Restrictive eating disorders

Aetiological, epidemiological and neurodevelopmental aspects

Lisa Dinkler

Gillberg Neuropsychiatry Centre
Institute of Neuroscience and Physiology
Sahlgrenska Academy
University of Gothenburg

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UNIVERSITY OF
GOTHENBURG

ABSTRACT

Restrictive Eating Disorders (EDs), including Avoidant/Restrictive Food Intake Disorder (ARFID) and Anorexia Nervosa (AN), are characterised by severely restricted food intake, commonly leading to substantial weight loss and significantly low weight, and the need for nutritional supplementation. The overarching aim of this thesis was to elucidate specific aetiological, epidemiological, and neurodevelopmental aspects of ARFID and AN, including the genetic aetiology of AN, the link between AN and autism spectrum disorder (ASD), the prevalence of ARFID, and the comorbidity of ARFID with neurodevelopmental disorders (NDDs).

Studies I and II were based on the Child and Adolescent Twin Study in Sweden, making use of parent- and/or child-reported survey data and clinical diagnoses from the Swedish National Patient Register. Using twin modelling, **Study I** examined whether adolescent-onset EDs (excluding ARFID) can be viewed aetiologically as the extreme manifestation of continuous variation in ED traits in the population (e.g., drive for thinness). Genetic factors influencing continuous variation of ED traits were less associated with AN than with other EDs, suggesting that EDs other than AN are on an aetiological continuum with ED traits, while AN is more genetically demarcated. Considering the previously observed overrepresentation of autistic traits in individuals with AN, **Study II** prospectively examined whether autistic traits in AN are already present in childhood. Individuals later diagnosed with AN did not show elevated autistic traits at age 9. At age 18, autistic traits were elevated in girls with acute AN, but not in girls with a history of AN. Potential elevations of autistic traits in childhood might have been concealed by coping strategies and the different/less overt female ASD phenotype. Using a novel experimental design, **Study III** examined the ability and strategy to recognise facial emotional expressions—often impaired in ASD—in women recovered from AN who were part of the 30-year follow-up in a Swedish case-control study. Women recovered from AN without ASD did not have deficits in emotion recognition, suggesting that impairments might be limited to the acute AN phase and/or the ASD subgroup. **Studies IV and V** were based on a parent-reported screening tool for ARFID developed by our group, applied in a sub-cohort of 4-7-year-old children from the Japan Environment and Children's Study. **Study IV** aimed to estimate the prevalence of ARFID and found a point prevalence of ~1%. ARFID was equally common in boys and girls. Using ICD-11 diagnostic criteria resulted in a higher prevalence than using DSM-5 criteria. Taking advantage of additional parent-reported data, **Study V** found that children with ARFID had an elevated risk of a broadly atypical/delayed neurodevelopment and a 3-4 times increased likelihood of being diagnosed with NDDs.

In summary, this thesis showed that AN might have a different aetiology than other adolescent-onset EDs, and that prospective studies are important to help disentangle the relationship between AN and ASD. Contrary to AN, ARFID is associated with increased risk for a range of neurodevelopmental problems/NDDs. Future studies should investigate whether ARFID in young children might be more strongly associated with NDDs than with later-onset EDs.

Keywords

SAMMANFATTNING PÅ SVENSKA

Undvikande/restriktiv ätstörning (på engelska: Avoidant/Restrictive Food Intake Disorder; ARFID) och Anorexia Nervosa (AN) är ätstörningar som kännetecknas av ett kraftigt begränsat matintag. Detta begränsade matintag leder ofta till en markant viktnedgång och låg kroppsvikt, avstannad tillväxt samt ett behov av näringstillskott. Individer med AN begränsar sitt matintag på grund av en intensiv rädsla för att gå upp i vikt eller bli tjock, medan det selektiva ätandet hos individer med ARFID styrs av ett starkt ointresse för mat, rädslor i samband med matintag på grund av tidigare negativa upplevelser (t.ex. kvävning, magvärk), och/eller en stark motvilja mot matens utseende, lukt, smak eller konsistens. Syftet med föreliggande avhandling är att belysa specifika aspekter av AN och ARFID, nämligen genetiska faktorers inverkan på ätstörningar (delstudie I), sambandet mellan AN och autismspektrumstörning (delstudie II-III), förekomst av ARFID (delstudie IV), och samsjuklighet av ARFID med utvecklingsrelaterade avvikelser såsom autism och ADHD (delstudie V).

Delstudierna I och II baserades på kohortstudien Child and Adolescent Twin Study in Sweden (CATSS), där data från föräldra- och/eller självrapporterade frågeformulär och kliniska diagnoser från det svenska patientregistret samlats in. I **delstudie I** undersöktes med hjälp av tvillingmodellering huruvida genetiska faktorer som påverkar ätstörningar som debuterar i tonåren (t.ex. AN, Bulimia Nervosa och ospecificerad ätstörning, men icke ARFID) också påverkar ätstört tänkande och beteende (t.ex. kroppsmissnöje, bantning) i befolkningen. Genetiska faktorer som påverkar den kontinuerliga fördelningen av ätstört tänkande och beteende var mindre associerade med AN än med de andra ätstörningar, vilket antyder att AN är mer genetiskt avgränsat från ätstört tänkande och beteende i befolkningen än de andra ätstörningarna.

Med tanke på tidigare rapporterad överrepresentation av autistiska drag hos individer med AN, undersöktes i en longitudinell kohortstudie (**delstudie II**), om autistiska drag hos individer med AN kan observeras redan i barndomen. Individer som senare diagnostiserades med AN rapporterades inte ha förhöjda autistiska drag vid 9 års ålder. Vid 18 års ålder fanns förhöjda autistiska drag hos flickor med pågående AN, men inte hos flickor med tidigare AN. Eventuellt ökad förekomst av autistiska drag vid 9 års ålder kan ha dolts av strategier för att hantera sociala situationer hos individer med autism (kamouflering av svårigheter), och genom att autismsymtomatologin manifesteras annorlunda och är mindre uppenbar hos flickor med autism än hos pojkar med autism. Med hjälp av en ny experimentell design undersöktes i **delstudie III** förmågan att känna igen känslomässiga ansiktsuttryck (vilken ofta är avvikande hos

individer med autism) hos kvinnor som tillfrisknat från AN. Kvinnorna ingick i en 30-års uppföljning i en svensk fall-kontrollstudie. Kvinnor som efter tillfrisknande från AN inte uppvisade autistiska drag, hade inga svårigheter att känna igen känslo-uttryck, vilket tyder på att potentiella brister i känsloigenkänning är begränsade till fasen av pågående AN och/eller till undergruppen med autism.

Delstudierna IV och V baserades på ett föräldrarapporterat screeningverktyg för ARFID som utvecklats av vår forskargrupp. Screeningverktyget användes i en kohort av 4-7-åriga barn födda i prefekturen Kochi i Japan, vilken är en del av studien Japan Environment and Children's Study (JECS). **Delstudie IV** syftade till att uppskatta förekomsten av ARFID i den allmänna barnpopulationen och visade en punktpreva-lens på ~1%. ARFID var lika vanligt hos pojkar och flickor. Tillämpning av ICD-11 diagnostiska kriterier resulterade i en högre förekomst av ARFID än tillämpning av DSM-5-kriterier. Genom användning av ytterligare föräldrarapporterade data visade **delstudie V** att barn med ARFID hade en förhöjd risk för många symptom som tyder på en atypisk eller fördröjd "neuroutveckling", och en 3-4 gånger ökad risk för att diagnostiseras med en eller fler utvecklingsrelaterade funktionsavvikelser.

Sammanfattningsvis har denna avhandling visat att AN kan ha en annan bakgrund än andra ätstörningar som debuterar i tonåren, och att det är viktigt att genomföra pro-spektiva studier avseende AN och autism för att förklara hur de påverkar varandra. Till skillnad från AN verkar ARFID vara associerad med ökad risk för ett brett spekt-rum av utvecklingsrelaterade funktionsavvikelser. Framtida studier bör undersöka om ARFID hos små barn kan vara starkare kopplad till utvecklingsrelaterade funktions-avvikelser än vad som är fallet med ätstörningar som oftast debuterar i tonåren, såsom AN.

LIST OF PAPERS

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

I.   **Dinkler L**, Taylor MJ, Råstam M, Hadjikhani N, Bulik CM, Lichtenstein P, Gillberg C, Lundström S. Association of aetiological factors across the extreme end and continuous variation in disordered eating in female Swedish twins. *Psychological Medicine*. 2019;Dec 17:1-11. E-pub ahead of print.

II. **Dinkler L**, Taylor MJ, Råstam M, Hadjikhani N, Bulik CM, Lichtenstein P, Gillberg C, Lundström S. Anorexia nervosa and autism: A prospective twin cohort study. *Journal of Child Psychology and Psychiatry*. 2020;Jun 4:1-11. E-pub ahead of print.

III. **Dinkler L**, Rydberg Dobrescu S, Råstam M, Gillberg IC, Gillberg C, Wentz, E, Hadjikhani N. Visual scanning during emotion recognition in long-term recovered anorexia nervosa: An eye-tracking study. *International Journal of Eating Disorders*. 2019;*52*(6):691-700.

IV. **Dinkler L**, Yasumitsu-Lovell K, Eitoku M, Fujieda M, Suganuma N, Hatakenaka Y, Hadjikhani N, Bryant-Waugh R, Råstam M, Gillberg C. Prevalence of Avoidant/Restrictive Food Intake Disorder (ARFID) based on DSM-5 vs. ICD-11 in a Japanese birth cohort. *Submitted*.

V.   **Dinkler L**, Yasumitsu-Lovell K, Eitoku M, Fujieda M, Suganuma N, Hatakenaka Y, Hadjikhani N, Bryant-Waugh R, Råstam M, Gillberg C. Neurodevelopment and clinical characteristics in children screening positive for Avoidant/Restrictive Food Intake Disorder (ARFID): a Japanese birth cohort study. *Submitted.*

CONTENT

ABBREVIATIONS

A	Additive genetic effects
ADHD	Attention-Deficit/Hyperactivity Disorder
AN	Anorexia Nervosa
AN-BP	Anorexia Nervosa Binge-eating/purging type
AN-R	Anorexia Nervosa Restricting type
AOI	Area of Interest
ARFID	Avoidant/Restrictive Food Intake Disorder
ARFID-BS	ARFID–Brief Screener
ASD	Autism Spectrum Disorder
ASQ-3	Ages and Stages Questionnaire-3
A-TAC	Autism-Tics, ADHD, and other Comorbidities inventory
BED	Binge-Eating Disorder
BMI	Body mass index
BN	Bulimia Nervosa
BPFAS	Behavioural Paediatric Feeding Assessment Scale
C	Shared environmental effects
CATSS	Child and Adolescent Twin Study in Sweden
CI	Confidence interval
COMP	Comparison group of healthy women in Study III
D	Non-additive genetic effects
DSM	Diagnostic and Statistical Manual of Mental Disorders
DZ	Dizygotic
E	Non-shared environmental effects
ED	Eating Disorder
EDI-2	Eating Disorder Inventory-2
EDNOS	Eating Disorder Not Otherwise Specified (DSM-IV)
EDY-Q	Eating Disorders in Youth-Questionnaire
EEBQ	Early Eating Behaviour Questionnaire
ESSENCE-Q	Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations-Questionnaire
FD	Fixation duration
FER	Facial emotion recognition
GEE	Generalized estimating equations
GWAS	Genome-wide association study
h^2	Heritability
h^2_g	Group heritability

ICD	International Classification of Diseases
IRR	Incidence rate ratio
JECS	Japan Environment and Children's Study
MZ	Monozygotic
NDD	Neurodevelopmental Disorder
NPR	National Patient Register
OED	Other Eating Disorder (other than Anorexia Nervosa)
OR	Odds ratio
OSFED	Other Specified Feeding or Eating Disorder (DSM-5)
r_E	Non-shared environmental correlation
RecAN±ASD	Recovered Anorexia Nervosa with/without Autism Spectrum Disorder
r_g	Genetic correlation
ROC	Receiver operating characteristic
r_{Ph}	Phenotypic correlation
RR	Relative risk
RRBI	Restricted/repetitive behaviour and interests
SOC	Social communication problems

1 INTRODUCTION

Eating disorders (EDs) are characterised by a persistent disturbance of eating or eating-related behaviour, which results in dysregulated food consumption and significantly impairs physical health and/or psychosocial functioning.[1] EDs are described and categorised in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5)[1] and the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10).[2] While ICD is used to assign diagnoses in clinical practice worldwide, DSM is the prevailing system in the research of mental disorders. With the publication of DSM-5 in 2013, the classification systems differed in important ways regarding the definition of EDs, which complicates comparability in research. In 2022, a new version of ICD will officially come into effect (ICD-11),[3] which will be consistent with DSM-5 in terms of ED diagnoses. While this thesis investigates and discusses DSM-5 ED diagnoses, the register-based studies in this thesis also include ICD-10 ED diagnoses.

EDs can broadly be differentiated into *restrictive EDs* and *binge-spectrum EDs*. Restrictive EDs are characterized by the restriction of food/energy intake, leading to substantial weight loss, significantly low weight, nutritional deficiency, and/or dependence on nutritional supplements or enteral feeding. This thesis focuses on the restrictive EDs *Anorexia Nervosa* (AN) and *Avoidant/Restrictive Food Intake Disorder* (ARFID). While underweight is a diagnostic criterion for AN, individuals with ARFID can be within or above the normal weight range. Importantly, the motivations underlying weight loss differ between AN and ARFID: while it is intentional in AN, it is not necessarily deliberate but rather a by-product in ARFID, where factors such as lack of interest in eating, sensory sensitivity to food qualities, and fear of aversive consequences of eating motivate the restriction of food intake. Another DSM-5 ED within the restrictive spectrum is *Atypical AN*, where almost all criteria for AN are met, but despite significant weight loss, the individual is of normal weight or overweight. Atypical AN is a subtype of the diagnosis *Other Specified Feeding or Eating Disorder* (OSFED) and not a separate diagnosis in its own right. It is not considered further in this thesis.

Binge-spectrum EDs, on the other hand, are characterised by recurrent episodes of binge eating and compensatory behaviours to prevent weight gain such as purging (i.e., self-induced vomiting or misuse of laxatives, diuretics, and other medications), fasting, or excessive exercise. Binge-spectrum EDs include *Bulimia Nervosa* (BN) and *Binge-Eating Disorder* (BED), and their corresponding "subthreshold" types in

the residual OSFED category. Binge-spectrum EDs are not associated with under-weight or weight loss, but occur in individuals with normal weight, overweight and obesity.[1] Diagnostic crossover within the ED spectrum is common, especially from AN to BN, but less so from BN to AN.[4-6]

1.1 Anorexia Nervosa (AN)

AN is characterised by (1) a persistent **restriction of food intake** leading to **under-weight**, (2) an **intense fear of gaining weight** or becoming fat, and (3) a **disturbed perception of one's own body** or disproportionate influence of body weight and shape on self-evaluation (Diagnostic criteria in **Box 1.1**).[1] DSM-5 provides a severity grading based on the body mass index (BMI, in kg/m^2): extreme (BMI<15), severe (BMI 15–15.99), moderate (BMI 16–16.99), and mild (BMI≥17). In children, BMI-for-age percentiles (e.g., <5th percentile) and growth trajectories should be considered to determine significantly low weight.

Malnutrition and very low weight in patients with AN are associated with a range of **medical complications**, which sometimes can be life-threatening:[7,8] individuals with AN often require hospitalisation for medical stabilisation and weight restoration.[9] AN has one of the highest **mortality rates** among psychiatric disorders with a standard-ised mortality ratio of 5.2–6.2,[7,10,11] although the rate might be overestimated due to the disproportional inclusion of severe inpatient cases with index treatment in adult-hood in many follow-up studies.[11-14] Epidemiological studies and studies including patients with index treatment in adolescence find lower rates.[15-17] Circa 20% of deaths are due to suicide.[18]

DSM-5 differentiates two subtypes: the restricting type (AN-R) and the binge-eat-ing/purging type (AN-BP). Individuals with AN-R primarily use fasting and exces-sive exercise to achieve and maintain their low weight, while individuals with AN-BP regularly engage in binge-eating behaviour and/or compensatory behaviours such as self-induced vomiting or abuse of laxatives, diuretics, or enemas. Crossover be-tween the two subtypes is very common, that is, approximately half of all patients with AN-R shift to AN-BP within 7 years, and the same applies vice versa.[5]

The **onset of AN** is typically in mid-puberty,[19,20] while onset before the age of 8 years and after the age of 30 years is rare.[21] The **lifetime prevalence** of AN ranges from <1–4%, depending on sex and the diagnostic system used. In addition, AN seems to be less common in Africa and Latin America than in other global regions, although research data from these regions are still scarce.[22,23] It is common to differentiate

between *narrowly defined AN,* corresponding to DSM-IV/ICD-10 AN (<85% of expected body weight and amenorrhea required), and *broadly defined AN,* comprising DSM-IV AN, ICD-10 atypical AN (amenorrhea not required), and DSM-5 AN (weight criterion relaxed, amenorrhea not required). The lifetime prevalence of narrowly defined AN in females is 0.4–2.2%,[24-29] while that of broadly defined AN is 1.4–4.2%.[24,25,27,30,31] In males, the lifetime prevalence is 0.0–0.3% for narrowly and broadly defined AN.[26-30]

Box 1.1 DSM-5 diagnostic criteria for AN (without remission and severity specifiers).[1]

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 that 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 behaviour (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas). This subtype describes presentations in which weight loss is accomplished primarily through dieting, fasting, and/or excessive exercise.

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

The overwhelming part of the existing literature on AN is based on females, as, historically, **men with AN** were considered so rare and atypical that they were systematically excluded. Recently, it has been increasingly recognised that men, although in the minority, make up a substantial part of individuals with AN.[32-35] In general, there seem to be more similarities than differences between men and women with AN.[36] Men's body image concerns are however typically characterised by drive for muscularity rather than drive for thinness, and accordingly, men show higher levels of over-exercising and lower levels of laxative abuse (for a review see [36]).

AN is characterised by a striking **ego-syntonic nature**; that is, affected individuals value their illness and lack insight into the seriousness of their condition, leading to a reluctance towards treatment,[37] despite the detrimental effects of the condition.[38] For

instance, individuals with AN report that losing weight gives an inner sense of strength, the strict adherence to schedules and rules provides a sense of structure and stability, and the fixation on food and weight helps avoid negative emotions.[37] The ego-syntonic nature of AN might partly explain why AN is often described as a notoriously difficult to treat disorder[39,40] with high rates of drop-out from treatment (20–60%)[41-43] and **low recovery rates**.[44-46] A large proportion of individuals with AN (23–50%) do not seek/receive treatment.[15,25,26] Within 10 years, 31%–47% of individuals with AN are reported to recover fully, and additional 32% recover partially (i.e., on some symptom domains).[44-46] Circa 20–30% will develop a chronic, sometimes lifelong, course of illness, including the development of other EDs.[15,45,47,48]

1.2 Avoidant/Restrictive Food Intake Disorder (ARFID)

ARFID is characterised by an extreme avoidance or restriction of food intake resulting in a **persistent failure to meet nutritional and/or energy needs** with one or more of the following sequelae: (1) significant weight loss (in children insufficient weight gain or faltering growth), (2) significant nutritional deficiency, (3) dependence on enteral feeding or oral nutritional supplementation, or (4) marked interference with psychosocial functioning (**Box 1.2**).[1] ARFID has been added as an **age-neutral diagnosis** to the DSM-5 in 2013, replacing and extending the DSM-IV diagnosis *Feeding disorder of infancy or early childhood,* which had limited clinical utility for several reasons, for instance, by restricting the age of onset to below six years. The ARFID diagnosis is also included in the ICD-11.[3]

Contrary to what is observed in AN, individuals with ARFID **lack body weight and shape concerns** or drive for thinness.[49] Instead, the food avoidance or restriction in ARFID is often based on (1) a sensitivity to sensory qualities of foods, (2) a lack of interest in food/eating (e.g., because of low appetite), and/or (3) a fear of aversive consequence to food intake (e.g., choking, vomiting, stomach pain, and other gastrointestinal symptoms).[1] These three factors are commonly described as the ***drivers* or *presentations* of food avoidance/restriction** in ARFID. The drivers are not exhaustive and not mutually exclusive, that is, other not yet well-known causal processes might underlie restrictive eating in ARFID, and several drivers can co-exist and be equally or differently dominant.[50,51] These distinct yet overlapping causal pathways have led to ARFID being a very heterogeneous disorder—an umbrella diagnosis.

Avoidant/Restrictive Food Intake Disorder

A. An eating or feeding disturbance (e.g., apparent lack of interest in eating or food; avoidance based on the sensory characteristics of food; concern about aversive consequences of eating) as manifested by persistent failure to meet appropriate nutritional and/or energy needs associated with one (or more) of the following:

    A1. Significant weight loss (or failure to achieve expected weight gain or faltering growth in children).
    A2. Significant nutritional deficiency.
    A3. Dependence on enteral feeding or oral nutritional supplements.
    A4. Marked interference with psychosocial functioning.

B. The disturbance is not better explained by lack of available food or by an associated culturally sanctioned practice.

C. The eating disturbance does not occur exclusively during the course of anorexia nervosa or bulimia nervosa, and there is no evidence of a disturbance in the way in which one's body weight or shape is experienced.

D. The eating disturbance is not attributable to a concurrent medical condition or not better explained by another mental disorder. When the eating disturbance occurs in the context of another condition or disorder, the severity of the eating disturbance exceeds that routinely associated with the condition or disorder and warrants additional clinical attention.

Unlike AN, where a low-calorie diet is adopted in order to control/lose weight, children with ARFID can have a **high-calorie diet** that sustains normal weight (or even leads to overweight), but that is so limited in variety that these children are nutritionally compromised.[52] However, in many clinical studies, children with ARFID on average presented with circa 85% of healthy body weight, although they were heavier than AN patients.[51,53-56] The true ratio of underweight, normal weight, and overweight in ARFID is not known. It is furthermore important to **differentiate ARFID from "normal" picky eating**. Picky eating at some point in early childhood is very common in typically developing children and seen to some degree as part of normative development.[57-59] Persistent picky eating occurs much less frequently;[60,61] furthermore, an ARFID diagnosis requires failure to meet nutritional and/or energy needs, which is an uncommon consequence of "normal" picky eating.

Similar to AN, ARFID is associated with a high rate of **medical conditions** as a consequence of starvation and malnutrition, and patients often require hospitalisation due to medical instability.[55,62] Especially common in ARFID are gastrointestinal problems, some of which pre-date and likely contribute to the development of ARFID.[63-65] Although the DSM-5 ARFID criteria stipulate that the eating disturbance should not be "attributable to a concurrent medical condition"[1] (**Box 1.2**), ARFID can very

well be triggered by medical conditions such as food allergies, gastroesophageal reflux, gastroenteritis, and other gastrointestinal problems. In such cases, patients develop a fear of aversive consequences of eating, such as pain or vomiting (conditioned food aversion).[66-68]

Since ARFID is a fairly new diagnosis, research on its **prevalence** in the general population is still very limited and partly hampered by the lack of validated screening tools. The **rate of males** is higher in patients with ARFID than in patients with AN and BN,[53-55,69] and an epidemiological study suggests that in the general population the male-female ratio might be 1:1.[70] As ARFID was defined as an age-neutral diagnosis in the DSM-5, its **onset** can be at any age, however it is most common in childhood.[1] The age of onset might also differ by the predominant driver such that fear-based food avoidance on average has a later onset than food avoidance based on lack of interest in eating.[1]

Research on the short- and long-term **prognosis** of ARFID is still scarce and largely based on retrospective chart reviews that compare patients retrospectively identified with ARFID to patients with AN. These studies indicate similar[71,72] or better[62,73,74] outcome for individuals with ARFID at follow-up. A prospective study following 113 children with infantile anorexia (which corresponds to the ARFID presentation *lack of interest in eating*) from age 2 years onwards, found that 63% still showed moderate to severe malnutrition at age 11.[75]

1.3 Are Eating Disorders (EDs) on an aetiological continuum with ED traits?

EDs are not easily ascertained with questionnaires and their prevalence is relatively low, especially that of AN. To circumvent the necessity of a reliable (clinical) diagnosis and to increase statistical power, ED researchers often study *ED traits* instead. ED traits comprise ED-related cognitions and behaviours such as overvaluation of weight and shape, body dissatisfaction, fear of weight gain, perceived pressure for thinness, internalisation of the thin-ideal, irregular eating, restrictive eating, binge-eating, purging, and excessive exercise. These ED traits are continuously distributed in the population[76] and it is assumed—but not known—that diagnosed EDs are the extreme manifestation of these continuously distributed traits. If this assumption is incorrect, ED traits and diagnosed EDs might have a different aetiology, and studying ED traits might not be as useful as previously believed for expanding the knowledge on EDs.[77]

Whether psychopathology is best conceptualised into discrete or dimensional constructs has been a longstanding debate.[78] Traditionally, psychiatric disorders have been considered as *discrete entities* that are qualitatively different from typical behaviour, that is, there is a clear distinction between affected and unaffected individuals (i.e., they vary in kind). This is reflected by the prevailing nosological systems DSM and ICD. In the alternative *dimensional* model, psychiatric disorders are conceptualised as the extreme manifestation of continuously distributed traits in the population, without a clear demarcation between affected and unaffected individuals (i.e., they vary in degree).

Which is the best model for psychiatric disorders can, for instance, be investigated at the phenotypic level (i.e., studying symptoms) or at the aetiological level (i.e., studying the relative contribution of genetic and environmental factors). At the *phenotypic level*, taxometric and factor mixture models—examining whether symptom data are of categorical or dimensional structure, or both[79,80]—have provided mixed results for EDs.[81-87] At the *aetiological level*, studies investigating shared genetic risk across disorders and their trait variation have shown that a broad range of psychiatric and neurodevelopmental disorders are on an *aetiological continuum*, that is, genetically, there is no clear distinction between affected and unaffected individuals.[88] Disorders on an aetiological continuum include, for instance, Autism Spectrum Disorder (ASD),[89-91] Attention-Deficit/Hyperactivity Disorder (ADHD),[92-94] depression,[95,96] and anxiety disorders,[97] while a potential aetiological continuum (i.e., shared genetic risk across disorders and trait variation) has not yet been examined in EDs.

AN has a twin-based heritability[a] of 48%–74%[98], and genome-wide association studies (GWAS) of AN have demonstrated that—in line with other psychiatric disorders[99-101]—thousands of common genetic variants with small, but cumulative and likely interacting effects contribute to the risk for AN.[102,103] This polygenic architecture suggests a continuously distributed genetic vulnerability to AN and potentially supports an aetiological continuum in EDs. That *ED traits* also are heritable[104,105] does not directly imply that they are influenced by the same genetic variants as diagnosed EDs (varying only in number), which would be expected under a continuous model. Rather it is possible that different genetic variants contribute to diagnosed EDs and ED traits. In **Study I**, we therefore examined the *aetiological continuum hypothesis* for EDs, that is, whether EDs can be viewed as the extreme manifestation of continuous genetic variation in ED traits in the population (scenario A), rather than as genetically distinct entities (scenario B). **Figure 1** illustrates the two potential scenarios.

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[a] Heritability is the proportion of individual differences in a trait that is explained by genetic variation between individuals.
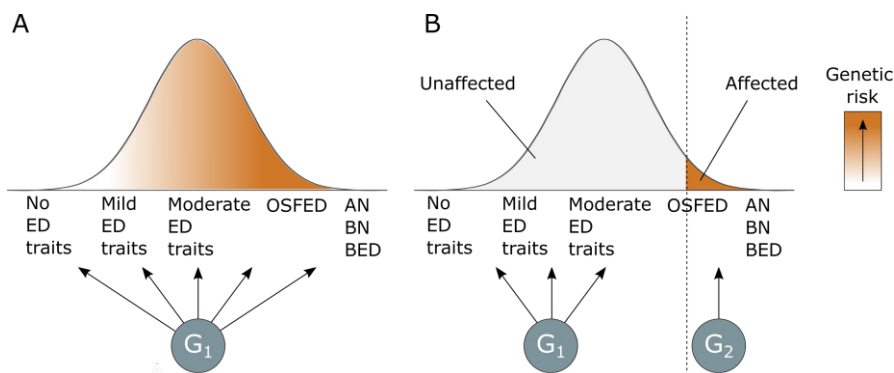
Figure 1.1 *The aetiological continuum hypothesis in Study I. Scenario A: EDs as the extreme manifestation of continuous genetic variation in ED traits in the population, Scenario B: EDs as genetically distinct entities. G1 and G2 represent different sets of genetic factors. BED: Binge-Eating Disorder, BN: Bulimia Nervosa, OSFED: Other Specified Feeding or Eating Disorder.*

1.4 Neurodevelopmental Disorders (NDDs)

NDDs comprise conditions characterised by developmental deficits and onset in early life, such as intellectual disability, ASD, ADHD, specific learning disorder (e.g., dyslexia), developmental coordination disorder, and tic disorders.[1] Multiple comorbid diagnoses of NDDs are very common,[106-108] which is one of the reasons Gillberg coined the acronym ESSENCE (Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations) in 2010. ESSENCE comprises a broad range of early neurodevelopmental symptoms that might indicate the presence of (multiple) NDDs, and advocates for a holistic approach to the clinical examination of children presenting with such symptoms.[106] The NDDs mainly discussed in this thesis are ASD and ADHD.

ASD is characterised by (1) pervasive deficits in social communication and social interaction, and (2) restricted and repetitive behaviours, interests or activities, as well as abnormalities in sensory processing (including both hyper- *and* hyposensitivity to sensory stimuli).[1] ASD has a prevalence of about 1–2.5% in children and adults of the general population and is more commonly diagnosed in males.[109-114] A recent meta-analysis concluded that the male-female ratio in ASD is approximately 3:1, while it is slightly less skewed in autistic individuals with intellectual disability than in autistic individuals with normal-range intelligence.[115,116]

ADHD is characterised by symptoms of inattention and/or hyperactivity-impulsivity, which severely interfere with functioning and development.[1] It affects about 3.4%–

7.2% of children and adolescents,[117-119] and about 2.5% of adults.[120,121] Like ASD, ADHD is more common in males, with a male-female ratio of roughly 2:1.[119,122] Three subtypes are differentiated: predominantly inattentive type, predominantly hyperactive/impulsive type, and combined type.[1] While the inattentive type is more common in females with ADHD, males with ADHD are more likely to meet criteria for the combined type.[123]

1.5 The relationship between AN and NDDs

In relation to AN, ASD is certainly the most studied and most robustly associated NDD (see chapter 1.6). Research on the relationship of ADHD with AN is rare and further hampered by small samples and samples of mixed EDs;[124,125] many studies have investigated ADHD and *restrictive eating* instead.[124] Data on the association between ADHD and restrictive eating/AN are inconsistent;[124] however, it does seem that ADHD is less common in AN-R than in AN-BP,[126-128] which is partly supported by the *negative* genetic correlation of AN-R with ADHD that was reported in the recent AN GWAS (while the genetic correlation of AN-BP with ADHD was close to zero).[102] Furthermore, the association between restrictive eating and the hyperactivity symptoms of ADHD seems to be stronger in males,[129-131] which might be explained by higher rates of hyperactivity in males.[123] In contrast to restrictive eating/AN, there is moderate to strong evidence for an association of ADHD with binge-spectrum EDs,[124,125] including prospective studies showing that ADHD in childhood predicts later BN symptoms and diagnosis.[132,133] The association between ADHD and binge-spectrum EDs might mainly be driven by impulsivity, which is shared between them (binge-eating and purging are considered impulsive behaviours).[133] Studies on the comorbidity of AN with *other* NDDs are scarce and mainly consist of case reports, for instance, for Tourette syndrome[134-136] and intellectual disability (although mainly in relation to genetic syndromes);[137-139] in fact, AN might be rather associated with higher than average IQ.[140] This thesis focuses on the link between AN and ASD.

1.6 Disentangling the link between AN and Autism Spectrum Disorder (ASD)

It has been suggested as early as in 1983 that AN and ASD might be related conditions with a shared vulnerability, manifesting as AN in girls and as ASD in boys.[141] The research body on AN, ASD, and the possible link between them has grown considerably since then. We now know that more girls than previously thought have ASD[115] and the same applies to boys with AN,[30] although both are still often overlooked.[115,142-144] The issue of a potential shared vulnerability underlying ASD and AN has rarely been investigated and will be discussed in chapter 7.

AN and ASD co-occur more frequently than expected by chance; however, estimates for the prevalence of ASD in individuals with AN vary widely (4–53%).[145] A number of studies have furthermore found increased *autistic traits* in AN, for instance, as measured with the Autism-Spectrum Quotient[146] (for a review see [147]). AN and ASD have some striking phenotypic similarities: individuals with AN are often perceived as socially withdrawn and rigid, and they exhibit obsessive, ritualistic behaviours—all distinctive features of ASD as well.[148] There is also vast evidence that individuals with AN show neurocognitive and social-emotional difficulties typically associated with ASD (*ASD-related traits*), for instance, cognitive inflexibility,[149,150] reduced global processing,[151-153] social anxiety,[154,155] alexithymia,[156,157] and emotion recognition.[158,159,b]

Such neurocognitive and social-emotional difficulties have been proposed to contribute to the development and maintenance of AN within the *Cognitive-interpersonal model of anorexia nervosa*.[162] In line with this, a recent meta-analysis found that cognitive inflexibility, reduced global processing, and impaired emotion recognition were associated with longer illness duration in AN.[163] High autistic traits and ASD diagnosis itself have furthermore been associated with a more severe illness trajectory in AN, including increased risk for involuntary treatment,[164] less improvement of cognitive symptoms after treatment,[165,166] and poorer long-term outcome in terms of overall functioning.[167,168] It therefore seems important to identify the subgroup with ASD in individuals with AN.

AN and ASD are, however, difficult to disentangle. It is uncertain to what extent neurocognitive and social-emotional difficulties in AN indeed reflect an underlying ASD condition, or whether they are *epiphenomena* (i.e., by-products) of AN, which only superficially resemble autistic symptoms. Starvation in the acute phase of AN has profound effects on brain functioning,[169,170] and might provoke or exacerbate certain symptoms such as social withdrawal and obsessive-ritualistic behaviour around food and eating,[169] which mimic problems experienced in ASD. Assessing ASD during the acute phase of AN is therefore highly problematic. Alternatively, it is possible that

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[b] *Cognitive inflexibility*: the ability to move back and forth ("shift") between different tasks, operations, or mental sets; commonly referred to as *set-shifting*. *Global processing*: the global integration of details as a gestalt (i.e., seeing the bigger picture) as opposed to local processing (i.e., attention to detail); commonly referred to as *central coherence*. *Alexithymia*: the inability to describe and/or recognise one's own emotions. *Theory of mind* (sometimes also referred to as *cognitive empathy*) as part of social-emotional functioning is commonly considered to be impaired in both ASD[158] and AN.[160] Recently, it has however been strongly questioned whether the claim of impaired theory of mind in ASD is valid at all.[161] Therefore, potential theory of mind impairment in ASD remains an open question and is not discussed here as a trait shared by ASD and AN.

neurocognitive and social-emotional difficulties in AN are *predisposing traits* present before AN onset, but that they are different from autistic traits in nature and severity.

1.6.1 Are autistic traits in AN already present in childhood?

Importantly, autistic symptoms need to have been present in early childhood in order to diagnose ASD,[1] and it is therefore crucial to consider the early developmental history when assessing ASD in adolescents or adults. Many studies describing the co-occurrence of AN and ASD/autistic traits are limited by their cross-sectional nature (i.e., autistic traits were assessed only during the acute state of AN while early developmental history was not considered[145,147]), and might therefore have overestimated the prevalence of ASD in AN. Some studies tried to overcome this limitation by examining early autistic traits retrospectively, using validated parent-report measures for ASD. Indeed, they report a much lower number of individuals with AN meeting clinical cut-off for ASD (4–10%)[136,171-173] than the cross-sectional studies that did not take into account childhood autistic traits (10–52.5%).[174-176]

Several retrospective studies that focused on social difficulties in AN have furthermore found that these difficulties existed premorbidly, including fewer social activities, no or few close friends, and less social support from others.[136,177-182] These findings indicate that social difficulties in AN are not limited to the acute phase of illness. However, the majority of these studies did not differentiate between individuals with and without likely ASD; it is therefore unknown whether premorbid social difficulties were confined to the potential subgroup with ASD. One of the studies found that premorbid social difficulties extended beyond the subgroup with likely ASD.[136]

As retrospective reports are prone to recall bias,[183-185] it is generally preferable to collect data prospectively, that is, to assess autistic traits at a young age and then follow these children over time, in order to see whether they develop AN or not. However, no such prospective studies are available. It is therefore unclear whether the observed overrepresentation of autistic traits in AN is present from early childhood, or whether it is mainly linked to the acute phase of AN. **Study II** addresses the lack of prospective studies and investigates whether individuals who later develop AN show elevated autistic traits in childhood (measured at age 9).

1.6.2 Is emotion recognition impaired in AN or only in the ASD subgroup?

The ability to correctly recognize facial emotional expressions of other people (Facial Emotion Recognition; FER) is critical for successful social communication and relationships,[186] and often discussed as one of the socio-emotional difficulties that AN and ASD might have in common. Here, we focus only on FER of *basic* emotions such as happiness, anger, sadness, fear, surprise, and disgust.[187] FER deficits are a robust finding in ASD,[158] while studies in acute AN provide inconsistent results: some reported impaired FER in AN compared to healthy control groups (although often only for a subset of the tested emotions),[188-192] while others did not find differences[193-198] (for a review of studies until 2014 see [199]). The only meta-analysis on basic FER in AN reported an overall small effect size, but included only five studies.[159] Importantly, only two previous studies controlled for comorbid ASD by excluding individuals with both AN and ASD,[192,196] which might have contributed to the inconsistent results. It is therefore uncertain whether potential FER deficits in AN are limited to the subgroup with ASD.

Findings of FER deficits in acute AN might furthermore be confounded by impairments in brain functioning due to malnutrition, and therefore limited to the acute phase. If FER deficits are present in individuals recovered from AN, they could either be a consequence of starvation (i.e., scarring effect) or pre-dating AN onset. This ambiguity can potentially be disentangled by differentiating individuals recovered from AN with and without ASD: if FER deficits are present in recovered individuals with ASD, but not in those without ASD, this would be indicative of a trait pre-dating AN onset in a subgroup rather than scarring effects. At the time Study III was designed, no study had examined FER of basic emotions in individuals recovered from AN.

Inconsistent findings regarding FER in AN might also have resulted from the use of high-intensity emotional expressions in almost all previous studies. Basic emotional expressions of high intensity might be too easy to recognise, therefore producing ceiling effects (i.e., the scores of both the AN group and the control group are so close to the maximum scores that the groups cannot be discriminated). It is possible that group differences can only be detected using subtle and/or blended emotional expressions, which are frequently encountered in everyday life and more difficult to identify. Three studies on FER in AN included lower-intensity/blended emotional expressions,[192,197,200] of which two studies found FER deficits in acute AN.[192,200]

Our understanding of the mechanisms underlying FER deficits is limited. Differences in face viewing might potentially be important, for instance, in terms of attention to the eyes versus the mouth, or hyperscanning behaviour (i.e., increased fixations of shorter duration than "normal").[201] These mechanisms have rarely been investigated

in EDs.[194,200] In summary, it is uncertain whether FER ability is impaired in AN, and if so, whether deficits persist after recovery and/or pre-date AN onset. It is also unknown, which mechanisms contribute to possible FER deficits. The design of **Study III** addresses the described issues that have potentially produced inconsistent results, and examines FER deficits and underlying mechanisms in individuals recovered from AN with and without ASD, using different intensities of emotional expressions.

1.7 Prevalence of ARFID and comorbidity with NDDs

Little is known about how common ARFID is in the general population. Point prevalence estimates range from 0.3–15.5%,[70,202-204] clearly indicating that the prevalence depends heavily on how ARFID is measured, while it might also differ between age groups. The prevalence of ARFID in children under 7 years is unknown. A related problem is the lack of validated screening tools for ARFID. Two self-reported screening tools have been developed specifically to measure ARFID symptoms; one for adolescents (Eating Disorders in Youth-Questionnaire, EDY-Q)[205] and one for adults (Nine Item ARFID Screen, NIAS).[206] Both screening tools have not yet been validated against clinical ARFID diagnoses. There is no parent-reported screening tool that has been developed specifically for ARFID and validated against clinical diagnoses.

The only study that used a parental questionnaire clearly stands out in the reported ARFID prevalence, which was 15.5% in 5-10-year-old Portuguese children.[207] The high prevalence might partly be explained by the fact that the study did not evaluate any exclusion criteria as specified in the DSM-5. Furthermore, the authors note that cultural differences could have played a role such that the concern about their child's eating and weight is generally high in Portuguese parents. This circumstance together with a *yes/no* response format might have resulted in the high endorsement of ARFID symptoms (assessed with only five items), while a quantifying scale such as the one used in the EDY-Q might have been better able to differentiate, for example, between severe and less severe selective eating.

A better understanding of the prevalence of ARFID is essential to assess the impact of this disorder on the population and to allocate health care resources. Most of our current knowledge of ARFID is based on (small) clinical samples, which are subject to selection bias for different reasons. First, not all children with ARFID receive treatment. Second, children with ARFID are encountered in paediatric as well as psychiatric clinics. To which clinic or treatment setting (e.g., inpatient vs. outpatient) a child is referred might depend on age, specific ARFID presentation, severity of malnutrition, and comorbid medical conditions. Studying ARFID in samples representative of the general population is therefore urgently needed to, for instance, determine the

"true" distribution of the underlying drivers of food avoidance and the "true" male-female ratio, which seems to be more skewed in clinical samples[53-55,69] than in non-clinical samples.[70] In **Study IV**, we therefore describe the development of a new parent-reported screening tool for ARFID and its application in a large birth cohort of Japanese children aged 4-7 years, in order to estimate the prevalence of ARFID.

While research on the neurodevelopmental comorbidity of ARFID is still very limited, it seems that ARFID might have a broader (i.e., more types of NDDs) and possibly stronger comorbidity with NDDs than AN.[53] The few studies investigating the occurrence of NDDs in children with ARFID report an ASD prevalence of 3–13%, and an ADHD prevalence of 4–39%.[51,53,208-210] General developmental delay and intellectual disability also seem to be overrepresented in patients with ARFID.[1,53,211] From the literature on picky eating we know that strong food selectivity is considered a problem in 46–89% of children with ASD,[212] and that inadequate nutrient intake is common in these children.[213,214] Selective eating has also been found to be more frequent than usual in children with ADHD, intellectual disability, and Tourette syndrome,[215-217] although some studies have indicated that this was largely associated with comorbid ASD.[218,219] Nevertheless, previous research indicates that ARFID might be linked to a wider range of NDDs. The stronger association between ARFID and NDDs than between AN and NDDs might also be a reason for the higher proportion of males in ARFID as compared to AN, as there is an overall male preponderance in NDDs.

Knowledge on the comorbidity of ARFID with NDDs is so far exclusively based on clinical samples, however, the rate of NDDs might be associated with ARFID presentation, ARFID severity, and treatment-seeking, and therefore be potentially biased in clinical samples. Furthermore, as single NDDs are not very common in the population (ca. 1–6%[106]), they might be difficult to study in small clinical groups, even if probably present at an increased rate. Studying the comorbidity of ARFID with NDDs might improve our knowledge of underlying mechanisms and treatment targets. As with prevalence, doing so in the general population might be more representative of the entire group of individuals with ARFID. **Study V** therefore examines the presence of a variety of neurodevelopmental symptoms and NDDs in children with and without ARFID from the Japanese birth cohort.

2 AIMS

The overarching aim of this thesis was to elucidate certain aetiological, epidemiological, and neurodevelopmental aspects of the restrictive eating disorders AN and ARFID, including the genetic aetiology of AN, the link between AN and ASD, the prevalence of ARFID, and the association between ARFID and NDDs.

The thesis comprises five studies with the following specific aims:

 I.   To investigate in a nationwide twin sample whether EDs can be viewed aetiologically as the extreme manifestation of continuous variation in ED traits (such as drive for thinness or body dissatisfaction), rather than being distinct entities.

 II. To examine the previously observed overrepresentation of autistic traits in individuals with AN prospectively, by investigating whether there is an elevation of autistic traits at age 9 in individuals who later develop AN.

 III. To investigate potential deficits in facial emotion recognition ability and visual scanning behaviour as a possible underlying mechanism in women long-term recovered from adolescent-onset AN, with and without ASD.

 IV. To develop a parent-reported screening instrument for ARFID in children, and to estimate the prevalence of ARFID in a large birth cohort of Japanese children aged 4 to 7 years, using this newly developed instrument.

 V.   To examine neurodevelopmental symptoms and NDDs in 4-7-year-old children with ARFID screened from a large Japanese general population sample.

3 MATERIALS AND METHODS

3.1 Study populations

3.1.1 Child and Adolescent Twin Study in Sweden (CATSS cohort)

The Child and Adolescent Twin Study in Sweden (CATSS) is an ongoing nationwide longitudinal study aiming to include all twins born in Sweden since 1st July 1992.[220] The twins are identified through the Swedish Twin Registry at Karolinska Institutet. In connection with the twins' 9th birthday (the first three years of the study also included 12-year-old twins), their parents are invited to participate in a telephone interview about the somatic and mental health of the twins (CATSS-9, response rate 70%). Zygosity is either ascertained using a panel of 48 single nucleotide polymorhisms, or an algorithm of five questions regarding twin similarity. Independently of their participation in CATSS-9, the twins and their parents are invited to complete (follow-up) questionnaires when the twins reach ages 15, 18 and 24 (CATSS-15, CATSS-18, CATSS-24). The CATSS data are collected continuously by Karolinska Institutet in Stockholm.

Study I included twins born between 1992 and 1999 who had responded to CATSS-18 (response rate: 59%). Data were extracted in November 2018. The final sample consisted of 1,481 female twin pairs (**Table 3.1**). Study II includes twins born between 1992 and 1999 whose *parents* had responded to CATSS-9 and CATSS-18 (response rate: 47% of baseline). Data were extracted in May 2019. The final sample consisted of 5,987 individuals (52.4% female).

3.1.2 Gothenburg Study on Anorexia Nervosa (AN cohort)

Study III is based on the Gothenburg Study on Anorexia Nervosa, a prospective population- and community-based case-control study ongoing since the mid-1980s. A screening of the total 1970-birth cohort in Gothenburg in 1985 resulted in a population-based group of former or current AN cases. This group was pooled together with a group of AN cases born in the adjacent years, who were referred to the research team by school health nurses and doctors. The total examined AN group consisted of 51 cases (48 females, 3 males) who all met or had met criteria for AN. A comparison group, consisting of 51 healthy age-, gender- and school-matched individuals, was selected by the school nurses. Both groups have been examined five times over a period of 30 years (on average at 16, 21, 24, 32, and 44 years of age).[44,168,221-223]

Data for the 30-year follow-up were collected from May 2015 through November 2016. Thirty-three participants in the AN group and 37 participants in the comparison group completed a computerised FER task. In the AN group we excluded individuals with current ED (n=6) or history of severe traumatic brain injury (n=1). In the comparison group we excluded men (n=3, as the three men in the AN group did not participate in the 30-year follow-up), and individuals with current psychiatric disorders (n=3). The final sample consisted of 26 women recovered from AN and 31 healthy comparison women (COMP). Women who had been assigned a diagnosis of ASD in at least three of the four previous examinations were classified as recovered from AN with stable ASD (recAN+ASD, n=6). The remaining 20 women were classified as recovered from AN without ASD (recAN–ASD).

3.1.3 Japan Environment and Children's Study (JECS cohort)

Studies IV and V included a sub-sample of the Japan Environment and Children's Study (JECS). The JECS is an ongoing nationwide birth cohort study following approximately 100,000 children from pregnancy/birth until the age of 13 and aiming to elucidate environmental factors that affect children's health and development.[224,225] JECS includes 15 Regional Centres that recruited pregnant women via the collaborating local health care providers and local government offices where women registered their pregnancy. The Regional Centres were requested to cover more than 50% of pregnancies in the defined area of study. In collaboration with the Kochi Regional Centre at Kochi Medical School we collected additional data in a sub-cohort including 6,633 children born in Kochi prefecture between July 2011 and December 2014 (Kochi cohort). The EEBQ was sent out to all parents in the Kochi cohort in December 2018. Responses were collected up until 31st October 2019. The response rate was 56.5% (n=3,746).

Table 3.1 *Overview of participants, methods, and type of ED and NDD investigated in each study*

	Study I	Study II	Study III	Study IV	Study V
Research question/topic	Are EDs on an aetiological continuum with ED traits?	Childhood autistic traits in individuals with AN	Facial emotion recognition in AN with or without ASD	Prevalence of ARFID in 4-7-year-old children	Comorbidity of ARFID with NDDs
Type of ED	AN vs. OEDs	AN	Recovered AN	ARFID	ARFID
Type of NDD	----	ASD	ASD	----	NDDs
Cohort	Child and Adolescent Twin Study in Sweden	Child and Adolescent Twin Study in Sweden	Gothenburg Study on Anorexia Nervosa	Japan Environment and Children's Study	Japan Environment and Children's Study
Type of study	Genetic epidemiology (nationwide twin cohort)	Epidemiology (nationwide twin cohort)	Experimental (community-based case-control study)	Epidemiology (regional birth cohort)	Epidemiology (regional birth cohort)
Study design	Cross-sectional	Prospective	Cross-sectional	Cross-sectional	Cross-sectional & prospective
Sample Size	1,481 twin pairs	5,987 individuals	26 recAN+ASD 6 recAN−ASD 31 healthy controls	3,728 individuals	3,728 individuals
Male-female ratio	Female only	52.4% female	Female only	49.1% female	49.1% female
Age of participants	18 y. (born 1992-1999)	9 y. (baseline) & 18 y. (follow-up) (born 1992-1999)	38-46 y. (born 1969-1974)	4-7 y. (born 2011-2014)	4-7 y. (born 2011-2014)
Data source	Questionnaires (self/parent), NPR diagnoses	Questionnaires (parent), NPR diagnoses	Experimental (Emotion recognition task), Clinical examination	Questionnaires (parent)	Questionnaires (parent)

NPR: National Patient Register; recAN±ASD: individuals recovered from AN with/without ASD, OED: EDs other than AN.

3.2 Measures by cohort

3.2.1 Measures in the CATSS cohort (Studies I & II)

3.2.1.1 ED & ASD diagnoses

Registered diagnoses of ED and ASD: The Swedish National Patient Register (NPR) contains diagnoses from psychiatric inpatient care since 1973 and from specialised outpatient care since 2001.[226] NPR diagnoses are based on ICD-8 (1973–1986), ICD-9 (1987–1996) and ICD-10 (since 1997). CATSS is continuously linked to the NPR. In Studies I and II, diagnoses in the NPR up until 31st December 2016 were included. The follow-up age for each individual therefore depended on their birth year (birth years: 1992–1999; ages at the end of follow-up: 17–24 years). For Study I, we retrieved diagnoses of the following EDs: AN (F50.0), Atypical AN (F50.1), BN (F50.2), Atypical BN (F50.3), and unspecified ED/Eating Disorder Not Otherwise Specified (EDNOS, F50.9). For Study II we retrieved diagnoses of AN (F50.0) and atypical AN (F50.1), as well as Autistic Disorder (299.00), Childhood autism (F84.0), Atypical autism (F84.1), Asperger's syndrome (F84.5), Other pervasive developmental disorders (F84.8), and Unspecified pervasive developmental disorder (F84.9; **Table 3.2**). NPR diagnoses show high validity for a range of mental disorders, including ASD,[226-228] while the validity of ED diagnoses has not been formally examined.

Parent-reported treatment for AN/BN: In CATSS-18, parents were asked in separate questions if their twin had been treated for AN or BN. If they responded "Yes, earlier" or "Yes, now", the twin was considered having/having had a diagnosis of AN/BN.

Self-reported purging behaviour: In CATSS-18, twins were asked if they engaged in purging behaviour (i.e., if they had ever used vomiting, laxatives, diuretics, or enemas to lose or control their weight). If twins responded "Yes, repeatedly over at least three months" or "Yes, repeatedly over the last three months" they were considered as having/having had an ED, as individuals with recurrent purging behaviour over a period of three months would meet criteria for DSM-5 OSFED, and possibly even for AN-BP or BN.

ED diagnoses were considered from a lifetime perspective (i.e., having had an ED at some point until the point of measurement). In Study I, we differentiated EDs into AN (including NPR diagnoses of AN and atypical AN, and parent-reported treatment for AN) and other EDs (OEDs, including NPR diagnoses of BN, atypical BN, and

EDNOS, as well as parent-reported treatment for BN and self-reported purging behaviour; **Table 3.2**). In Study II, OEDs were not considered, and lifetime AN was furthermore differentiated into *acute AN* and *history of AN* at the time parents responded to CATSS-18 (i.e., during the assessment of autistic traits at age 18). Individuals were identified with acute AN (1) if parents reported current treatment (as opposed to earlier treatment), (2) if they had received an AN diagnosis in the NPR within 6 months before or after their parents' response to CATSS-18, and/or (3) if they had a BMI below 17 during CATSS-18.

3.2.1.2 ED traits

Eating Disorder Inventory-2 (EDI-2): In CATSS-18, twins filled in the three symptom subscales of the EDI-2,[76] a self-report questionnaire screening for ED pathology. The subscale *Drive for Thinness* (7 items) measures excessive concern with dieting, preoccupation with weight, and fear of weight gain. The subscale *Bulimia* (7 items) measures the tendency to engage in binge eating and to think about purging. The subscale *Body Dissatisfaction* (9 items) measures dissatisfaction with one's overall body shape and the size of specific parts of the body. Items are rated on a 6-point scale from *never* to *always*. A total *EDI-2 score* was computed as the mean of all items on the three subscales. The EDI-2 discriminates reliably between individuals with EDs and healthy controls cross-culturally, but less well between different EDs. It can therefore be used for screening, but not as a diagnostic instrument.[76,229-231]

Table 3.2 *Overview of measurements in the studies based on the Child and Adolescent Twin Study in Sweden (CATSS)*

Disorder/traits	Study I	Study II
AN	F50.0, F50.1, parent-reported treatment for AN	F50.0, F50.1, parent-reported treatment for AN
OED	F50.2, F50.3, F50.9, parent-reported treatment for BN, self-reported purging behaviour	----
Any ED	Any of the above	----
ED traits	EDI-2 score (self-report)	----
ASD diagnoses	----	299.00, F84.0, F84.1, F84.5, F84.8, F84.9
Autistic traits	----	A-TAC ASD score (parent-report)

A-TAC: Autism-Tics, ADHD, and other Comorbidities inventory; EDI-2: Eating Disorder Inventory-2, OED: EDs other than AN.

3.2.1.3 Autistic traits

Autism–Tics, AD/HD, and other Comorbidities inventory (A-TAC): The A-TAC is a fully structured parental telephone interview developed in Sweden for large-scale epidemiological research. It is designed to screen for neurodevelopmental and other psychiatric disorders in childhood based on symptom criteria and well-known clinical features.[232] In the CATSS-9, the ASD module in the A-TAC consists of 17 items— rated with "No" (0), "Yes, to some extent" (0.5), or "Yes" (1)—which together yield an ASD score. The A-TAC has shown high validity for clinical ASD diagnoses in cross-sectional[232,233] and longitudinal studies.[234,235] In CATSS-18, the ASD module includes only 12 of the 17 items. To make the ASD scores comparable across ages, we used the same 12 items to compute the ASD score at age 9. The area under the curve for those 12 items at age 9 was .92 (95% confidence interval [CI] .89-.94) in a community sample.[233] The ASD score was split into two subscales that align with the DSM-5 criteria: *social communication problems* (8 items) and *restricted/repetitive interests and behaviours* (4 items).

3.2.2 Measures in the AN cohort (Study III)

3.2.2.1 Facial emotion recognition task

Participants performed a FER task that was built and conducted with the software Tobii Studio 3.4.0.[236] On an eye tracking screen, participants were presented with a set of faces showing emotional expressions (fear, anger, and happiness) at varying intensity, or neutral expressions on a black background (**Figure 3.1**). Full emotional (100% intensity) and neutral expressions (0% intensity) of eight different people (i.e., identities) were taken from the NimStim Set of Facial Expressions,[237] and morphed expressions were created at 80%, 60%, and 40% intensity using the software Morph Age (http://creaceed.com/morphage).

The total test set consisted of 104 stimuli pictures (targets). These had to be matched to four prototypical (i.e., high-intensity) facial expressions representing fear, anger, happiness and neutral. The participants were instructed to as quickly and accurately as possible select one of the four prototypical images that best described the emotion of the target by pressing the number of the matching image on a button box. The images remained on the screen until a response was given. Accuracy and response time were measured, and eye gaze during the task was recorded.
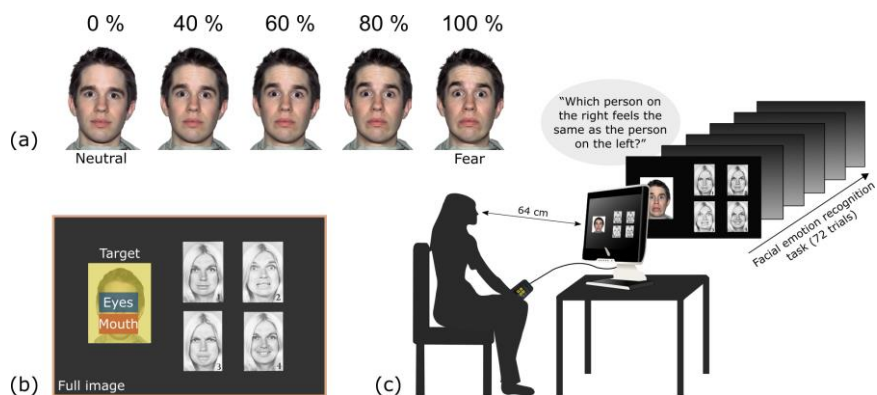
Figure 3.1. *The facial emotion recognition (FER) task in Study III. (a) Example for the morphing of a fear expression: 0% (neutral), 40%, 60%, 80%, and 100% (full emotion). (b) Example image from the FER task with areas of interest. The target on the left (anger at 40% intensity) had to be matched to one of the four images on the right, portraying the fully expressed emotions fear, anger and happiness, as well as a neutral expression. The correct response in this example is image number 3 (anger). (c) Experimental setup. Participants are sitting 64 cm from the eye tracking screen with a button box in their hand to indicate their response. The figure is reprinted with modifications from Paper III.*

3.2.2.2 Clinical examination for EDs

Eating disorders were assessed using the Mini International Neuropsychiatric Interview (M.I.N.I. 6.0, Swedish Version),[238] the Structured Clinical Interview for DSM-IV-TR Axis I Disorders—eating disorders module,[239] and a DSM-5 criteria checklist for feeding and eating disorders.[1] Recovery from AN was defined as having been free from all criterion symptoms of AN, BN, or BED for at least six months.

3.2.2.3 ASD diagnoses

Individuals were not examined for ASD in the current follow-up, though ASD was assessed at each of the previous follow-ups by trained clinicians, blinded to any previously given diagnosis. In the current follow-up, individuals were therefore considered having ASD if they had been assigned a diagnosis of ASD by our group in at least three of the four previous examinations.

3.2.3 Measures in the JECS cohort (Studies IV & V)

In the Kochi cohort, data were collected cross-sectionally with the Early Eating Behaviour Questionnaire (EEBQ). At this point, the children in the Kochi cohort were 4 to 7 years old. While Study IV was based solely on the EEBQ, Study V also used data from the JECS main study, where data were collected longitudinally (i.e., each child was assessed when it was 6 months old, 12 months old, etc.). All data used in Studies IV and V were collected via parent-reported questionnaires.

3.2.3.1 ARFID

Development of the EEBQ: To remedy the lack of parent-reported screening tools for ARFID we started developing such a tool in 2017. The EEBQ is an epidemiological tool with the purpose of screening for ARFID while also providing a comprehensive picture of a broader range of eating problems in young children. The EEBQ consists of 68 items in three sections (see Supplement 1 in Paper IV) and two main instruments to screen for ARFID: (1) the child part (first 25 items) of the Behavioural Paediatric Feeding Assessment Scale (BPFAS),[240,241] and (2) a set of ten items assessing the DSM-5 diagnostic criteria for ARFID.

(1) The BPFAS is a parent-rated questionnaire measuring children's problem behaviours related to mealtimes and nutritional intake. BPFAS items are rated on 5-point frequency scale (*never* to *always*) yielding the *BPFAS Frequency Score*, and on a problem scale ("Is this a problem for you?" *no/yes*) yielding the *BPFAS Problem Score*. Although a British study identified cut-off values for both BPFAS scores to discriminate between 2- to 7-year-old children with ARFID and a normative population, the BPFAS was not specifically developed for ARFID.[242]

(2) The diagnostic items map closely on to the DSM-5 diagnostic criteria for ARFID (see **Box 1.2** and Table 2 in Paper IV). Children were identified with current/previous DSM-5 ARFID when they met criterion A, plus at least one of the criteria A1, A2, and A3, as well as criteria C and D. Criterion B was not assessed. If criterion A together with one of the criteria A1, A2, and A3 were currently met, the child was identified with current ARFID. If A or A1/A2/A3 (or both) were previously met, the child was identified with previous ARFID. For DSM-5 ARFID, criterion A4 was not considered, as the DSM-5 requires physical impairment ("persistent failure to meet nutritional and/or energy needs") for an ARFID diagnosis. We also identified children with current/previous ARFID according to the ICD-11 criteria, where ARFID is also

diagnosed when the avoidance/restriction of food intake is "only" leading to psycho-social impairment, but not to physical impairment (i.e., if only criterion A4 is met, but not any of the criteria A1, A2, or A3).

Further, the EEBQ contains one question each to screen for the three drivers of food avoidance in ARFID (Lack of interest in eating: Q3, Fear of aversive consequences of eating: Q53, Sensory sensitivity to characteristics of food: Q54). The items were rated on a 5-point Likert scale from *never* (1) to *always* (5). A driver was considered to be present if it was rated with at least *sometimes* (3).

3.2.3.2 Neurodevelopment

Data from the EEBQ

NDD diagnoses: Parents were asked to indicate whether their child had received a diagnosis of ASD, ADHD, developmental coordination disorder, intellectual disability, specific learning disorder (e.g., dyslexia), tic disorder/Tourette Syndrome, oppositional defiant disorder, or conduct disorder.

Data from the JECS main study

Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations Questionnaire (ESSENCE-Q): The ESSENCE-Q screens for a broad range of early neurodevelopmental symptoms that might indicate the presence of NDDs and therefore suggest that clinical examination is needed.[243] It is intended for use in both clinical practice and epidemiological research and shows good validity when used for screening by health professionals in Japanese public health settings.[244,245] The ESSENCE-Q consists of 11 short questions on whether there is any concern in the different developmental areas, which are rated with "Yes", "Maybe/a little" or "No". In the JECS, the answer format was changed to "Yes" or "No" (modified ESSENCE-Q). Data were available at child age 2.5 years.

Ages and Stages Questionnaire-3 (ASQ-3), Japanese Version: The ASQ-3 is a parent-rated screening tool assessing developmental delay in five skill domains: communication, gross motor, fine motor, problem-solving and personal-social.[246] Each domain consists of six questions on whether a certain activity can be done by the child. Data were available at ages 6, 12, 18, 24, 30, and 36 months. Children potentially at risk for developmental delay are identified with age- and domain-dependent cut-off values ("monitoring cut-off" at 1 standard deviation below the mean and a "referral cut-off" at 2 standard deviations below the mean).[247] In Study V only

the referral cut-off was used. A score below the referral cut-off value of a domain is labelled as "failing the domain".

3.3 Analytical and statistical methods by study

Data analyses were performed in Stata,[248] R,[249] and SPSS.[250] The statistical significance level was set to p<.05 in all studies.

3.3.1 Study I

3.3.1.1 Quantitative genetic twin modelling

Quantitative genetic modelling aims to investigate the aetiology of phenotypes in terms of the proportions of genetic and environmental factors explaining the individual variation in a phenotype. The term *phenotype* refers to observable traits of individuals (e.g., symptoms). Quantitative genetic *twin* modelling takes advantage of the genetic and environmental factors shared by twins (for an extensive description of the twin design see [251-253]). Monozygotic (MZ) twins share all of their segregating alleles[c], while dizygotic (DZ) twins on average share 50%. Furthermore, if twins grow up in the same home environment at the same age, they share influences such as parental education, certain parenting behaviours, and the amount of conflict in the household; these influences are therefore called the *shared environment*. Shared environmental influences make twins more similar to each other, and these influences should have the same effect regardless of zygosity (*equal environments assumption*). Other environmental factors might not be shared between twins (e.g., having different peers, teachers, hobbies, and diseases) and in that case make them less similar to each other (*non-shared environment*).

The twin model is based on comparing the resemblance of MZ twins for a certain phenotype with the resemblance of DZ twins for the same phenotype. The resemblance is expressed in correlations. The variance of the phenotype is decomposed into the following genetic and environmental effects: **Additive genetic effects** (*A*, also: *heritability h²*), indicated when MZ correlations are higher than DZ correlations; **non-additive genetic effects** (*D*), indicated when MZ correlations are more than twice as

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[c] An allele is one of the variants a gene can take. Humans share circa 99.9% of their DNA. The 0.1% of the DNA that are not shared cause individual differences and are called *segregating alleles*. The assumption that MZ twins share 100% of their segregating alleles is not always true. Certain mutations (called de novo mutations) can arise after the fertilised maternal egg has split and lead to genetic differences between MZ twins.

high as DZ correlations; **shared environmental effects** (*C*), indicated when DZ correlations are more than half as high as MZ correlations; and **non-shared environmental effects** (*E*), indicated by differences within MZ pairs (i.e., a MZ correlation smaller than 1). *E* also includes measurement error. The simplest and most common twin models are *ACE* and *ADE* models. As *C* and *D* confound each other, the twin model can only contain either or.

3.3.1.2 Extremes analyses of EDI-2 score

We used three different analytical methods to investigate whether genetic and environmental factors that contribute to EDs also influence the variation in ED traits in the population (**Figure 3.2**). The first two methods are extremes analyses. They relate to only one phenotype (ED traits measured by the EDI-2 score), and examined whether the aetiology of the EDI-2 score was consistent across the entire sample *and* among those showing extreme EDI-2 scores. We identified different groups of extreme scorers (*probands*) using percentile-based cut-offs (i.e., scoring within the *upper* 1st, 3rd, 5th and 10th percentile of the EDI-2).

Liability threshold modelling is based on dichotomous data, but assumes an underlying continuous distribution of liability to the categorical construct (i.e., being a proband or not). Using liability threshold models, we estimated the proportions with which genetic and environmental factors explained the variation in the liability to being a proband (**Figure 3.2**). We did this for each of the different groups of probands (i.e., the upper 1st, 3rd, 5th and 10th percentile of the EDI-2 score).

DeFries-Fulker extremes analysis assesses consistency in the aetiology of a trait across different severity levels (here the upper 1st, 3rd, 5th and 10th percentile of the EDI-2 score) by modelling an individual's expected score as a function of their co-twin's proband status.[254,255] DeFries-Fulker analysis returns an estimate for group heritability (h^2_g) that indicates the degree to which the genetic influences on extreme scores for a trait also influence the continuous variation in this trait (**Figure 3.2**). While the classical procedure is regression-based, we used a model fitting implementation of the procedure.[255]

3.3.1.3 Joint categorical-continuous models of ED diagnoses and EDI-2 score

The third method we used–**joint categorical-continuous modelling**–relates to two different phenotypes, here the EDI-2 score and AN/OED diagnoses. It estimates the degree to which genetic and environmental factors that contribute to the EDI-2 score also contribute to ED diagnoses, and therefore provides the most direct evidence for

the continuum hypothesis. The joint categorical-continuous model combines a liability threshold model (here for AN/OED diagnoses) with a model for a continuous variable (here for EDI-2 score). Apart from estimating the degree of genetic and environmental influences on EDI-2 score and AN/OED diagnoses, the model estimates the genetic, shared environmental, and non-shared environmental correlations *between* EDI-2 score and AN/OED diagnoses (**Figure 3.2**). The genetic correlation (r_g) indicates the degree to which genetic influences on the EDI-2 score are shared with those on AN/OED diagnoses. A genetic correlation of 1.0 (0.0) implies that all (none) of the additive genetic influence on EDI-2 score and AN/OED diagnoses is shared between them. Using the genetic correlation and the heritability of each trait, we can calculate the *bivariate heritability*; that is, the degree to which the overlapping genetic factors on EDI-2 score and AN/OED diagnoses explain the phenotypic correlation between them.

In all three analytical methods we fitted ACE (instead of ADE) models, as the DZ twin correlation for EDI-2 score was larger than half of the MZ twin correlation.

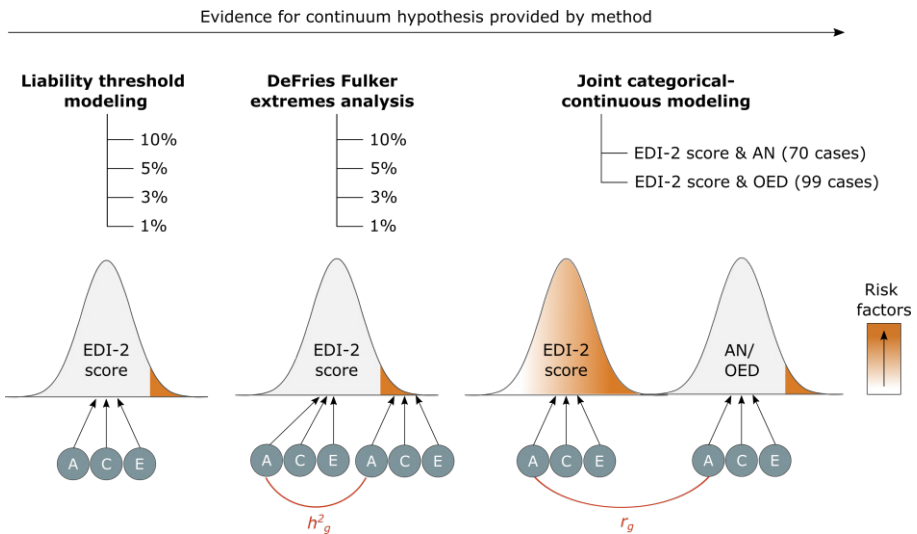***Figure 3.2*** *Illustration of the three different analytical methods used in Study I. A: additive genetic effects, C: shared environmental effects, E: non-shared environmental effects, EDI-2: Eating Disorder Inventory-2, OED: EDs other than AN, h^2_g = group heritability, r_g = genetic correlation, 10%, 5%, 3%, 1% = different groups of extreme scorers based on scoring in the upper 10th, 5th, 3rd or 1st percentile of the EDI-2.*

3.3.2 Study II

The ASD subscale scores (social communication problems and restricted/repetitive behaviour and interests) were compared between individuals with AN and individuals without AN, separately for boys and girls, at ages 9 and 18. Assuming that there is an increased prevalence of ASD in AN, we expected to see some elevation of childhood autistic traits in individuals with later AN. Next, we compared the ASD score at age 18 between individuals with a history of AN and individuals with acute AN. This analysis could only be done for girls, as the number of boys with AN was too low for meaningful interpretations. As a statistical method, we applied generalised estimating equations (GEE) with a robust sandwich estimator, to account for the dependency between twins of a pair (i.e., each pair is treated as a cluster).[256] The GEE models were run using a negative binomial distribution with log link function, since the ASD score was extremely skewed and log-transformation failed. The models therefore yielded incidence rate ratios (IRR) as parameter estimates. In the case of a binary predictor variable (AN vs. no AN), the IRR can be interpreted as the ratio of the ASD score in individuals with AN to the ASD score in the individuals without AN.

3.3.3 Study III

Expressions at 100% intensity and neutral expressions were not used in the data analysis, therefore the FER task yielded data for 72 trials per participant. Trials with extremely short or extremely long response times were considered invalid and discarded. For the eye gaze analyses, we also discarded trials where the participant was looking at the screen for less than 90% of the trial time. Areas of interest (AOIs) were created for the target (whole face, eye region, mouth region; **Figure 3.1**). For each trial, we computed the fixation duration and the number of fixations on these AOIs. We conducted analyses for four outcome variables: 1. accuracy, 2. eye-to-mouth viewing ratio, 3. average fixation duration, and 4. fixation count (3. and 4. are measures for hyperscanning). The computation of and statistical method for each outcome variable is presented in **Table 3.3**.

Predictor variables were the between-factor *group*, and the within-factors *emotion intensity* (40%, 60%, 80%) and *type of emotion* (fear, anger, happiness). Since the recAN+ASD group was very small (n=6), we only conducted exploratory analyses for this group (comparing it to recAN–ASD), while the main analysis consisted of comparing recAN–ASD with COMP. For each outcome, we first ran the full model, including group, emotion intensity, and type of emotion, their 2-way and 3-way interactions, and response time as a covariate. Statistically non-significant predictors were then removed successively until only significant predictors were left in the

model (except for *group*, which was kept in the final model even if non-significant). All statistical models were adjusted for repeated measurements within participants, by modelling each participant as a cluster using cluster-robust standard errors (robust sandwich estimator).

Table 3.3 *Computation of and statistical method for each outcome variable in Study III*

Outcome	Computed as	Type of data	Statistical model	Distribution, link function
Accuracy	----	Binary (correct/incorrect)	GEE	Binomial, logit link
Eye-to-mouth viewing ratio	FD on eye AOI / (FD on eye AOI + FD on mouth AOI) *per trial*	Proportion [0, 1]	Fractional logistic regression	
Average fixation duration	Total FD/number of fixations (per trial)	Continuous in milliseconds, approx. normal	GEE	Gaussian, identity link
Fixation count	Number of fixations per trial	Count	GEE	Negative binomial, log link

All models were computed with cluster-robust standard errors to account for repeated measurements within participants. AOI: Area of interest, FD: Fixation duration; GEE: Generalised estimating equations.

3.3.4 Study IV

Descriptive statistics were used to report the prevalence estimates of ARFID. Point prevalence was determined as the proportion of children with current ARFID. Lifetime prevalence was determined as the proportion of children with current and/or previous ARFID. The prevalence of ARFID was furthermore estimated based on the cut-off values that have been proposed for the two BPFAS scores.[242] To measure the diagnostic accuracy of the BPFAS scores, we conducted receiver operating characteristic (ROC) analyses against ARFID "diagnosis" as defined by the DSM-5 diagnostic criteria assessed with the EEBQ.

3.3.5 Study V

Descriptive statistics were used to report characteristics of children with ARFID and children without ARFID. To measure the relative association between ARFID status and the binary outcomes we estimated relative risks (RRs) using log-poisson models with a robust variance estimator.[257] In cohort studies, RRs are a good alternative to odds ratios (ORs) to measure relative association, as ORs are often misinterpreted while RRs are more intuitive.[257] When the outcome is rare, ORs and RRs are very similar, but the more common the outcome, the more they diverge.[257]

3.4 Ethical considerations

All procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. Written, verbal, or digital informed consent was obtained from all participants. All studies were approved by ethical review boards:

Studies I & II: Regional Ethical Review Board in Stockholm (02-289, 03-672, 2010/597-31/1, 2010/322-31/2, 2010/1410-31/1, 2016/2135-31)

Study III: Regional Ethical Review Board in Gothenburg (398-14)

Studies IV & V: Kochi Medical School (ERB-102925 and ERB-104083)

4 RESULTS

4.1 Study I: Are EDs on an aetiological continuum with ED traits?

Across all analytical methods, AE models showed the best fit, which means shared environmental factors did not have a significant[d] influence on EDI-2 score and ED diagnoses. The group heritability estimates in the DeFries-Fulker extremes analyses (h^2_g) ranged from 0.59 to 0.65. They were significant and consistent over the different extreme groups (i.e., upper 1st, 3rd, 5th, and 10th percentile of the EDI-2 score; **Figure 4.1**). The group heritability estimates were also similar to the heritability of EDI-2 score in the full sample (h^2=0.65, **Figure 4.2**). Together, this indicates genetic continuity between severe ED traits and milder manifestations. In the liability threshold models, the heritability estimates of EDI-2 score were consistent over the different extreme groups (h^2=0.64–0.70; **Figure 4.1**), further indicating consistent aetiology for different severity levels of ED traits. The liability threshold analysis could not be conducted for the 1st percentile due to low power.
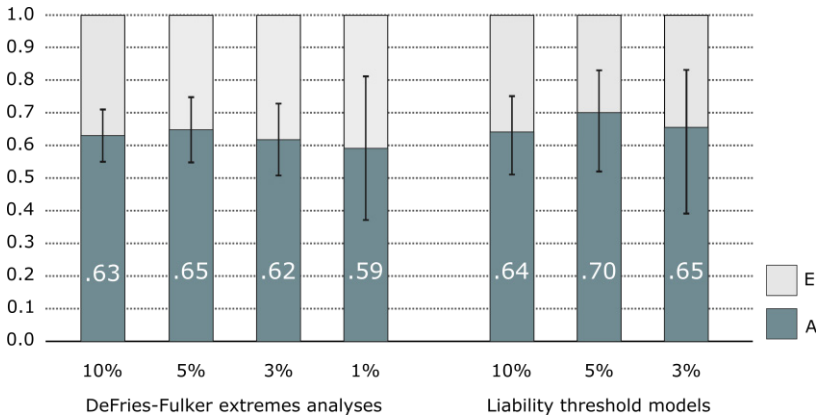

Figure 4.1 *Variance component estimates in the DeFries-Fulker extremes analyses and the liability threshold models of the Eating Disorder Inventory-2 (EDI-2) score (Study I). 10%, 5%, 3%, and 1% on the x-axis relate to the percentile-based extreme groups. The numbers on the bars indicate the point estimate of the additive genetic effects. Error bars visualise the 95% confidence interval for the additive genetic effects. A: additive genetic effects (in the DeFries-Fulker extremes analyses, A corresponds to the group heritability, h^2_g, while in the Liability threshold models, A corresponds to the heritability, h^2), E: non-shared environmental effects. The figure is reprinted with modifications from Paper I.*

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[d] Throughout chapter 4, the term "significant" specifically and consistently denotes *statistical* significance.

AN was identified in 70 individuals (2.4%) and OEDs were identified in 99 individuals (3.3%). The joint categorical-continuous models revealed similar heritability estimates for EDI-2 score (h^2=0.65), AN (h^2=0.63), and OEDs (h^2=0.67; **Figure 4.2**). EDI-2 score and AN had a lower phenotypic correlation (r_{Ph}=0.39) than EDI-2 score and OEDs (r_{Ph}=0.52). Similarly, the genetic correlation was lower for EDI-2 score and AN (r_g=0.26) than for EDI-2 score and OEDs (r_g=0.52; **Figure 4.2**). The bivariate heritability of EDI-2 score and AN was 0.43, that is, genetic factors accounted for 43% of the phenotypic correlation between EDI-2 score and AN. The bivariate heritability of EDI-2 score and OEDs was 0.66. The non-shared environmental correlations were similar for AN and EDI-2 score (r_E=0.60), and for OEDs and EDI-2 score (r_E=0.52).
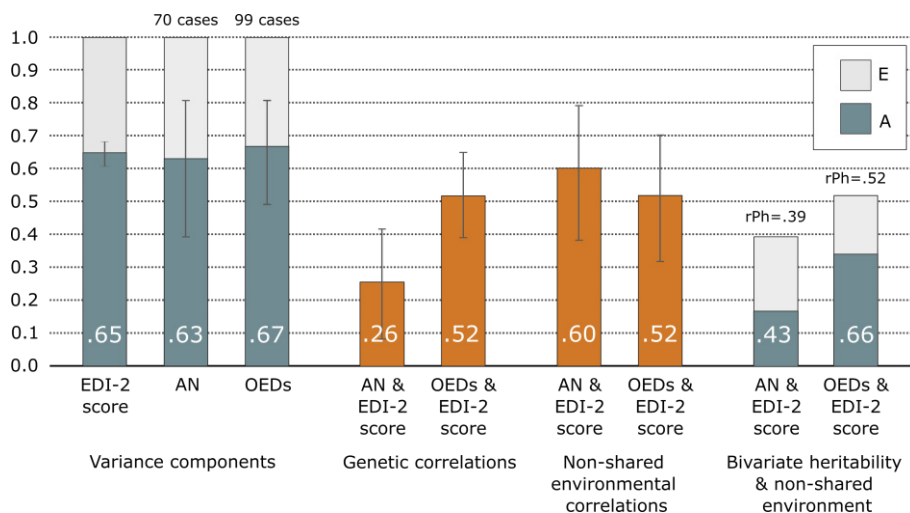

Figure 4.2 *Variance components, correlations, and bivariate estimates from the joint categorical-continuous models (Study I). Orange bars depict the genetic and non-shared environmental correlations. The numbers on the bars indicate the point estimate of the additive genetic effects/the correlation. Error bars visualise the 95% confidence interval for the additive genetic effects/the correlations. A: additive genetic effects (corresponds to heritability, h^2), E: non-shared environmental effects, EDI-2: Eating Disorder Inventory-2, OEDs: EDs other than AN; r_{Ph}: phenotypic correlation. The figure is reprinted with modifications from Paper I.*

4.2 Study II: Childhood autistic traits in individuals with AN

Ongoing or previous AN was identified in 76 girls (2.4%) and 20 boys (0.7%). ASD scores were compared between individuals with and without AN *before* the first diagnosis of AN (age 9) and *after* the first diagnosis of AN (age 18). At age 9, social communication problems and restricted/repetitive behaviour and interests were *not* significantly increased in girls and boys with later AN, as indicated by the confidence intervals that included the baseline of 1 (**Figure 4.3**).
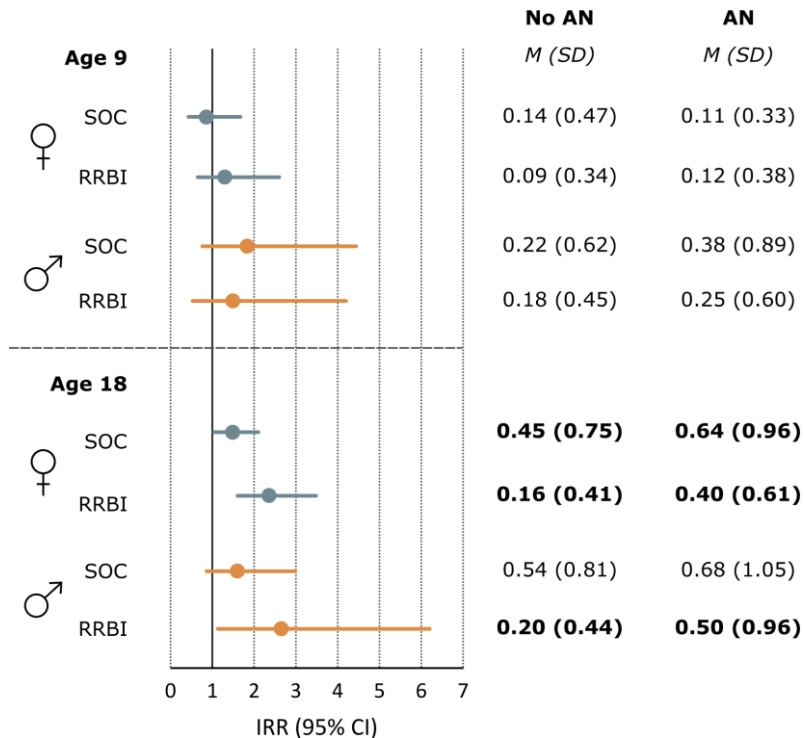
Figure 4.3 *Comparison of scores on the ASD module of the Autism–Tics, AD/HD, and other Comorbidities inventory (A-TAC) between children with and without AN at age 9 and age 18 (Study II). Mean values (M) and standard deviations (SD) are presented on the right, incidence rate ratios (IRRs) and 95% confidence intervals (CI) are presented on the left. Mean values differing significantly from each other are printed in bold. SOC: social communication problems, RRBI: restricted/repetitive behaviour and interests. The figure is reprinted with modifications from Paper II.*

At age 18, both social communication problems and restricted/repetitive behaviour and interests were significantly increased in girls with AN compared to girls without AN (**Figure 4.3**). This elevation was, however, confined to restricted/repetitive behaviour and interests in the subgroup of girls with acute AN, while girls with a history of AN had the same level of social communication problems and restricted/repetitive behaviour and interests as girls who never had AN (**Figure 4.4**). In boys with AN, restricted/repetitive behaviour and interests, but not social communication problems, were significantly increased at age 18. A subgroup analysis could not be conducted due to few boys with AN (n=20).
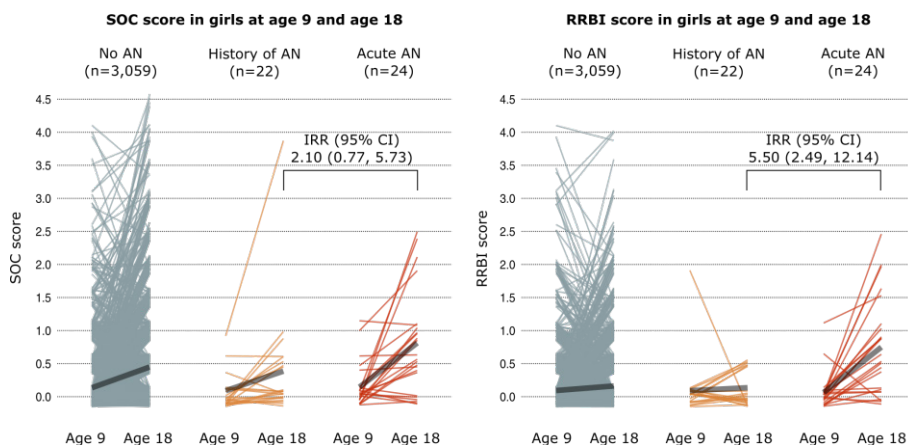

Figure 4.4 *Within-individual change in ASD subscale scores from age 9 to age 18 by group. Each coloured line corresponds to one individual (Study II). The thicker black line is the group average. Incidence ratio ratios (IRRs) are given for the comparison of mean scores between individuals with a history of AN and individuals with acute AN at age 18. SOC: social communication problems, RRBI: restricted/repetitive behaviour and interests. The figure is reprinted with modifications from Paper II.*

4.3 Study III: Facial emotion recognition in AN with or without ASD

Accuracy: The average accuracy for targets at 60% and 80% intensity was ≥90%, indicating ceiling effects, while the average accuracy was 47% for targets at 40% intensity. There was no significant main effect of group, nor were there any significant interaction effects of group with emotion intensity or type of emotion. This means that recAN–ASD did not differ significantly in accuracy from the COMP group. In the exploratory analysis (recAN–ASD vs. recAN+ASD), we found a significant interaction effect of group with emotion intensity, meaning that the group difference depended on the level of emotion intensity. Post-hoc comparisons revealed that the

recAN+ASD group was significantly better than the recAN–ASD group at recognising emotions at 40% intensity (60% accuracy [95% CI 46–75%] vs. 41% accuracy [95% CI 32–49%]; **Figure 4.5**). The recAN+ASD group took on average 0.8s longer than the recAN–ASD group to complete correct trials at 40% intensity.
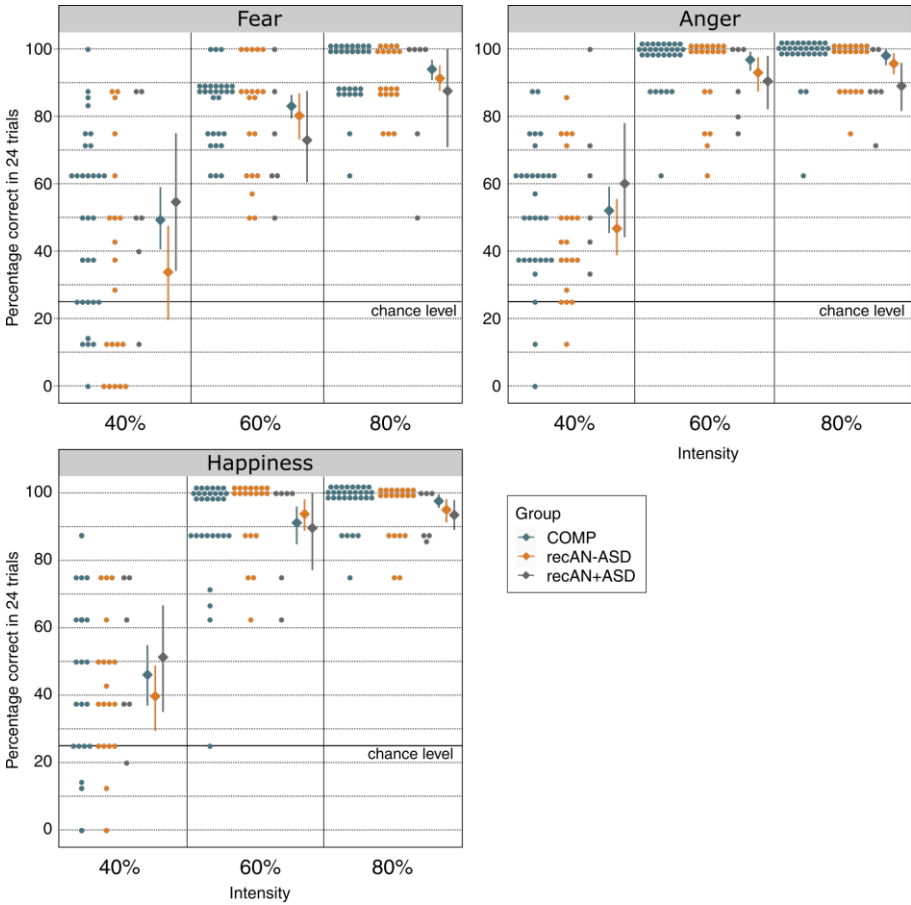
Figure 4.5 *Distribution of accuracy by type of emotion, emotion intensity, and group (Study III). On the left of each column, each dot represents the percentage of accuracy of one participant averaged over eight trials (i.e., 8 identities). On the right of each column, diamonds and error bars present the group mean and the 95% confidence interval of the group mean. The figure illustrates that healthy comparison women (COMP) and women recovered from AN without ASD (recAN–ASD) performed very similarly. It also illustrates a main effect of emotion intensity (40% < 60% < 80%) and a main effect of type of emotion (fear < anger = happiness). recAN+ASD: women recovered from AN with ASD. The figure is reprinted with modifications from Paper III.*

Visual scanning behaviour (eye-to-mouth viewing ratio, average fixation duration, fixation count): In both the main analysis (recAN–ASD vs. COMP) and the exploratory analysis (recAN–ASD vs. recAN+ASD) there were no significant main effects of group nor significant interaction effects including group for any of the three outcome variables. **Figure 4.6** shows the eye-to-mouth viewing ratio by type of emotion and group. Eye-to-mouth viewing ratio did not predict accuracy.
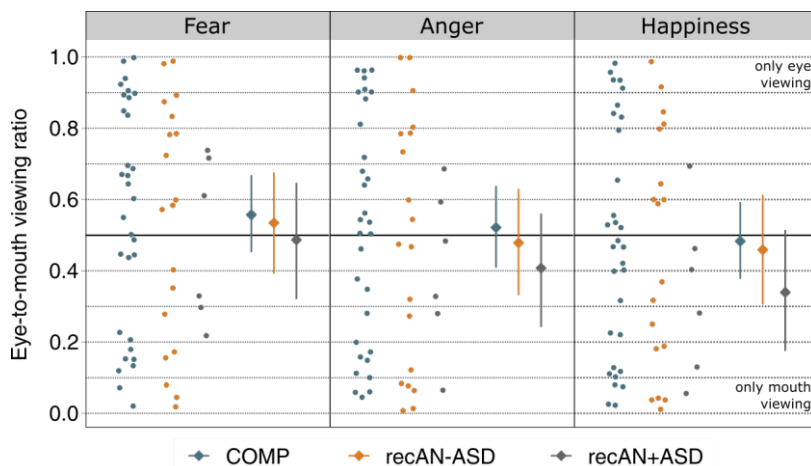

Figure 4.6 *Distribution of eye-to-mouth viewing ratio by type of emotion and group (Study III). An eye-to-mouth viewing ratio of 0.5 means that equal time was spent looking at the eye region and looking at the mouth region of the target. Each dot represents the eye-to-mouth viewing ratio of one participant averaged over 24 trials (3 intensities x 8 identities). Diamonds and error bars present the group mean and the 95% confidence interval of the group mean. COMP: healthy comparison women, recAN±ASD: women recovered from AN with/without ASD. The figure is reprinted with modifications from Paper III.*

4.4 Study IV: Prevalence of ARFID in 4-7-year-old children

Figure 4.7 summarises the most important results of Study IV. The point prevalence of ARFID according to DSM-5 criteria was 0.7% (n=27). Girls and boys were equally affected. When ICD-11 criteria were applied (i.e., allowing for the A4 criterion to be critical for the diagnosis), the point prevalence almost doubled (1.3%). However, the ICD-11 point prevalence varied from 0.9–1.6%, based on the applied threshold for the A4 criterion (see Table 3 in Paper IV). With the strictest threshold, DSM-5 and ICD-11 prevalence were very similar (0.7% and 0.9%), however, we decided that a moderate threshold would be most appropriate (see Supplement 2 in Paper IV). Both sensory sensitivity to food characteristics and lack of interest in eating were drivers

of food avoidance in more than half of all children with ARFID. Roughly a third of children with ARFID had more than one driver.
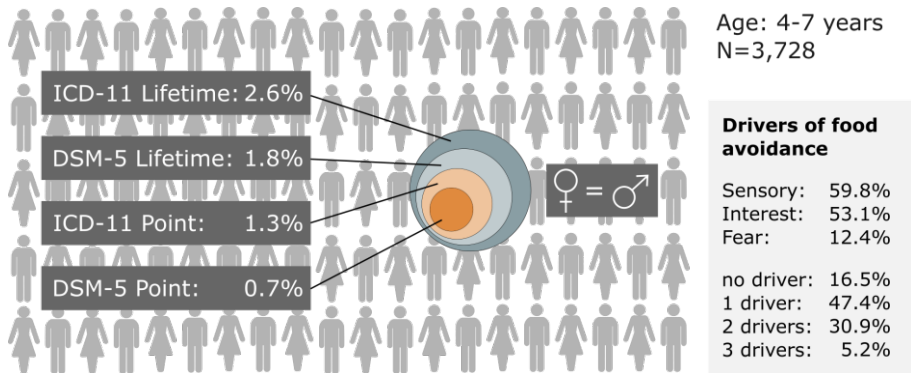

Figure 4.7 Summary of results regarding the prevalence of ARFID in Study IV. ICD-11 Life/DSM-5 Life: lifetime prevalence of ARFID according to the ICD-11/DSM-5 criteria, the lifetime prevalence includes children with current and/or previous ARFID; ICD-11/DSM-5 Point: point prevalence of ARFID according to the ICD-11/DSM-5 criteria, the point prevalence includes children with current ARFID; Sensory: sensory sensitivity to food characteristics, Interest: lack of interest in eating, Fear: fear of aversive consequences of eating.

We conducted ROC analyses for both BPFAS scores, to measure their diagnostic accuracy in classifying children with or without ARFID. Children identified with current and/or previous ARFID according to the DSM-5 diagnostic criteria assessed with the EEBQ were considered "true" cases (1.8%, see **Figure 4.7**). The area under the curve was 0.80 for the BPFAS Frequency Score and 0.78 for BPFAS Problem Score, indicating a 78–80% probability that a randomly selected child with ARFID will have higher BPFAS scores than a randomly selected child without ARFID. When applying the previously proposed cut-off values to the BPFAS scores, the prevalence of ARFID was 5.2% according to the BPFAS Frequency Score and 11.7% according to the BPFAS Problem Score. While both scores had a high specificity (95%/89%; i.e., proportion of correctly identified children without ARFID [true negatives]), their sensitivity was low (39%/53%; i.e., proportion of correctly identified children with ARFID [true cases]). **Figure 4.8** illustrates that the BPFAS scores and the DSM-5 diagnostic criteria assessed with the EEBQ largely identified different groups of children with ARFID. For instance, using the BPFAS Frequency Score, only 39% of the true cases were detected (sensitivity) and only 13% of the children identified with the BPFAS Frequency Score were true cases (positive predictive value).
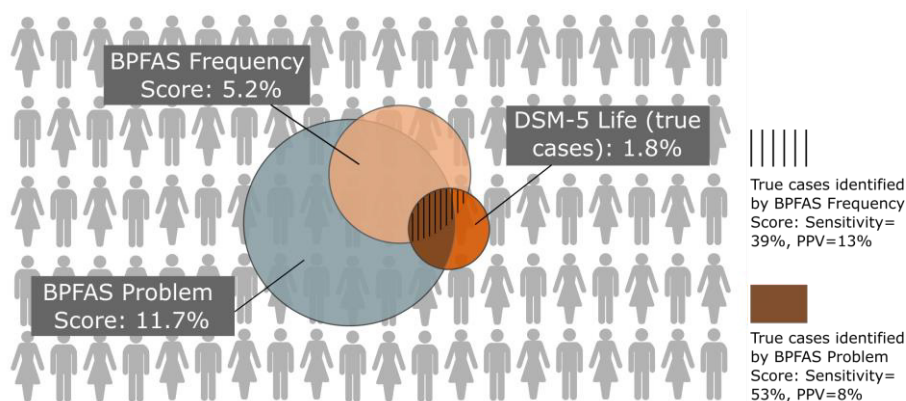
Figure 4.8 *Overlap of the groups of children with ARFID identified by the Behavioural Paediatric Feeding Assessment Scale (BPFAS) scores and the DSM-5 diagnostic criteria assessed with the Early Eating Behaviour Questionnaire (EEBQ) in Study IV. Percentages in the dark grey boxes indicate prevalence. DSM-5 Life: includes children with current and/or previous ARFID according to the DSM-5 criteria, PPV: positive predictive value.*

Based on the experience of evaluating the EEBQ in this cohort and the above presented data, we have converted the 68-item EEBQ into a short screening instrument: the ARFID-Brief Screener (ARFID-BS, see Supplement 4 in Paper IV). The ARFID-BS consists of the EEBQ items assessing the DSM-5/ICD-11 diagnostic criteria and the drivers of food avoidance (although with small changes to their wording and/or response formats). The modifications are described in detail in supplementary Table 6 of Paper IV.

4.5 Study V: Comorbidity of ARFID with NDDs

The neurodevelopmental comorbidity of ARFID was investigated in the group of children with current and/or previous ARFID according to the DSM-5 criteria (n=67, 1.8%; compare **Figure 4.7**, DSM-5 Lifetime). Of these, 27 children currently had ARFID and 40 children previously had ARFID. Overall, children with ARFID had a higher risk of neurodevelopmental problems and NDDs. **Figure 4.9** shows the relative risks for (1) NDD diagnoses reported in the EEBQ (at age 4–7 years), (2) neurodevelopmental problems indicated in the modified ESSENCE-Q (at age 2.5 years), and (3) developmental delay demonstrated by failing an ASQ-3 domain at least twice out of the six biannual measurements (up to age 3 years).
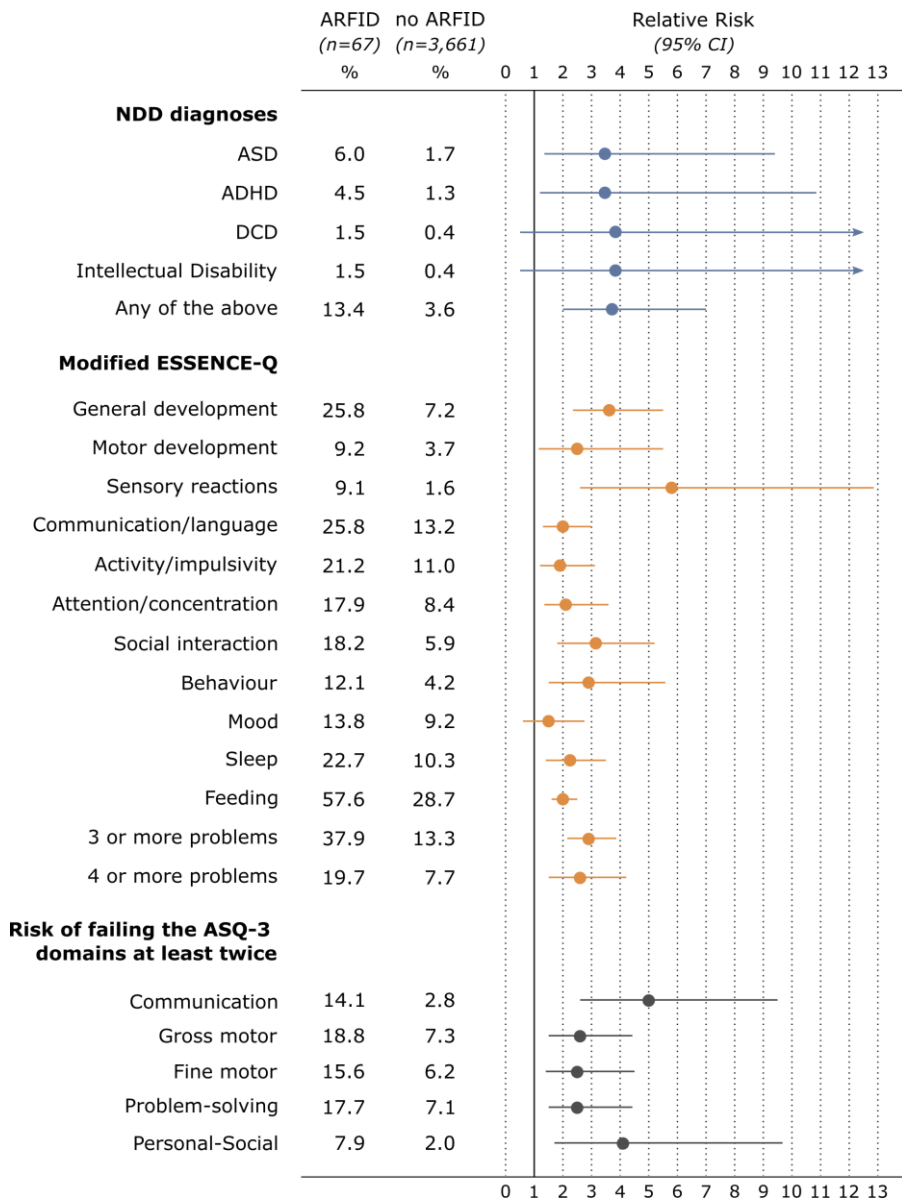
	ARFID (n=67) %	no ARFID (n=3,661) %	Relative Risk (95% CI)
NDD diagnoses			
ASD	6.0	1.7	
ADHD	4.5	1.3	
DCD	1.5	0.4	
Intellectual Disability	1.5	0.4	
Any of the above	13.4	3.6	
Modified ESSENCE-Q			
General development	25.8	7.2	
Motor development	9.2	3.7	
Sensory reactions	9.1	1.6	
Communication/language	25.8	13.2	
Activity/impulsivity	21.2	11.0	
Attention/concentration	17.9	8.4	
Social interaction	18.2	5.9	
Behaviour	12.1	4.2	
Mood	13.8	9.2	
Sleep	22.7	10.3	
Feeding	57.6	28.7	
3 or more problems	37.9	13.3	
4 or more problems	19.7	7.7	
Risk of failing the ASQ-3 domains at least twice			
Communication	14.1	2.8	
Gross motor	18.8	7.3	
Fine motor	15.6	6.2	
Problem-solving	17.7	7.1	
Personal-Social	7.9	2.0	

Figure 4.9 Relative risk of neurodevelopmental problems and NDDs in children with ARFID compared to children without ARFID (Study V). Error bars present 95% confidence intervals (CIs). The arrows at the CIs of Developmental Coordination Disorder (DCD) and intellectual disability indicate that the CIs extend beyond the plotted scale; the upper CI limit is 29.3 for both CIs. ASQ-3: Ages and Stages Questionnaire-3, ESSENCE-Q: Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations-Questionnaire.

The prevalence of any NDD was 13.4% in the ARFID group and 3.6% in children without ARFID (RR=3.7; **Figure 4.9**). The risk of ASD and ADHD was 3-4 times higher in children with ARFID, although their absolute prevalence was lower than expected (ASD: 6%, ADHD: 4.5%). The prevalence of ASD and ADHD in the whole sample was 1.8% and 1.3%, respectively. On the modified ESSENCE-Q, every neuro-developmental problem—except mood—was 2–6 times more common in children with ARFID. Abnormal sensory reactions to stimuli such as touch, sound, light, smell, or taste showed the highest risk increase (**Figure 4.9**). In the ARFID group, 38% had four or more neurodevelopmental problems on the ESSENCE-Q, as opposed to 13% in the group without ARFID. On the ASQ-3, children with ARFID had a 2–5 times higher risk of failing a domain at least twice. The highest risk increase was found for the Communication domain and the Personal-Social domain. Sensory sensitivity to food characteristics and lack of interest in eating as drivers of food avoidance were more common in children with ARFID *and NDDs* than in children with ARFID without NDDs; for instance, 77.8% of children with NDDs presented with sensory sensitivity, but only 51.7% of children without NDDs presented with sensory sensitivity (**Figure 4.10**).
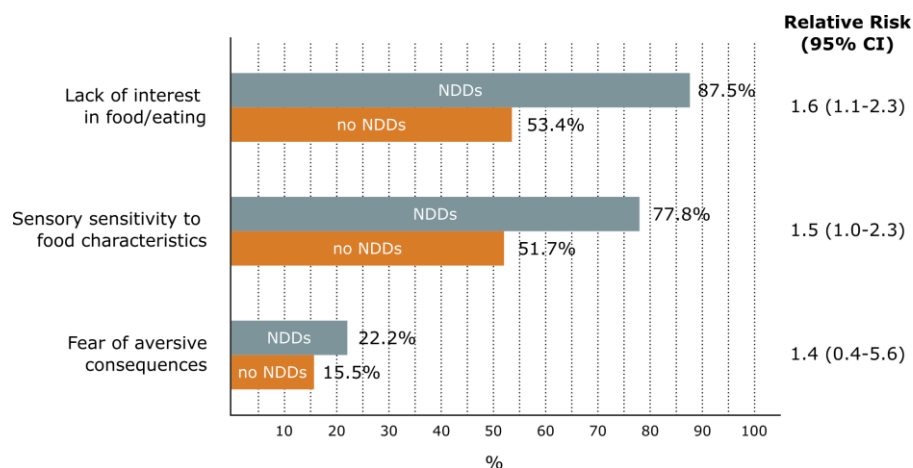

Figure 4.10 *Frequency of the three drivers of food avoidance in children with ARFID, depending on comorbid NDDs as reported by parents in the Early Eating Behaviour Questionnaire (EEBQ) in Study V. ARFID with NDDs: n=9 (of these: n=8 with ≥1 driver), ARFID without NDDs: n=58 (of these: n=47 with ≥1 driver).*

5 DISCUSSION

5.1 Discussion of main findings

5.1.1 Study I

Study I examined whether adolescent-onset EDs can be viewed aetiologically as the extreme manifestation of continuous variation in ED traits. The aetiology of ED traits (i.e., the extent of genetic and environmental influences) measured with the EDI-2 was consistent across different levels of severity in the extremes analyses. When examining the genetic correlation between ED traits and ED diagnoses in joint categorical-continuous models, we found a moderate genetic correlation of *OEDs* and ED traits, while there was a lower genetic correlation between *AN* and ED traits. This suggests that **OEDs can**, at an aetiological level, **be conceptualised as the extreme manifestation of continuously distributed traits** (scenario A in **Figure 5.1**), which is in line with other psychiatric and neurodevelopmental disorders.[88,97] This finding is also in agreement with previous evidence for a dimensional nature of ED pathology from phenotypic studies using taxometric and mixture modelling approaches,[84-86] and it concurs with recent endeavours of a dimensional classification of EDs within the Hierarchical Taxonomy of Psychopathology (HiTOP).[258]

That **AN seems to be more genetically demarcated from ED traits** (scenario B in **Figure 5.1**) than OEDs, is an intriguing finding, which confirms previous reports that the heritability of AN decreased with the broadening of diagnostic criteria, while this was not the case for BN.[27,259] Interestingly, the most recent GWAS of AN found that AN shares genetic variation with metabolic traits (e.g., higher levels of high-density lipoprotein cholesterol, lower levels of leptin and insulin resistance), which is not accounted for by common genetic variants associated with BMI.[102] This poses the question whether AN might be not only a psychiatric, but also a metabolic disorder[102]—a notion that is further supported by the recent finding that individuals who go on to develop AN in adolescence have significantly lower BMIs throughout childhood (2–12 years), which suggests that premorbid metabolic factors could be involved in the aetiology of AN.[260] The EDI-2 and dimensional measures of ED traits in general may not capture this metabolic component, which might have led to the low genetic correlation between AN and ED traits. Another potential explanation for the genetic discontinuity between AN and ED traits could be that the psychological and behavioural dimensions measured with the EDI-2 do not optimally reflect the psychological and behavioural AN phenotype. It is, however, unclear what would

characterise more suitable dimensions of AN. In summary, our results indicate that the risk for AN might be less continuously distributed than the risk for (most) other psychiatric disorders. Future studies should examine this potential difference further by using different measures of ED traits.
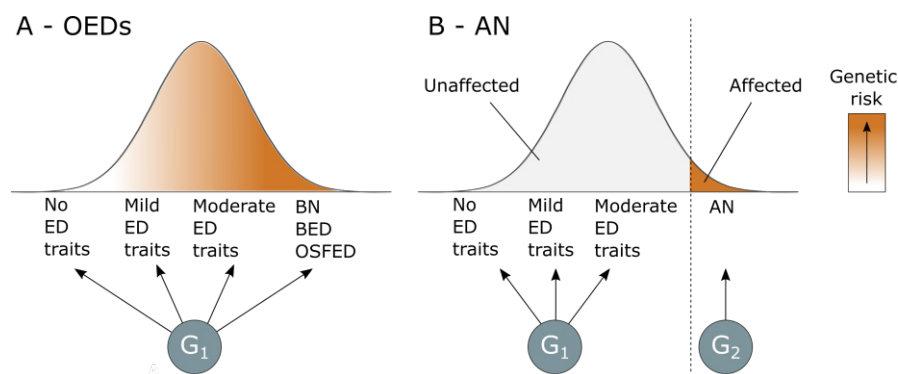

Figure 5.1 Result for the aetiological continuum hypothesis in Study I. Scenario A: Other Eating Disorders (OEDs) as the extreme manifestation of continuous genetic variation in ED traits in the population, Scenario B: AN as a genetically distinct entity. G1 and G2 represent different sets of genetic factors. BED: Binge-Eating Disorder, BN: Bulimia Nervosa, OSFED: Other Specified Feeding or Eating Disorder.

Another interesting result was that the **non-shared environmental correlations** between ED diagnoses and ED traits were **higher than what is usually observed** in other disorders.[97] This might (partly) be explained by the *idealisation of thinness* (thin-ideal) in Westernised cultures, which is an important environmental risk factor for EDs, but less relevant for other disorders. Indeed, there is evidence that increased media exposure to the thin-ideal, perceived pressure to be thin, and thinness expectations (e.g., expecting life improvements when being thin) are risk factors for both ED traits as well as EDs.[261]

5.1.2 Study II

Study II examined prospectively whether there is an elevation of autistic traits at age 9 in individuals who later develop AN. The finding that children later diagnosed with AN did *not* show elevated autistic traits at age 9, compared to children without AN, was surprising at first sight, as it seems to contradict previous findings of an overrepresentation of ASD in AN.[136,172,173,262] That the elevation of autistic traits at age 18 was confined to the subgroup with acute AN, but not visible in girls with a history of AN,

furthermore supports the notion that symptoms of the acute AN phase might only mimic autistic traits. For example, parents might have been referring to their children's strict routines around eating and exercise when rating their children's restricted and repetitive behaviour and interests.

There are however several **other possible explanations** for these findings. For example, successful **camouflaging** behaviour of children with ASD (especially girls) might underlie the result that autistic traits were not elevated in children who later developed AN. Camouflaging describes coping strategies by cognitively able individuals with ASD—in particular autistic females—in order to socially fit in, by either hiding behaviours associated with ASD or purposely performing behaviours deemed to be neurotypical.[263,264] Such behaviours can be observed in children as young as 5 to 11 years,[265,266] and might be especially common in the group with later AN, as individuals with AN are often characterised by high academic achievement[267,268] and above average cognitive ability.[140] Camouflaging can be very demanding and might—together with other problems in adolescence such as the emergence of AN—lead to a depletion of mental resources,[263,264] which in turn exacerbates autistic traits and makes them more noticeable. Especially during acute AN, when brain functioning is affected by starvation, the ability to camouflage might be impaired, leading to an exacerbation of the previously subtle autistic traits. After weight recovery, the ability to camouflage could be restored, however. This might also explain the result that at age 18, autistic traits were only elevated in girls with acute AN, while girls with a history of AN had the same low level of autistic traits as girls who never had AN.

A second but related explanation for our findings is that girls with ASD show a somewhat **different phenotype** and their autistic traits are often more subtle and more difficult to detect with the existing assessment instruments that were developed based on the male ASD phenotype.[265,269,270] This commonly leads to many females with ASD not being diagnosed until they seek health care for other mental health problems such as AN in adolescence or adulthood.[144] Previous studies also show that, as opposed to boys, autistic social traits in girls only become **more overt in adolescence**, when social contexts become more complex and demanding.[271] In summary, the somewhat different and less overt female ASD phenotype, and coping strategies in individuals with ASD may explain the finding that autistic traits were not elevated in children who would later go on to develop AN. Alternatively, the described overlap between ASD and AN may be less strong than previously thought. It remains unclear whether autistic traits in AN are an epiphenomenon of the acute AN phase or if they represent "true" ASD.

5.1.3 Study III

Study III tested potential deficits in FER ability, and visual scanning behaviour as a possible underlying mechanism, in women long-term recovered from adolescent-onset AN with and without ASD. The finding that women recovered from AN *without* ASD did not show impairments in FER ability compared to healthy controls is in line with recent results from the only other study investigating basic FER in recovered AN.[272] Like us, Kerr-Gaffney and colleagues found that differences in FER ability depended on the degree of autistic traits rather than AN status. Furthermore, to our knowledge, all available studies that controlled for comorbid ASD found that basic FER ability was not impaired in *acute* AN without ASD either,[196,272] or only very minimally (i.e., for only one of five emotions: disgust).[192] Moreover, the preserved FER ability in AN without ASD seems to extend to complex emotions.[272] Overall, our and other's results indicate that **deficits in FER ability are likely not an inherent characteristic in AN**, neither as a trait, nor as a state. Instead, deficits in FER **might be limited to the subgroup with ASD**. Differences in the number of individuals with comorbid ASD between previously studied samples might have contributed to inconsistent results regarding FER in AN.

Contrary to our expectations, and to Kerr-Gaffney et al.'s results,[272] women recovered from AN *with* ASD were better, instead of worse, at identifying emotions, however, this only applied for low-intensity emotional expressions and in comparison to women recovered from AN without ASD, while no differences were found for higher-intensity emotional expressions or in comparison to healthy controls. One explanation for this finding might be that women recovered from AN with ASD took on average almost one second longer to respond in trials where they correctly identified low-intensity expressions than women recovered from AN without ASD. As the group of women recovered from AN with ASD was very small (n=6), these analyses were only exploratory and we refrain from interpreting the results further.

We found ceiling effects for emotional expressions at 80% and also at 60% intensity, while average accuracy was approximately 50% for expressions at 40% intensity. This was in line with a previous study of FER in AN using blends of basic emotions at different intensities[192] and suggests that tasks employing only high-intensity basic emotions in earlier studies might not have been sensitive enough to detect potential group differences; a caveat that has previously been brought forward.[273] The use of **lower-intensity emotional expressions might resolve** the problem of **ceiling effects** in basic emotion recognition experiments.

No significant group differences emerged for visual scanning behaviour (attention to the eyes vs. the mouth, hyperscanning) during the FER task, which furthermore was

not related to task performance. These results are difficult to interpret, as research on visual scanning behaviour as a potential underlying mechanism of FER deficits is still scarce and furthermore limited to acute AN. One study found hyperscanning behaviour in individuals with acute AN, albeit this was not related to FER task performance.[194] A second study reported that eye avoidance was associated with poorer FER task performance within a group of individuals with acute AN, however, they did not differ from healthy controls in their average attention to the eyes.[200] No study apart from the current one has examined visual scanning behaviour during FER in individuals recovered from AN, but a recent study that compared saccadic eye movements unrelated to emotion recognition in individuals with acute and recovered AN suggested that differences in saccadic eye movements might be limited to the acute state of AN.[274]

5.1.4 Study IV

Study IV applied a newly developed screening tool for ARFID in a large birth cohort of Japanese children aged 4–7 years, and thus extends the very small body of literature on the prevalence of ARFID in the general population (especially in children under 7 years). Using the parent-reported screening tool, we found a point prevalence of 0.7% for DSM-5 ARFID in 4-7-year-old Japanese children. In general, it is difficult to compare to existing prevalence estimates due to the different measurements used. Our estimate is similar to that of a previous study in older Taiwanese children (0.3%),[203] but lower than estimates reported from Germany and Switzerland (3.2–5.5%).[70,202] When using the ICD-11 criteria, the point prevalence was 1.3%, showing that the **psychosocial impairment criterion** being critical for diagnosis by itself **in ICD-11 leads to a higher ARFID prevalence**. Furthermore, the ICD-11 prevalence was very sensitive to the threshold applied to measure "marked interference with psychosocial functioning". It needs to be more clearly defined how this criterion should best be evaluated.

In the general population of Japanese children, the male-female ratio of ARFID was 1:1. *Sensory sensitivity to food characteristics* and *lack of interest in eating* were more common as drivers of food avoidance than was *fear of aversive consequences of eating*. These findings are in line with a previous study in the general child population,[70] but in contrast to studies from child and adolescent ED services (age ca. 8–17 years): in these settings, the proportion of males is 21–29%,[53-55,69] and fear-based avoidance is the most common driver of food avoidance.[275,276] In younger samples receiving intensive multidisciplinary treatment for chronic food refusal and tube dependence,

boys are equally as affected as girls, or even slightly overrepresented.[64,211] These differences depending on the treatment setting **underscore the value of studying non-selected groups**.

The male-female ratio in ARFID is in striking contrast to that in AN. One reason for this might be that the drivers of food avoidance in ARFID are less gender-specific than body image concerns and drive for thinness in females with AN.[277,278] The dominance of sensory sensitivity as a driver of food avoidance furthermore **suggests a link between ARFID and the neurodevelopmental spectrum**, where abnormal sensory processing is common.[279,280] That more than a third of children showed evidence of more than one driver of food avoidance confirms the previous proposition that the **drivers are not mutually exclusive**.[50] A significant proportion (17%) did not show evidence for any of the three drivers, which could either indicate the existence of other potential (yet unknown) reasons for food avoidance, or reflect the relatively crude measurement of the drivers, which were only evaluated with one question each. Indeed, in a clinical study using somewhat more detailed questions to assess the three drivers of food avoidance, all children with ARFID presented with at least one driver, and almost two thirds of children with ARFID presented with more than one driver,[51] as opposed to slightly more than one third in our sample.

The agreement of the newly developed screening tool for ARFID with the BPFAS was poor: only a small proportion of children identified through the DSM-5 diagnostic criteria were also identified by applying the proposed cut-off values to the BPFAS scores, and vice versa. As the ARFID screening tool has not yet been validated against clinical diagnoses and the BPFAS has not been used in Japan before, these results are difficult to interpret.

5.1.5 Study V

Study V examined neurodevelopmental symptoms and NDDs in 4-7-year-old children with ARFID screened from a large Japanese general population sample. Children with ARFID had a three times higher risk of having NDDs (including ASD, ADHD, developmental coordination disorder, and intellectual disability), although the **absolute prevalence of** these **NDDs might have been underestimated** both in the ARFID group (13.4%) and in children without ARFID (3.6%). This is likely a consequence of the young age of the children (especially for assessing ADHD) and the way NDDs were measured (parent-report of *diagnoses*). The number of neurodevelopmental problems reported on the modified ESSENCE-Q might also be indicative of the presence of NDDs. The proportion of children having three or more (7.7%)/four or more problems (13.3%) on the ESSENCE-Q corresponded approximately to the population

prevalence of NDDs of around 10%.[106] The corresponding estimates in the ARFID group were 38% (three or more problems) and 20% (four or more problems), which might be closer to the true prevalence of NDDs in ARFID. However, the diagnostic validity of these cut-off values is unclear, as their positive and negative predictive values for clinical NDD diagnoses are unknown. Still, the 2–6 times increased prevalence of a broad range of neurodevelopmental problems on the ESSENCE-Q *and* the ASQ-3 in the ARFID group indicates a **more generally atypical/delayed neurodevelopment in children with ARFID**, with problems in the domains of sensory processing and communication being most distinct.

The prevalence of ASD in the total sample (1.8%) was lower than a recently reported estimate for the Japanese child population (3.2%).[108] Therefore—although the prevalence of ASD in children with ARFID (6%) was in the range of previously reported estimates (3–13%)[51,53,208,209]—the "true" prevalence of ASD in ARFID is likely higher than 6%. ADHD was only reported for 1.3% of the whole sample, compared to an expected 5%, if the children had been somewhat older.[119] Previous studies have reported an ADHD prevalence of 4–39% in children with ARFID,[51,53,208-210] which corresponds to a 1–7 times increase in risk when comparing to the expected population prevalence of 5%.[117-119] The risk estimate in this sample (3.5) lies in the middle of this range.

Interestingly, all drivers of food avoidance (sensory sensitivity to food characteristics, low interest in eating, fear of aversive consequences of eating) were more common in children with ARFID and NDDs (although this was only significant for sensory sensitivity and lack of interest in eating). This suggests that **children with NDDs might have a higher overall number of drivers** underlying their ARFID, and might therefore be more prone to develop ARFID. Indeed, there is evidence of a link between NDDs and at least two of the three known drivers of food avoidance in ARFID. First, abnormal sensory processing is a well-known marker of ASD[280] and also associated with other NDDs over and above ASD.[216,281,282] This abnormality might underlie the *sensory sensitivity presentation* of ARFID in children with NDDs. Indeed, sensitivity to taste and smell have been shown to be a mediator of selective eating in children with NDDs.[216] Second, in children with ADHD, impulsivity and hyperactivity might make it difficult to remain seated at meals and to keep focus on eating, resulting in the *low interest in eating presentation* of ARFID.[283] Furthermore, it has been observed that the initiation of stimulant medication for ADHD (e.g., lisdexamfetamine)—known for its appetite suppressing side effects[284]—led to increased food avoidance and significant weight loss or stunted weight and height in children with a history of selective/avoidant eating.[285]

5.2 Implications for research and clinical practice

The finding that OEDs aetiologically can be viewed as the extreme manifestation of continuously distributed ED traits (**Study I**) has important implications for genomic research in EDs that is lagging behind other psychiatric disorders; in fact, data collection for GWAS on binge-spectrum EDs has only just begun.[286] Molecular genetic studies might benefit from including continuous ED traits in the general population (as a complement to diagnoses), in order to quickly increase sample size and reach the necessary statistical power for identifying common genetic variants. This could help accelerate genetic findings for EDs significantly and has already been done for ADHD traits and depressive symptoms.[92,95,287,288] In general, our findings suggest that insights from studying ED traits can translate to OEDs but not necessarily to AN.

Study II showed that the parent-reported screening assessment was not able to detect elevated autistic traits in young children with later AN, if such elevations were present. Instruments that are better tailored to capture the qualitative differences in the ASD phenotype of (young) girls, especially the cognitively able ones, are needed for future research; one such instrument could be the *Autism Spectrum Screening Questionnaire-Revised Extended Version* (ASSQ-REV).[269] Our findings also confirmed previous concerns about the assessment of ASD in the acute phase of AN, as certain symptoms associated with AN might only mimic ASD. Here, it is crucial to collect information on autistic traits in the early development. More prospective studies using different measurements to assess autistic traits in childhood *before* the development of AN are needed to clarify whether autistic traits in AN represent an underlying ASD condition.

Women recovered from AN *without* ASD did not seem to have deficits in recognising basic emotions from facial expressions (**Study III**), and other research suggested that such deficits might not either be present during the acute state of AN, nor for complex emotions.[196,272] This implies that treatment strategies focusing on improving the recognition of other's emotions (see e.g.,[289]) might be dispensable in AN without ASD. The same implications might not apply to AN *with* comorbid ASD. Although our results were inconclusive for this group, previous research strongly suggests that individuals with ASD have difficulties in recognizing other people's facial emotional expressions.[158,290] Therefore, treatments targeting these deficits might potentially be useful in individuals having both AN and ASD. We also showed that task sensitivity was improved when low-intensity emotional expressions were used. This should be considered by future research studying FER ability.

The prevalence of ARFID is still largely unknown. The prevalence rates reported in **Study IV** give an approximate estimate of children that might need access to health care for ARFID. This study also for the first time reports an estimate for the prevalence of ARFID based on the ICD-11 criteria. Future research needs to validate the newly developed screening tool against clinical diagnoses of ARFID. Furthermore, it needs to be clarified how the psychosocial impairment criterion should best be evaluated in research as well as in clinical practice. **Study V** showed that—due to the relatively low prevalence of the conditions—even larger population samples (n>4,000) as well as older children need to be studied in order to examine the overlap of ARFID with NDDs and the possible interaction of NDDs with drivers of food avoidance. The results also suggest that clinicians treating children with ARFID should be aware of a possibly atypical/delayed neurodevelopment, and ADHD and ASD in particular. If underlying NDDs are present, treatment should be adjusted accordingly.

5.3 Methodological considerations

5.3.1 Generalisability

AN, ARFID, and ASD all have a relatively low prevalence of 1–2% in the population. This leads to issues with **small sample sizes** in the subgroups with the respective disorder, even if "large" samples of several thousand individuals are studied. This is furthermore aggravated by the inversely skewed sex ratios in AN and ASD (i.e., more females with AN, more males with ASD). Small sample sizes lead to high uncertainty in estimates (see e.g., Study V) and weaken generalisability. Because of the small number of males with AN/EDs, males were excluded in Studies I and III, which are therefore limited in that the conclusions only apply to females. In Study III, the number of women recovered from AN *with* ASD was so small that it prevented us from drawing firm conclusions for this group regarding potential deficits in FER.

Another question to be considered in connection with Studies I and II is whether results from **twin samples** generalise to the non-twin general population. A Swedish total population study suggested that multiple births are associated with a higher risk of AN (but not of BN or EDNOS), which was unexpected and cannot easily be explained.[291] However, the aim of Studies I and II was not to estimate the prevalence of EDs—which could potentially have been overestimated in this case—but to investigate genetic and environmental influences on EDs and the link between AN and ASD. Population-based studies of ASD show that twins can be considered representative of the general population.[292,293] We therefore believe that the results of Studies I and II can be generalized to the non-twin population.

All studies except Study III were based on epidemiological surveys in a twin cohort and a birth cohort, which are characterised by **high attrition rates** in line with other cohort studies on child development.[294,295] It is known for both the CATSS and the JECS that non-responding parents and their children on average have more mental and physical health problems.[220,296] For instance, in the CATSS, parents of children with NDDs, identified by NPR diagnoses, were less likely to participate in the baseline assessment at age 9.[220] While this might introduce bias in the form of underestimation when studying absolute prevalence rates (Study IV), the impact is less clear in association studies (Studies I, II, & V). It is, however, likely that having fewer individuals with the disorders of interest in the studied sample decreases variation, which in turn might attenuate (and therefore underestimate) the associations of interest. On the other hand, parents of children with some disorders may be more likely to participate in research studies to contribute to furthering knowledge about these disorders. It is not entirely clear whether this is the case for EDs. Our attrition analyses from baseline to follow-up assessment in Studies I and II showed that the prevalence of twins' NPR-registered *ED diagnoses* was roughly comparable between responders and non-responders, especially when the twins themselves were the responders (Study I). In contrast, the prevalence of NPR-registered *ASD diagnoses* in children of parents who responded at follow-up was lower than in children of parents who did not respond at follow-up (especially for boys, Study II). In Study II, we were furthermore able to examine the association of parent-reported autistic traits at age 9 with NPR-registered diagnoses of AN in children whose parents did *not* respond in the follow-up at age 18. In line with our main results, we did not find evidence of such association, which provides support that attrition from baseline to follow-up has not biased our results.

It can be questioned, whether we can translate the results from the **Japanese cohort** in Studies IV and V to European/North-American populations. For example, the prevalence of ASD has traditionally[297] and currently[108] been estimated to be somewhat higher in Japan than in Europe and North America. It is therefore conceivable that also the prevalence of ARFID might be somewhat higher in Japan than in other countries, assuming that ASD and ARFID are related to some degree. Furthermore, it is possible that there are cultural differences in how concerned parents are about their child's eating in general, which possibly has influenced how parents responded to the EEBQ-items screening for ARFID. Cross-cultural comparison studies are needed to examine potential cultural differences; with this in mind we have started to use the ARFID-BS in Swedish children. Nevertheless, the items screening for ARFID pertain very closely to the DSM-5/ICD-11 criteria, which are also used in Japan, and therefore should measure the same underlying disorder.

Lastly, Study III included a **community-based sample** with a history of AN, with an average illness length of 3.7 years (compare e.g.,[298]). The results might therefore not generalise to individuals with longer illness duration. The only directly comparable study produced similar results in women recovered from AN with an average illness length of 5.4 years.[272]

5.3.2 Measurement error and misclassifications

Misclassification might have happened when identifying individuals with EDs. In the **register-based studies**, EDs might have been **underreported** in the NPR, since not all individuals with EDs seek treatment[15,299] and not all health care units treating ED patients report to the NPR.[226] Although the NPR shows high validity for a range of mental disorders, including ASD,[226-228] it has not yet been formally validated for EDs. We tried to identify additional cases not captured by the NPR through other measures such as parent-reported treatment for an ED and self-reported purging behaviour recurring over at least three months, a behaviour that would fulfil criteria for DSM-5 OSFED, and—in combination with other symptoms—possibly even for AN-BP or BN. The proportion of additionally identified cases was circa 45% in both Study I and Study II, indicating a significant underreporting of EDs in the NPR. Prevalence estimates can be difficult to compare between studies due to differences in the applied diagnostic criteria and methods of ascertainment, as well as in age range and country studied. The prevalence rates of EDs resulting from combining the methods described above (2.4% AN, 3.3% EDs other than AN) were within the expected range for girls in the general population,[300,301] while the prevalence of AN in boys (0.7%) was slightly higher than expected.[29,30] The majority of boys with AN (75%) were identified through parent-report of treatment for AN, and it is difficult to imagine that parents potentially would falsely report treatment for AN that has not occurred. In summary, the ED prevalence rates in Study I and Study II suggest that a significant underestimation of EDs is unlikely.

Furthermore, we were **not able to differentiate AN-R from AN-BP** as neither the NPR nor the CATSS contain this subtype information. In Study I, this prevented us from investigating whether, from an aetiological perspective, AN-BP would be closer associated with AN-R than with OEDs. Since AN-BP includes binge eating behaviour in addition to restrictive eating, it has been questioned whether AN-BP really is a restrictive ED or if it should rather be classified as a binge-spectrum ED,[81] and some studies have excluded AN-BP when investigating restrictive EDs.[56,302] If AN-BP indeed was part of the binge-eating spectrum, we would have overestimated the genetic correlation of AN with ED traits in Study I (since AN-BP was classified as AN), and therefore underestimated the difference in the genetic correlations of AN with ED

traits and OEDs with ED traits. However, it has also been questioned how useful the differentiation between AN-R and AN-BP is at all,[303] since crossover between the subtypes is extremely common: in fact, by 7–12 years of follow-up, only 12–19% of circa 100 women with AN never had an episode of regular binge-purge behaviour, while circa 51% were restrictive for the majority of the time.[5,304] Furthermore, no significant differences in the genetic correlations with metabolic traits emerged between AN-R and AN-BP in the recent AN GWAS.[102] It therefore seems likely that the differentiation based on underweight (i.e., AN vs. OEDs) is (here) more relevant than the differentiation based on the presence or absence of binge eating. Generally, the distinction between restrictive EDs and binge-spectrum EDs is not trivial, as EDs might indeed lie on a spectrum from restriction/control to loss of control (compare e.g.,[305]), where disorders in the middle of the spectrum (e.g., AN-BP) are characterised by both restrictive eating as well as binge eating.

In both Studies I and II, it is possible that false negative classification has occurred due to the relatively young age of a large part of the sample when NPR diagnoses were extracted (age range: 17–24 years), especially for BN, which on average has a later age of onset than AN.[19,20] Misclassification might furthermore have occurred when differentiating acute AN from previous AN in Study II (due to the relatively crude measures used), and when classifying the presence of self-reported regular purging behaviour as OEDs in Study I, as purging behaviour could indeed have been part of AN-BP, although it is more likely to occur in BN. The results from Studies I and II need to be replicated in older individuals with longer follow-up time of potential ED diagnoses. Using the Swedish register for the quality assurance of specialised ED treatment[306] could be of assistance in achieving a more fine-grained classification of ED diagnoses.

In Study III, the use of isolated and static facial expressions of emotions—which are rarely encountered in real life—may have limited the ecological validity of the FER test. It is possible that using video sequences showing dynamic facial emotional expressions and including other nonverbal cues (e.g., sounds) provide more ecologically valid results (see e.g.,[307]).

The main caveat of Studies IV and V is that the set of items screening for ARFID has not yet been validated against clinical diagnoses, although such efforts are underway. In fact, the data collection with the EEBQ in the Japanese cohort provided useful information for improving the screening items, based on which we developed the ARFID-BS. The changes are documented item-by-item in supplementary Table 6 of Paper IV. For example, the measure of *previous ARFID*, used to determine the life-time prevalence of ARFID, was based on the assumption that the ARFID criteria were met simultaneously at some point, although we did not have information on the onset and duration of symptoms. This procedure might be justified by the young age of the children and the fact that restrictive eating in childhood often persists over some years.[61,308] Furthermore, the resulting lifetime prevalence of ARFID was not unrea-sonably higher than the point prevalence. In the ARFID-BS, we ask parents to indicate at which age each criterion was present, that is, when the respective problem started and when it ceased (see Supplement 4 of Paper IV). On the other hand, the set of screening items used in Studies IV and V likely has high construct validity, as the items are closely mapped onto the DSM-5 ARFID criteria. A similar procedure has been used when developing the A-TAC, where the items measuring ASD and ADHD almost verbatim reflect the DSM-IV diagnostic criteria.[232,233] The A-TAC has proved to have high criterion validity for diagnoses of ASD and ADHD.[232-235] In Study V, it is likely that we have underestimated the absolute prevalence of NDDs in both chil-dren with ARFID and the total cohort, due to the way NDD diagnoses were assessed (by parent-report) and due to young age of the children, especially for diagnoses of ADHD (see also discussion in chapter 5.1.5).

6 CONCLUSIONS

The studies included in this thesis have found that:

I.   EDs other than AN might best be viewed aetiologically as the extreme manifestation of continuous variation in ED traits and may therefore be added to the range of psychiatric disorders that can be defined dimensionally. AN might be more genetically demarcated from ED traits.

II.   Individuals who later went on to develop AN did not show elevated autistic traits in childhood; however, potential elevations might have been concealed by coping strategies of individuals with ASD and the different/less overt female ASD phenotype, resulting in parental underreporting. It remains unclear, whether autistic traits in AN are present from childhood and therefore represent an underlying ASD condition in some cases.

III.   Facial emotion recognition was not impaired in women recovered from AN without ASD. Deficits in basic emotion recognition ability should therefore probably not be considered an underlying trait in AN. Instead such deficits might be limited to the acute phase of AN and/or the subgroup with ASD.

IV.   ARFID was equally common in boys and girls with a point prevalence of circa 1%. Several drivers of food avoidance are likely to co-exist in ARFID, with sensory sensitivity to food characteristics and lack of interest in eating perhaps being the dominant drivers. Use of ICD-11 diagnostic criteria resulted in a higher prevalence than use of DSM-5 criteria.

V.   Children with ARFID had a three to four times increased likelihood of being diagnosed with NDDs (especially ASD and ADHD) and they showed a generally more atypical/delayed neurodevelopment, with abnormal sensory processing and communication problems being most prominent.

AN and ARFID both are characterised by restrictive eating and both show associations with the spectrum of NDDs (**Figure 6.1**). Individuals with AN and comorbid ASD might have more severe illness trajectories and it is therefore important to identify this subgroup. However, ASD and ASD-*related* traits in AN are difficult to disentangle, as this thesis also has shown in line with previous studies. In large prospective epidemiological studies such as ours it might be challenging to find evidence of child-

hood autistic traits in individuals with AN, which would indicate an underlying ASD condition, although this could potentially be achieved with more fine-grained instruments. Furthermore, fewer ASD-related traits might be inherent in AN than previously believed and in fact be limited to the subgroup with "underlying" ASD (such as seemed to be the case for emotion recognition deficits in this thesis). AN is a heterogeneous group, potentially with three subgroups: (1) a subgroup with "true" ASD, possibly around 10%;[309] these individuals show autistic symptoms long before the onset of AN (e.g., ritualistic behaviour and tendency to social oddities), (2) a subgroup with ASD-related personality traits (e.g., obsessive-compulsive, social difficulties) that might increase risk for AN, and (3) a subgroup unrelated to ASD with better outcome compared to the other groups (i.e., AN is limited to adolescence, and with positive outcome when promptly treated). The delineation of these potential subgroups remains however difficult. It is very important that future research considers the potential subgroup with ASD when studying ASD-related traits in AN and furthermore considers childhood autistic traits when assessing ASD in AN. While AN might be more specifically related to ASD, Study V's findings suggested that ARFID might be associated more generally with broader neurodevelopmental problems. Both ASD and ADHD show some association with the drivers underlying food avoidance in ARFID, and children with NDDs might have a higher number of drivers of food avoidance contributing to their ARFID condition than children without NDDs.
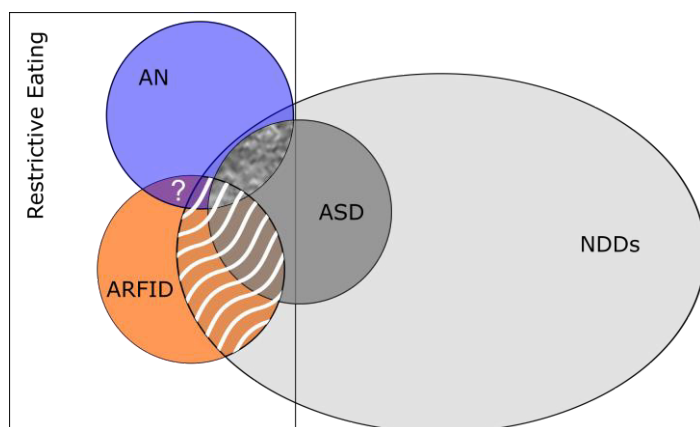

Figure 6.1 *Hypothetical overlap of restrictive EDs and NDDs. Patterned areas illustrate the intersections investigated in this thesis. ASD in ARFID: previous studies 3-13%,[53,208] Study V 6%, but potentially higher; NDDs other than ASD in ARFID: previous studies up to 39%,[51,53] Study V 20-38% (based on having 3-4 neurodevelopmental problems in the modified ESSENCE-Q); ASD in AN: ~10%,[309] NDDs other than ASD in AN: little evidence for overrepresentation; Restrictive eating in ASD: ~50% (up to 89%);[212] Restrictive eating in NDDs: not known; ARFID & AN: no empirical evidence of overlap, as represented by the question mark. The size of each area is only approximately proportionate, assuming a prevalence of ca. 1-2% for each AN, ARFID, and ASD, and ca. 10% for NDDs, while the prevalence of restrictive eating is unknown.*

7 FUTURE PERSPECTIVES

Future studies should focus on the type and extent of overlap between **AN and ASD** by examining, for instance, if they **share genetic influence**. Both conditions are comorbid and aggregate in families,[141,262] suggesting a potential underlying common genetic vulnerability. A register-based study of the Danish population found that having a family member with ASD increased the risk for developing AN, and vice versa, having a family member with AN increased the risk for developing ASD. However, the risks of developing AN/ASD were similarly increased by having a family member with depression or any psychiatric disorder, suggesting that the genetic relationship between AN and ASD is non-specific.[262] To which degree AN and ASD are genetically correlated has not yet been investigated in twin studies. Molecular genetic studies still have low power to estimate the genetic correlation between AN and ASD. Interestingly, the most recent AN GWAS reported a larger genetic correlation of ASD with AN-R than with AN-BP, although both were statistically non-significant.[102] These correlations were based on common variants only, while twin correlations capture multiple sources of genetic covariation and will therefore likely be higher. That ASD might be more closely associated with AN-R than with AN-BP is conceivable, as AN-BP is characterised by impulsivity and loss of control (in addition to restrictive eating)—traits *not* characteristic of ASD. Nevertheless, as discussed in chapter 5.3.2, the differentiation between AN-R and AN-BP is not straightforward. Understanding their possible shared genetic influence can be useful for understanding the comorbidity of ASD and AN and its underlying causes.

It is an important question whether early-onset ARFID potentially could develop into other EDs—especially AN—later, since, for example, picky eating has been found to increase risk for later AN.[310,311] The motivations for food avoidance are very different in AN and ARFID, and it is indeed not entirely clear, why these motivations would change at some point during development. So far, only two studies have examined this question. Both of them conducted retrospective chart reviews and had a small sample size; none of them provided evidence for a progression from ARFID to AN. In the first study, 19 patients treated for ARFID before age 13 were followed up in adulthood (age range 19–41 years): five still had ARFID and none had migrated to another ED diagnosis.[72] In the second study, 27 women identified with ARFID in late adolescence or adulthood (age range 15–40 years) did not show signs of body image concerns, binge eating, or purging behaviour at follow-up after on average 7 years.[74] Recently, Becker et al.[312] reported that they regularly encounter cases with clear

ARFID in their clinical practice, who also present with "traditional" ED psychopathology (i.e., body checking, dieting to lose weight, binge eating), developed in the wake of ARFID. The authors suggest that ARFID and traditional EDs (AN, BN, BED, & OSFED) may not be completely separate disorders (as suggested in DSM-5), but may have connected underlying mechanisms. For example, extreme disgust responses due to sensory sensitivity in individuals with ARFID might generalise to disgust responses to their body shape during puberty. Furthermore, weight loss (often occurring in ARFID) in itself is a risk factor for traditional ED psychopathology, as is weight-related teasing that individuals with ARFID might encounter when losing or gaining weight.[312] Considering the association of both AN and ARFID with ASD, it is possible, that in some individuals the pathway from ASD to developing AN goes via ARFID. Hence, investigating the association of ARFID with AN and other traditional EDs is an important task for the future. Especially prospective studies monitoring children with ARFID for the development of traditional ED psychopathology might be able to shed light on this issue.

Screening tools for ARFID need to be further developed in order to assess the prevalence and impact of the disorder, and to identify children at risk for ARFID who should be clinically examined and/or followed up closely. The ARFID screener that was developed for this thesis still has uncertain diagnostic validity, which needs to be tested using clinically ascertained cases. Comprehensive validation studies of the ARFID screener are currently being conducted in several Swedish birth cohorts and clinical samples.

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REFERENCES

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Arlington, VA: American Psychiatric Association; 2013.

2. World Health Organization. International Statistical Classification of Diseases and Related Health Problems, Tenth Revision. Geneva: World Health Organization; 1992.

3. World Health Organization. International Classification of Diseases for Mortality and Morbidity Statistics, Eleventh Revision 2018. Available from: https://icd.who.int/browse11/l-m/en.

4. Castellini G, Lo Sauro C, Mannucci E, Ravaldi C, Rotella CM, Faravelli C, et al. Diagnostic crossover and outcome predictors in eating disorders according to DSM-IV and DSM-V proposed criteria: a 6-year follow-up study. Psychosom Med. 2011;73(3):270-9.

5. Eddy KT, Dorer DJ, Franko DL, Tahilani K, Thompson-Brenner H, Herzog DB. Diagnostic crossover in anorexia nervosa and bulimia nervosa: implications for DSM-V. Am J Psychiatry. 2008;165(2):245-50.

6. Welch E, Jangmo A, Thornton LM, Norring C, von Hausswolff-Juhlin Y, Herman BK, et al. Treatment-seeking patients with binge-eating disorder in the Swedish national registers: clinical course and psychiatric comorbidity. BMC Psychiatry. 2016;16:163.

7. Papadopoulos FC, Ekbom A, Brandt L, Ekselius L. Excess mortality, causes of death and prognostic factors in anorexia nervosa. Br J Psychiatry. 2009;194(1):10-7.

8. Reas DL, Kjelsås E, Heggestad T, Eriksen L, Nielsen S, Gjertsen F, et al. Characteristics of anorexia nervosa-related deaths in Norway (1992-2000): data from the National Patient Register and the Causes of Death Register. Int J Eat Disord. 2005;37(3):181-7.

9. Toulany A, Wong M, Katzman DK, Akseer N, Steinegger C, Hancock-Howard RL, et al. Cost analysis of inpatient treatment of anorexia nervosa in adolescents: hospital and caregiver perspectives. CMAJ Open. 2015;3(2):E192-7.

10. Keshaviah A, Edkins K, Hastings ER, Krishna M, Franko DL, Herzog DB, et al. Re-examining premature mortality in anorexia nervosa: a meta-analysis redux. Compr Psychiatry. 2014;55(8):1773-84.

11. Fichter MM, Quadflieg N. Mortality in eating disorders - results of a large prospective clinical longitudinal study. Int J Eat Disord. 2016;49(4):391-401.

12. Chesney E, Goodwin GM, Fazel S. Risks of all-cause and suicide mortality in mental disorders: a meta-review. World Psychiatry. 2014;13(2):153-60.

13. Crump C, Ioannidis JPA, Sundquist K, Winkleby MA, Sundquist J. Mortality in persons with mental disorders is substantially overestimated using inpatient psychiatric diagnoses. J Psychiatr Res. 2013;47(10):1298-303.

14. Rosling AM, Sparén P, Norring C, von Knorring A-L. Mortality of eating disorders: A follow-up study of treatment in a specialist unit 1974–2000. Int J Eat Disord. 2011;44(4):304-10.

15. Dobrescu SR, Dinkler L, Gillberg C, Rastam M, Gillberg C, Wentz E. Anorexia nervosa: 30-year outcome. Br J Psychiatry. 2020;216(2):97-104.

16. Strober M, Freeman R, Morrell W. The long-term course of severe anorexia nervosa in adolescents: survival analysis of recovery, relapse, and outcome predictors over 10-15 years in a prospective study. Int J Eat Disord. 1997;22(4):339-60.

17. Herpertz-Dahlmann B, Wewetzer C, Hennighausen K, Remschmidt H. Outcome, psychosocial functioning, and prognostic factors in adolescent anorexia nervosa as determined by prospective follow-up assessment. J Youth Adolesc. 1996;25(4):455-71.

18. Arcelus J, Mitchell AJ, Wales J, Nielsen S. Mortality rates in patients with anorexia nervosa and other eating disorders. A meta-analysis of 36 studies. Arch Gen Psychiatry. 2011;68(7):724-31.

19. Micali N, Hagberg KW, Petersen I, Treasure JL. The incidence of eating disorders in the UK in 2000-2009: findings from the General Practice Research Database. BMJ Open. 2013;3(5):e002646.

20. Zerwas S, Larsen JT, Petersen L, Thornton LM, Mortensen PB, Bulik CM. The incidence of eating disorders in a Danish register study: Associations with suicide risk and mortality. J Psychiatr Res. 2015;65:16-22.

21. Javaras KN, Runfola CD, Thornton LM, Agerbo E, Birgegård A, Norring C, et al. Sex- and age-specific incidence of healthcare-register-recorded eating disorders in the complete swedish 1979-2001 birth cohort. Int J Eat Disord. 2015;48(8):1070-81.

22. Kolar DR, Rodriguez DLM, Chams MM, Hoek HW. Epidemiology of eating disorders in Latin America: a systematic review and meta-analysis. Curr Opin Psychiatry. 2016;29(6):363-71.

23. van Hoeken D, Burns JK, Hoek HW. Epidemiology of eating disorders in Africa. Curr Opin Psychiatry. 2016;29(6):372-7.

24. Wade TD, Bergin JL, Tiggemann M, Bulik CM, Fairburn CG. Prevalence and long-term course of lifetime eating disorders in an adult Australian twin cohort. Aust N Z J Psychiatry. 2006;40(2):121-8.

25. Keski-Rahkonen A, Hoek HW, Susser ES, Linna MS, Sihvola E, Raevuori A, et al. Epidemiology and course of anorexia nervosa in the community. Am J Psychiatry. 2007;164(8):1259-65.

26. Preti A, Girolamo G, Vilagut G, Alonso J, Graaf R, Bruffaerts R, et al. The epidemiology of eating disorders in six European countries: results of the ESEMeD-WMH project. J Psychiatr Res. 2009;43(14):1125-32.

27. Bulik CM, Thornton LM, Root TL, Pisetsky EM, Lichtenstein P, Pedersen NL. Understanding the relation between anorexia nervosa and bulimia nervosa in a Swedish national twin sample. Biol Psychiatry. 2010;67(1):71-7.

28. Hudson JI, Hiripi E, Pope HG, Jr., Kessler RC. The prevalence and correlates of eating disorders in the National Comorbidity Survey Replication. Biol Psychiatry. 2007;61(3):348-58.

29. Duncan AE, Ziobrowski HN, Nicol G. The Prevalence of Past 12-Month and Lifetime DSM-IV Eating Disorders by BMI Category in US Men and Women. Eur Eat Disord Rev. 2017;25(3):165-71.

30. Udo T, Grilo CM. Prevalence and Correlates of DSM-5-Defined Eating Disorders in a Nationally Representative Sample of U.S. Adults. Biol Psychiatry. 2018;84(5):345-54.

31. Micali N, Martini MG, Thomas JJ, Eddy KT, Kothari R, Russell E, et al. Lifetime and 12-month prevalence of eating disorders amongst women in mid-life: a population-based study of diagnoses and risk factors. BMC Med. 2017;15(1):12.

32. Gueguen J, Godart N, Chambry J, Brun-Eberentz A, Foulon C, Divac Phd SM, et al. Severe anorexia nervosa in men: comparison with severe AN in women and analysis of mortality. Int J Eat Disord. 2012;45(4):537-45.

33. Strobel C, Quadflieg N, Naab S, Voderholzer U, Fichter MM. Long-term outcomes in treated males with anorexia nervosa and bulimia nervosa-A prospective, gender-matched study. Int J Eat Disord. 2019;52(12):1353-64.

34. El Ghoch M, Calugi S, Milanese C, Bazzani PV, Dalle Grave R. Body composition in men with anorexia nervosa: Longitudinal study. Int J Eat Disord. 2017;50(7):856-60.

35. Kask J, Ramklint M, Kolia N, Panagiotakos D, Ekbom A, Ekselius L, et al. Anorexia nervosa in males: excess mortality and psychiatric co-morbidity in 609 Swedish in-patients. Psychol Med. 2017;47(8):1489-99.

36. Voderholzer U, Hessler JB, Naab S, Fichter M, Graetz A, Greetfeld M, et al. Are there differences between men and women in outcome of intensive inpatient treatment for anorexia nervosa? An analysis of routine data. Eur Eat Disord Rev. 2019;27(1):59-66.

37. Gregertsen EC, Mandy W, Serpell L. The Egosyntonic Nature of Anorexia: An Impediment to Recovery in Anorexia Nervosa Treatment. Front Psychol. 2017;8:2273.

38. Klump KL, Bulik CM, Kaye WH, Treasure J, Tyson E. Academy for eating disorders position paper: eating disorders are serious mental illnesses. Int J Eat Disord. 2009;42(2):97-103.

39. Gregertsen EC, Mandy W, Kanakam N, Armstrong S, Serpell L. Pre-treatment patient characteristics as predictors of drop-out and treatment outcome in individual and family therapy for adolescents and adults with anorexia nervosa: A systematic review and meta-analysis. Psychiatry Res. 2019;271:484-501.

40. Steiner H, Mazer C, Litt IF. Compliance and outcome in anorexia nervosa. West J Med. 1990;153(2):133-9.

41. Hubert T, Pioggiosi P, Huas C, Wallier J, Maria AS, Apfel A, et al. Drop-out from adolescent and young adult inpatient treatment for anorexia nervosa. Psychiatry Res. 2013;209(3):632-7.

42. Huas C, Godart N, Foulon C, Pham-Scottez A, Divac S, Fedorowicz V, et al. Predictors of dropout from inpatient treatment for anorexia nervosa: data from a large French sample. Psychiatry Res. 2011;185(3):421-6.

43. Wallier J, Vibert S, Berthoz S, Huas C, Hubert T, Godart N. Dropout from inpatient treatment for anorexia nervosa: critical review of the literature. Int J Eat Disord. 2009;42(7):636-47.

44. Wentz E, Gillberg C, Gillberg IC, Råstam M. Ten-year follow-up of adolescent-onset anorexia nervosa: psychiatric disorders and overall functioning scales. J Child Psychol Psychiatry. 2001;42(5):613-22.

45. Steinhausen HC. The outcome of anorexia nervosa in the 20th century. Am J Psychiatry. 2002;159(8):1284-93.

46. Eddy KT, Tabri N, Thomas JJ, Murray HB, Keshaviah A, Hastings E, et al. Recovery From Anorexia Nervosa and Bulimia Nervosa at 22-Year Follow-Up. J Clin Psychiatry. 2017;78(2):184-9.

47. Fichter MM, Quadflieg N, Hedlund S. Twelve-year course and outcome predictors of anorexia nervosa. Int J Eat Disord. 2006;39(2):87-100.

48. Herpertz-Dahlmann B, Dempfle A, Egberts KM, Kappel V, Konrad K, Vloet JA, et al. Outcome of childhood anorexia nervosa—The results of a five- to ten-year follow-up study. Int J Eat Disord. 2018;51(4):295-304.

49. Izquierdo A, Plessow F, Becker KR, Mancuso CJ, Slattery M, Murray HB, et al. Implicit attitudes toward dieting and thinness distinguish fat-phobic and non-fat-phobic anorexia nervosa from avoidant/restrictive food intake disorder in adolescents. Int J Eat Disord. 2019;52(4):419-27.

50. Thomas JJ, Lawson EA, Micali N, Misra M, Deckersbach T, Eddy KT. Avoidant/Restrictive Food Intake Disorder: a Three-Dimensional Model of Neurobiology with Implications for Etiology and Treatment. Curr Psychiatry Rep. 2017;19(8):54.

51. Reilly EE, Brown TA, Gray EK, Kaye WH, Menzel JE. Exploring the cooccurrence of behavioural phenotypes for avoidant/restrictive food intake disorder in a partial hospitalization sample. Eur Eat Disord Rev. 2019;27(4):429-35.

52. Harshman SG, Wons O, Rogers MS, Izquierdo AM, Holmes TM, Pulumo RL, et al. A Diet High in Processed Foods, Total Carbohydrates and Added Sugars, and Low in Vegetables and Protein Is Characteristic of Youth with Avoidant/Restrictive Food Intake Disorder. Nutrients. 2019;11(9):2013.

53. Nicely TA, Lane-Loney S, Masciulli E, Hollenbeak CS, Ornstein RM. Prevalence and characteristics of avoidant/restrictive food intake disorder in a cohort of young patients in day treatment for eating disorders. J Eat Disord. 2014;2(1):21.

54. Fisher MM, Rosen DS, Ornstein RM, Mammel KA, Katzman DK, Rome ES, et al. Characteristics of avoidant/restrictive food intake disorder in children and adolescents: a "new disorder" in DSM-5. J Adolesc Health. 2014;55(1):49-52.

55. Norris ML, Robinson A, Obeid N, Harrison M, Spettigue W, Henderson K. Exploring avoidant/restrictive food intake disorder in eating disordered patients: a descriptive study. Int J Eat Disord. 2014;47(5):495-9.

56. Zanna V, Criscuolo M, Mereu A, Cinelli G, Marchetto C, Pasqualetti P, et al. Restrictive eating disorders in children and adolescents: a comparison between clinical and psychopathological profiles. Eat Weight Disord. 2020.

57. Manikam R, Perman JA. Pediatric feeding disorders. J Clin Gastroenterol. 2000;30(1):34-46.

58. Bryant-Waugh R, Markham L, Kreipe RE, Walsh BT. Feeding and eating disorders in childhood. Int J Eat Disord. 2010;43(2):98-111.

59. Taylor CM, Wernimont SM, Northstone K, Emmett PM. Picky/fussy eating in children: Review of definitions, assessment, prevalence and dietary intakes. Appetite. 2015;95:349-59.

60. Cardona Cano S, Tiemeier H, Van Hoeken D, Tharner A, Jaddoe VW, Hofman A, et al. Trajectories of picky eating during childhood: A general population study. Int J Eat Disord. 2015;48(6):570-9.

61. Herle M, Stavola B, Hubel C, Ferreira DLS, Abdulkadir M, Yilmaz Z, et al. Eating behavior trajectories in the first 10 years of life and their relationship with BMI. Int J Obes (Lond). 2020;44(8):1766-75.

62. Strandjord SE, Sieke EH, Richmond M, Rome ES. Avoidant/Restrictive Food Intake Disorder: Illness and Hospital Course in Patients Hospitalized for Nutritional Insufficiency. J Adolesc Health. 2015;57(6):673-8.

63. Williams KE, Hendy HM, Field DG, Belousov Y, Riegel K, Harclerode W. Implications of Avoidant/Restrictive Food Intake Disorder (ARFID) on Children with Feeding Problems. Child Health Care. 2015;44(4):307-21.

64. Sharp WG, Volkert VM, Scahill L, McCracken CE, McElhanon B. A Systematic Review and Meta-Analysis of Intensive Multidisciplinary Intervention for Pediatric Feeding Disorders: How Standard Is the Standard of Care? J Pediatr. 2017;181:116-24.

65. Aulinas A, Marengi DA, Galbiati F, Asanza E, Slattery M, Mancuso CJ, et al. Medical comorbidities and endocrine dysfunction in low-weight females with avoidant/restrictive food intake disorder compared to anorexia nervosa and healthy controls. Int J Eat Disord. 2020;53(4):631-6.

66. King LA, Urbach JR, Stewart KE. Illness anxiety and avoidant/restrictive food intake disorder: Cognitive-behavioral conceptualization and treatment. Eat Behav. 2015;19:106-9.

67. Murphy J, Zlomke KR. A behavioral parent-training intervention for a child with avoidant/restrictive food intake disorder. Clin Pract Pediatr Psychol. 2016;4(1):23-34.

68. Maertens C, Couturier J, Grant C, Johnson N. Fear of Vomiting and Low Body Weight in Two Pediatric Patients: Diagnostic Challenges. J Can Acad Child Adolesc Psychiatry. 2017;26(1):59-61.

69. Forman SF, McKenzie N, Hehn R, Monge MC, Kapphahn CJ, Mammel KA, et al. Predictors of outcome at 1 year in adolescents with DSM-5 restrictive eating disorders: report of the national eating disorders quality improvement collaborative. J Adolesc Health. 2014;55(6):750-6.

70. Kurz S, van Dyck Z, Dremmel D, Munsch S, Hilbert A. Early-onset restrictive eating disturbances in primary school boys and girls. Eur Child Adolesc Psychiatry. 2015;24(7):779-85.

71. Bryson AE, Scipioni AM, Essayli JH, Mahoney JR, Ornstein RM. Outcomes of low-weight patients with avoidant/restrictive food intake disorder and anorexia nervosa at long-term follow-up after treatment in a partial hospitalization program for eating disorders. Int J Eat Disord. 2018;51(5):470-4.

72. Lange CRA, Ekedahl Fjertorp H, Holmer R, Wijk E, Wallin U. Long-term follow-up study of low-weight avoidant restrictive food intake disorder compared with childhood-onset anorexia nervosa: Psychiatric and occupational outcome in 56 patients. Int J Eat Disord. 2019;52(4):435-8.

73. Kurotori I, Shioda K, Abe T, Kato R, Ishikawa S, Suda S. An Inpatient Observational Study: Characteristics And Outcomes Of Avoidant/Restrictive Food Intake Disorder (ARFID) In Children And Adolescents In Japan. Neuropsychiatr Dis Treat. 2019;15:3313-21.

74. Nakai Y, Nin K, Noma S, Hamagaki S, Takagi R, Teramukai S, et al. Clinical presentation and outcome of avoidant/restrictive food intake disorder in a Japanese sample. Eat Behav. 2017;24:49-53.

75. Lucarelli L, Sechi C, Cimino S, Chatoor I. Avoidant/Restrictive Food Intake Disorder: A Longitudinal Study of Malnutrition and Psychopathological Risk Factors From 2 to 11 Years of Age. Front Psychol. 2018;9:1608.

76. Garner DM. Eating Disorder Inventory-2. Professional Manual. Odessa, FL: Psychological Assessment Resources, Inc.; 1991.

77. Bulik CM. Towards a science of eating disorders: Replacing myths with realities: The fourth Birgit Olsson lecture. Nord J Psychiatry. 2016;70(3):224-30.

78. Krueger RF, Kotov R, Watson D, Forbes MK, Eaton NR, Ruggero CJ, et al. Progress in achieving quantitative classification of psychopathology. World Psychiatry. 2018;17(3):282-93.

79. Meehl PE. Bootstraps taxometrics. Solving the classification problem in psychopathology. Am Psychol. 1995;50(4):266-75.

80. Lubke GH, Muthén B. Investigating population heterogeneity with factor mixture models. Psychol Methods. 2005;10(1):21-39.

81. Gleaves DH, Lowe MR, Green BA, Cororve MB, Williams TL. Do anorexia and bulimia nervosa occur on a continuum? A taxometric analysis. Behav Ther. 2000;31(2):195-219.

82. Gleaves DH, Lowe MR, Snow AC, Green BA, Murphy-Eberenz KP. Continuity and discontinuity models of bulimia nervosa: a taxometric investigation. J Abnorm Psychol. 2000;109(1):56-68.

83. Williamson DA, Womble LG, Smeets MAM, Netemeyer RG, Thaw JM, Kutlesic V, et al. Latent Structure of Eating Disorder Symptoms: A Factor Analytic and Taxometric Investigation. Am J Psychiatry. 2002;159(3):412-8.

84. Luo X, Donnellan MB, Burt SA, Klump KL. The dimensional nature of eating pathology: Evidence from a direct comparison of categorical, dimensional, and hybrid models. J Abnorm Psychol. 2016;125(5):715-26.

85. Tylka TL, Mezydlo Subich L. Revisiting the Latent Structure of Eating Disorders: Taxometric Analyses With Nonbehavioral Indicators. J Couns Psychol. 2003;50(3):276-86.

86. Holm-Denoma JM, Richey JA, Joiner TE. The latent structure of dietary restraint, body dissatisfaction, and drive for thinness: a series of taxometric analyses. Psychol Assess. 2010;22(4):788-97.

87. Forbush KT, Wildes JE. Application of structural equation mixture modeling to characterize the latent structure of eating pathology. Int J Eat Disord. 2017;50(5):542-50.

88. Martin J, Taylor MJ, Lichtenstein P. Assessing the evidence for shared genetic risks across psychiatric disorders and traits. Psychol Med. 2018;48(11):1759-74.

89. Lundström S, Chang Z, Råstam M, Gillberg C, Larsson H, Anckarsäter H, et al. Autism spectrum disorders and autistic like traits: similar etiology in the extreme end and the normal variation. Arch Gen Psychiatry. 2012;69(1):46-52.

90. Colvert E, Tick B, McEwen F, Stewart C, Curran SR, Woodhouse E, et al. Heritability of Autism Spectrum Disorder in a UK Population-Based Twin Sample. JAMA Psychiatry. 2015;72(5):415-23.

91. Robinson EB, St Pourcain B, Anttila V, Kosmicki JA, Bulik-Sullivan B, Grove J, et al. Genetic risk for autism spectrum disorders and neuropsychiatric variation in the general population. Nat Genet. 2016;48(5):552-5.

92. Demontis D, Walters RK, Martin J, Mattheisen M, Als TD, Agerbo E, et al. Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. Nat Genet. 2019;51(1):63-75.

93. Greven CU, Merwood A, van der Meer JM, Haworth CM, Rommelse N, Buitelaar JK. The opposite end of the attention deficit hyperactivity disorder continuum: genetic and environmental aetiologies of extremely low ADHD traits. J Child Psychol Psychiatry. 2016;57(4):523-31.

94. Larsson H, Anckarsäter H, Råstam M, Chang Z, Lichtenstein P. Childhood attention-deficit hyperactivity disorder as an extreme of a continuous trait: a quantitative genetic study of 8,500 twin pairs. Journal of Child Psychology and Psychiatry. 2012;53(1):73-80.

95. Direk N, Williams S, Smith JA, Ripke S, Air T, Amare AT, et al. An Analysis of Two Genome-wide Association Meta-analyses Identifies a New Locus for Broad Depression Phenotype. Biol Psychiatry. 2017;82(5):322-9.

96. Eley TC. Depressive symptoms in children and adolescents: etiological links between normality and abnormality: a research note. J Child Psychol Psychiatry. 1997;38(7):861-5.

97. Taylor MJ, Martin J, Lu Y, Brikell I, Lundstrom S, Larsson H, et al. Association of Genetic Risk Factors for Psychiatric Disorders and Traits of These Disorders in a Swedish Population Twin Sample. JAMA Psychiatry. 2019;76(3):280-9.

98. Yilmaz Z, Hardaway JA, Bulik CM. Genetics and Epigenetics of Eating Disorders. Adv Genomics Genet. 2015;5:131-50.

99. Sullivan PF, Daly MJ, O'Donovan M. Genetic architectures of psychiatric disorders: the emerging picture and its implications. Nat Rev Genet. 2012;13(8):537-51.

100. Plomin R, Haworth CMA, Davis OSP. Common disorders are quantitative traits. Nat Rev Genet. 2009;10(12):872-8.

101. Cross-Disorder Group of the Psychiatric Genomics Consortium. Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. Nat Genet. 2013;45(9):984-94.

102. Watson HJ, Yilmaz Z, Thornton LM, Hubel C, Coleman JRI, Gaspar HA, et al. Genome-wide association study identifies eight risk loci and implicates metabo-psychiatric origins for anorexia nervosa. Nat Genet. 2019;51(8):1207-14.

103. Duncan L, Yilmaz Z, Gaspar H, Walters R, Goldstein J, Anttila V, et al. Significant Locus and Metabolic Genetic Correlations Revealed in Genome-Wide Association Study of Anorexia Nervosa. Am J Psychiatry. 2017;174(9):850-8.

104. Baker JH, Maes HH, Lissner L, Aggen SH, Lichtenstein P, Kendler KS. Genetic risk factors for disordered eating in adolescent males and females. J Abnorm Psychol. 2009;118(3):576-86.

105. Wade T, Martin NG, Neale MC, Tiggemann M, Treloar SA, Bucholz KK, et al. The structure of genetic and environmental risk factors for three measures of disordered eating. Psychol Med. 1999;29(4):925-34.

106. Gillberg C. The ESSENCE in child psychiatry: Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations. Res Dev Disabil. 2010;31(6):1543-51.

107. Lundström S, Reichenberg A, Melke J, Råstam M, Kerekes N, Lichtenstein P, et al. Autism spectrum disorders and coexisting disorders in a nationwide Swedish twin study. J Child Psychol Psychiatry. 2015;56(6):702-10.

108. Saito M, Hirota T, Sakamoto Y, Adachi M, Takahashi M, Osato-Kaneda A, et al. Prevalence and cumulative incidence of autism spectrum disorders and the patterns of co-occurring neurodevelopmental disorders in a total population sample of 5-year-old children. Mol Autism. 2020;11(1):35.

109. Baird G, Simonoff E, Pickles A, Chandler S, Loucas T, Meldrum D, et al. Prevalence of disorders of the autism spectrum in a population cohort of children in South Thames: the Special Needs and Autism Project (SNAP). Lancet. 2006;368(9531):210-5.

110. Baxter AJ, Brugha TS, Erskine HE, Scheurer RW, Vos T, Scott JG. The epidemiology and global burden of autism spectrum disorders. Psychol Med. 2015;45(3):601-13.

111. Brugha TS, McManus S, Bankart J, Scott F, Purdon S, Smith J, et al. Epidemiology of autism spectrum disorders in adults in the community in England. Arch Gen Psychiatry. 2011;68(5):459-65.

112. Kim YS, Leventhal BL, Koh YJ, Fombonne E, Laska E, Lim EC, et al. Prevalence of autism spectrum disorders in a total population sample. Am J Psychiatry. 2011;168(9):904-12.

113. Idring S, Lundberg M, Sturm H, Dalman C, Gumpert C, Rai D, et al. Changes in prevalence of autism spectrum disorders in 2001-2011: findings from the Stockholm youth cohort. J Autism Dev Disord. 2015;45(6):1766-73.

114. Christensen DL, Van Naarden Braun K, Baio J, Bilder D, Charles J, Constantino JN, et al. Prevalence and characteristics of autism spectrum disorder among children aged 8 years–autism and developmental disabilities monitoring network, 11 sites, United States, 2012. MMWR Surveill Summ. 2018;65(No. SS-13):1-23.

115. Loomes R, Hull L, Mandy WPL. What Is the Male-to-Female Ratio in Autism Spectrum Disorder? A Systematic Review and Meta-Analysis. J Am Acad Child Adolesc Psychiatry. 2017;56(6):466-74.

116. Volkmar FR, Szatmari P, Sparrow SS. Sex differences in pervasive developmental disorders. J Autism Dev Disord. 1993;23(4):579-91.

117. Polanczyk GV, Salum GA, Sugaya LS, Caye A, Rohde LA. Annual research review: A meta-analysis of the worldwide prevalence of mental disorders in children and adolescents. J Child Psychol Psychiatry. 2015;56(3):345-65.

118. Thomas R, Sanders S, Doust J, Beller E, Glasziou P. Prevalence of attention-deficit/hyperactivity disorder: a systematic review and meta-analysis. Pediatrics. 2015;135(4):e994-1001.

119. Polanczyk G, de Lima MS, Horta BL, Biederman J, Rohde LA. The worldwide prevalence of ADHD: a systematic review and metaregression analysis. Am J Psychiatry. 2007;164(6):942-8.

120. Simon V, Czobor P, Balint S, Meszaros A, Bitter I. Prevalence and correlates of adult attention-deficit hyperactivity disorder: meta-analysis. Br J Psychiatry. 2009;194(3):204-11.

121. Fayyad J, Sampson NA, Hwang I, Adamowski T, Aguilar-Gaxiola S, Al-Hamzawi A, et al. The descriptive epidemiology of DSM-IV Adult ADHD in the World Health Organization World Mental Health Surveys. Atten Defic Hyperact Disord. 2017;9(1):47-65.

122. Danielson ML, Bitsko RH, Ghandour RM, Holbrook JR, Kogan MD, Blumberg SJ. Prevalence of Parent-Reported ADHD Diagnosis and Associated Treatment Among U.S. Children and Adolescents, 2016. J Clin Child Adolesc Psychol. 2018;47(2):199-212.

123. Willcutt EG. The prevalence of DSM-IV attention-deficit/hyperactivity disorder: a meta-analytic review. Neurotherapeutics. 2012;9(3):490-9.

124. Kaisari P, Dourish CT, Higgs S. Attention Deficit Hyperactivity Disorder (ADHD) and disordered eating behaviour: A systematic review and a framework for future research. Clin Psychol Rev. 2017;53:109-21.

125. Nickel K, Maier S, Endres D, Joos A, Maier V, Tebartz van Elst L, et al. Systematic Review: Overlap Between Eating, Autism Spectrum, and Attention-Deficit/Hyperactivity Disorder. Front Psychiatry. 2019;10(708):708.

126. Wentz E, Lacey JH, Waller G, Råstam M, Turk J, Gillberg C. Childhood onset neuropsychiatric disorders in adult eating disorder patients. Eur Child Adolesc Psychiatry. 2005;14(8):431-7.

127. Sala L, Martinotti G, Carenti ML, Romo L, Oumaya M, Pham-Scottez A, et al. Attention-deficit/hyperactivity disorder symptoms and psychological comorbidity in eating disorder patients. Eat Weight Disord. 2018;23(4):513-9.

128. Yates WR, Lund BC, Johnson C, Mitchell J, McKee P. Attention-deficit hyperactivity symptoms and disorder in eating disorder inpatients. Int J Eat Disord. 2009;42(4):375-8.

129. Råstam M, Täljemark J, Tajnia A, Lundström S, Gustafsson P, Lichtenstein P, et al. Eating Problems and Overlap with ADHD and Autism Spectrum Disorders in a Nationwide Twin Study of 9- and 12-Year-Old Children. Sci World J. 2013;2013:315429.

130. Slane JD, Burt SA, Klump KL. The road less traveled: Associations between externalizing behaviors and eating pathology. Int J Eat Disord. 2010;43(2):149-60.

131. Grabarek C, Cooper S. Graduate Students' Social and Emotional Functioning Relative to Characteristics of Eating Disorders. J Gen Psychol. 2008;135(4):425-52.

132. Biederman J, Petty CR, Monuteaux MC, Fried R, Byrne D, Mirto T, et al. Adult Psychiatric Outcomes of Girls With Attention Deficit Hyperactivity Disorder: 11-Year Follow-Up in a Longitudinal Case-Control Study. Am J Psychiatry. 2010;167(4):409-17.

133. Mikami AY, Hinshaw SP, Arnold LE, Hoza B, Hechtman L, Newcorn JH, et al. Bulimia nervosa symptoms in the multimodal treatment study of children with ADHD. Int J Eat Disord. 2010;43(3):248-59.

134. Annibali JA, Kales JD, Tan TL. Anorexia nervosa in a young man with Tourette's syndrome. J Clin Psychiatry. 1986;47(6):324-6.

135. Kerbeshian J, Burd L. Is anorexia nervosa a neuropsychiatric developmental disorder? An illustrative case report. World J Biol Psychiatry. 2009;10(4-2):648-57.

136. Gillberg C, Råstam M. Do some cases of anorexia nervosa reflect underlying autistic-like conditions? Behav Neurol. 1992;5(1):27-32.

137. Gritti A, Salerno F, Pisano S, Formicola F, Melis D, Franzese A. A case of Klinefelter syndrome, mosaicism (46,XY/47,XXY), associated with anorexia nervosa. Eat Weight Disord. 2011;16(1):e69-71.

138. Raitasuo S, Virtanen H, Raitasuo J. Anorexia nervosa, major depression, and obsessive-compulsive disorder in a Down's syndrome patient. Int J Eat Disord. 1998;23(1):107-9.

139. Dymek M, le Grange D. Anorexia nervosa with comorbid psychosis and borderline mental retardation: a case report. Int J Eat Disord. 2002;31(4):478-82.

140. Lopez C, Stahl D, Tchanturia K. Estimated intelligence quotient in anorexia nervosa: a systematic review and meta-analysis of the literature. Ann Gen Psychiatry. 2010;9:40.

141. Gillberg C. Are autism and anorexia nervosa related? Br J Psychiatry. 1983;142:428.

142. Räisänen U, Hunt K. The role of gendered constructions of eating disorders in delayed help-seeking in men: a qualitative interview study. BMJ Open. 2014;4(4):e004342.

143. Strother E, Lemberg R, Stanford SC, Turberville D. Eating disorders in men: underdiagnosed, undertreated, and misunderstood. Eat Disord. 2012;20(5):346-55.

144. Gould J, Ashton-Smith J. Missed diagnosis or misdiagnosis? Girls and women on the autism spectrum. Good Autism Practice (GAP). 2011;12(1):34-41.

145. Westwood H, Tchanturia K. Autism Spectrum Disorder in Anorexia Nervosa: An Updated Literature Review. Curr Psychiatry Rep. 2017;19(7):41.

146. Baron-Cohen S, Wheelwright S, Skinner R, Martin J, Clubley E. The autism-spectrum quotient (AQ): evidence from Asperger syndrome/high-functioning autism, males and females, scientists and mathematicians. J Autism Dev Disord. 2001;31(1):5-17.

147. Westwood H, Eisler I, Mandy W, Leppanen J, Treasure J, Tchanturia K. Using the Autism-Spectrum Quotient to Measure Autistic Traits in Anorexia Nervosa: A Systematic Review and Meta-Analysis. J Autism Dev Disord. 2016;46(3):964-77.

148. Zucker NL, Losh M, Bulik CM, LaBar KS, Piven J, Pelphrey KA. Anorexia nervosa and autism spectrum disorders: guided investigation of social cognitive endophenotypes. Psychol Bull. 2007;133(6):976-1006.

149. Westwood H, Stahl D, Mandy W, Tchanturia K. The set-shifting profiles of anorexia nervosa and autism spectrum disorder using the Wisconsin Card Sorting Test: a systematic review and meta-analysis. Psychol Med. 2016;46(9):1809-27.

150. Smith KE, Mason TB, Johnson JS, Lavender JM, Wonderlich SA. A systematic review of reviews of neurocognitive functioning in eating disorders: The state-of-the-literature and future directions. Int J Eat Disord. 2018;51(8):798-821.

151. Lang K, Lopez C, Stahl D, Tchanturia K, Treasure J. Central coherence in eating disorders: An updated systematic review and meta-analysis. World J Biol Psychiatry. 2014;15(8):586-98.

152. Van der Hallen R, Evers K, Brewaeys K, Van den Noortgate W, Wagemans J. Global processing takes time: A meta-analysis on local-global visual processing in ASD. Psychol Bull. 2015;141(3):549-73.

153. Neufeld J, Hagstrom A, Van't Westeinde A, Lundin K, Cauvet E, Willfors C, et al. Global and local visual processing in autism - a co-twin-control study. J Child Psychol Psychiatry. 2020;61(4):470-9.

154. Kerr-Gaffney J, Harrison A, Tchanturia K. Social anxiety in the eating disorders: a systematic review and meta-analysis. Psychol Med. 2018;48(15):2477-91.

155. Spain D, Sin J, Linder KB, McMahon J, Happé F. Social anxiety in autism spectrum disorder: A systematic review. Res Autism Spectr Disord. 2018;52:51-68.

156. Kinnaird E, Stewart C, Tchanturia K. Investigating alexithymia in autism: A systematic review and meta-analysis. Eur Psychiatry. 2019;55:80-9.

157. Westwood H, Kerr-Gaffney J, Stahl D, Tchanturia K. Alexithymia in eating disorders: Systematic review and meta-analyses of studies using the Toronto Alexithymia Scale. J Psychosom Res. 2017;99:66-81.

158. Velikonja T, Fett AK, Velthorst E. Patterns of Nonsocial and Social Cognitive Functioning in Adults With Autism Spectrum Disorder: A Systematic Review and Meta-analysis. JAMA Psychiatry. 2019;76(2):135-51.

159. Caglar-Nazali HP, Corfield F, Cardi V, Ambwani S, Leppanen J, Olabintan O, et al. A systematic review and meta-analysis of 'Systems for Social Processes' in eating disorders. Neurosci Biobehav Rev. 2014;42:55-92.

160. Kerr-Gaffney J, Harrison A, Tchanturia K. Cognitive and Affective Empathy in Eating Disorders: A Systematic Review and Meta-Analysis. Front Psychiatry. 2019;10:102.

161. Gernsbacher MA, Yergeau M. Empirical Failures of the Claim That Autistic People Lack a Theory of Mind. Arch Sci Psychol. 2019;7(1):102-18.

162. Treasure J, Willmott D, Ambwani S, Cardi V, Clark Bryan D, Rowlands K, et al. Cognitive Interpersonal Model for Anorexia Nervosa Revisited: The Perpetuating Factors that Contribute to the Development of the Severe and Enduring Illness. J Clin Med. 2020;9(3):630.

163. Saure E, Laasonen M, Lepisto-Paisley T, Mikkola K, Algars M, Raevuori A. Characteristics of autism spectrum disorders are associated with longer duration of anorexia nervosa: A systematic review and meta-analysis. Int J Eat Disord. 2020;53(7):1056-79.

164. Clausen L, Larsen JT, Bulik CM, Petersen L. A Danish register-based study on involuntary treatment in anorexia nervosa. Int J Eat Disord. 2018;51(11):1213-22.

165. Stewart CS, McEwen FS, Konstantellou A, Eisler I, Simic M. Impact of ASD Traits on Treatment Outcomes of Eating Disorders in Girls. Eur Eat Disord Rev. 2017;25(2):123-8.

166. Tchanturia K, Larsson E, Adamson J. How anorexia nervosa patients with high and low autistic traits respond to group Cognitive Remediation Therapy. BMC Psychiatry. 2016;16(1):334.

167. Nielsen S, Anckarsäter H, Gillberg C, Gillberg C, Råstam M, Wentz E. Effects of autism spectrum disorders on outcome in teenage-onset anorexia nervosa evaluated by the Morgan-Russell outcome assessment schedule: a controlled community-based study. Mol Autism. 2015;6:14.

168. Wentz E, Gillberg IC, Anckarsäter H, Gillberg C, Råstam M. Adolescent-onset anorexia nervosa: 18-year outcome. Br J Psychiatry. 2009;194(2):168-74.

169. Keys A, Brozek J, Henschel A, Mickelsen O, Taylor HL, Simonson E, et al. The biology of human starvation. Minneapolis, MN: University of Minnesota Press; 1950.

170. Phillipou A, Rossell SL, Castle DJ. Anorexia nervosa or starvation? Eur J Neurosci. 2018;48(11):3317-8.

171. Pooni J, Ninteman A, Bryant-Waugh R, Nicholls D, Mandy W. Investigating autism spectrum disorder and autistic traits in early onset eating disorder. Int J Eat Disord. 2012;45(4):583-91.

172. Rhind C, Bonfioli E, Hibbs R, Goddard E, Macdonald P, Gowers S, et al. An examination of autism spectrum traits in adolescents with anorexia nervosa and their parents. Mol Autism. 2014;5(1):56.

173. Westwood H, Mandy W, Simic M, Tchanturia K. Assessing ASD in Adolescent Females with Anorexia Nervosa using Clinical and Developmental Measures: a Preliminary Investigation. J Abnorm Child Psychol. 2018;46(1):183-92.

174. Bentz M, Jepsen JR, Pedersen T, Bulik CM, Pedersen L, Pagsberg AK, et al. Impairment of Social Function in Young Females With Recent-Onset Anorexia Nervosa and Recovered Individuals. J Adolesc Health. 2017;60(1):23-32.

175. Postorino V, Scahill L, De Peppo L, Fatta LM, Zanna V, Castiglioni MC, et al. Investigation of Autism Spectrum Disorder and Autistic Traits in an Adolescent Sample with Anorexia Nervosa. J Autism Dev Disord. 2017;47(4):1051-61.

176. Westwood H, Mandy W, Tchanturia K. Clinical evaluation of autistic symptoms in women with anorexia nervosa. Mol Autism. 2017;8:12.

177. Westwood H, Lawrence V, Fleming C, Tchanturia K. Exploration of Friendship Experiences, before and after Illness Onset in Females with Anorexia Nervosa: A Qualitative Study. PLoS One. 2016;11(9):e0163528.

178. Doris E, Westwood H, Mandy W, Tchanturia K. A Qualitative Study of Friendship in Patients with Anorexia Nervosa and Possible Autism Spectrum Disorder. Psychology. 2014;5(11):1338-49.

179. Krug I, Penelo E, Fernandez-Aranda F, Anderluh M, Bellodi L, Cellini E, et al. Low social interactions in eating disorder patients in childhood and adulthood: a multi-centre European case control study. J Health Psychol. 2013;18(1):26-37.

180. Cardi V, Mallorqui-Bague N, Albano G, Monteleone AM, Fernandez-Aranda F, Treasure J. Social Difficulties As Risk and Maintaining Factors in Anorexia Nervosa: A Mixed-Method Investigation. Front Psychiatry. 2018;9:12.

181. Kim YR, Heo SY, Kang H, Song KJ, Treasure J. Childhood risk factors in Korean women with anorexia nervosa: two sets of case-control studies with retrospective comparisons. Int J Eat Disord. 2010;43(7):589-95.

182. Karwautz A, Rabe-Hesketh S, Hu X, Zhao J, Sham P, Collier DA, et al. Individual-specific risk factors for anorexia nervosa: a pilot study using a discordant sister-pair design. Psychol Med. 2001;31(2):317-29.

183. Pearson N, Charman T, Happé F, Bolton PF, McEwen FS. Regression in autism spectrum disorder: Reconciling findings from retrospective and prospective research. Autism Res. 2018;11(12):1602-20.

184. Brewin CR, Andrews B, Gotlib IH. Psychopathology and early experience: A reappraisal of retrospective reports. Psychol Bull. 1993;113(1):82-98.

185. Simon GE, VonKorff M. Recall of psychiatric history in cross-sectional surveys: implications for epidemiologic research. Epidemiol Rev. 1995;17(1):221-7.

186. Frith C. Role of facial expressions in social interactions. Philos Trans R Soc Lond B Biol Sci. 2009;364(1535):3453-8.

187. Ekman P, Cordaro D. What is Meant by Calling Emotions Basic. Emot Rev. 2011;3(4):364-70.

188. Castro L, Davies H, Hale L, Surguladze S, Tchanturia K. Facial affect recognition in anorexia nervosa: is obsessionality a missing piece of the puzzle? Aust N Z J Psychiatry. 2010;44(12):1118-25.

189. Pollatos O, Herbert BM, Schandry R, Gramann K. Impaired central processing of emotional faces in anorexia nervosa. Psychosom Med. 2008;70(6):701-8.

190. Jänsch C, Harmer C, Cooper MJ. Emotional processing in women with anorexia nervosa and in healthy volunteers. Eat Behav. 2009;10(3):184-91.

191. Kucharska-Pietura K, Nikolaou V, Masiak M, Treasure J. The recognition of emotion in the faces and voice of anorexia nervosa. Int J Eat Disord. 2004;35(1):42-7.

192. Dapelo MM, Surguladze S, Morris R, Tchanturia K. Emotion Recognition in Blended Facial Expressions in Women with Anorexia Nervosa. Eur Eat Disord Rev. 2016;24(1):34-42.

193. Gramaglia C, Ressico F, Gambaro E, Palazzolo A, Mazzarino M, Bert F, et al. Alexithymia, empathy, emotion identification and social inference in anorexia nervosa: A case-control study. Eat Behav. 2016;22:46-50.

194. Phillipou A, Abel LA, Castle DJ, Hughes ME, Gurvich C, Nibbs RG, et al. Self perception and facial emotion perception of others in anorexia nervosa. Front Psychol. 2015;6:1181.

195. Kucharska K, Jeschke J, Mafi R. Intact social cognitive processes in outpatients with anorexia nervosa: a pilot study. Ann Gen Psychiatry. 2016;15(1):24.

196. Kim YR, Eom JS, Yang JW, Kang J, Treasure J. The Impact of Oxytocin on Food Intake and Emotion Recognition in Patients with Eating Disorders: A Double Blind Single Dose Within-Subject Cross-Over Design. PLoS One. 2015;10(9):e0137514.

197. Mendlewicz L, Linkowski P, Bazelmans C, Philippot P. Decoding emotional facial expressions in depressed and anorexic patients. J Affect Disord. 2005;89(1-3):195-9.

198. Wyssen A, Lao J, Rodger H, Humbel N, Lennertz J, Schuck K, et al. Facial Emotion Recognition Abilities in Women Experiencing Eating Disorders. Psychosom Med. 2019;81(2):155-64.

199. Tchanturia K, Dapelo MA, Harrison A, Hambrook D. Why study positive emotions in the context of eating disorders? Curr Psychiatry Rep. 2015;17(1):537.

200. Fujiwara E, Kube VL, Rochman D, Macrae-Korobkov AK, Peynenburg V, The University of Alberta Hospital Eating Disorder Program. Visual Attention to Ambiguous Emotional Faces in Eating Disorders: Role of Alexithymia. Eur Eat Disord Rev. 2017;25(6):451-60.

201. Tanaka JW, Sung A. The "Eye Avoidance" Hypothesis of Autism Face Processing. J Autism Dev Disord. 2016;46(5):1538-52.

202. Schmidt R, Vogel M, Hiemisch A, Kiess W, Hilbert A. Pathological and non-pathological variants of restrictive eating behaviors in middle childhood: A latent class analysis. Appetite. 2018;127:257-65.

203. Chen YL, Chen WJ, Lin KC, Shen LJ, Gau SS. Prevalence of DSM-5 mental disorders in a nationally representative sample of children in Taiwan: methodology and main findings. Epidemiol Psychiatr Sci. 2019;29:e15.

204. Hay P, Mitchison D, Collado AEL, Gonzalez-Chica DA, Stocks N, Touyz S. Burden and health-related quality of life of eating disorders, including Avoidant/Restrictive Food Intake Disorder (ARFID), in the Australian population. J Eat Disord. 2017;5:21.

205. van Dyck Z, Bellwald, Kurz S, Dremmel D, Munsch S, Hilbert A. Essprobleme im Kindesalter. Screening in der allgemeinen Bevölkerung [Eating disorders in childhood and adolescence]. Zeitschrift für Gesundheitspsychologie. 2013;21(2):91-100.

206. Zickgraf HF, Ellis JM. Initial validation of the Nine Item Avoidant/Restrictive Food Intake disorder screen (NIAS): A measure of three restrictive eating patterns. Appetite. 2018;123:32-42.

207. Gonçalves S, Vieira AI, Machado BC, Costa R, Pinheiro J, Conceiçao E. Avoidant/restrictive food intake disorder symptoms in children: Associations with child and family variables. Child Health Care. 2019;48(3):301-13.

208. Kambanis PE, Kuhnle MC, Wons OB, Jo JH, Keshishian AC, Hauser K, et al. Prevalence and correlates of psychiatric comorbidities in children and adolescents with full and subthreshold avoidant/restrictive food intake disorder. Int J Eat Disord. 2020;53(2):256-65.

209. Duncombe Lowe K, Barnes TL, Martell C, Keery H, Eckhardt S, Peterson CB, et al. Youth with Avoidant/Restrictive Food Intake Disorder: Examining Differences by Age, Weight Status, and Symptom Duration. Nutrients. 2019;11(8):1955.

210. Cooney M, Lieberman M, Guimond T, Katzman DK. Clinical and psychological features of children and adolescents diagnosed with avoidant/restrictive food intake disorder in a pediatric tertiary care eating disorder program: a descriptive study. J Eat Disord. 2018;6:7.

211. Sharp WG, Volkert VM, Stubbs KH, Berry RC, Clark MC, Bettermann EL, et al. Intensive Multidisciplinary Intervention for Young Children with Feeding Tube Dependence and Chronic Food Refusal: An Electronic Health Record Review. J Pediatr. 2020;223:73-80 e2.

212. Ledford JR, Gast DL. Feeding Problems in Children With Autism Spectrum Disorders: A Review. Focus Autism Other Dev Disabl. 2016;21(3):153-66.

213. Sharp WG, Berry RC, McCracken C, Nuhu NN, Marvel E, Saulnier CA, et al. Feeding problems and nutrient intake in children with autism spectrum disorders: a meta-analysis and comprehensive review of the literature. J Autism Dev Disord. 2013;43(9):2159-73.

214. Sharp WG, Postorino V, McCracken CE, Berry RC, Criado KK, Burrell TL, et al. Dietary Intake, Nutrient Status, and Growth Parameters in Children with Autism Spectrum Disorder and Severe Food Selectivity: An Electronic Medical Record Review. J Acad Nutr Diet. 2018;118(10):1943-50.

215. Leventakou V, Micali N, Georgiou V, Sarri K, Koutra K, Koinaki S, et al. Is there an association between eating behaviour and attention-deficit/hyperactivity disorder symptoms in preschool children? J Child Psychol Psychiatry. 2016;57(6):676-84.

216. Smith B, Rogers SL, Blissett J, Ludlow AK. The relationship between sensory sensitivity, food fussiness and food preferences in children with neurodevelopmental disorders. Appetite. 2020;150:104643.

217. Gal E, Hardal-Nasser R, Engel-Yeger B. The relationship between the severity of eating problems and intellectual developmental deficit level. Res Dev Disabl. 2011;32(5):1464-9.

218. Bandini LG, Curtin C, Eliasziw M, Phillips S, Jay L, Maslin M, et al. Food selectivity in a diverse sample of young children with and without intellectual disabilities. Appetite. 2019;133:433-40.

219. Dickerson Mayes S, Zickgraf H. Atypical eating behaviors in children and adolescents with autism, ADHD, other disorders, and typical development. Res Autism Spectr Disord. 2019;64:76-83.

220. Anckarsater H, Lundstrom S, Kollberg L, Kerekes N, Palm C, Carlstrom E, et al. The Child and Adolescent Twin Study in Sweden (CATSS). Twin Res Hum Genet. 2011;14(6):495-508.

221. Rastam M, Gillberg C, Garton M. Anorexia nervosa in a Swedish urban region. A population-based study. Br J Psychiatry. 1989;155:642-6.

222. Råstam M. Anorexia nervosa in 51 Swedish adolescents: premorbid problems and comorbidity. J Am Acad Child Adolesc Psychiatry. 1992;31(5):819-29.

223. Råstam M, Gillberg IC, Gillberg C. Anorexia nervosa 6 years after onset: Part II. Comorbid psychiatric problems. Compr Psychiatry. 1995;36(1):70-6.

224. Kawamoto T, Nitta H, Murata K, Toda E, Tsukamoto N, Hasegawa M, et al. Rationale and study design of the Japan environment and children's study (JECS). BMC Public Health. 2014;14:25.

225. Michikawa T, Nitta H, Nakayama SF, Yamazaki S, Isobe T, Tamura K, et al. Baseline Profile of Participants in the Japan Environment and Children's Study (JECS). J Epidemiol. 2018;28(2):99-104.

226. Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. BMC Public Health. 2011;11:450.

227. Rück C, Larsson KJ, Lind K, Perez-Vigil A, Isomura K, Sariaslan A, et al. Validity and reliability of chronic tic disorder and obsessive-compulsive disorder diagnoses in the Swedish National Patient Register. BMJ Open. 2015;5(6):e007520.

228. Ludvigsson JF, Reichenberg A, Hultman CM, Murray JA. A nationwide study of the association between celiac disease and the risk of autistic spectrum disorders. JAMA Psychiatry. 2013;70(11):1224-30.

229. Nevonen L, Broberg AG. Validating the Eating Disorder Inventory-2 (EDI-2) in Sweden. Eat Weight Disord. 2001;6(2):59-67.

230. Nevonen L, Clinton D, Norring C. Validating the EDI-2 in three Swedish female samples: eating disorders patients, psychiatric outpatients and normal controls. Nord J Psychiatry. 2006;60(1):44-50.

231. Clausen L, Rokkedal K, Rosenvinge JH. Validating the eating disorder inventory (EDI-2) in two Danish samples: a comparison between female eating disorder patients and females from the general population. Eur Eat Disord Rev. 2009;17(6):462-7.

232. Hansson SL, Svanstrom Rojvall A, Rastam M, Gillberg C, Gillberg C, Anckarsater H. Psychiatric telephone interview with parents for screening of childhood autism - tics, attention-deficit hyperactivity disorder and other comorbidities (A-TAC): preliminary reliability and validity. Br J Psychiatry. 2005;187(3):262-7.

233. Larson T, Anckarsäter H, Gillberg C, Ståhlberg O, Carlström E, Kadesjö B, et al. The Autism - Tics, AD/HD and other Comorbidities inventory (A-TAC): further validation of a telephone interview for epidemiological research. BMC Psychiatry. 2010;10(1):1.

234. Larson T, Lundström S, Nilsson T, Selinus E, Råstam M, Lichtenstein P, et al. Predictive properties of the A-TAC inventory when screening for childhood-onset neurodevelopmental problems in a population-based sample. BMC Psychiatry. 2013;13(1):233.

235. Mårland C, Lichtenstein P, Degl'Innocenti A, Larson T, Råstam M, Anckarsäter H, et al. The Autism-Tics, ADHD and other Comorbidities inventory (A-TAC): previous and predictive validity. BMC Psychiatry. 2017;17(1):403.

236. Tobii Technology AB. Tobii Studio Version 3.3.0. Danderyd, Sweden: Tobii Technology AB; 2014.

237. Tottenham N, Tanaka JW, Leon AC, McCarry T, Nurse M, Hare TA, et al. The NimStim set of facial expressions: judgments from untrained research participants. Psychiatry Res. 2009;168(3):242-9.

238. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry. 1998;59 Suppl 20:22-33.

239. First MB, Spitzer RL, Gibbon M, Williams JBW. Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition. (SCID-I/P). New York: Biometrics Research, New York State Psychiatric Institute; 2002.

240. Crist W, Napier-Phillips A. Mealtime behaviors of young children: a comparison of normative and clinical data. J Dev Behav Pediatr. 2001;22(5):279-86.

241. Crist W, McDonnell P, Beck M, Gillespie CT, Barrett P, Mathews J. Behavior at Mealtimes and the Young Child with Cystic Fibrosis. J Dev Behav Pediatr. 1994;15(3):157-61.

242. Dovey TM, Aldridge VK, Martin CI, Wilken M, Meyer C. Screening Avoidant/Restrictive Food Intake Disorder (ARFID) in children: Outcomes from utilitarian versus specialist psychometrics. Eat Behav. 2016;23:162-7.

243. Hatakenaka Y, Fernell E, Sakaguchi M, Ninomiya H, Fukunaga I, Gillberg C. ESSENCE-Q - a first clinical validation study of a new screening questionnaire for young children with suspected neurodevelopmental problems in south Japan. Neuropsychiatr Dis Treat. 2016;12:1739-46.

244. Hatakenaka Y, Maeda M, Ninomiya H, Hachiya K, Fernell E, Gillberg C. ESSENCE-Q obtained in routine Japanese public child health check-ups may be a valuable tool in neurodevelopmental screening. Acta Paediatr. 2020;109(4):764-73.

245. Hatakenaka Y, Ninomiya H, Billstedt E, Fernell E, Gillberg C. ESSENCE-Q - used as a screening tool for neurodevelopmental problems in public health checkups for young children in south Japan. Neuropsychiatr Dis Treat. 2017;13:1271-80.

246. Squires J, Bricker D. Ages & Stages Questionnaires, Third Edition (ASQ-3). Baltimore, MD: Brookes Publishing; 2009.

247. Mezawa H, Aoki S, Nakayama SF, Nitta H, Ikeda N, Kato K, et al. Psychometric profile of the Ages and Stages Questionnaires, Japanese translation. Pediatr Int. 2019;61(11):1086-95.

248. StataCorp. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC; 2019.

249. R Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing; 2020.

250. IBM Corp. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp; 2017.

251. Plomin R, DeFries JC, Knopik VS, Neiderhiser JM. Behavioral Genetics. 6 ed. New York: Worth Publishers; 2013.

252. Rijsdijk FV, Sham PC. Analytic approaches to twin data using structural equation models. Brief Bioinform. 2002;3(2):119-33.

253. Neale MC, Maes HHM. Methodology for Genetic Studies of Twins and Families. Dordrecht, The Netherlands: Kluwer Academic Publishers B.V.; 2004.

254. DeFries JC, Fulker DW. Multiple regression analysis of twin data. Behav Genet. 1985;15(5):467-73.

255. Purcell S, Sham PC. A model-fitting implementation of the DeFries-Fulker model for selected twin data. Behav Genet. 2003;33(3):271-8.

256. Carlin JB, Gurrin LC, Sterne JA, Morley R, Dwyer T. Regression models for twin studies: a critical review. Int J Epidemiol. 2005;34(5):1089-99.

257. Gallis JA, Turner EL. Relative Measures of Association for Binary Outcomes: Challenges and Recommendations for the Global Health Researcher. Ann Glob Health. 2019;85(1):137.

258. Forbush KT, Chen PY, Hagan KE, Chapa DAN, Gould SR, Eaton NR, et al. A new approach to eating-disorder classification: Using empirical methods to delineate diagnostic dimensions and inform care. Int J Eat Disord. 2018;51(7):710-21.

259. Dellava JE, Thornton LM, Lichtenstein P, Pedersen NL, Bulik CM. Impact of broadening definitions of anorexia nervosa on sample characteristics. J Psychiatr Res. 2011;45(5):691-8.

260. Yilmaz Z, Gottfredson NC, Zerwas SC, Bulik CM, Micali N. Developmental Premorbid Body Mass Index Trajectories of Adolescents With Eating Disorders in a Longitudinal Population Cohort. J Am Acad Child Adolesc Psychiatry. 2019;58(2):191-9.

261. Culbert KM, Racine SE, Klump KL. Research Review: What we have learned about the causes of eating disorders - a synthesis of sociocultural, psychological, and biological research. J Child Psychol Psychiatry. 2015;56(11):1141-64.

262. Koch SV, Larsen JT, Mouridsen SE, Bentz M, Petersen L, Bulik C, et al. Autism spectrum disorder in individuals with anorexia nervosa and in their first- and second-degree relatives: Danish nationwide register-based cohort-study. Br J Psychiatry. 2015;206(5):401-7.

263. Lai M-C, Lombardo MV, Ruigrok ANV, Chakrabarti B, Auyeung B, Szatmari P, et al. Quantifying and exploring camouflaging in men and women with autism. Autism. 2016;21(6):690-702.

264. Hull L, Petrides KV, Allison C, Smith P, Baron-Cohen S, Lai MC, et al. "Putting on My Best Normal": Social Camouflaging in Adults with Autism Spectrum Conditions. J Autism Dev Disord. 2017;47(8):2519-34.

265. Dean M, Harwood R, Kasari C. The art of camouflage: Gender differences in the social behaviors of girls and boys with autism spectrum disorder. Autism. 2017;21(6):678-89.

266. Rynkiewicz A, Schuller B, Marchi E, Piana S, Camurri A, Lassalle A, et al. An investigation of the 'female camouflage effect' in autism using a computerized ADOS-2 and a test of sex/gender differences. Mol Autism. 2016;7:10.

267. Sundquist J, Ohlsson H, Winkleby MA, Sundquist K, Crump C. School Achievement and Risk of Eating Disorders in a Swedish National Cohort. J Am Acad Child Adolesc Psychiatry. 2016;55(1):41-6.e1.

268. Claydon E, Zullig KJ. Eating disorders and academic performance among college students. J Am Coll Health. 2020;68(3):320-5.

269. Kopp S, Gillberg C. The Autism Spectrum Screening Questionnaire (ASSQ)-Revised Extended Version (ASSQ-REV): An instrument for better capturing the autism phenotype in girls? A preliminary study involving 191 clinical cases and community controls. Res Dev Disabil. 2011;32(6):2875-88.

270. Hiller RM, Young RL, Weber N. Sex differences in autism spectrum disorder based on DSM-5 criteria: evidence from clinician and teacher reporting. J Abnorm Child Psychol. 2014;42(8):1381-93.

271. Mandy W, Pellicano L, St Pourcain B, Skuse D, Heron J. The development of autistic social traits across childhood and adolescence in males and females. J Child Psychol Psychiatry. 2018;59(11):1143-51.

272. Kerr-Gaffney J, Mason L, Jones E, Hayward H, Ahmad J, Harrison A, et al. Emotion Recognition Abilities in Adults with Anorexia Nervosa are Associated with Autistic Traits. J Clin Med. 2020;9(4).

273. Oldershaw A, Hambrook D, Stahl D, Tchanturia K, Treasure J, Schmidt U. The socio-emotional processing stream in Anorexia Nervosa. Neurosci Biobehav Rev. 2011;35(3):970-88.

274. Phillipou A, Abel LA, Gurvich C, Castle DJ, Rossell SL. Eye movements in anorexia nervosa: State or trait markers? Int J Eat Disord. 2020;53(10):1678–84.

275. Norris ML, Spettigue W, Hammond NG, Katzman DK, Zucker N, Yelle K, et al. Building evidence for the use of descriptive subtypes in youth with avoidant restrictive food intake disorder. Int J Eat Disord. 2018;51(2):170-3.

276. Zickgraf HF, Lane-Loney S, Essayli JH, Ornstein RM. Further support for diagnostically meaningful ARFID symptom presentations in an adolescent medicine partial hospitalization program. Int J Eat Disord. 2019;52(4):402-9.

277. Nunez-Navarro A, Aguera Z, Krug I, Jimenez-Murcia S, Sanchez I, Araguz N, et al. Do men with eating disorders differ from women in clinics, psychopathology and personality? Eur Eat Disord Rev. 2012;20(1):23-31.

278. Anderson CB, Bulik CM. Gender differences in compensatory behaviors, weight and shape salience, and drive for thinness. Eat Behav. 2004;5(1):1-11.

279. Ghanizadeh A. Sensory Processing Problems in Children with ADHD, a Systematic Review. Psychiatry Investig. 2011;8(2):89-94.

280. Robertson CE, Baron-Cohen S. Sensory perception in autism. Nat Rev Neurosci. 2017;18(11):671-84.

281. Brimo K, Dinkler L, Gillberg C, Lichtenstein P, Lundström S, Åsberg Johnels J. The co-occurrence of neurodevelopmental problems in dyslexia. Unpublished results.

282. Little LM, Dean E, Tomchek S, Dunn W. Sensory Processing Patterns in Autism, Attention Deficit Hyperactivity Disorder, and Typical Development. Phys Occup Ther Pediatr. 2018;38(3):243-54.

283. Micali N, Cooper-Vince C. Aetiology and epidemiology. In: Bryant-Waugh R, Higgins C, editors. Avoidant Restrictive Food Intake Disorder in Childhood and Adolescence A Clinical Guide. Abingdon, Oxon: Routledge; 2020.

284. Najib J, Didenko E, Meleshkina D, Yusupov K, Maw K, Ramnarain J, et al. Review of lisdexamfetamine dimesylate in children and adolescents with attention deficit/hyperactivity disorder. Curr Med Res Opin. 2020;36(10):1717-35.

285. Pennell A, Couturier J, Grant C, Johnson N. Severe avoidant/restrictive food intake disorder and coexisting stimulant treated attention deficit hyperactivity disorder. Int J Eat Disord. 2016;49(11):1036-9.

286. Bulik CM, Butner JE, Tregarthen J, Thornton LM, Flatt RE, Smith T, et al. The Binge Eating Genetics Initiative (BEGIN): study protocol. BMC Psychiatry. 2020;20(1):307.

287. Middeldorp CM, Hammerschlag AR, Ouwens KG, Groen-Blokhuis MM, Pourcain BS, Greven CU, et al. A Genome-Wide Association Meta-Analysis of Attention-Deficit/Hyperactivity Disorder Symptoms in Population-Based Pediatric Cohorts. J Am Acad Child Adolesc Psychiatry. 2016;55(10):896-905.e6.

288. Stergiakouli E, Martin J, Hamshere ML, Langley K, Evans DM, St Pourcain B, et al. Shared genetic influences between attention-deficit/hyperactivity disorder (ADHD) traits in children and clinical ADHD. J Am Acad Child Adolesc Psychiatry. 2015;54(4):322-7.

289. Preis MA, Schlegel K, Stoll L, Blomberg M, Schmidt H, Wunsch-Leiteritz W, et al. Improving emotion recognition in anorexia nervosa: An experimental proof-of-concept study. Int J Eat Disord. 2020;53(6):945-53.

290. Uljarevic M, Hamilton A. Recognition of Emotions in Autism: A Formal Meta-Analysis. J Autism Dev Disord. 2013;43(7):1517-26.

291. Goodman A, Heshmati A, Malki N, Koupil I. Associations between birth characteristics and eating disorders across the life course: findings from 2 million males and females born in Sweden, 1975-1998. Am J Epidemiol. 2014;179(7):852-63.

292. Curran S, Dworzynski K, Happe F, Ronald A, Allison C, Baron-Cohen S, et al. No major effect of twinning on autistic traits. Autism Res. 2011;4(5):377-82.

293. Hallmayer J, Glasson EJ, Bower C, Petterson B, Croen L, Grether J, et al. On the twin risk in autism. Am J Hum Genet. 2002;71(4):941-6.

294. Fraser A, Macdonald-Wallis C, Tilling K, Boyd A, Golding J, Davey Smith G, et al. Cohort Profile: the Avon Longitudinal Study of Parents and Children: ALSPAC mothers cohort. Int J Epidemiol. 2013;42(1):97-110.

295. Olsen EM, Rask CU, Elberling H, Jeppesen P, Clemmensen L, Munkholm A, et al. Cohort Profile: The Copenhagen Child Cohort Study (CCC2000). Int J Epidemiol. 2020;49(2):370-1.

296. Kigawa M, Tsuchida A, Matsumura K, Takamori A, Ito M, Tanaka T, et al. Factors of non-responsive or lost-to-follow-up Japanese mothers during the first year post partum following the Japan Environment and Children's Study: a longitudinal cohort study. BMJ Open. 2019;9(11):e031222.

297. Williams JG, Higgins JP, Brayne CE. Systematic review of prevalence studies of autism spectrum disorders. Arch Dis Child. 2006;91(1):8-15.

298. Fichter MM, Quadflieg N, Crosby RD, Koch S. Long-term outcome of anorexia nervosa: Results from a large clinical longitudinal study. Int J Eat Disord. 2017;50(9):1018-30.

299. Forsén Mantilla E, Birgegård A. The enemy within: the association between self-image and eating disorder symptoms in healthy, non help-seeking and clinical young women. J Eat Disord. 2015;3:30.

300. Smink FR, van Hoeken D, Oldehinkel AJ, Hoek HW. Prevalence and severity of DSM-5 eating disorders in a community cohort of adolescents. Int J Eat Disord. 2014;47(6):610-9.

301. Keski-Rahkonen A, Mustelin L. Epidemiology of eating disorders in Europe: prevalence, incidence, comorbidity, course, consequences, and risk factors. Curr Opin Psychiatry. 2016;29(6):340-5.

302. Peñas-Lledó EM, Rodriguez Santos L, Vaz Leal FJ, Waller G. Pattern of birth in restrictive and bulimic eating disorders. Eat Behav. 2003;3(4):325-8.

303. Peat C, Mitchell JE, Hoek HW, Wonderlich SA. Validity and utility of subtyping anorexia nervosa. Int J Eat Disord. 2009;42(7):590-4.

304. Eddy KT, Keel PK, Dorer DJ, Delinsky SS, Franko DL, Herzog DB. Longitudinal comparison of anorexia nervosa subtypes. Int J Eat Disord. 2002;31(2):191-201.

305. Brooks SJ, Rask-Andersen M, Benedict C, Schioth HB. A debate on current eating disorder diagnoses in light of neurobiological findings: is it time for a spectrum model? BMC Psychiatry. 2012;12:76.

306. Birgegard A, Bjorck C, Clinton D. Quality assurance of specialised treatment of eating disorders using large-scale Internet-based collection systems: methods, results and lessons learned from designing the Stepwise database. Eur Eat Disord Rev. 2010;18(4):251-9.

307. Schlegel K, Grandjean D, Scherer KR. Introducing the Geneva Emotion Recognition Test: An example of Rasch-based test development. Psychol Assess. 2014;26(2):666.

308. Cardona Cano S, Hoek HW, Bryant-Waugh R. Picky eating: the current state of research. Curr Opin Psychiatry. 2015;28(6):448-54.

309. Anckarsäter H, Hofvander B, Billstedt E, Gillberg IC, Gillberg C, Wentz E, et al. The sociocommunicative deficit subgroup in anorexia nervosa: autism spectrum disorders and neurocognition in a community-based, longitudinal study. Psychol Med. 2012;42(9):1957-67.

310. Marchi M, Cohen P. Early childhood eating behaviors and adolescent eating disorders. J Am Acad Child Adolesc Psychiatry. 1990;29(1):112-7.

311. Herle M, Stavola B, Hubel C, Abdulkadir M, Ferreira DS, Loos RJF, et al. A longitudinal study of eating behaviours in childhood and later eating disorder behaviours and diagnoses. Br J Psychiatry. 2020;216(2):113-9.

312. Becker KR, Breithaupt L, Lawson EA, Eddy KT, Thomas JJ. Co-occurrence of Avoidant/Restrictive Food Intake Disorder and Traditional Eating Psychopathology. J Am Acad Child Adolesc Psychiatry. 2020;59(2):209-12.