autism och ADHD. **Resultaten** visade att 30 år efter insjuknande i AN, levde alla individer, 64% var fullt tillfrisknade från ätstörningssymtom, 19% hade en ätstörning och 38% hade annan psykiatrisk sjuklighet. Högre ålder vid insjuknande i AN och premorbid perfektionism var prediktivt för en bättre prognos. Födelsevikt och längd samt huvudomfång var lägre hos barnen i AN gruppen jämfört med barnen i COMP gruppen. Det var få skillnader mellan barngrupperna gällande psykisk ohälsa, vissa resultat indikerade på att psykiatriska diagnoser var vanligare förekommande hos barnen i AN gruppen. Fysiska diagnoser inom gruppen endokrina, metabola och autoimmuna sjukdomar var mer frekvent förekommande hos barnen i AN gruppen. Högre vårdkonsumtion framkom i AN gruppen och ca var femte individ hade fått sjukpension. Studie IV visade att en mer detaljorienterad kognitiv stil återfanns hos ungdomar med AN efter viktåterhämtning. Resultaten kunde dock inte bekräfta ett samband mellan kognitiva nedsättningar och symptom på autism och ADHD.

**Sammanfattningsvis** har denna avhandling visat att 30 år efter insjuknande i AN med tonårsdebut var utfallet gott för majoriteten. Var femte individ hade en kvarvarande ätstörning, 22% hade fått sjukpension och vissa negativa hälsoutfall återfanns hos barn födda till mödrar med en historia av AN. Det är av stor vikt att vidta åtgärder för att minska risken för att AN utvecklas till ett kroniskt förlopp, både för den drabbade individen och ur ett hälsoekonomiskt

perspektiv. Med målsättningen att minska negativa födelseutfall hos barn födda av mödrar med pågående eller tidigare AN föreslås att screening för ätstörningar implementeras i mödravården. Teorierna kring en mer detaljorienterad kognitiv stil på bekostnad av att uppfatta helheten vid AN stöds av resultat från avhandlingen och har implikationer för behandlingsstrategier som inriktar sig på denna kognitiva stil.

# LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals:

- I. Dobrescu SR\*, Dinkler L\*, Gillberg CI, Råstam M, Gillberg C, Wentz E. Anorexia nervosa: 30-year outcome. *British Journal of Psychiatry*, 2020. 216 (2): p. 97-104. \* Shared contribution.
- II. Dobrescu SR, Dinkler L, Gillberg CI, Gillberg C, Råstam M, Wentz E. Mental and physical health in children of women with a history of anorexia nervosa. *European Child and Adolescent Psychiatry*, 2024. 33 (10): p. 3481-3493.
- III. Dobrescu SR, Dinkler L, Gillberg IC, Gillberg C, Råstam M, Bolin K, Wentz E. Anorexia nervosa 30 years later: health care utilisation and social welfare benefits. *Submitted*.
- IV. Dobrescu SR, Dahlin K, Karjalainen L, Montonen AB, Klint H, Stenberg I, Paulsson Karlsson G, Wentz E. The cognitive profile in adolescents with anorexia nervosa and the relationship with autism and ADHD: a pilot study. *European Eating Disorders Review*, 2024. Online ahead of print.

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# ABBREVIATIONS

AN	Anorexia Nervosa
ADHD	Attention-Deficit/Hyperactivity Disorder
ADHD-RS	Attention-Deficit/Hyperactivity Disorder Rating Scale
AN-A	Anorexia Nervosa, Acute phase
AN-WR	Anorexia Nervosa, Weight Restored
AQ	Autism spectrum Quotient
ARFID	Avoidant/Restrictive Food Intake Disorder
ASD	Autism Spectrum Disorder
ASRS	ADHD Self-Report Scale
ASSQ	Autism Spectrum Screening Questionnaire
BED	Binge-Eating Disorders
BMI	Body Mass Index
BN	Bulimia Nervosa
CBT-E	Enhanced Cognitive Behavioral Therapy for Eating Disorders
CBT-ED	Eating-Disorder-focused Cognitive Behavioral Therapy
CCI	Central Coherence Index
COMP	Comparison group
DAWBA	Developmental and Well-Being Assessment
DISCO	Diagnostic Interview for Social and Communications Disorders
DSM	Diagnostic and Statistical Manual
ED	Eating Disorder
EDE-Q	Eating Disorder Examination Questionnaire

EDI	Eating Disorder Inventory
EDNOS	Eating Disorders Not Otherwise Specified
FBT	Family Based Treatment
GAF	Global Assessment of Functioning scale
GEE	Generalized Estimating Equations
GEFT	Group Embedded Figures Test
HRQoL	Health Related Quality of Life
ICD	International Classification of Disease
IQ	Intelligence Quotient
MCS	Mental Composite Score (SF-36)
MINI	Mini-International Neuropsychiatric Interview
MROAS	Morgan-Russel Assessment Scale
NPR	National Patient Register
OCD	Obsessive-Compulsive Disorder
OSFED	Other Specified Feeding and Eating Disorder
PCS	Physical Composite Score (SF-36)
PEACE	Pathway for Eating disorders and Autism developed from Clinical Experience
RCFT	Rey Complex Figure Test
SCID-I	Structured Clinical Interview for DSM IV
SDQ	Strengths and Difficulties Questionnaire
SF-36	Short Form Health Survey
SIAS	Swedish Social Insurance Agency
SMBR	Swedish Medical Birth Register

SPDR	Swedish Prescribed Drug Register
SWEAA	SWedish Eating Assessment for Autism spectrum disorders
TMT-4	Trail Making Test condition four
WASI	Wechsler Abbreviated Scale of Intelligence
WCST	Wisconsin Card Sorting Test
WHODAS	World Health Organization Disability Assessment Schedule



# INTRODUCTION

Anorexia nervosa (AN) is a severe eating disorder (ED), mainly affecting young females. The core characteristics of AN are restricted food intake leading to a low body weight, obsessive fear of weight gain and disturbances in the way in which one's body weight or shape is experienced (1). AN typically has its onset during adolescence—at a crucial stage in young individuals development (2). AN is accompanied by numerous somatic and psychiatric comorbidities and carries a considerable risk of a chronic course (3-6). Moreover, the disorder has the highest mortality rate of all psychiatric illnesses (6, 7). Subsequently, AN is associated with high costs for the affected individuals, their families, and society in general (8, 9).

Research pertaining to the long-term outcome of AN is of great importance as it can provide valuable insights into the course, prognosis, and lasting impact of EDs. Such long-term outcome studies stretching over more than two decades are very rare. Moreover, despite treatment advances, the past decades' interventions targeting AN are of limited success and a considerable minority of individuals develop a chronic course. Improving our understanding of factors that contribute to this prolonged course of AN, including comorbidity and neuropsychological deficits, is crucial for improving outcomes and developing more effective treatment approaches.

This thesis will summarize the outcome of adolescent-onset AN 30 years after the onset by exploring different aspects including recovery, mortality, comorbidity, quality of life, health in offspring and health economic outcomes. Further, the thesis encompasses a study of adolescents in the early stages of AN that contributes to the field of research on the neuropsychological profile in AN by exploring its link to autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD).

The following sections give an introduction to AN and the four studies (Study I-IV) included in this thesis.

## ANOREXIA NERVOSA- A HISTORICAL REVIEW

Over 150 years ago, Sir William Gull was one of the pioneering physicians to recognize and describe the disorder that he named anorexia nervosa (10). The term “anorexia” comes from Greek and means “loss of appetite” while “nervosa” indicates that the condition is related to psychological factors. Individuals with this disorder often do not lack an appetite, as indicated by the term “anorexia”, but may avoid food due to fear of gaining weight or a distorted body image.

Gull described several young female patients with extreme emaciation, the majority in the ages 16 to 23 (10). He observed that his patients were persistent and urged themselves to exhaustion if allowed. Restlessness and over-activity, despite severe weight loss, were noted in all the cases and seemed to have made a strong clinical impression (11). Gull published his medical description of three of his patients in 1873, initially referring to this condition as ‘Hysteria Apepsia’. Later on, he concluded that ‘anorexia nervosa’ was more suitable (10). Around the same time, Dr. Lasègue, a psychiatrist in Paris, made similar observations independently and described the condition from his perspective (12).

However, long before the concept of anorexia nervosa was clear, in the Middle Ages there were instances of self-induced starvation often linked to religious fasting, ascetic practices, or spiritual experiences. Catherine de Siena (1347-1380), an Italian patron saint, is a well-known historical figure who exhibited self-starvation. Her preaching practices were characterized by an extreme holy form of fasting, which may eventually have contributed to her death at the young age of 33 (13).

Many of the presenting features of AN described by Gull are similar to cases observed in modern times and can be categorized as AN according to one of the diagnostic manuals used today, the Diagnostic and Statistical manual- fifth edition (DSM-5) (1, 11). In contrast to Gull, who regarded the prognosis of AN as “for the most part favorable”, the prognosis of AN has been considered as relatively poor throughout the 20<sup>th</sup> century (6).

# ANOREXIA NERVOSA

## DIAGNOSTIC CRITERIA

AN is characterized by (1) a restricted food intake leading to significantly low weight and (2) an intense fear of gaining weight or becoming fat and (3) a distorted perception of the body (for diagnostic criteria see Figure 1.) (1). A severity index is defined in the DSM-5, based on the body mass index (BMI), derived from the World Health Organization categories for thinness in adults. The severity indices are categorised as: extreme (BMI<15), severe (BMI 15-15.99), moderate (BMI 16-16.99), and mild (BMI ≥17).

*Figure 1. DSM-5 diagnostic criteria for AN (excluding remission and severity specifiers)*

### *Anorexia Nervosa*

- A. Restriction of energy intake relative to requirements, leading to a significantly low body weight in the context of age, sex, developmental trajectory, and physical health. Significantly low weight is defined as a weight that is less than minimally normal or, for children and adolescents, less than minimally expected.
- B. Intense fear of gaining weight or of becoming fat, or persistent behaviour that interferes with weight gain, even though at a significantly low weight.
- 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 persistent lack of recognition of the seriousness of the current low body weight.

#### *Specify whether:*

(F50.01) *Restricting type*: During the last 3 months, the individual has not engaged in recurrent episodes of binge eating or purging behavior (i.e. self-induced vomiting or the misuse of laxatives, diuretic, or enemas).

(F50.02) *Binge-eating/purging type*: During the last 3 months, the individual has engaged in recurrent episodes of binge eating or purging behavior (i.e. self-induced vomiting or the misuse of laxatives, diuretics, or enemas).

### *Diagnostic criteria- change over time*

The first version of the DSM to include AN as a distinct diagnostic category was the DSM-III (published in 1980). The weight loss criteria for AN was defined as “25% below original body weight” in the DSM-III (14) and was revised in the DSM-III-R and DSM-IV to “body weight less than 85% of that expected” (15, 16). In the DSM-5 the criteria was redefined to a “significantly low weight” to allow for a broader interpretation (1). Both DSM-III and DSM-IV included amenorrhea (absence of menstruation) as a diagnostic criteria for AN, the criteria was removed in the DSM-5. Regarding EDs other than AN, DSM-5 intended to decrease the number of individuals being diagnosed with “eating disorder not otherwise specified” (EDNOS) according to the DSM-IV. Subsequently, EDNOS was replaced by “other specified feeding or eating disorders” (OSFED) comprising; atypical AN, subthreshold bulimia nervosa (BN) and subthreshold binge-eating disorder (BED), purging disorder, night eating syndrome and unspecified feeding and eating disorders. BED from the DSM-IV EDNOS group, became an independent DSM-5 diagnosis. Moreover, the diagnosis avoidant/restrictive food intake disorder (ARFID) was added in the DSM-5 as an age-neutral diagnosis (1). It was formerly recognized as Feeding disorder of infancy or early childhood in the DSM-IV (15). Findings from a large database study indicated that the implementation of the DSM-5 have reduced the residual category EDNOS substantially, as intended (17).

Diagnostic cross over between ED diagnoses is common. AN cross over to BN or OSFED is common (18, 19) while BN cross over to AN is rare (19).

## **INCIDENCE AND PREVALENCE**

The incidence rates for AN have been relatively stable the last decades (20, 21), although a noticeable increase in the incidence of AN in the lower age span has been reported (21, 22). It remains unclear whether this reflect an actual earlier age of onset or if it reflects other factors such as earlier detection and increased public awareness (21). The peak age of onset in AN is usually in mid-puberty, with the most common age of onset being 15 years (2). The onset of the disorder rarely occurs before the age of 8 years and over the age of 30 (23).

The lifetime prevalence of AN varies depending on the methodology applied and diagnostic system used. According to a comprehensive systematic review by Galmiche et al. the lifetime prevalence of AN ranged from 0.1% - 3.6% in females and 0% - 0.3% in males (24).

## ETIOLOGY

The etiology of AN is not fully understood but most consider it a multifactorial disorder. The biopsychosocial model is an integrative framework that considers the biological, psychological and sociocultural factors that contribute to the development and maintenance of AN. The model suggests that AN is not caused by any one factor but is instead the result of complex interactions across these three domains (25). Genetic factors seem to be of great importance as shown in twin studies, with heritability estimates of AN ranging from 0.48 to 0.74 (26). Moreover, Genome-Wide association studies have provided insight into the genetic underpinnings of AN, illuminating its psychobiology. Findings pertaining to a genetic correlation between AN and a range of metabolic and anthropometric traits, indicate the AN is not solely a psychiatric disorder (27). Based on the findings a reframing of AN as a “metabopsychiatric” disorder has been suggested (28). The findings enhance our understanding of the complex biology of AN and have opened up to new pathways for research and intervention.

Socio-cultural influences such as the societal ideal of thinness as desirable and a symbol of success and control are conveyed through a variety of socio-cultural means (25, 29). Media often promote an unrealistic idealized image of the body, and these portrayals can create pressure to conform to these standards, leading to body dissatisfaction, especially in adolescents and young adults (30). A majority of adolescent girls experience dissatisfaction with their body shape and size (31). Factors that may contribute to negative body image in early adolescence include the perception of having a deficient appearance compared with peers (e.g., being taller/shorter, larger/thinner), exposure to negative peer influences such as appearance teasing and appearance pressure and general dissatisfaction with life (32). The socio-cultural influences may lead to periodic dieting in young individuals. Not everyone who diets develops AN, however, restrictive eating can trigger the disorder in individuals who may already be vulnerable due to a genetic predisposition. Perfectionism is common in individuals with EDs and involves exceedingly high standards, i.e. regarding body image and self-control. The perfectionism often extends beyond appearance and may affect other areas in life such as academic achievement and interpersonal relationships (33). The interaction of genetic risk with other identified risk factors including anxiety, perfectionism, cognitive rigidity, and early feeding problems may increase the vulnerability of an individual to develop AN (34).

Emotion regulation problems and low self-esteem are other factors associated with the development of AN. When faced with overwhelming emotions

individuals may turn to maladaptive coping mechanisms, such as starvation or over-activity. The starvation numbs or suppresses emotions, temporarily by reducing anxiety (25).

## COMORBIDITY IN AN

AN is frequently accompanied by psychiatric comorbidity among which depressive disorders, anxiety disorders, obsessive-compulsive disorder (OCD), alcohol abuse, personality disorders (especially cluster C) and neuropsychiatric disorders are common co-occurring conditions (4, 5, 35). As some comorbidities seem to subside after weight recovery, premorbid vulnerabilities may also be present and persist beyond recovery.

### *The relationship between AN, autism and ADHD*

ASD has been repeatedly associated with AN and the link between AN and ASD has gained increased attention the past two decades (36-39). Already in the 1980s a link between AN and ASD was suggested by Gillberg who proposed that a shared genetic vulnerability may interact with environmental factors to manifest as AN in girls and ASD in boys (40).

**ASD** is a neurodevelopmental disorder with onset in early childhood. It is characterized by a number of features including pervasive deficits in social communication and social interaction together with repetitive behaviors and interests, and deviances in sensory processing. ASD has a prevalence of 1% with a median male-to-female ratio of 4.2 (41).

Patients with AN are often described as socially reserved, presenting with rigid, repetitive behaviors and specific eating deviances, characteristics that are also distinctive in individuals with ASD. It is especially the restrictive subtype of AN that has been linked to ASD (36) while primarily the bingeing/purging subtype has been associated with ADHD (37). Estimates of the prevalence of ASD in individuals with AN vary widely, in adults between 8.8% and 32% meet the criteria for a possible autistic condition (36, 39, 42, 43). Studies exploring younger AN samples indicate slightly lower rates with between 4-22% scoring above cutoff for ASD (44-46).

The similarities between AN and ASD also manifest in neuropsychological characteristics, including weak central coherence, impaired cognitive flexibility (see page 12), and problems in emotion recognition. Recognizing

emotions in other people is important for successful social communication and individuals with AN may experience difficulty in this area (47). In the acute stages of AN difficulties in emotion recognition has been demonstrated (48). However, it remains unclear whether the impairments persist after recovery, as some studies have confirmed problems in emotion recognition beyond recovery (49) while others report no deficiencies in individuals recovered from AN (50).

A growing body of evidence suggests that elevated ASD traits in AN are associated with a worse overall outcome, longer duration of AN and poorer response to existing treatments (51-54).

**ADHD** is a neurodevelopmental disorder characterized by persistent symptoms of inattention and/or hyperactivity-impulsivity that interfere with functioning and development. It affects about 4.2%-7.6% of children and adolescents (55, 56) and the prevalence of ADHD in boys is 2-2.5 times higher than in girls (57). Three subtypes of ADHD exist: predominantly inattentive type, predominantly hyperactive/impulsive type and combined type.

The relationship between AN and ADHD has received less attention. Traditionally ADHD has been associated with BN and BED. These conditions are mainly driven by impulsivity, which is shared between them. It is primarily the bingeing/purging subtype of AN that has been associated with ADHD (4, 58). Lower recovery rates have been reported for individuals with AN and a high degree of ADHD symptoms (59).

## TREATMENT IN AN

AN is often described as a disorder that is challenging to treat with high rates of drop-out from treatment and low recovery rates (6, 60). The lack of insight into the seriousness of the disorder and the strong ambivalence regarding weight gain and recovery, complicates and often impedes the recovery process (61). Patients seem to value the behaviors that contribute to their illness such as self-control, mastery and perfection, and neglect the risks of these behaviors (62).

Among adolescents with AN, family-based treatment (FBT) is considered the first-line treatment (63). Parents accompany their child in treatment and are seen as important resources in therapy. Positive short-term as well as long-term outcomes can be achieved with this form of treatment (64). Despite treatment

advances and a growing body of research focused on evidence-based ED treatment, interventions for adults have been less successful, and relapse occurs frequently, especially within the first year following treatment (65, 66). The National Institute of Health and Care Excellence (NICE) recommends psychological treatments for adults comprising individual eating-disorder-focused cognitive behavioral therapy (CBT-ED), Maudsley model of anorexia nervosa treatment for adults (MANTRA) or Specialist supportive clinical management (SSCM) (67). As such, among adults, there is a continued need for development of novel treatment approaches to better target the core symptoms of AN.

In several countries evidence-based guidelines have been developed to guide the treatment of different EDs. Treatment guidelines suggest recommendations based on current scientific evidence and, in cases where there is a lack of scientific evidence available, based on expert opinion. In May 2024 the Swedish National Board of Health and Welfare introduced Swedish guidelines on treatment for EDs (68). The guidelines highlight the importance of early detection and individualized care plans. A multidisciplinary approach involving healthcare professionals such as psychologists, psychiatrists and dietitians is emphasized in the guidelines. Regarding children and adolescents with AN, FBT and eating-disorder-focused cognitive behavioral therapy (e.g. enhanced cognitive behavioral therapy for EDs, CBT-E) (69) have the highest recommendation score in the Swedish guidelines and are equally highly recommended.

Outpatient treatment is preferred and most individuals with AN can be treated in an outpatient setting. However, a subgroup needs more intensive treatment options in the course of their illness, such as day-patient- and inpatient care (19, 70).

Not all individuals with AN seek treatment, a significant proportion of individuals with AN (23-50%) are not seen in ED clinics (71-73). This fact sheds light on the importance of studying community-based samples in order to capture a broader group of individuals affected by AN.

## LONG-TERM OUTCOME STUDIES OF ANOREXIA NERVOSA

Longitudinal, prospective studies of EDs provide essential information on long-term outcome including prognostic factors. The literature on follow-up studies of AN conducted during the second half of the 20<sup>th</sup> century, has been reviewed in depth by Steinhausen (6). According to the review almost half of the individuals with AN were fully recovered, while one in three had improved and 20% developed a chronic course over the long-term. A more recent systematic review and meta-analysis, included cohort studies and clinical trials conducted between 1980-2021, and presented outcome of all EDs pooled together. At follow-up of 10-years or longer 67% had recovered while 18% developed a chronic course (19).

Generally, compared to adult-onset AN, outcome studies of adolescent-onset AN indicate better outcomes with over 80% no longer fulfilling an ED diagnosis at long-term follow-up (72, 74-76). Favorable outcomes have also been reported in the nationwide 'Finn twin' study that has prospectively followed twins and explored the outcome of AN. Out of 2825 female twins screened, 55 met the criteria for AN. At 10-year follow-up, at mean age 34, the individuals with previous AN were all alive and 88% were weight recovered, although they had a lower mean BMI compared with unaffected controls (77).

Studies with very long-term follow-up periods, longer than 20 years are rare. Three studies have followed up patients with AN more than two decades after treatment; the studies were conducted in Sweden (78), Germany (79), and the USA (80). The recovery rates ranged from 51-76% and two of the studies reported discouraging mortality rates of 16% and 18%, respectively (78, 79).

The trajectories of AN can be highly variable (6, 72). Relapses are frequently occurring, especially within the first year after treatment, but remain elevated up to two years after discharge (81). Commonly, the recovery rates increases with longer follow-ups, although there is also an increase in deaths (6). However, there are also findings indicating stabilization in recovery rates in the long-term. Results from a prospective study exploring the outcome of adult patients with longstanding EDs, from 5 to 17-year follow-up, showed that the recovery rates were stable over the long term, with recovery seeming more unlikely with a long duration of illness (82).

AN is associated with high mortality rates and according to two meta-analyses the standardized mortality ratio varied between 5.2 and 5.86 for AN (7, 83).

Some more encouraging data from two Scandinavian register studies imply that mortality from AN has decreased in the 21<sup>st</sup> century compared to the late 20<sup>th</sup> century (84, 85). The development of specialized ED care units was stated as one factor likely contributing to the reduced mortality rates (85).

## **THE GOTHENBURG ANOREXIA NERVOSA STUDY**

The Gothenburg AN study is a prospective follow-up study of individuals with AN onset in adolescence. The study was initiated by Maria Råstam and Christopher Gillberg in 1985 and has followed a community-based group of individuals with adolescent-onset AN and a healthy comparison group for three decades so far (study sample described in the methods section) (86). The participants of the Gothenburg AN study have been examined on five occasions, the fifth examination presented in this thesis (72, 86-88). The latest previous follow-up study was conducted 18-years after AN-onset. At the time, 12% had a persisting ED and 39% had other psychiatric morbidity. Furthermore, one in five reported that they had no paid employment due to psychiatric problems. ASD traits, premorbid obsessive-compulsive personality disorder and age at onset of AN were predictors of worse outcome at 18-year follow-up (89).

## **CHILDREN OF MOTHERS WITH ANOREXIA NERVOSA**

Long-term follow-up studies stretching over several decades open up to the possibility of studying health outcomes in the next generation. Previous literature on birth and perinatal outcomes in offspring of individuals with EDs has indicated an increased rate of birth complications. Elevated rates of preterm deliveries, lower birth weight, smaller head circumference, lower Apgar scores and perinatal mortality have been reported in offspring of mothers with ongoing or previous AN compared with controls (90-94). However, more favorable perinatal outcomes have also been reported (95, 96).

The psychiatric health in the offspring in childhood and adolescence has received some attention with findings indicating that children of mothers with EDs have poorer developmental outcomes including feeding and eating problems, socio-emotional difficulties and psychopathology (97, 98). The offspring of individuals with AN are at particularly increased risk of

developing AN themselves compared to offspring of controls with no history of ED (99). Moreover, the risk to offspring may extend transdiagnostically to psychiatric disorders other than that of the parent (100). ALSPAC (the Avon Longitudinal Study of parents and children,), which is a large prospective population-based study, has shown that 3-year old children of women with lifetime AN were at increased risk of emotional problems compared with children of unexposed women (101). Later in childhood, the children from the ALSPAC cohort had an overrepresentation of emotional and anxiety problems compared to controls (102). Furthermore, two register studies, one Swedish and one Finnish, have indicated that children born to females with EDs are at increased risk of neurodevelopmental disorders (103, 104), at highest risk were children with a mother who had an ongoing ED during pregnancy (103).

The physical health in offspring of mothers with AN has not been systematically investigated previously. However, offspring of parents with other mental disorders, such as depression, seem to have an increased risk of negative physical outcomes including injuries, asthma, malnutrition and diarrhea (105).

## HEALTH CARE UTILISATION AND SOCIAL WELFARE NEEDS

AN is associated with high costs for the affected individuals their families and the society. The risk of a chronic course, the numerous comorbidities, the incapacity for work and the risk of premature death imply that the burden of AN is significant. Increased rates of health care utilisation in individuals with AN, including in- and outpatient care, and a higher rate of emergency visits compared with healthy controls have been reported (8, 9). Moreover, a history of AN may have negative long-term consequences with regard to work-life and educational achievement (89, 106, 107). A large Swedish register study of former inpatients with AN reported lower employment rates and a subgroup of circa 20% who depended on societal benefits for their income (106). In the 18-year follow-up of the Gothenburg AN study 25% had no employment due to psychiatric morbidity (89). Lower employment rates have been reported in follow-up studies on inpatients with AN, where 50-71% were unemployed after about 20 years (107, 108). In contrast, employment rates similar to those of controls have also been reported in population-based samples (77). Educational levels have been reported to be either similar to or lower than among unaffected peers (77, 109, 110).

## NEUROPSYCHOLOGY IN AN

General intellectual functioning (IQ) was for long considered to be higher than average in AN. However, more recent studies have revealed no differences in overall IQ in adults as well as adolescents with AN, compared to controls (111-113). It has been hypothesized that there is a specific neuropsychological profile in individuals with AN. Impaired set-shifting (cognitive flexibility) and weak central coherence (information processing bias towards detail at the expense of seeing the “bigger picture”) is part of this typical neuropsychological profile (114, 115). Moreover, there is some evidence supporting working memory deficits in AN (116). Working memory refers to the ability to hold and work with information in mind and use the information to guide behavior. Few studies have however examined the possible influence of other relevant factors on working memory such as duration of illness or comorbid psychopathology (117, 118). This specific neuropsychological profile also manifests in individuals with ASD and ADHD and is one of several features suggesting a link between these disorders (see page. 6).

**Set-shifting** is an executive function referring to the ability to move flexibly from one task, thought, or strategy to another (119). Multiple studies have reported poor set-shifting in adults who have recovered from AN (114, 115, 120, 121). Deficiencies in set-shifting are associated with a limited range of interests, challenges in shifting perspectives, perseveration and repetitive behavior (122). Poor set-shifting may contribute to the restrictive and rigid behavior toward weight and eating in individuals with AN and prevent the behavioral change that is essential for recovery (123).

**Central coherence** refers to the ability to integrate global information into a coherent whole. Weak central coherence is the tendency to prioritize focusing on details and difficulty processing information in a global context. Weak central coherence has been found in adults with AN, in the acute stages, after recovery and in their unaffected relatives (115, 124, 125). Weak central coherence may contribute to poor treatment outcomes as it has been linked to exaggerated obsessive compulsive traits hampering behavioral change (126, 127). Further, it has been suggested that a detailed processing style can lead to restricted food choices, fixations in numbers e.g. relating to weight, calories, and/or exercise (126, 128). Furthermore, focus on details rather than the global context may be linked to the body image disturbances observed in AN. The poor global integration of visual information may exaggerate the obsession of thinness with certain body areas and underlie a distorted body image (112, 129).

Regarding younger populations with AN, the findings on impaired set-shifting and weak central coherence are inconclusive. Some studies report deviances in set-shifting and central coherence (111, 126, 130) while others reveal no impairments compared with controls (131-133). Some have hypothesized that there may be an underlying cognitive impairment that becomes exacerbated by starvation and contributes to the maintenances of AN, a “neurological scar effect” (53). An increased understanding of the neuropsychological function in adolescents with AN could lead to greater insight into the cognitions and behaviours that define the disorder, which potentially could guide treatment.

### *The state or trait question*

It has long been debated whether the neuropsychological deviances in AN are a predisposing phenomenon i.e. representing an endophenotype, or if it may be sequels, i.e. scars of the starvation and malnourishment in the acute disease stage. Already in 1945, the Minnesota Starvation Experiment investigated the impact of long-term starvation on cognitive functioning (134). The psychological impact was substantial. Many participants became obsessed with food, persistently thinking about eating. Some experienced irritability, depression and anxiety and showed signs of social withdrawal and isolation. Moreover, the refeeding phase was psychologically challenging and marked by slow, gradual weight gain. The intense obsession with food remained beyond the starvation phase for many individuals. It has been suggested that the negative impact on cognitive and social functioning associated with being in a state of starvation represents pseudo-autistic traits, which resolve after weight restoration (135). In contrast, higher rates of autistic traits in people with EDs have also been found in retrospect reports before onset of starvation as well as in individuals who have recovered from AN (37, 39, 136).

To ultimately explore the “state-trait” question, premorbid traits of AN in high risk groups has recently been examined. Dahlin et al. explored set-shifting and central coherence in young girls, 6-12 years old, of mothers with ongoing or previous AN. No cognitive deficits were detected in the high-risk girls supporting the notion that central coherence and set-shifting are likely not premorbid traits (137). In contrast preliminary findings from another family high risk study showed set-shifting deficiencies in daughters of mothers with EDs indicating that cognitive flexibility may in fact be a premorbid trait (138).

Taking both the state and trait perspectives into account, it has been suggested that some individuals with AN have underlying neuropsychological features (i.e. impaired set-shifting; weak central coherence) and may not recover from

traditional treatments, which leads to a prolonged illness. The prolonged illness, per se, may cause a “neurological scar”, further consolidating the underlying neuropsychological characteristics. As a sequel, due to the exacerbated neuropsychological features, treatment efforts may become less and less effective as the illness withstands (53).

## AIMS

The overarching aim of the present thesis was to examine individuals with adolescent-onset AN in the acute phase and 30 years after onset of AN. The thesis comprises four studies with the following specific aims:

- I. To examine the very long-term outcome of adolescent-onset AN, including recovery from ED symptoms, psychiatric morbidity, mortality, global functioning and quality of life. An additional aim was to identify predictors of outcome of AN.
- II. To investigate the outcome of children of mothers with a history of AN compared to children of mothers with no ED with regard to (a) perinatal status, (b) the prevalence of EDs and other psychiatric disorders, and (c) the prevalence of physical disorders.
- III. To explore the long-term utilisation of health care and medications, amount of social assistance received and days of sick leave and disability pension in individuals with a history of adolescent-onset AN. An additional aim was to identify early predictors of health care utilisation in the individuals with former AN.
- IV. To investigate if adolescent females with AN have a specific neuropsychological profile (deficits in central coherence and set-shifting) and its putative associations with traits of ASD and ADHD. An additional aim was to explore the resemblance between the neuropsychological profile of youths with AN and that of their parents.

## METHODS

An overview of participants, study design and data sources regarding the four papers in this thesis is shown in Table 1.

**Table 1.** Overview of participants, study design and data sources, Study I-IV.

<b>Study</b>	<b>I</b>	<b>II</b>	<b>III</b>	<b>IV</b>
<i>Study design</i>	Prospective longitudinal	Prospective longitudinal	Prospective longitudinal	Cross-sectional, 1-yr follow-up
<i>Type of study</i>	Community-based, case-control	Community-based, case-control	Community-based, case-control	Clinical group, case-control
<i>Sample size</i>	47 AN 51 COMP	83 offspring of 40 mothers with previous AN 86 offspring of 40 mothers with no ED history	51 AN 51 COMP	20 AN 28 COMP 31 AN parents
<i>Age (mean) of participants</i>	44.4 (born 1969-1977)	AN mothers: 44.5 COMP mothers: 44.4 AN offspring: 13.3 COMP offspring: 12.2	44.4	14.2 (born 1996-2003)
<i>Data source</i>	Interview, questionnaires (self-report)	Interview, questionnaires (parental) Swedish national registers	Swedish national registers, interview	Neuropsychological tests, Interview, questionnaires (self/parent)
<i>Instruments</i>	MINI, SCID-I (ED module), MROAS, GAF, SF-36	SDQ, DAWBA, MINI, SCID-I (ED module), ADHD-RS	N/A	WASI, TMT-4, WCST, RCFT, GEFT, Object assembly, AQ, SWEAA, ASSQ, DISCO, ADHD-RS, ASRS, MINI-KID (ED module)

## STUDY POPULATIONS

### STUDY I-III: THE GOTHENBURG ANOREXIA NERVOSA STUDY

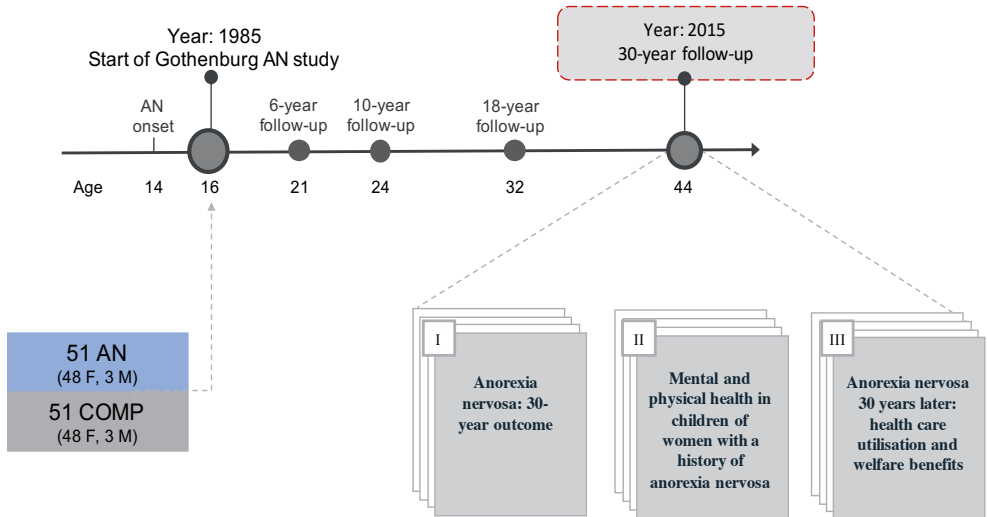
Study I-III are based on a prospective population- and community-based study ongoing since the 1980s called the Gothenburg AN Study. At the start of the study, in 1985, all 4291 individuals born in 1970 and living in Gothenburg, Sweden, attending eighth grade, were examined by the school health nurse and had his/her growth charts scrutinized in detail (by M.R.). M.R. established a close collaboration with all 36 school health nurses, including the principle school health nurse, to guarantee that all children born in 1970 experiencing symptoms of AN were traced. All individuals completed a brief questionnaire comprising food interests, weight perception, desire to lose weight and menstrual problems. The adolescents were followed by the school health nurse until leaving upper secondary school, typically after age 18 years. All individuals who raised any suspicion of suffering from symptoms of AN were repeatedly checked for weight by the school health nurses. M.R. personally examined all teenagers where AN could not be ruled out. In addition, not to miss any AN cases in this population, a register search was performed together with a screening among pediatricians and psychiatrist.

In total, 25 individuals (23 females and two males) met the criteria for AN in the 1970 birth cohort. One of the girls refused an in-depth examination, leaving 22 females and two males to constitute the *population-based group*. This group was pooled together with a group of AN cases (26 females and 1 male) born in the adjacent years, who had been recruited through community screening and referred to the research group by school health nurses and doctors (*the population screening group*). All 51 individuals (48 females, 3 males) met the DSM-III criteria (16) for AN. *The population-based group* and the *population screening group* was compared at the start of the Gothenburg AN study and found to be similar in all aspects, except treatment received (139).

A comparison group, consisting of 51 age-, gender- and school-matched adolescents with no history of EDs was selected by the school nurses (the *COMP group*). The COMP group took part in the same examinations as the AN cases.

The AN and COMP groups have been examined on five occasions, over a period of 30-years, at mean ages of 16 (AN Study 1: the original study), 21 (AN Study 2: the 6-year follow-up), 24 (AN Study 3: the 10-year follow-up), 32 (AN Study 4: the 18-year follow-up) and 44 years (AN Study 5: the 30-year

follow-up) (72, 86, 88, 89, 140, 141) (Figure 2). There has been no attrition in the first four examinations. In the present study, data were collected from May 2015 through November 2016.



**Figure 2.** The four previous examinations and the 30-year follow-up are illustrated with mean ages of the AN group at each examination displayed. AN: Anorexia nervosa; COMP: Comparison group; F: female; M: male.

At the 30-year follow-up, all 102 participants of the Gothenburg AN study were traced (51 AN and 51 COMP). Four persons belonging to the AN group declined to participate (two females, two males; total drop-out rate: 4%). All individuals were alive. In the COMP group, all individuals (n=51) agreed to take part in the fifth examination.

In Study II, only the females (48 AN and 48 COMP) were included due to the small number of male participants.

Study III was based on all participants (51 AN and 51 COMP), and data were mainly collected from Swedish national registers.

## STUDY IV: ADOLESCENTS WITH ACUTE ANOREXIA NERVOSA AT THE EATING DISORDER CENTRE FOR CHILDREN AND YOUNG ADULTS

Study IV is based on a group of female adolescents ( $n=20$ ) recruited from a specialized unit for outpatient treatment, the Eating Disorder Centre for Children and Young Adults, Sahlgrenska University Hospital, Gothenburg, Sweden. All participants met the criteria for AN according to the DSM-IV criteria (15) and were diagnosed by a psychiatrist. The participants were recruited in the acute phase of the illness (*AN-A group*) together with one or both parents. To be included in the study the following criteria had to be met: (1) a current DSM-IV diagnosis of AN, (2) age between 12 and 18 years, and (3) Swedish-speaking. A known intellectual disability (IQ below 70) was the only exclusion criterion.

A healthy comparison group ( $n=28$ ) of female adolescents with no history of EDs (*COMP group*) was recruited from three different schools in Gothenburg. The inclusion criteria were (1) absence of current or previous eating disorder (ED), and (2) age between 12 and 18 years. The exclusion criterion was known intellectual disability.

Parents (biological) of the adolescents with AN were also recruited to the study. Parents of 18 of the individuals in the AN group (mothers  $n = 15$ , fathers  $n = 16$ ) agreed to participate in the assessments.

## PROCEDURES

### STUDY I-III

The AN and COMP groups were assessed regarding psychiatric disorders (including EDs), ED outcome, general outcome and quality of life. Height and weight were taken at the day of the examination. Well known interviews and self-reports were administered (described below). The majority of the interviews were performed face-to-face (AN group: 36 face-to-face interviews; 11 online video or telephone interviews; COMP group: 42 face-to-face interviews; 9 online video or telephone interviews).

All participants were asked brief general questions about reproduction and offspring. Participants who confirmed they had offspring were asked if they would agree to take part in interviews regarding health and development in their offspring. Of the 40 women in each group who had given birth, 33 and 38 in the AN and COMP group respectively, agreed to perform the interviews. The interviewer was blinded to the group status of the participants throughout all the parental interviews until the data acquisition was completed. In addition, data regarding psychiatric diagnosis in offspring, 0-17 years old, (ICD codes: F00-F99) were collected from the National Patient register (NPR). The Swedish medical birth register (SMBR) was used to collect data on perinatal measures in the offspring.

Study III relied mainly on data from Swedish national registers. As part of the 30-year follow-up examination the participants (47 AN; 51 COMP) took part in a brief interview comprising questions about current living situation, level of education and current employment.

The 30-year follow-up examination also included other various elements of data collection, including blood samples and eye tracking, not presented in this thesis (for details see (50, 51, 142)).

### STUDY IV

After recruitment, the AN-A group completed baseline assessments: a battery of neuropsychological tests and self-reports. Parental reports covering childhood traits of ASD and ADHD were administered. The COMP group underwent the same neuropsychological tests and self-reports. In addition, a screening to rule out any current or previous ED occurrence was administered. The students were assessed at school by a clinical psychologist. Moreover, the researchers were in contact with the school health nurses regarding whether

any student in the COMP group had shown any deviances in weight raising suspicion of AN.

A follow-up assessment of the AN group was conducted approximately one year after baseline when the participants were no longer classified as underweight. One participant declined participation in the follow-up assessment leaving 19 individuals to constitute the weight restored AN group (*AN-WR group*). At the time of the follow-up the parents of the adolescents with AN also performed neuropsychological tests and self-reports. An interview pertaining to childhood symptoms of ASD was conducted with a subgroup of the parents (n = 10).

## INSTRUMENTS AND OUTCOME MEASURES BY STUDY

### STUDY I

The **Mini-International Neuropsychiatric Interview** (MINI 6.0) is a short structured diagnostic interview for DSM-IV and ICD-10 psychiatric disorders (143) and was used to assess psychiatric disorders. In addition, the ED domain of the **Structured Clinical Interview for DSM IV** (SCID-I) (144) and a **DSM-5 checklist** (1) for feeding and eating disorders were added to assess EDs.

To assess quality of life, the **36-item Short Form Health Survey** (SF-36) (145) was used. The instrument is a self-report questionnaire consisting of four physical and four mental subscales. It generates two composite scores: The *Physical Composite Score* (PCS) and the *Mental Composite score* (MCS). The Health related quality of life (HRQoL) instrument is commonly used in ED research (65).

The **Morgan-Russel Assessment Scale** (MROAS) is a semi-structured interview for estimating ED outcome. It covers clinical features central to the syndrome of AN and was launched by Morgan & Russell in the 1970's (146) and modified by Morgan and Hayward later on (147). The instrument comprises five scales (A to E) with questions focused on the six past months. Scale A is entitled Food intake, B; Menstrual pattern, C: Mental state, D: Psychosexual state, E: Socioeconomic state. A Morgan Russel averages scale

score which is an average composite score of all scales (A+B+C+D+E) can be calculated. The MROAS has been widely used in research and in clinical practice (147).

The **Global Assessment of Functioning scale (GAF)**, a global rating that estimates the degree of psychiatric symptoms and level of functioning was used. The GAF scale consists of a 100-point scale (range: 1-100) with poor functioning and severe psychiatric symptoms at the lower end and superior functioning in a wide range of activities with no psychiatric symptoms at the other end. The GAF has been shown to be a reliable and valid measure (148).

## STUDY II

In Study II the data collection was based on parental interviews, parental reports as well as register data. Interview instruments were selected based on the age of the offspring and the children were divided into three groups: 0-4 year old; 5-17 year old; and adult offspring (> 18 years).

### *Perinatal status measures in the offspring*

The **Swedish Medical Birth Register (SMBR)** was used to collect data on gestational age, birth weight and length, head circumference, Apgar score (Appearance, Pulse, Grimace response, Activity, Respiration) at 1, 5 and 10 minutes and perinatal death (death within six days of birth) (149). The *ponderal index (PI)* (a ratio indicating the body proportions of an infant; kg/m<sup>3</sup>) was also calculated.

### *Assessment of mental health in the offspring*

*0-4 year old children:* In order to assess developmental problems in infancy a **brief semi-structured parental interview** was carried out. The interview targeted sleep, colic, breastfeeding, selective eating, parental concern regarding weight and psychomotor development. The interview has been used previously (95), but has not been tested for validity or reliability. **The Strengths and Difficulties Questionnaire (SDQ)** is a validated, well established brief questionnaire used for general mental health screening in children aged 2-17 years (150). The SDQ comprises 25 items divided into five subscales: emotional symptoms, conduct problems, hyperactivity, peer

problems and prosocial behavior. The SDQ is completed by the parent and covers the child's behavior the past six months.

*5-17 year old children:* In addition to the SDQ, the **Developmental and Well-Being Assessment** (DAWBA) (151), a well validated parental interview was administered in this age group. A web-based version of the DAWBA was used. The instrument assesses psychiatric disorders in children 5-17 years old. The DAWBA generates ICD-10 and DSM-IV diagnoses and comprises separate sections covering individual, emotional, behavioral and hyperactivity disorders, including a section examining EDs. Further, the **ADHD Rating Scale** (ADHD-RS) (152) was administered to investigate Attention-Deficit/Hyperactivity Disorder for children at or above age 5. Psychiatric diagnoses (ICD codes: F00-F99) were collected from the **Swedish National Patient Register** (NPR) regarding offspring aged 0-17 years old at the time of the examination of the mother.

*Adult offspring (>18 years):* The **MINI 6.0** (143) was used to assess psychiatric disorders and the ED domain, specifically, of the **SCID-I**. In addition, the **ADHD-RS** (152) was administered to explore Attention-Deficit/Hyperactivity Disorder i.e. the mother responded to the questions regarding their adult offspring.

### *Outcome measures physical health of the offspring*

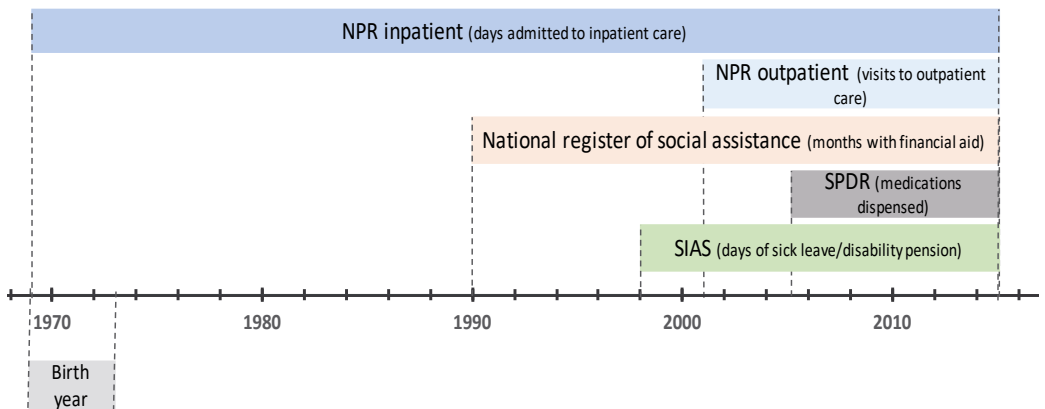
Physical disorders were identified in the NPR using ICD-10 codes regarding children 0-17 years old. In addition, all mothers were asked to report weight and height of their child (aged 5-25 years).

## **STUDY III**

Register data were collected from the **Swedish National Board of Health and Welfare** as well as from the **Swedish Social Insurance Agency** (SIAS). The **NPR** stores data from 1964 on inpatient care and visits to specialized outpatient care. Data on outpatient visits were included in the NPR from 2001. The NPR gathers information on main and secondary diagnoses coded according to the International Classification of Disease, eighth revision [ICD-8] (153), in use between 1968 and 1986, the International Classification of Disease, ninth revision [ICD-9] (154) in use between 1987 and 1996, and the International Statistical Classification of Diseases and Related Health Problems, tenth revision [ICD-10] (155), in use since 1997. The validity of the NPR is high

(156). From the NPR data on days admitted to inpatient care including observed hospitalizations with a registered ED diagnosis was collected. The utilization of outpatient care was defined as the number of visits in specialized outpatient care. The **Swedish Prescribed Drug Register (SPDR)** contains all prescribed medicines since 2005, classified according to the Anatomic Therapeutic Chemical Classification system (ATC). The drug register has almost complete coverage (157). The main outcome variable collected was the number of prescribed psychotropic medications (ATC codes N05, N06). The **Swedish register of social assistance** stores data on social assistance (financial aid) from the year 1990. Information was collected on the number of months that each group had received social assistance.

The SIAS administers the area of the social insurance that provides financial security if an individual were to be ill, disabled to work and for families with children. The SIAS hold registers that contain information on benefits within social insurance. Sick leave was defined as absence due to illness/disability >14 days, as the Swedish social insurance agency only stores information about sick leave from day 15. The net number of days with sick leave and/or disability pension was collected from the SIAS register. An overview of the registers used is displayed in Figure 3.



**Figure 3.** Overview of the registers used in Study III. NPR: National patient register; SPDR: Swedish prescribed drug register; SIAS: The Swedish social insurance agency.

In addition to the register information, data on highest attained level of education and current employment were collected at the 30-year follow-up study by a brief interview. The participants also reported upon their marital status in the interview.

## STUDY IV

### *Neuropsychological assessments*

The **Wechsler Abbreviated Scale of Intelligence** (WASI) (158) was used at baseline to assess general intellectual ability in the acute phase of AN (AN-A group) and in the COMP group. The WASI comprises four subtests: Block design, Matrix reasoning, Vocabulary and Similarities. Set-shifting ability was assessed with the **Trail Making Test** (TMT-4), a subtest of the Delis Kaplan Executive Function system (159) and the computerized version of the **Wisconsin Card Sorting Test** (WCST) (160) (an overview of the tests is shown in Table 2). A central coherence index (CCI) was obtained from the copy condition of the **Rey Complex Figure Test** (RCFT) (161). The CCI (range: 0-2) comprises an order of construction index (OCI) as well as a drawing style index (SI) (162, 163). A higher CCI score indicates a more global or holistic processing ability. The original scoring procedure was presented by Booth (162), in Study IV the slightly modified scoring instruction described by Lang et al. (164) was used. **The Group Embedded Figures Test** (GEFT) (165) was used as an additional measure of central coherence. Individuals with a more detail-oriented approach tend to achieve higher scores on the GEFT. Moreover, the **object assembly subtest** from the Wechsler adult/child intelligence scale III was used.

**Table 2.** Overview of the neuropsychological tests used

Assessed area	Test/task	Description
Intelligence quotient, IQ	WASI	Comprises four subtests from the Wechsler intelligence scales: Block design, Matrix reasoning, Vocabulary and Similarities. Provides intelligence estimates in perceptual and verbal reasoning as well as full scale IQ.
Set-shifting	TMT-4	The condition prompts the individual to connect a sequence, alternating between numbers and letters (e.g. 1-A-2-B). Time required to complete the task is the outcome.
	WCST	The test person has to match cards according to an unknown sorting rule. The sorting rule changes every 10 cards and the proband must adapt to the new rule.
Central coherence	RCFT (CCI)	CCI consists of organization index, OCI (range:0-3.3), and style index, SI (range: 0-2). OCI assesses the order in which the elements of the RCFT figure are drawn (global, detailed) and SI captures the style of drawing (coherent, fragmented).
	GEFT	The test consists of a series of complex figures, each containing a simple figure that is embedded within it. The task requires the individual to identify the simple figure within the more complex image as quickly and accurately as possible.
	Object assembly	The task requires the participant to complete jigsaw puzzles depicting familial objects. In order to complete the test fast and accurately, the ability to disregard concrete detail in the construction of a coherent "whole" is favorable.

### *Self-reports and interviews*

**The Autism Spectrum Questionnaire (AQ)** is a self-report questionnaire based on the autism spectrum symptomatology and was first introduced by Baron-Cohen and colleagues (166). The questionnaire contains 50 items based on five different areas with a cutoff of 32 points to identify levels of autistic traits considered to be clinically significant. **The Swedish Eating Assessment for Autism spectrum disorders (SWEAA)**, a self-report questionnaire, targets typical eating and mealtime problems in individuals with ASD and normal intelligence (167). The SWEAA comprises 60 items divided into different subscales (A-J) targeting deviant eating behavior: A. Perception; B. Motor control; C. Purchase of food; D. Eating behavior; E. Mealtime surroundings; F. Social situation at mealtime; G. Other behaviors associated with disturbed eating; H. Hunger/satiety; I. Simultaneous capacity, and J. Pica. The SWEAA has shown reliability in terms of Cronbach's alpha and good test-retest ability (167). The total score cutoff is 12 while the subscale based cutoff score (based on subscale F and I; developed to differentiate between ASD and no ASD) has a value of 10 (42).

**The Autism Spectrum Screening Questionnaire (ASSQ)** is a screening questionnaire for autism (168). It is based on 27 items and is rated on a three-point scale, (0 = indicating normality, 1 = some abnormality, and 2 = definite abnormality), with a possible maximum score of 54 points. Eleven items cover topics regarding social interaction, six target communication problems and five refer to restricted and repetitive behavior. The remaining five items embrace motor clumsiness and other associated symptoms including motor and vocal tics. Cutoff scores of 19 or more for the parental version have been recommended in Sweden for screening to identify ASDs in children. To more accurately capture the phenotype of autism in females, 18 items were added by Kopp and colleagues (ASSQ-REV) (169).

**The Diagnostic Interview for Social and Communication disorders (DISCO)** (170) is a standardized interview used to assist clinicians in the diagnostic work-up and care of persons with ASD. The interview takes 2-4 hours and is intended for interviewing a person who has known the individual with suspected ASD from early childhood.

**ADHD-RS** (described in Study II) was administered as a parental interview regarding the current and childhood symptoms of their child at baseline. In order to assess ADHD symptoms in the AN parent group the **ADHD Self-Report Scale (ASRS v.1.1)** was used. The ASRS is one of various self-report measures developed to assess current manifestations of ADHD symptoms in

individuals aged 18 years or older (171). It covers inattentive, hyperactive, and impulsive symptoms including 18 items to measure the symptoms specified in the DSM-IV. Respondents are required to use a five-item Likert scale to indicate the frequency of the occurrence of symptoms (0 = never; 1 = rarely; 2 = sometimes; 3 = often; 4 = very often). The first six questions (Part A) were found to be the most predictive of symptoms consistent with ADHD (172). A global score (range 0-72) was also calculated.

In order to rule out EDs in the COMP group the ED module of the **Mini-International Neuropsychiatric Interview for Children and Adolescents** (MINI-KID) was used to screen the students in the COMP group. MINI-KID is a structured clinical diagnostic interview designed to assess the presence of current DSM-IV and ICD-10 psychiatric disorders in children and adolescents aged 6 to 17 years (173).

## STATISTICAL ANALYSES BY STUDY

Data analyses were performed in SPSS, SAS/STAT and R. The statistical significance level was set to  $p < 0.05$  in all studies.

### STUDY I

Comparisons between the AN group and the COMP group were performed with the Mann–Whitney test for continuous variables and the Chi-squared test or Fisher’s exact test were used for dichotomous variables. Change over time was assessed by using McNemar’s test for dichotomous variables and the Wilcoxon signed-rank test for continuous variables.

Predictive factors were selected in line with a previous follow-up study (18-year follow-up) and focused on variables measured at AN Study 1, the original study, and premorbid childhood data. The predictors were: age at AN onset; premorbid BMI; lowest BMI ever assessed at AN Study 2; perinatal factors; social class; early gastrointestinal problems; primary amenorrhea; premorbid problems with friends; major problems in the family; major life events; parental divorce; death of family member; affective disorder; overweight; obsessive-compulsive disorder; obsessive-compulsive personality traits; premorbid perfectionism; ASD before AN Study 1 and/or at AN Study 2. The outcome variables were: GAF, Morgan-Russel averaged scale score, PCS, MCS and full recovery from ED symptoms. Spearman correlations were used to examine the association of two continuous variables and the Mann-Whitney test was used for associations of continuous with dichotomous variables. Logistic regression was performed for the univariate associations of predictors with the dichotomous variable ‘full recovery from ED symptoms’. Variables with  $p < 0.10$  in the univariate analysis were entered as possible predictors in the multiple stepwise regression analyses.

### STUDY II

In order to analyze offspring data statistical methods that could deal with clustered data were used as most of the mothers contributed with multiple births to the dataset. A mixed model analysis was performed for continuous variables and Generalized Estimating Equations (GEE) was used for dichotomous variables. Group comparisons between the mothers in the AN and COMP group were carried out with non-parametric tests, due to small

sample and non-normal distribution. The Mann–Whitney test was used for continuous variables and Chi-squared test or Fisher’s Exact test were used for dichotomous variables.

### STUDY III

For comparisons between groups, mainly non-parametric tests were used, as the scale scores were not normally distributed, and the group sizes were relatively small. The Chi-squared test or Fisher’s Exact test were used for dichotomous variables and the Mann-Whitney test for continuous variables. Analysis of predictive factors for binary outcomes (e.g. ever admitted to psychiatric inpatient care, ever visited psychiatric outpatient care) were performed with logistic regression in both univariable and multivariable analyses. For discrete count variables (e.g. days in psychiatric inpatient care, days in somatic inpatient care, visits to somatic outpatient care), log-linear quasi-Poisson regression was performed in both univariable and multivariable analyses. Correlations between health care utilisation outcomes and predictors were performed using Spearman correlation coefficients.

### STUDY IV

In Study IV, comparisons between groups were conducted with Fishers non-parametric permutation test for continuous variables and Fisher’s exact test for dichotomous variables. Fisher’s non-parametric permutation test for paired observations was used to analyze change over time, from baseline to follow-up, within the AN group. Spearman’s correlation coefficient was used to analyze associations between variables.

Predictor analyses were performed using univariable logistic regression followed by multivariable regression. Variables with p-values  $<0.10$ , in the univariable analysis, were entered in a multivariable regression. The model was evaluated using Tjur’s discrimination index.

## ETHICAL CONSIDERATIONS

All four studies were approved by the Regional Ethical Review Board, University of Gothenburg or the Swedish Ethical Review Authority and followed the World Medical Association's Declaration of Helsinki. All participants received oral and/or written information about the study and consented to participate voluntarily. For participants <18 years their parent/s also received oral and/or written information about the study.

Study I-III:           The Regional Ethical Review Board at the University of Gothenburg (reg. no. 398–14) and the Swedish Ethical Review Authority in 2023 (2023-03127-02) (Study III, amendment).

Study IV:             The Regional Ethical Review Board at the University of Gothenburg (reg. no. 395-12).

Although ethical considerations were made throughout this thesis, various ethical questions still arose. One such consideration is the fact that participants with previous AN, taking part in the 30-year follow-up study, could be reminded of a time when they were severely ill which can bring back unpleasant thoughts and feelings. However, as all the participants agreed to participate in the four previous examinations it may indicate that taking part in the study has not been perceived as a negative experience. Moreover, the parents could be troubled/worried with regard to psychiatric diagnoses that may be identified in their children. If psychiatric morbidity were identified/suspected regarding the offspring, referral to appropriate healthcare department was offered to the participating parent.

In Study I, II and IV, the research group was prepared to handle possible co-occurring conditions that were identified through the diagnostic interviews. The participants were offered to be referred to treatment if applicable.

In Study IV the adolescents with AN could screen positive for a neuropsychiatric disorder, which may be challenging to cope with. On the other hand, such information could enable treatment adaptations to prevent a possibly prolonged course of AN. From an ethical point of view the test

procedure could be perceived as very challenging or exhausting when severely starved, as in the acute phase of AN. Most adolescents found the tasks acceptable and some even found the tasks exciting. It would not have been possible to perform the tasks if the adolescent/child was not willing to participate. In cases where the test procedure appeared clearly tiring, the test-leader made sure to administer the tests on two occasions. Furthermore, as the participants were in treatment they (and their parents) were also well informed that participating or declining did not affect their course of treatment in any way.

Another ethical aspect that was discussed pertains to the adult offspring in Study II. No register data were collected for offspring over 18 years of age and therefore all information regarding adult offspring was reported by the mothers.

## RESULTS

### STUDY I: AN: 30-YEAR OUTCOME

#### EATING DISORDERS, PSYCHIATRIC MORBIDITY AND RECOVERY

All 102 individuals in the AN and COMP group were alive at the 30-year follow-up. Nine individuals in the AN group (19%) met the criteria for a current ED (Table 3). The mean duration of all aggregated episodes of AN was 4.9 years (SD: 5.1) while the mean duration of all aggregated episodes of EDs was 10.2 years (SD: 8.1).

*Table 3. Prevalence of psychiatric diagnoses at the 30-year follow-up and the prevalence of psychiatric diagnoses between AN Study 4 and AN Study 5.*

	Current diagnoses		Diagnoses between AN Study 4 and AN Study 5	
	AN group (N=47) <sup>a</sup>	COMP group (N=51)	AN group (N=46) <sup>b</sup>	COMP group (N=51)
	n (%)	n (%)	n (%)	n (%)
ED	9 <sup>c**</sup> (19.1)	1 (2)	16 <sup>d***</sup> (34.8)	1 <sup>e</sup> (2)
AN	3 (6.4)	0	8 <sup>**</sup> (17.4)	0
Any affective disorder	8 (17.8)	3 (5.9)	22 <sup>*</sup> (48.9)	13 (25.5)
Any anxiety disorder	13 <sup>*</sup> (28.9)	5 (9.8)	19 <sup>**</sup> (42.2)	7 (13.7)
Any psychiatric disorder excluding EDs	17 <sup>**</sup> (37.8)	6 (11.8)	26 <sup>**</sup> (57.8)	15 (29.4)
Any psychiatric disorder including EDs	21 <sup>***</sup> (46)	6 (11.8)	31 <sup>***</sup> (67.4)	15 (29.4)

ED: eating disorder; AN: anorexia nervosa; COMP: Comparison.

<sup>a</sup> Two individuals were interviewed regarding EDs but not regarding other psychiatric disorders.

<sup>b</sup> One individual was interviewed only regarding current psychiatric disorders, leaving 46 individuals who were interviewed regarding psychiatric disorders between AN Study 4 and AN Study 5.

<sup>c</sup> AN n=3; Other specified feeding or eating disorders (OSFED) n=5; Binge-eating disorder (BED) n=1

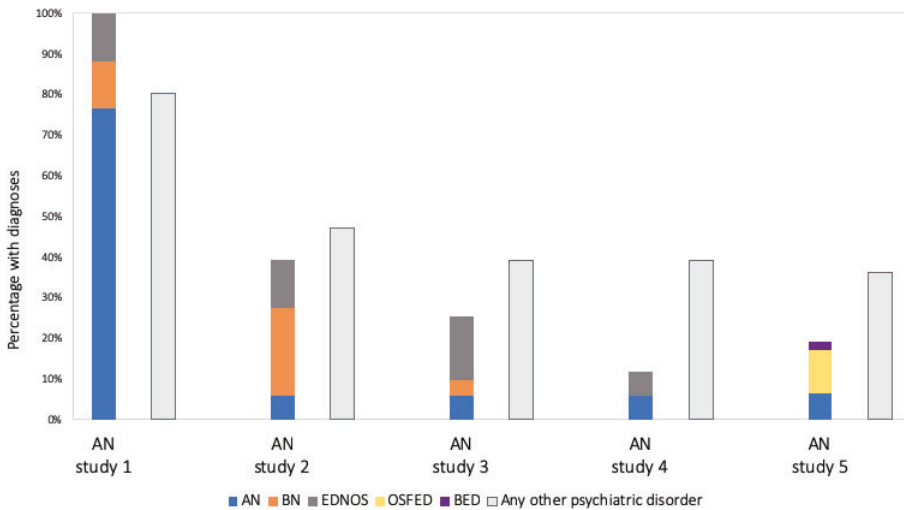
<sup>d</sup> One individual had fulfilled the criteria for both AN and BED between AN Study 4 and AN Study 5. i.e. 15 individuals with EDs including one individual with two EDs; cross-over from BED to AN between AN Study 4 and AN Study 5.

<sup>e</sup> OSFED night eating syndrome.

\* p<0.05, \*\*p<0.01, \*\*\*p<0.001; AN group vs. COMP group.

Psychiatric morbidity, other than EDs, was common and significantly overrepresented in the AN group, affecting 37.8%. Anxiety disorders were the most prevalent psychiatric disorder in both groups (Table 3).

With regard to full ED symptom recovery, 64% were considered fully recovered in the AN group. In the AN group, the Morgan-Russell average scale score was 9.60 (SD: 1.82) compared to 10.67 (SD: 1.63) in the COMP group ( $p = 0.003$ ). The AN group had a significantly lower mean GAF score than the COMP group (AN: 60.7; SD: 17.2; COMP: 80.2; SD: 14.8;  $p < 0.0001$ ). While our previous follow-up studies have indicated a gradual decrease in ED prevalence over time, the present study showed an increase in the number of individuals meeting the criteria for an ED compared to the 18-year follow-up (AN Study 4). ED diagnoses and psychiatric morbidity in the AN group at the original study (AN Study 1) and across the four follow-up studies are shown in Figure 4.



**Figure 4.** Eating disorders and other psychiatric disorders in the AN group at the original study (AN study 1) and across the four follow-up studies. Note: AN Study 1-4, based on 51 cases; AN Study 5, based on 47 cases. AN: Anorexia nervosa; BN: Bulimia nervosa; EDNOS: Eating disorders not otherwise specified; OSFED: Other specified feeding or eating disorders; BED: Binge-eating disorder.

Relapses between the two most recent follow-up studies (AN Study 4 and AN Study 5) were frequent in the AN group, including 17% (n=8) fulfilling the criteria for AN at some point between AN Study 4 and AN Study 5. The individuals who fulfilled the criteria for AN in the 18-year follow-up (n=3) were all free from any ED in the 30-year follow-up.

## **QUALITY OF LIFE**

Thirty-seven individuals in the AN group and 47 from the COMP group completed the SF-36. The Mental Composite Score (MCS) was significantly lower in the AN group compared to the COMP group (AN mean: 45.0, SD: 13.4; COMP mean: 51.2, SD: 7.8,  $p=0.011$ ) while the Physical Composite Score (PCS) did not differ across groups (AN mean: 54.8, SD: 7.3; COMP mean: 54.9, SD: 7.4,  $p=0.937$ ). Individuals in the AN group with a current ED did not score significantly lower on the MCS, compared to those who had no ED at the 30-year follow-up.

## **TREATMENT**

Twenty-three percent had never received treatment for an ED. At the 30-year examination two individuals were in treatment for an ED, one of the individuals received compulsory treatment. There were no difference between those who had received treatment and those who had not with respect to outcome as measured by MROAS average scale score and GAF score.

## **PREDICTORS OF GOOD OUTCOME**

Full ED symptom recovery was predicted by a higher age at onset of adolescent onset AN. Higher age at AN onset and perfectionism before onset of AN were predictors of better outcome with regard to GAF, Morgan-Russel average scale score and the HRQoL mental composite score. In addition, gastrointestinal problems in childhood predicted a better outcome on the Morgan-Russel average scale score. A summary of the predictors is shown in Table 4.

*Table 4. Predictors of good outcome in different outcome measures*

<b>Predictor</b>	<b>Outcome measure</b>
Higher age at AN onset	Full ED symptom recovery GAF score MROAS HRQoL mental composite score
Premorbid perfectionism	GAF score MROAS HRQoL mental composite score
Early gastrointestinal problems	MROAS

ED: eating disorder; GAF: Global assessment of functioning; MROAS: Morgan-Russel average scale score; HRQoL: Health related quality of life.

## STUDY II: HEALTH IN CHILDREN OF MOTHERS WITH A HISTORY OF AN

### REPRODUCTION AND PERINATAL OUTCOMES

There was no difference between the AN group and the COMP group regarding childbirth, 40 (83%) women in each group had given birth to at least one child. Altogether 93 children (46 girls; 47 boys) were born to the AN group and 86 children (33 girls; 53 boys) to women in the COMP group. The mean number of children born was 1.98 (SD: 1.33) and 1.79 (SD: 1.05) in the AN and COMP group respectively ( $p=0.45$ ). Six of the mothers in the AN group had a current ED at the time of the 30-year follow-up examination. In the AN group, the age of the offspring ranged from 0-25 (mean age: 13.3, SD: 6.0) and in the COMP group the age range was 0-24 years (mean age: 12.2, SD: 4.9). Thirty-six of the women in the AN group and 32 of the mothers in the COMP group were found in the SMBR, providing data on 82 (88%) and 68 (79%) newborns, respectively. The perinatal outcome showed that all of birth weight and length, head circumference and ponderal index were significantly reduced in the offspring of the mothers in the AN group (Table 5).

**Table 5.** Comparison of the perinatal status of offspring of women with a history of AN and offspring of women in the COMP group based on SMBR data.

	<b>Children of mothers in the AN group<sup>a</sup></b> (N = 82)	<b>Children of mothers in the COMP group<sup>c</sup></b> (N = 68)
	Mean (SD)	Mean (SD)
Birth weight (g)	3267 <sup>a*</sup> (598)	3633 <sup>a</sup> (682)
Birth length (cm)	49.4 <sup>b*</sup> (2.8)	50.7 <sup>c</sup> (2.6)
Ponderal index (kg/m <sup>3</sup> )	26.7 <sup>b*</sup> (2.6)	27.8 <sup>c</sup> (2.7)
Head circumference (cm)	34.3 <sup>*</sup> (1.6)	35.3 (1.9)

Results are based on a mixed model analysis adjusted for clusters within mothers that contributed with multiple births to the dataset. Adjusted means are shown. CI: confidence interval; SMBR: Swedish medical birth register. Note. Ponderal index: a standard measure for reporting body mass index in newborns (kg/m<sup>3</sup>).

<sup>a</sup>Data missing of 1 child.

<sup>b</sup>Data missing of 2 children of the AN mothers.

<sup>c</sup>Data missing of 2 children of the COMP mothers. \* p<0.05

## MENTAL AND PHYSICAL HEALTH IN OFFSPRING

In the AN group, 33 mothers of 59 children took part in the parental interviews regarding health in the offspring. In the COMP group, there were 38 mothers of 73 children participating. The seven mothers who declined the offspring interviews did not differ from the mothers who took part in the interviews with regard to age, BMI and ED duration. In the offspring in the AN group, an overrepresentation of current psychiatric disorders based on the parental interviews was found (Table 6). Psychiatric or neurodevelopmental disorders, in a lifetime perspective, did not differ significantly across groups (p=0.11). Lifetime EDs affected 7.2 % (5 girls, 1 boy) of the children in the AN group and 1.2% (1 girl) of the offspring in the COMP group, the difference across groups failed to reach statistical significance (p=0.061). Among the offspring in the AN group it was more common to have a physical condition within the group of endocrine, immune and metabolic diseases compared to the offspring in the COMP group (p=0.002) (Table 6).

**Table 6.** Psychiatric- and physical disorders in the offspring of the AN group and the offspring in the COMP group

	AN offspring n = 59		COMP offspring n = 73	
	n	%	n	%
<i>Current psychiatric disorders</i>				
Any eating disorder	3 <sup>a</sup>	5.1	1 <sup>b</sup>	1.4
Any psychiatric disorder	11*	18.6	3	4.1
	AN offspring n = 83		COMP offspring n = 86	
	n	%	n	%
<i>Lifetime psychiatric disorders</i>				
Any eating disorder	6 <sup>c</sup>	7.2	1 <sup>b</sup>	1.2
Any affective disorder	8	9.6	4	4.7
Any anxiety disorder	11	13.3	6	7
<i>Lifetime physical disorders</i>				
Any endocrine, immune, nutritional and metabolic disease	13 <sup>d**</sup>	15.7	2	2.3
Any disease of the digestive system	7	8.4	7	8.1
Any disease of the nervous system including seizures	6	7.2	3	3.5
Any disease of the respiratory system	15	18.1	8	9.3

AN: Anorexia nervosa; COMP: Comparison; EDNOS: Eating disorders not otherwise specified; BED: Binge-eating disorder

<sup>a</sup> EDNOS n=3 (1 male, 2 female)

<sup>b</sup> AN; n=1 (female)

<sup>c</sup> AN; n=1 (female); EDNOS n=4 (1 male, 3 female); BED n=1 (female)

<sup>d</sup> Juvenile arthritis n=3; Celiac disorder n=2; Hypothyroidism n=2; Deviant growth n=2; Gilberts syndrome n=1; Diabetes type 2 n=1; Disorders of puberty n=2; Iron deficiency n=1 note. One individual had two conditions.

\* p<0.05, \*\* p<0.01; AN group offspring vs. COMP group offspring

## STUDY III: HEALTHCARE UTILISATION AND SOCIAL WELFARE NEEDS

### HEALTHCARE UTILISATION AND MEDICATION

The overall healthcare utilisation in the AN group was higher compared to the COMP group, and most prominent around the time of the study start (in 1985) and the following years. The AN group had significantly more days of psychiatric and somatic inpatient care (psychiatric:  $p < 0.001$ ; somatic:  $p < 0.001$ ) and had more visits to psychiatric outpatient care compared with the COMP group ( $p < 0.001$ ) (Table 7). The distribution of the total number of days in inpatient care, in the AN group, in different healthcare departments is presented in Figure 5.

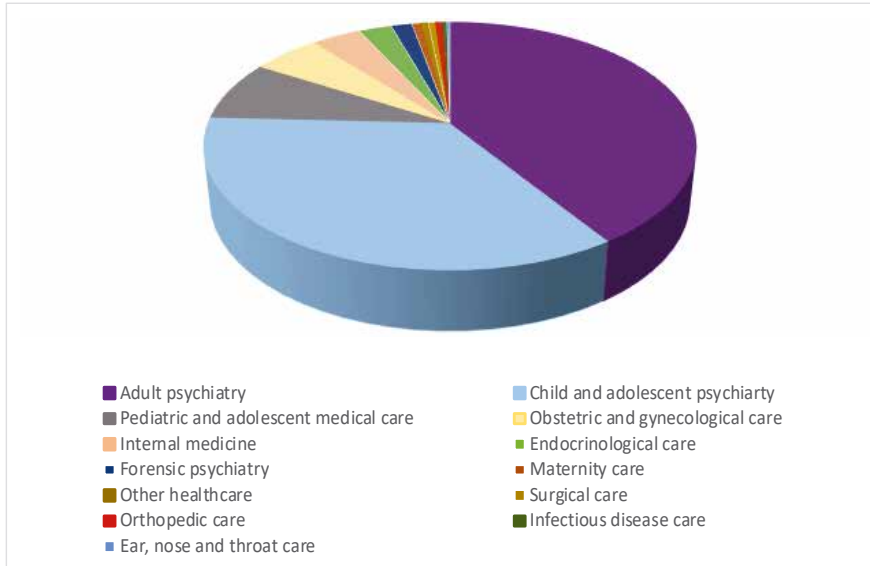
*Table 7. Utilisation of in- and outpatient care in the AN and COMP groups.*

	<b>AN group</b> N = 51	<b>COMP group</b> N = 51
<b>Inpatient care, 1972-2015</b>		
Ever admitted to inpatient care, n (%)	46 (90.2)	43 (84.3)
Total no. of days in inpatient care	7419	1232
Ever admitted to <i>psychiatric</i> inpatient care, n (%)	17*** (33.3)	2 (3.9)
Ever admitted to <i>inpatient care for ED</i> , n (%)	12 (23.5)	0
No. of days in <i>psychiatric</i> inpatient care, mean (SD; range)	111.0*** (295.2; 0-1331)	6.5 (43.0; 0-307)
<b>Outpatient care, 2001-2015</b>		
Ever had a visit to outpatient care, n (%)	45 (88.2)	44 (86.3)
Ever had a visit to <i>psychiatric</i> outpatient care, n (%)	20*** (39.2)	3 (5.9)
No. of outpatient visits to <i>psychiatric</i> care, mean (SD; range)	6.9*** (16.6; 1-91)	1.1 (6.0; 1-42)

AN: anorexia nervosa; COMP: Comparison; SD: Standard deviation. ED: Eating disorder.

\*\*\*  $p < 0.001$

The number of prescribed psychotropic medications, from year 2005-2015, was significantly higher in the AN group (AN mean: 78.9, SD: 257.8; COMP mean: 6.4, SD: 25.6,  $p=0.045$ ). The two most frequently prescribed groups of medications in the AN group were psycholeptic (e.g. anxiolytics) and psychoanaleptic drugs (e.g. antidepressants).



**Figure 5.** Distribution of the total number of days in inpatient care in different healthcare departments in the AN group.

## SICK LEAVE, DISABILITY PENSION AND SOCIAL ASSISTANCE

The mean number of days with sick leave was 424.1 (SD: 749.6) and 153.6 (SD: 425.6) in the AN and COMP group respectively ( $p=0.006$ ). Twenty-two per cent in the AN group had ever received a disability pension compared with 2% in the COMP group ( $p=0.004$ ). In the AN group 45.1% had received social assistance at some point compared to 21.6% in the COMP group ( $p=0.02$ ).

Age at AN onset emerged as a predictor with statistically significant ORs for psychiatric inpatient (OR = 0.61, 95% CI: 0.39, 0.94;  $p=0.027$ ), outpatient care (OR = 0.63, 95% CI: 0.40, 0.98;  $p=0.042$ ) and use of psychotropic medication (OR=0.66, 95% CI: 0.43, 1.00;  $p=0.048$ ), meaning that individuals

with a later onset of AN were less likely to require psychiatric in- and outpatient care and psychotropic medication.

## **STUDY IV: THE COGNITIVE PROFILE IN ADOLESCENTS WITH AN**

### **NEUROPSYCHOLOGICAL ASSESSMENTS**

At the baseline assessments there were no differences across the AN group and the COMP group with regard to the neuropsychological test results (Table 8). At the one-year follow-up results showed a significant difference across groups with regard to performance on the GEFT task, indicating a superior detail processing in weight-recovered adolescents with AN (Table 8) (note: only baseline data of the COMP group were available).

### **ASD TRAITS AND ADHD SYMPTOMS**

The mean AQ score was significantly higher in the AN group compared to the COMP group at baseline (AN mean: 19.6, SD: 8.6; COMP mean: 12.9, SD: 4.9,  $p=0.0017$ ) and follow-up (AN mean: 17.9, SD: 9.0; COMP mean: 12.9, SD: 4.9,  $p=0.02$ ). In the AN group, 10% ( $n=2$ ) and 5.3% ( $n=1$ ) scored above the cutoff for ASD in the first and second assessment respectively. After weight restoration 10.5% ( $n=2$ ) in the AN group scored above the cutoff of the ADHD-RS and another two adolescents in the AN group had been assigned a diagnosis of ADHD at the ED unit or after referral to a child and adolescent psychiatric clinic. Parental reports of ASD traits and ADHD symptoms were all below the cutoff. No associations were found between set-shifting or central coherence data and AQ scores or between set-shifting data and ADHD-RS results.

### **RESEMBLANCE IN NEUROPSYCHOLOGICAL PROFILE OF THE ADOLESCENTS WITH AN AND THEIR PARENTS**

The object assembly task, a subtest assessing central coherence, was the only parent-child resemblance found in this study. There was a significant positive correlation between the adolescents with AN and their fathers ( $r=0.53$ ;  $p=0.035$ ) indicating that the weaker the central coherence in the adolescent with AN, the weaker the central coherence in their father.

**Table 8.** Neuropsychological test results of adolescents with acute anorexia nervosa and after weight restoration contrasted with a healthy comparison group

	Baseline		1-year follow-up		Effect size	
	AN-A (n = 20)	COMP (n = 28)	Difference between groups <sup>a</sup> mean (95% CI)	AN-WR (n = 19)		Difference between groups <sup>b</sup> mean (95% CI)
TMT-4	mean (SD) 10.0 (1.62)	mean (SD) 10.4 (2.2)	-0.429 (-1.583; 0.727)	mean (SD) 9.6 (2.3)	-0.850 (-2.20; 0.545)	0.372
WCST perseverative responses	18.4 (24.9)	13.7 (13.8)	4.65 (-6.67; 14.78)	9.41 (5.16)	-4.30 (-11.67; 1.60)	0.371
WCST perseverative errors	15.6 (18.4)	12.4 (11.3)	3.19 (-5.58; 11.00)	8.59 (4.93)	-3.80 (-9.90; 1.20)	0.396
GEFT	10.6 (4.8)	8.8 (4.6)	1.76 (-1.07; 4.50)	13.3** (3.5)	4.53 (2.08; 7.09)	1.06
RCFT, Central coherence index	1.24 (0.37)	1.34 (0.27)	-0.103 (-0.287; 0.087)	1.42 (0.36)	0.078 (-0.106; 0.264)	0.251
Object assembly	10.4 (2.4)	11.4 (2.4)	-1.04 (-2.44; 0.33)	11.3 (3.2)	-0.077 (-1.700; 1.583)	0.028

AN-A: Acute anorexia nervosa; COMP: Comparison; AN-WR: Anorexia nervosa weight restored; SD: Standard deviation; CI: Confidence interval;

TMT-4: Trail making test condition 4; WCST: Wisconsin card sorting test; GEFT: Group embedded figures test; RCFT: Rey Complex figures test.

<sup>a</sup> AN-A vs. COMP<sup>b</sup> AN-WR vs. COMP

\*\*p &lt; 0.001

## DISCUSSION

### DISCUSSION OF MAIN FINDINGS

This prospective community-based 30-year follow-up study of adolescent-onset AN has shown that the majority are doing well with regard to mortality and full ED symptom recovery. The individuals with a history of AN resembled their unaffected comparisons regarding relationship status, childbearing, number of children born and educational achievements. However, 30 years after the onset of AN, one in five in the AN group fulfilled the diagnostic criteria for an ED. One fifth of the AN group were disabled and depended on disability pension, this group included two individuals with persistent ED and the majority of those with prominent ASD. Children born to mothers with a history of AN had reduced birth sizes (weight and length, ponderal index and head circumference) compared to the offspring in the COMP group. Regarding psychiatric disorders in the offspring, the results were inconsistent. Parental interviews showed an overrepresentation of current psychiatric disorders, whereas lifetime psychiatric disorders, based on both register data and interview data from a larger group, did not differ significantly across groups. Compared with the offspring in the COMP group, endocrinological, immune and metabolic disorders were more common in the offspring of the AN group. Further, an increased rate of healthcare utilisation and a negatively affected employment status were found in the AN group, informing us about the long-term consequences of adolescent-onset AN at a health economic level.

#### *Outcome compared to other very long-term follow-up studies of AN*

Compared with other very long-term outcome studies of AN, we had expected that the outcome of the present study would be better, due to our community-based, partly population-based, sample. There is one study on AN with a longer observation period than ours. It was conducted in the southern part of Sweden by Sten Theander. He reported that after 33 years there was a recovery rate of 76% and only 6% had persisting ED (78). However, the mortality rate of 18% differed markedly from the present study. Theander's study is not immediately comparable to our 30-year follow-up, because the patients in Theander's sample had all been diagnosed in adulthood while our sample consisted of a more homogenous group of adolescent-onset AN cases. The outcome, in general, is reported to be better in adolescent-onset AN cases compared to those with a later onset (6). Furthermore, Theander's study focused on women

hospitalized due to AN, whereas our study consisted of a community-based sample. Additionally, the studies were conducted in different time periods: Theander's patient group was hospitalized 1931-1960, while our study identified AN cases in the mid 1980s, which may have implications for the outcome. With no individuals deceased in our study, results are in line with the mortality outcome at ten-year follow-up of the community-based Finn Twin study (77).

Sixty-four percent in the AN group were considered fully ED symptom recovered. The recovery rate was on par with a 22-year follow-up study, of a *clinical AN sample* in the USA, where 63% of the patients had recovered (80). Our recovery rate was only slightly better than a German 21-year follow-up study of inpatients with AN, where half of the patients had recovered (79). However, as there is still no consensus regarding the definition of full ED recovery (66), results across studies are not easily compared. It has been suggested that a definition of recovery should include physical, behavioral, and psychological/cognitive criteria as well as absence of any ED (174).

Regarding quality of life, the mental dimension of the SF-36 (MCS) reflected a poorer outcome in the AN group while the physical domain (PCS) was on par with the COMP group. The lower MCS results in the AN group may be partly attributed to the overrepresentation of psychiatric morbidity among the individuals who completed the SF-36 compared to those who did not. Individuals in our sample with a current ED did not report a lower HRQoL compared to those without a current ED. In contrast, the 22-year follow-up study by Eddy et al. found lower quality of life among individuals who had not recovered from AN (80).

Long-term follow-up studies clearly vary regarding many aspects such as patient group and sample selection (outpatients versus inpatients, population-/community-based versus clinical-cases), age group (adolescent onset versus adult onset), and data collection methods (registers versus interviews). These variations contribute to the limits of comparing the outcomes in our study with those of other long-term follow-up studies.

### *ED prevalence and relapses*

Nine-teen percent in the AN group had an ED at 30-year follow-up, it was unexpected to find a slight increase in ED prevalence compared to the 18-year follow-up. This finding disrupts the pattern of gradual decrease in ED prevalence over time. It was also surprising that over one third in the AN group experienced a relapse at some point during the past 12 years. EDs generally

have a high rate of relapse (81), but these findings show that relapses can occur, even after two decades in remission.

### *Factors influencing the outcome*

Some factors may also have positively influenced the course of the illness. For instance, the AN screening, in 1985, could be considered a form of early identification of the individuals with AN. The screening likely raised awareness among the parents, of the adolescents with AN, about the ED problems. Moreover, following the participants for 30 years with several follow-up examinations during this period could also be considered an intervention.

### *Treatment received*

It is important to acknowledge that at the time the Gothenburg AN study was initiated (in 1985) there was no specialized ED unit for children and adolescents in Gothenburg. The first specialized ED unit in Gothenburg opened in 1994 at Queen Silvia Children's Hospital. Despite the research teams efforts to encourage the families to seek child psychiatric treatment around the start of the Gothenburg AN study, the majority of the adolescents did not seek help for their ED (139). Nonetheless, over the period of 30 years 77% reported that they had received treatment for an ED at some point. Unexpectedly, there was no difference in outcome between individuals who had received ED treatment and those who had not.

### *Premorbid perfectionism-an unexpected predictor of good outcome*

Premorbid perfectionism emerged as one of the predictors of good outcome in Study I. Most research has described perfectionism as a risk factor for developing and maintaining AN and associated the trait with poor outcomes (175, 176). Further, to address clinical perfectionism a specific module with the aim of reducing these behaviours has been included in the CBT-E manual (69). In the literature, two different types of perfectionism have been distinguished; adaptive (healthy) and maladaptive (unhealthy). The first type is marked by a more flexible action, where individuals accept the differences between their level of performance and their standards, allowing room for mistakes. In contrast, unhealthy perfectionism is characterized by very high standards set for oneself, a feeling that one's efforts are never good enough, a strong fear of failure, and a lack of satisfaction (177). One could speculate

whether our sample had more of the adaptive perfectionism, at least at AN Study 5, that seems to promote healthy behaviours?

Although perfectionism is considered a risk factor for developing AN, in the context of recovery from AN, it may be that the perfectionistic tendencies that initially contribute to the development of the disorder can be redirected to support recovery.

Further, when interpreting the results regarding premorbid perfectionism the fact that no validated instrument was used to assess premorbid perfectionism, as no such instrument existed 30 years ago, needs to be taken into account. Additionally, premorbid perfectionism has not previously been reported as a good prognostic factor and replication of this finding is needed.

### *Reproduction and perinatal outcome*

Childbearing and number of children born in the AN group was on par with the COMP group. In contrast, several studies have reported delays in reproduction and reduced fertility rates in individuals with AN (76, 178). In a large Swedish register study of individuals with a history of AN, born between 1950-1970, both males and females had reduced fertility ratios (178). A German follow-up study of inpatients with AN, showed much lower fertility rates compared to the general German population at 10-year follow-up (179). Additionally, in the Finn Twin study the females with AN, in their mid 30's, differed from their controls with regard to having children. Only half of the women in the AN group had children, compared to 66% of the unaffected women. The duration before recovery seemed to play a role in parity (77). In a previous 18-year follow-up study of our group, none of the women who had a persisting ED had become parents. However, in the 30-year follow-up, of the 40 women who had become mothers, 6 had a current ED. This may reflect that pregnancy and the transition to motherhood, which can be especially challenging for individuals with a history of EDs, was triggering relapses. Even women who have been in stable remission from an ED before pregnancy have a high risk of relapse (180).

Our findings regarding perinatal outcomes support previous studies reporting lower birth weight and smaller head circumference in offspring of mothers with AN (90, 91). The mechanisms behind the adverse birth outcomes are not clear. The nutritional status prior to and during pregnancy is essential in fetal development and may be compromised in individuals with a history of EDs. Even though the majority of the mothers did not fulfill the criteria for an ED

during pregnancy, it is possible that some still had restrictive eating patterns and fear of losing control over their body weight and shape. Pregnancy can be a high-risk period for the development of disordered eating, even in women with no prior history of EDs (180).

Despite the growing evidence of adverse birth outcomes in mothers with EDs, no maternity care routines to screen for current or previous EDs have been implemented in Sweden so far. Dörsam et al. have outlined several challenges of screening for EDs in pregnancy including the fact that no solid screening tool specifically developed for use in antenatal populations exists (181). The SCOFF questionnaire (182), comprising five questions, could be used to elicit a discussion about disordered eating as suggested by the National Eating Disorders Collaboration (2015). ‘SCOFF’ (S: Sick, C: Control, O: One stone, F: Fat, F: Food) is an acronym for the five questions included in the questionnaire, that addresses the core features of AN and BN.

### *The mixed results in psychiatric health in offspring*

There were inconsistencies regarding whether the offspring in the AN group were at increased risk of psychiatric disorders. Results from the parental interviews, indicated more general psychiatric morbidity. Mothers affected by psychiatric disorders may have expressed more worry and concern about the health and development in their children compared to healthy mothers. Additionally, we expected to find an overrepresentation of EDs in the children born to mothers with AN, but the difference did not reach statistical significance. Only one child in the AN group had met the DSM-IV criteria for AN. Instead EDNOS was the most common ED diagnosis in the offspring group. Considering that a significant minority of the offspring had not yet reached puberty when EDs usually have their onset, the ED prevalence of 7.2% may increase in the future. Moreover, some ED behaviors such as binge-purging may go unnoticed by parents and would likely not be captured in the parental interviews. The design of our study, examining children of all ages born to a group of mothers with a history of AN, differed from other studies exploring offspring in a specific age range. For instance, Barona et al. explored children of mothers with EDs that were part of the Danish National Birth Cohort, at 18 months and 7 years of age (183). Moreover, Micali et al. examined the psychiatric health of the children in the ALSPAC cohort at age 3,5 and again at age 7, 10 and 13 and associations between maternal ED and psychiatric diagnoses in the offspring were explored (101, 102). Both these studies showed an increased risk of psychopathology in the children of mothers with EDs, in particular emotional problems including anxiety. The differences

in design limit the comparison of results between our study and these large register-based studies. To our knowledge, other very long-term follow-up studies of AN have so far not examined the health in the offspring. It would be valuable to examine the offspring regarding EDs and other psychiatric disorders in a future follow-up, when most offspring had passed puberty.

### *The physical health in offspring*

To the best of our knowledge, it has not previously been reported that offspring of mothers with AN have an overrepresentation of endocrine, immune and metabolic disorders. The results align with previous findings that suggest an association between EDs and various autoimmune disorders, including gastrointestinal-related autoimmune diseases such as, celiac disease and Crohn's disease and type 1 diabetes (184-186). Further, our findings are in line with a Swedish register-based cohort study showing that parental mental illness is associated with an increased risk of autoimmune diseases in the offspring. Maternal ED was specifically associated with an increased risk of type I diabetes mellitus in offspring (187). In our study hypothyroidism, juvenile arthritis and celiac disorders were among the more frequently occurring physical disorders in the offspring of the AN group.

### *Health economics in a long-term perspective*

Based on the good long-term outcome in terms of no mortality and full ED symptom recovery in most cases, we had expected healthcare utilisation to decline over time and employment status to normalize. In our Study III, the most prominent trend of high inpatient care occurred around the start of the original study and the following years. Other reports have found elevated rates of health care the year before the ED diagnosis was assigned and the following year (188, 189). Because outpatient register data have only been available since 2001, we were not able to study the patterns of outpatient care utilisation around the time of the onset of AN which occurred more than a decade earlier.

Interestingly, we could observe an increase in psychiatric inpatient care utilisation between the years 2004-2008. During this period a large subgroup went through pregnancies and gave birth and the increased rates may reflect this more vulnerable period in life (190).

Over the 30-year period, 33% in the AN group had been admitted to psychiatric inpatient care and 23% had been hospitalized due to an ED diagnosis. These numbers reflects the proportion of 20-30%, who are reported to be in need of

more intense treatment alternatives in the course of their treatment (191). Hospital stays in child- and adult psychiatry dominated the distribution of days in inpatient care in general, followed by pediatric medical care.

Not surprising, data on medical consumption showed that psycholeptics and psychoanaleptics were the most frequently prescribed drugs in the AN group. This likely reflects the relatively high prevalence of psychiatric morbidity at 30-year follow-up including anxiety and affective disorders.

Work capacity was markedly affected in the AN group. Over the 30-year-period, one in five had received a disability pension and less than half the group had a fulltime job. The result regarding disability pension is comparable to Hjerm et al. (106) who reported that 21% of individuals that had been hospitalized with AN, depended on society for their income. However, we had expected a better outcome in comparison to the study by Hjerm's group considering their sample included only inpatients. The community-based Finn Twin study also reported a better outcome, with their AN group showing an employment status and disability pension on par with their controls (77).

### *The neuropsychological profile in adolescents with AN*

In Study IV some support was found for a superior detail processing among the weight recovered adolescents with AN, indicating a weaker central coherence. A daughter-father association at a task measuring central coherence was also found. No support was found regarding set-shifting deficiencies in the group of adolescents. The results needs to be interpreted with consideration to some limitations. First, the number of father-daughter pairs analyzed was small (n=16). Second, the GEFT scores improved from baseline to follow-up which could reflect practice effects. Third, comparing the neuropsychological test scores of the weight recovered AN group to the score of the COMP group at baseline may be questionable. The AN group had grown one year older and recognized the test situation and the tasks administered. Unfortunately, we had not access to follow-up data of the COMP group which limits the interpretation of results. Fourth, although the acute starvation state may have affected the performance at baseline we would have expected to find a more detail-oriented processing style at both assessments.

Findings from Study IV could not confirm an association between higher levels of ASD/ADHD traits and poorer central coherence/set-shifting performances. Self-reports showed higher levels of ASD traits in the adolescents with AN, both in the acute stages and after weight recovery. Moreover, ADHD symptoms exceeding cutoff were found in two individuals and another two

adolescents had been assigned a diagnosis of ADHD. However, the parental interviews did not confirm that neither ASD traits nor ADHD symptoms were prominent during childhood. The discrepancies between the self-reports and the parental reports may reflect that the parents were not receptive to explore these childhood behaviours in the extremely stressful situation of having a child with acute AN. Alternatively, parents may not recognize these traits possibly due to the concept of camouflaging. Especially girls with ASD mask their symptoms well by using behavioral and cognitive strategies to engage intentionally in behaviours that are non-autistic. Camouflaging could be a partial explanation for the increased rates of missed or late ASD diagnoses found among females (192).

Moreover, a detailed focused cognitive style has also been associated with a good treatment outcome. Keegan et al. found that individuals with weak central coherence at start of treatment had a greater decrease in ED pathology and clinical impairment from baseline to 1-yr follow-up. The findings from the study suggest that the detailed-focused thinking style can function both as a vulnerability and a strength (193). The authors hypothesized that focusing on details, e.g. weight and food, could pose a vulnerability for the development of AN. On the other hand, the authors argued that the detailed focus cognitive style could also help break down the recovery process into smaller, less overwhelming and doable steps.

## METHODOLOGICAL CONSIDERATIONS

Throughout this thesis the majority of the instruments used were well established, valid and reliable. The instruments were selected with the intention of making the results comparable to those of other studies in the field. For instance, MROAS (used in Study I) is well used in ED research and has been applied as an outcome measure at all previous follow-up examinations of the Gothenburg AN study allowing for comparison with previous examinations. MROAS, has been questioned with regard to heteronormativity and another long-term follow-up study excluded Subscale D on sexuality aspects due to its implication of heteronormativity (194). Moreover, considering that the GAF scale was replaced in the DSM-5, the World Health Organization Disability Assessment Schedule (WHODAS) could have been used. WHODAS takes a broader and more holistic approach to assessing disability, including both mental and physical health factors (1). However, a strength of using the GAF scale was that it allowed us to compare the results

with our previous follow-ups. SF-36 on the other hand, contributed with a new aspect, quality of life, which was not assessed in previous examinations. The instrument is a well-used HRQoL measurement in EDs (65).

The ED diagnoses in Study I were based on MINI 6.0 and the SCID-I (ED-module) that are both based on DSM-IV diagnoses. A checklist for DSM-5 EDs was therefore included to enable diagnoses according to the DSM-5. However, in Study II, due to the use of DAWBA that generates DSM-IV diagnoses, the offspring diagnoses were presented based on DSM-IV in children 5-18 years old. The interviewer, who conducted the offspring interviews, was blinded to the participant's group status until all interviews were completed, reducing the risk of bias with regard to the offspring diagnoses.

In Study I, it would have been beneficial to include additional ED specific outcome measures e.g. the Eating Disorder Examination Questionnaire (EDE-Q) or the Eating Disorder Inventory (EDI) to capture more detailed aspects of ED symptoms (e.g. concerns about shape and weight, body dissatisfaction). EDE-Q is widely used in clinical settings and research and it has been suggested that the instrument should be included as part of an assessment of ED recovery and outcome (66).

### *Register data*

Data from Swedish national registers provided reliable objective information on offspring birth outcomes, diagnoses, healthcare utilisation and social welfare benefits. However, some limitations relate to the register data. First, only the inpatient part of the NPR covered the entire study period, whereas NPR outpatient diagnoses (2001→) and the Swedish prescribed drug register (2005→) were not available at the time the participants had their AN onset. Second, data from primary care visits are not included in the registers. Third, specialized outpatient care by other professionals than physicians was not stored. Although the national registers have high validity and coverage (156, 157), data were missing regarding individuals who had emigrated.

### *Neuropsychological assessment*

The neuropsychological tests in Study IV were well established and frequently used in other studies exploring the neuropsychological profile in individuals with EDs. Whether these results generalize to everyday life, i.e. the ecological validity, is a question to be considered. For instance, the ability to perceive details versus the bigger picture in an every-day task may differ from what we measure in a highly controlled test situation.

### *Generalizability*

AN has a relatively low prevalence in the population of circa 2%, which leads to issues with small sample sizes, which in turn lead to increased uncertainty in estimates and restrict the generalizability. Study I-III included a community-based and partly population-based sample and allow for generalizability beyond the more selected group of individuals seen in ED clinics. The sample was relatively small and only half the group was drawn from a total birth cohort which limits the generalizability to some extent.

In Study IV, the sample was small and represents a selected group of clinical cases. The results of this pilot study are likely not representative for the larger group of adolescents with AN. Furthermore, considering only females were part of the AN group, the findings only generalize to females.

### *Gender perspectives*

Another question to be considered is the gender perspective. The overwhelming part of existing research in AN is based on females. Males are often excluded from ED research because of the small number of cases available. At the start of the Gothenburg AN study, 4291 growth charts were scrutinized to identify individuals with AN, where about half of the charts belonged to male students. Two boys were identified in the cohort and another male was found in the population screening group, highlighting the fact that both genders were represented in the AN sample of the Gothenburg AN study. However, in the 30-year follow-up, unfortunately two out of three men in the AN group declined to participate, leaving only one male. Moreover, this made it difficult to possibly explore outcome in offspring from a paternal perspective in Study II. In Study IV, the original intention was to include males in the AN group but no males met the inclusion criteria during the time of recruitment. From a gender perspective, we consider it a strength that we managed to recruit both mothers and fathers to Study IV. The larger part of parent-child research has focused on mother-daughter associations.

### *Statistical considerations*

In Study II, the majority of the mothers had contributed with more than one child to the data set. To account for non-independent data, i.e. clustering of siblings and correlations between offspring of the same mother, GEE were used for dichotomous variables and a Mixed model analysis for continuous variables. If we would instead have used a t-test to compare the two groups of offspring we would more likely have found significant differences. However, the t-test assumes that the data from both groups are independent and follow a normal distribution, this assumption was not met due to non-independent data in the offspring sample. Moreover, in Study IV, missing values for one of the scales (scale G) of the SWEAA were addressed by replacing missing values with stochastic imputation. If the missing values had not been replaced with stochastic imputation, the total SWEAA score would have been lower. However, only three individuals at baseline and two individuals at follow-up had missing values of the G scale, meaning that the difference in total SWEAA score, due to the imputation of values, was small.

## **STRENGTHS AND LIMITATIONS**

The Gothenburg AN study is the only study, that has followed individuals with adolescent-onset AN prospectively for as long as 30 years. In addition, the sample was followed together with a matched comparison group over the same time period. The AN sample was community-based and half of the AN group consisted of a total birth cohort— a strength considering that a significant minority of individuals with EDs never seek treatment. The close collaboration with school health nurses, at the start of the study, stretching over several years ensured representativeness of the group. The majority of the AN cases were non-clinical cases identified by the research group. All individuals were traced at 30-year follow-up, and the drop-out rate was exceptionally low with 96% of the original sample agreeing to participate. Another strength pertains to the in-depth information obtained from the face-to-face interviews. The prospective design allowed for ED trajectories to be studied in detail, stretching over 30 years. Study II is to the best of our knowledge the first study examining several aspects of health in offspring of mothers with AN i.e. perinatal-, psychiatric- and physical health. Moreover, Study III is to our knowledge the first long-term follow-up study exploring health economic outcomes over a period of 30 years. The study relied on data from Swedish national registers which provided reliable information on outcome measures, stretching over up to three decades. In Study IV, we consider it a strength that fathers as well as mothers were

examined regarding their neuropsychological profile. To our knowledge, previous studies have not explored the neuropsychological profile in fathers of individuals with AN.

Throughout the thesis different data collection methods were used including self-reports and interviews, register data and neuropsychological assessments. This combination of objective measures and more subjective experiences enhances the accuracy and is considered a strength.

One of the obvious limitations pertain to small sample sizes. Other very long-term follow-up studies have included larger samples, varying between 84-121 (78-80). Only half the group in the Gothenburg AN study was drawn from a total birth cohort which limits the generalization to some extent. Study II was limited by some attrition with regard to both register data and parental interview data. By combining different data sources, we obtained at least some information on psychiatric and physical health in the majority of the children. The children were not examined by the researchers, instead the information relied on well-validated parental interviews. Having access to register data enabled complementary information regarding the children. The wide age range in the offspring sample (newborns to young adults) was a challenge considering that we had to use different assessment tools and compare outcome across age groups. In Study III, we did not calculate the years of life lost (YLL), the years lost to disability (YLD) or disability-adjusted life year (DALY). The use of such estimates, would have enabled comparison of the burdens in our AN group with that of other various diseases. Study IV, is considered a pilot study and the sample size was clearly small, and the generalizability limited.

In all studies multiple comparisons were performed. We did not correct for multiple testing which increases the risk of type I errors (finding significant results by chance when performing many tests). The samples of Study I-III were small but it was not possible to collect larger samples. To not miss any potential associations, we did not adjust for multiple comparisons.

A final limitation pertains to the fact that over ten years have elapsed since the first data were collected. In Study III, register data from SIAS were collected in 2023, however to match the data collected at the 30-year examination only data until 2015 could be used.

## CLINICAL IMPLICATIONS

From a clinical point of view, although the outcome after 30 years was favorable for the majority, it is discouraging that a significant minority had a persisting ED. To improve the long-term outcomes, more efforts need to be directed towards preventing AN from developing into a prolonged course. The high risk of relapse observed between AN Study 4 and AN Study 5, implies that we need to enable fast access to ED clinics for individuals who encounter relapses. Lower age at AN onset emerged as a risk factor for worse outcome in the 30-year follow-up, emphasizing the importance of the youngest being a highly prioritized group in specialized ED units.

To reduce the negative birth outcomes in the offspring of mothers with a history of AN, we suggest implementation of screening procedures in maternal care. Women who screen positive for AN need special consideration during their pregnancies and information about the increased risk of negative birth outcomes in the offspring. The screening could identify women who experience relapse during pregnancy and open up for a discussion about referral for ED treatment.

The typical neuropsychological profile was less pronounced in adolescents with AN, compared to adults, which highlights the importance of treatment in this early stage before neuropsychological deficits may manifest. The resemblance in detail-oriented thinking style may be shared between daughter and parent. An increased knowledge about how the cognitive profile of the parent/s might influence treatment outcome could be of value in family-based approaches.

The implementation of screening tools into clinical practice to assess traits of ASD and ADHD symptoms in adolescents not responding to treatment is an important action. These traits can be incorporated into the treatment plans of adolescents with AN. Such alternative approaches have begun to develop. The Pathway for eating disorders and autism derived from clinical experience (PEACE) is one such alternative approach that has shown promising results with regard to patient experiences and cost savings (195).

Clinicians need to be aware of the long-term health economic consequences of adolescent-onset AN, where a significant minority is at risk of an impaired occupational status, and at least one in five will likely need inpatient care for their ED at some point. Adolescents with a lower age at AN onset are at increased risk of requiring in- and outpatient care over the years. This fact

should be disseminated to all health care professionals who meet children. If they identify ED symptoms at an early stage and refer these children to treatment, a vicious circle with repeated in- and outpatient treatments could be prevented.

## CONCLUSION

To conclude, the 30-year outcome of adolescent-onset AN was favorable in many aspects: the majority had recovered from EDs, established relationships, had given birth, had achieved educational goals and were employed. Some outcomes were discouraging including one in five meeting the criteria for an ED, relapses had occurred frequently over the past decade and the occupational status was impaired in a significant minority. Offspring of the mothers with a history of AN exhibited some unfavorable health outcomes, although the majority did well. From a health economic perspective, health care utilisation in the AN group was increased, especially during the years following the onset of AN, and a minority depended on social welfare benefits for their income.

With regard to adolescents in the initial stage of AN, some support was found for the typical neuropsychological profile in individuals with AN i.e. a weaker central coherence. This finding is in line with previous theories of an endophenotype in AN defined by a detail-oriented processing style rather than focusing on the broader context. The father-daughter association regarding central coherence aligns with this theory, but needs to be further explored in larger samples.

## **FUTURE PERSPECTIVES**

The results of this thesis emphasize the importance of prospective very long-term follow-up studies of AN, especially using prospective design. Future long-term follow-up studies should continue exploring the course of AN throughout the lifespan. It would be of interest to study if the trend of the slightly increased prevalence of EDs at 30-year follow-up, compared with the 18-year follow-up, will stabilize, decline or increase 40 to 50 years after the onset of AN. Further, to gain a more comprehensive understanding of the health impact on offspring, these individuals could be included as participants alongside their parents in a future follow-up study, when all have reached adulthood. However, this would require careful ethical considerations, as the adult offspring may not be aware of the parent's history of AN. Additionally, the neuropsychological profile in young offspring of mothers with EDs have been explored in pioneering studies (137, 138). In line with those familial high-risk studies it would be valuable to investigate whether the specific neuropsychological profile (weak central coherence, impaired set-shifting) could be detected in the offspring of a community-based sample of parents with AN. Combining a quantitative approach with qualitative methods in long-term follow-up studies of AN would also allow for new insights. For instance, it would be of interest to explore experiences of the recovery journey, including relapses, and explore factors that essentially affected the recovery process.

The development and implementation of adequate ED screening tools in maternal care with the aim of reducing negative birth outcomes are needed. Future studies should also focus on identifying mechanisms underlying the negative perinatal outcomes in offspring of women with EDs.

Future studies should prospectively follow larger samples of individuals with adolescent-onset AN, including all genders, with regard to the cognitive profile and its relationship with traits of ASD and ADHD. Neuropsychological assessments could also be included as baseline variables in future treatment studies to explore their potential as predictors for better/ worse treatment outcome in adolescents with AN.

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