RESEARCH ARTICLE

A longitudinal study of autism spectrum disorder characteristics in adolescents with restrictive type anorexia nervosa during and after underweight

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ABSTRACT

Objectives: The aim of this prospective, longitudinal study is to compare the prevalence of autism spectrum disorder characteristics in adolescents with anorexia nervosa during and after underweight. We want to determine whether increased autism spectrum disorder characteristics in adolescents with anorexia nervosa can be regarded as a trait or as a state.

Methods: 24 adolescents with anorexia nervosa completed the youth self-report, autism spectrum quotient and a questionnaire designed by the researchers during a state of underweight and after weight recovery.

Results: Autism spectrum quotient total score and autism spectrum quotient subscale scores for attention switching, imagination and attention to detail at the time of underweight are significantly higher than after weight recovery. Linear regression modelling does not show a statistically significant association between weight gain and autism spectrum disorder characteristics, but suggests the presence of subgroups based on baseline autism spectrum quotient score. Association remains insignificant after adjusting for use of medication and youth self-report internalizing scale score and after subgroup analysis.

Conclusions: Our results indicate that autism spectrum disorder characteristics in patients with anorexia nervosa should sometimes be considered a state rather than a trait. Caution is advised when diagnosing autism spectrum disorder in patients with anorexia nervosa, especially during underweight. Despite reluctance to diagnose, we advocate further evaluation of autism spectrum disorder characteristics as they may predict a poorer outcome. Our preliminary results suggest subgroup analysis based on autism spectrum quotient score during underweight might help identify those patients in need of specific or more intensive treatment.

Keywords: Anorexia nervosa; Autism spectrum disorder; Autism spectrum quotient; Disorder; Diagnose

Abbreviations: AN: Anorexia Nervosa; ASD: Autism Spectrum Disorder; ASEBA: Achenbach System of Empirically Base Assessment; AQ: Autismspectrum Quotient; AQ-adolescent: Autism spectrum Quotient, adolescent version; BMI: Body Mass Index; Et al.: And Others; IQ: Intelligence Quotient; Kg: Kilogram; $Kg/m^{2:}$ Kilogram Per Square Meter; M: Mean; N: Number; R^2: Coefficient of determination; SD: Standard Deviation; SSRI: Selective Serotonin Reuptake Inhibitor; T^1: Time/moment one, start of the study, during underweight; T^2: Time/moment two, end of the study, after weight recovery; UKJA: University Hospital for child and Adolescent Psyhiatry Antwerp; YSR: Youth Self-Report

INTRODUCTION

Anorexia Nervosa (AN) is an eating disorder defined as a combination of restriction of energy intake relative to requirements, fear of gaining weight/becoming fat and a disturbance in body image, which is heavily influenced by one's weight [1]. The specifier "restrictive type" refers to the fact that there has not been any binge eating or purging over the last three months. "Binge eating/purging type" refers to these activities being present over the past three months. The disorder is more often found in women than in men. According to a recent review of van Eeden, et al. the lifetime prevalence is 4% for females and 0.3% for males, with a usual onset in adolescence [2]. Autism Spectrum Disorder (ASD) is a neurobiological developmental disorder defined by both persistent difficulties in social communication and restricted, repetitive, and sensory behavior and/or interests [3,4]. Both symptoms must be present at a young age, even if not recognized until later. More males are diagnosed with ASD than females [5-7]. Even though both disorders don't resemble each other at first sight, clinicians have reported behavioral overlap. Gillberg was the first to address this issue in 1983 [8]. He wondered if a common disturbance in biochemicals could cause ASD in young boys and AN in young girls.

Since then, research has shown that a lot of subjects with ASD experience eating problems on one hand and a lot of subjects with AN show ASD characteristics on the other hand. Subjects with ASD and AN share difficulties in cognitive tasks, set-shifting (the ability to unconsciously shift attention between one task and another), theory of mind (the capacity to understand other people by ascribing mental states to them) and central coherence (processing information in the context rather than focusing on details) [9-13]. However, the work of Timko, et al. contradicts these similarities [14].

Firstly, a lot of research is done on ASD and eating problems. Between 43% and 96% of children with a diagnosis of ASD experience eating problems [15-18]. Food selectivity is the most reported problem and leads to severe nutritional deficiencies in some cases. Other reported eating problems are food refusal, eating too little or too much, eating slowly, craving certain foods, rigidity concerning eating habits and disrupting behavior during meals. Studies also show that eating problems remain present: Adults with ASD report more eating rituals, more food selectivity, more problems with multitasking during meals and more problems with adapting their eating habits to other people [19,20]. Moreover, female adults with ASD reported specific symptoms consistent with eating disorders such as dieting, refusing to eat or inducing vomiting. One study showed that 6.7% of patients with an ASD diagnosis also had a diagnosis of AN.

Secondly, several studies have found a higher prevalence of ASD diagnosis or ASD characteristics in patients with AN. In both a meta-analysis of Huke, et al. and a cross-sectional study of Westwood, et al. an ASD prevalence of 23% in patients with AN was found. A more recent review from Nickel, et al. describes a prevalence of 25.4% for ASD symptoms and a prevalence of 4.7% for an ASD diagnosis in subjects with AN; both in adults

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and adolescents. Several other studies also found a higher score on the Autism spectrum Quotient (AQ), a self-reported questionnaire measuring characteristics of ASD, in adults with AN than in healthy controls. Specific differences between adult and adolescent populations are found. Several studies showed that while elevated levels of ASD characteristics and ASD diagnoses are present in adolescents with AN, the rate is lower than in adult studies. These characteristics are often not recognized by parents in early childhood, suggesting that they appear during the course of AN. The link between both disorders is complex, even more so in adults than in adolescents because the presence of features from an early age is required to make a diagnosis of ASD and this information is often missing in adult research. Moreover, in adults there often is a longer duration of AN and underweight, which possibly affects the ASD characteristics. Previous research has shown that underweight and even short time fasting in itself lead to increased rigidity, more coercion and more social withdrawal. This is further supported by the studies of Oldershaw, et al. showing ASD characteristics in severely underweight patients, but not in recovered patients. Contrarily, lasting ASD characteristics have been reported in patients who have already recovered from an eating disorder. This may indicate the presence of traits, but it may also be a consequence of long-term illness. Several studies concluded that examination of this state or trait nature is necessary.

Research specifically in young adolescents is valuable as the effect of long term illness can be minimized and because of the opportunity to collect information about earlier development. Little prospective longitudinal research, however, is available. In addition, several studies focus on adult patients or include both adults and adolescents as one group. Further prospective longitudinal research evaluating the effect of underweight on the occurrence of ASD characteristics in young adolescents with AN is therefore indicated.

Internalizing problems such as anxiety, depression, and compulsion have been suggested to play a role in the occurrence and impact of ASD characteristics in subjects with AN. On one hand they are often accompanied by weight change, on the other hand underweight can lead to increased internalizing complaints. This is probably due to their impact on cognitive functioning. Further investigation into the link between internalizing difficulties and the occurrence of ASD characteristics in adolescents with AN is warranted. In line with this, it stands to reason that other factors influencing cognitive functioning may also impact ASD characteristics in AN patients. One of these factors is the use of psychotropic medication. Both antidepressants and antipsychotics are sometimes used in the treatment of AN and its comorbidities. Both belong to the group of psychotropic medication that exert an influence on cognitive functioning. Evaluating their impact therefore seems valuable. To date, no studies have been known to show the impact of the use of psychotropic medication on the occurrence of ASD characteristics in patients with AN.

The aim of this prospective, longitudinal study in an adolescent, Flemish population is to compare the prevalence of ASD characteristics in adolescents with restrictive AN during and after underweight. Additionally, correlations for possible confounders such as internalizing problems and use of medication will be taken into account. It is the first Belgian study to assess this topic.

MATERIALS AND METHODS

Procedure

The study was approved by the ethical committee/institutional review board of Antwerp university hospital on May 13th 2020. An insurance policy was taken out that covered any damage or negative consequences that participants could experience as a result of participating in the study.(Insurer: Allianz global corporate and specialty SE-Policy number: EL000862). Written informed consent was obtained from all participants and their parents prior to participation.

It was a prospective, longitudinal follow-up study. Patients were recruited during the acute phase of the illness while underweight. After recruitment patients completed the following questionnaires: The AQ, the Youth Self-Report 11-18 (YSR) and a clinical questionnaire designed by the researchers. For patients younger than 16 years of age, the autism spectrum quotient adolescent version (AQ-adolescent) was used instead of the AQ. This was completed by the parents instead of the patient. When they had reached a stable healthy weight for at least one month, they were invited to complete all three questionnaires again. All data was anonymized before analysis by the researchers. In this article the first study moment (while underweight) and the second study moment (after weight recovery) are referred to as T1 and T2.

Participants

Participants were recruited at the inpatient and day patient eating disorder service of the university hospital for child and adolescent psychiatry Antwerp (UKJA) and at the outpatient eating disorder service care in balance in Antwerp. All adolescents (12-18 years) with AN, restrictive type, who consulted there between August 2020 and November 2021 were invited to participate in the study. The follow-up period ran between February 2021 and February 2023. Diagnosis of AN was made by a child and adolescent psychiatrist (in training) based on anamnesis and clinical examination. A minimum healthy weight was determined by a specialist pediatrician. Patients were included if they had at least 5 kg underweight in comparison to this minimum healthy weight. Patients from all Flemish regions and all genders were included. All patients attended high school. Patients with a known Intelligence Quotient (IQ) of <75 were excluded.

Measures

Autism spectrum Quotient (AQ) and Autism spectrum Quotient adolescent (AQ-adolescent). The AQ is a self-report questionnaire, developed in 2001 by Baron-Cohen, et al. designed to easily measure ASD characteristics in individuals of 16 years or older of normal intelligence. The AQ was translated and validated in a Dutch population in 2008 by Hoekstra, et al. The questionnaire is not intended as a diagnostic instrument, but as a screening instrument within scientific research. The advantage of the AQ is that it is not time consuming and does not require a specialized researcher. In addition, a version for adolescents (12-15 years of age) to be completed by the parents, exists as well. The questionnaire consists of 50 questions, each with four options: “Completely agree”, “somewhat agree”, “somewhat disagree” and “completely disagree”. The Dutch version uses a 4-point system for which scores vary between 50 and 200. A higher score correlates with a higher degree of ASD characteristics. The questionnaire is further divided into five subscales with a score between 10 and 40: Attention to detail, attention switching, imagination, communication and social skills and behavior. The test retest reliability of the Dutch AQ is good (r=0.78), as is the internal consistency (Cronbach's a between 0.71 and 0.81). Official norm scores are not yet available for the Dutch AQ. However both Hoekstra, et al.; Spek, et al. presented the questionnaire to a group of people with ASD diagnosis (n=12 and n=127) and a control group (n=302 and n=71). From Spek, et al. only gender specific scores are available. The reported averages from both studies can be used as a reference point. Spek, et al. suggests a cut off score of 110 for the Dutch AQ.

The AQ adolescent was developed by Baron-Cohen, et al. in 2006. It is indicated for 11 to 15 year olds. The test retest reliability of the AQ-adolescent is high (r=0.92). The internal consistency is also high (Cronbach's a=0.79). As both versions have comparable scoring, means and standard deviation, the data can be analyzed together. From now on “AQ score” in this article refers to the scores of all participants, both those who completed the AQ and those who completed the AQ-adolescent.

The Achenbach System of Empirically Base Assessment (ASEBA) Youth Self-Report 11-18 (YSR). The YSR is part of the ASEBA questionnaires developed by Achenbach and colleagues. The self-reported questionnaire evaluates competences, emotional and behavioral problems in the adolescent. There are always three options: “0 not applicable at all”, “1 somewhat or sometimes applicable” and “2 clearly or often applicable”. The questionnaire has three skill scales (social, school, activities), three problem summary scales (internalizing problems, externalizing problems, and total problem score), eight syndrome scales (anxiety/depressed, withdrawn/depressed, somatic complaints, social problems, thinking problems, attention problems, rule-breaking behavior and aggressive behavior) and six

DSM oriented scales (affective problems, anxiety problems, physical problems, attention deficit/hyperactivity problems, oppositional defiant problems, and behavioral problems). The questionnaire was translated into Dutch by Verhulst, et al.; van den Ende, et al. The scoring of the questionnaire is done *via* a computer program (ADM) which contains norm scores for more than thirty different countries, including a Dutch speaking population. The scores distinguish three areas: A normal area, a subclinical area and a clinical area.

Clinical questionnaire designed by the researchers

This questionnaire collects a number of additional data about the patient at the time of completing the questionnaires, unless otherwise specified: Gender, age, weight, length, use of medication, age at onset of AN, family history of ASD, completed counseling process for AN (outpatient, inpatient, day patient).

Primary and secondary outcomes

Body Mass Index (BMI) is computed using the available data about length and weight. Since weight and BMI naturally vary with age in adolescence, these variables are less suitable as a comparative parameter in this young age group. BMI is placed on the gender and age specific BMI curve according to Flemish standards to determine the BMI percentile for each patient. BMI percentile is comparable across different ages and is therefore used as variable in the further analyses instead of weight or BMI which are used in most studies.

As SSRI's and antipsychotics are the main drugs of interest when investigating AN, use of medication is redefined to a binary parameter: Use/no use of SSRI and/or antipsychotics. Use of other medication is not taken into account.

The main interest of the study is the evolution in different parameters between T1 and T2. Evolution in AQ scores, AQ subscale scores, BMI percentiles and YSR internalizing scale scores are computed as new variables, using the formula: T2 minus T1.

Statistical analysis

All statistical analyses are performed with the software package SPSS Statistics version 28. The normality of continuous variables is evaluated with Shapiro-Wilk tests, and inspection of histograms and QQ-plots. Alpha is set at 0.05, p-values between 0.05 and 0.1 are considered trend significant. All tests are two-tailed. All linear regression models are checked for linearity, normal distribution of residues, and independence from the variance of residues, interdependence and influencing factors.

Comparisons between paired groups (T1-T2) are performed with a paired t-test (normal distribution) or a Wilcoxon test (deviation of normal distribution). One sample t-tests are used to compare mean AQ scores of patients to the reference scores and to the cut-off point. If the paired t-tests show a significant difference in AQ scores between T1 and T2, a regression model is fitted to assess influence of "evolution in BMI percentile" on "evolution in AQ score". It is rationalized that the AQ score at T1 might interact with this association. An interaction effect between "evolution in BMI percentile" and "AQ score at T1" is therefore added to the regression model. To aid interpretation the AQ score at T1 is converted into a binary variable: Above (presence of ASD characteristics)/below (no presence of ASD characteristics) threshold. This results in a multiple linear regression model with "evolution of AQ score" as dependent variable and "evolution in BMI percentile" and "the interaction effect between evolution in BMI percentile and AQ score at T1" as independent variables. If the interaction effect is relevant, further analyses are made using subgroups (above/below threshold for AQ score at T1). In both groups a simple linear regression model with "evolution in AQ score" as dependent variable and "evolution in BMI percentile" as independent variable is performed. Simple linear regression models are also used to examine the effect of weight on AQ subscale scores. Lastly, the binary variable "use of medication" and the continuous variable "evolution in YSR internalizing score" are added as independent variables to the model. This results in a multiple linear regression model with dependent variable "evolution in AQ score" and independent variables "evolution in BMI percentile", "evolution in YSR internalizing scale score" and "use of medication".

RESULTS

Descriptive statistics

Twenty nine patients participated in T1: 27 girls, two boys. Twenty four patients participated in both T1 and T2: 23 girls, one boy. Four patients were not included for follow-up because they did not reach a healthy weight by the end of the study period. One patient did not wish to participate further in the study. None of the participants had AN for more than 2 years. None had a known diagnosis of ASD, nine had a positive family history for ASD. Eleven participants used a Selective Serotonin Re uptake Inhibitor (SSRI) or an antipsychotic (risperidone) at T1, 18 did not. Other used drugs were methylfenidate, laxative, vitamin supplements and inhalation corticoids. These were not further investigated. Table 1 shows the remaining characteristics of the study population at T1 and T2. Seven participants (29.2%) completed an outpatient treatment, seven (29.2%) a day patient treatment and 10 (41.7%) an inpatient treatment.

Table 1: Characteristics of the study population.

	Age T1 (years)	Age T2 (years)	Time between T1 and T2 (years)	BMI percentile T1	BMI percentile T2	Percent underweight with respect to MHW	Age at start eating disorder (years)
N valid	29	24	24	29	24	29	29
Missing	0	5	5	0	5	0	0
Mean	15,0	16,4	1,2	8.1	35	15.1	16.8
Median	14,6	16,1	1.2	3	26.5	13.5	13.7
Standard deviation	1,2	1,2	0.3	10.3	22.4	4.8	1.4
Minimum	12,75	14,50	0.05	1	10	8	8.83
Maximum	17,75	18,83	1.84	37	80	31	16.75

Note: T1: Time/moment one, start of the study, during underweight; T2: Time/moment two, end of the study, after weight recovery; BMI: Body Mass Index; MWH: Minimal Healthy Weight.

AQ scores

Mean BMI percentile is significantly different between T1 (M=8.14) and T2 (M=35.00) ($p<.001$). Total AQ scores and AQ subscale scores for T1 and T2 are reported in Table 2, along with representation of the significance level for the comparison between T1 and T2. AQ score at T1 is significantly higher than AQ score at T2. More specific, AQ subscale scores at T1 are significantly higher than AQ subscale scores at T2 for attention switching,

imagination and attention to detail, but not for social skills and communication.

Table 2: Mean and standard deviation of AQ scores and AQ subscale scores, with representation of the significance level for the comparison between T1 and T2.

	T1: M (SD)	T2: M (SD)	P value
Total AQ score	113.3 (3.3)	102.5 (5.6)	<.001
AQ score social skills	22.2 (1.1)	20.7 (4.2)	0.21
AQ score attention switching	26.3 (4.3)	22.2 (4.6)	<.001
AQ score Communication	21.3 (4.8)	20.4 (3.4)	0.374
AQ score imagination	26.0 (4.8)	23.2 (3.3)	0.009
AQ score attention to detail	22.7 (4.5)	20.8 (2.7)	0.028

Note: AQ: Autism spectrum Quotient; T1: Time/moment one, start of the study, during underweight; T2: Time/moment two, end of the study, after weight recovery; M (SD): Mean (Standard Deviation)

AQ score at T1 is significantly higher than the mean AQ score reported in both the study of Hoekstra (mean AQ score 102.93, p<.001) and the study of Spek, et al. (mean AQ score 85.44, p<.001). AQ score at T2 is higher than the female mean AQ score reported by Spek, et al. (p<.001), but does not differ from the mean AQ score reported by Hoekstra (p=.81). The mean AQ score at T1 does not differ significantly from the cut-off point of 110 (p=.127), while the mean AQ score at T2 is significantly lower than this cut-off point (p=.01). Ten patients score below and nineteen patients score above the threshold at T1. Eighteen patients score below and six patients score above the threshold at T2.

AQ score ranks at T1 are significantly higher for those who did not recover a healthy weight and were thus excluded from T2 (mean rank 22.8) than for those who did recover a healthy weight and participated in T2 (mean rank 13.38) (p=.023). This is also the case for AQ subscale scores social skills (p=.037), attention switching (p=.027) and attention to details (p=.032), but not for AQ subscale scores communication (p=.845) and imagination (p=.414).

Correlation between evolution in BMI percentile and evolution in AQ score

A multiple linear regression is fitted to assess influence of evolution in BMI percentile on evolution in AQ score, corrected for the interaction effect between evolution in BMI percentile and AQ score at T1. No deviations from the model assumptions are found and no highly influential observations are detected. Coefficients and p values for this and all the following regression models are displayed in Table 3. P value for the interaction effect is trend significant (p=.055). This indicates that the relation between evolution in BMI percentile and evolution in AQ score is influenced by AQ score at T1. Therefore further analyses are made separately for two subgroups: Those with AQ score at T1 above versus below the threshold of 110. A simple linear regression is fitted to assess influence of evolution in BMI percentile on evolution in AQ score. The regression analysis is repeated separately for evolution in AQ subscale attention switching, attention to details and imagination scores as dependent variable. Model assumptions are not met for subgroup "AQ score at T1 below threshold": Important deviations from linearity and dependency of the residuals are seen. The regression model for this subgroup is therefore considered unreliable. Results are not mentioned in Table 3. No major deviations from the model assumptions are found and no highly influential observations are detected for the subgroup "AQ score at T1 above threshold". Use of SSRI or antipsychotics (binary variable: Yes/no) and evolution in YSR internalizing scale score (continuous variable) are considered possible confounders and are added to the model with evolution in AQ total score as dependent variable. No major deviations from the model assumptions are found and no highly influential observations are detected. No significant correlations are seen in any of the analyses.

Table 3: Coefficients and p values of the six linear regression models.

Model 1, dependent variable: Evolution in AQ score		
Adjusted R^2=-.029		
Independent variable	**Unstandardized beta coefficient**	**P-value**
Constant	-6.12	0.465
Evolution in BMI percentile	-1.33	0.561
Interaction effect*	/	0.055
Model 2, dependent variable: Evolution in AQ score with AQ score at T1> threshold		
R^2=.176		
Independent variable	**Unstandardized beta coefficient**	**P value**
Constant	-4.22	0.582
Evolution in BMI percentile	-3.54	0.119
Model 3, dependent variable: Evolution in AQ score attention switching with AQ score at T1> threshold		
R^2=.14		
Independent variable	Unstandardized beta coefficient	P value

Constant	-0.75	0.837
Evolution in BMI percentile	-1.46	0.176
Model 4, dependent variable: Evolution in AQ score imagination with AQ score at T1> threshold		
R^2=.21		
Independent variable	**Unstandardized beta coefficient**	**P value**
Constant	1.36	0.643
Evolution in BMI percentile	-1.49	0.089
Model 5, dependent variable: Evolution in AQ score attention to details with AQ score at T1> threshold		
R^2=.005		
Independent variable	**Unstandardized beta coefficient**	**P value**
Constant	-1.44	0.712
Evolution in BMI percentile	-0.29	0.794
Model 6, dependent variable: Evolution in AQ score with AQ score at T1> threshold		
Adjusted R^2=.064		
Independent variable	**Unstandardized beta coefficient**	**P value**
Constant	-2.84	0.758
Evolution in BMI percentile	-3.17	0.191
Use of medication (yes/no)	0.35	0.276
Evolution in YSR internalizing scale score	1.73	0.764

Note: *Interaction effect between evolution in BMI and binary variable AQ score at T1 above/below threshold.

AQ: Autism spectrum Quotient; R^2: coefficient of determination; BMI: Body Mass Index; T1: Time/moment one, start of the study, during underweight

DISCUSSION

The aim of this prospective, longitudinal study was to compare the prevalence of ASD characteristics in adolescents with restrictive AN during and after underweight. This report is the only recent longitudinal study concerning this topic, and the first performed in a Belgian cohort. The main outcome of our study is that the AQ score at T1 is significantly higher than the AQ score at T2. Thus we were able to confirm our main hypothesis that ASD characteristics might be related to the state of underweight and are less likely to be a stable trait of AN patients. This is in line with the findings of Oldershaw, et al.; Kerr-Gaffney, et al. that the emotion recognition ability, the emotional theory of mind and social attention are impaired in underweight patients with AN, but not in recovered patients. However it does not reflect the findings from Rhind, et al.; Bentz, et al.; Pruccoli, et al. that adolescent AN patients show more ASD characteristics without correlation to BMI. The cross-sectional design of these studies and the focus on social skills and communication rather than general ASD characteristics might account for these differences. ASD characteristics as a state in AN is further supported by the following observation from earlier research, that shows that ASD characteristics are not continuously present in patients with AN: While elevated ASD characteristics are seen in AN patients, these characteristics are often not recognized by parents in earlier development. A recent longitudinal study from Susanin, et al. also observed fluctuations in ASD characteristics in adolescent patients before and after treatment. Thus, these studies do not advocate for ASD diagnosis despite ASD characteristics. This signifies that caution should be exercised when interpreting studies conducted with underweight AN patients. It also supports the notion that a diagnosis of ASD should not be made before patients have reached a stable healthy weight.

However, our findings partially contrast with several other studies reporting persistent problems in adult AN patients after recovery. In several studies with adolescents with AN the rate of reported ASD characteristics is lower than in adult studies, but it often remains elevated in comparison to the general population. Since AN usually starts during adolescence, adult patients often have a history of long term underweight. It is possible that the duration of the underweight affects patients to such an extent that recovery of ASD characteristics with weight gain does not ensue as easily as in younger patients. The review and meta-analysis by Saure, et al. and colleagues substantiates this theory: They found that long-term illness is associated with an increase in ASD characteristics. This may result in ASD characteristics reflecting a combination of state and trait features in adult AN patients with a long history of underweight. The combination of state and trait is also suggested by Kerr-Gaffney, et al. This duplicity is also found in our study. Despite the clear reduction in ASD characteristics in most of our study group, 25% still scores above the AQ score threshold at T2 and 33% scores below the AQ score threshold at T1. Thus there are patients in which ASD characteristics remain despite weight gain and there are patients without ASD characteristics despite underweight. This advocates for the presence of subgroups, presumably based on baseline AQ score. If this theory holds, it would be interesting to investigate potential risk and protective factors such as developmental issues, age of onset, speed of weight loss, family history of certain psychiatric disorders and/or strength of the available social network.

Interestingly, the difference between T1 and T2 is significant for those subscales of the AQ focusing on cognitive flexibility and attention functions, but not for those subscales focusing directly on social skills and communication. This is in line with the findings of Courty, et al. that revealed similarities between participants with ASD and participants with AN in a few cognitive domains (attention switching, perspective taking and fantasy, lack of emotional introspection) but not in social skills and with the findings of Kerr-Gaffney, et al. reporting similar scores for repetitive behavior and restricted interests but not for other ASD characteristics in patients with AN. All patients in these studies were underweight. Ghiotto, et al. also reported that lower BMI is associated with poorer executive

functioning in patients with AN. This is an important observation as it indicates that when examining ASD characteristics in patients with AN focus should not solely be on social and communicative measures. It further supports the theory that ASD characteristics should be considered a state rather than a trait in patients with AN, as research has shown that underweight mainly exerts an effect on those brain functions.

A significant evolution in both BMI percentile and AQ (subscale) score between T1 and T2 is seen in our study, suggesting that weight gain might influence the presence of ASD characteristics. The first regression model, with the interaction effect, suggests that there are several subgroups, based on AQ score at T1. Subgroup analyses (above/below threshold of AQ score at T1=110) are therefore used. The subgroup-analysis regression model is unable to prove a significant effect of weight gain on ASD characteristics. This is not what we expected, but is in line with the findings from Rhind, et al.; Bentz, et al.; Pruccoli, et al. that ASD characteristics in adolescents with AN are not correlated to BMI. All these studies had a cross-sectional instead of a longitudinal, prospective design and used BMI instead of BMI percentile. This raises the question how the earlier described effect of weight evolution on brain functioning can be explained. Our findings suggest that subgroups might be present within the AN patient group, based on AQ score at T1. Future research would benefit from further mapping of this interaction effect through baseline AQ score subgroup analysis to investigate whether this can account for the inconsistency between studies. The lack of a significant correlation in our study is presumably due to the limited power of the analyses because of our small study population, especially when investigating subgroups. However, it is also possible that there is another, as yet unknown factor that influences both the evolution in weight and the evolution in ASD characteristics/brain function. Literature suggests internalizing problems such as compulsion, anxiety and depression might be a confounding factor. It also stands to reason that the use of psychotropic medication will have an impact on cognitive functions such as flexibility and attention. Both possible confounders are entered into the regression model, but no evidence for effect is seen. This is in line with the results from Bentz that neither found a significant correlation with internalizing problems. Our study is the first to examine the effect of psychotropic medication such as SSRI's and antipsychotics on the link between weight and ASD characteristics in adolescent patients with AN. Due to our small study population we are unable to incorporate other possible confounders, but future research with larger patient groups should consider the following: Age of onset of AN, developmental problems, duration of AN.

We see that patients, who did not recover to a minimum healthy weight within the time period of the study (two years), achieve a significantly higher AQ score at T1 than patients who did recover. We also see a non-significant trend for the interaction effect between AQ score and difference in BMI percentile, suggesting that the AQ score at T1 is relevant to the further evolution of ASD characteristics and thus that subgroups based on AQ score at T1 might exist. Although the numbers in our study are too small to draw definite conclusions, this suggests that a higher AQ score at T1 might predict a less favorable outcome. This is in line with a bulk of recent research that showed that patients with more ASD characteristics often need a more intensive treatment and may show a lower satisfaction with treatment. Prucolli, et al.; Huke, et al. however did not find a difference in outcomes or treatment between patients with high and low ASD characteristics. These are important results as they suggest that measuring ASD characteristics at T1 might help to make a correct estimate of the need for intensive treatment and to facilitate early specific intervention for this vulnerable patient group. Both Tchanturia, et al.; Loomes, et al. suggested specific treatment adaptations for AN patients with elevated ASD characteristics. The evaluation of ASD characteristics at the start of treatment, during underweight, may therefore remain clinically relevant. The results of our study call for caution when assigning ASD diagnoses to patients with AN or even categorizing certain cognitive difficulties as ASD characteristics. It may be more correct to speak of difficulties due to underweight.

CONCLUSION

The results from our current study indicate that ASD characteristics in young patients with AN might in a subgroup of these patients be a state related to underweight, rather than a stable trait. Caution should be used when diagnosing ASD in patients with AN, as it should be avoided during underweight. Our study supports the theory that more ASD characteristics at T1 may result in a poorer outcome and a higher need for specified and intensive treatment. Our preliminary results suggest subgroup analysis based on AQ score during underweight might help identify those patients in need of specific or more intensive treatment. So despite reluctance to diagnose, we advocate further evaluation of these characteristics. Application of this study procedure in a larger, multicenter study is appropriate to further unravel the link between ASD characteristics and underweight in patients with AN. Subgroup analysis based on AQ score at T1 is advised. Future studies should also focus more on outcome and treatment intensity measures.

LIMITATIONS

The most important limitation of the current study is the sample size. This must be taken into account when interpreting all statistical results. As only one male participant is included in T1 and T2, gender specific comparisons were not possible. This comparison would have been particularly interesting as more and more research shows that ASD characteristics differ between the genders. In the regression analyses the effective sample sizes were small, which increased the risk for an over fitted model. To reduce this risk, recommendations by Babyak, et al. were followed: Pretesting of candidate predictors and dichotomization of continuous variables were avoided. All decisions were theory driven and not data driven. Despite the risk of overfitting, YSR internalizing scale score and use of medication were included in the last model as they were suggested to be confounding factors by literature. Another limitation was the lack of official norm scores for the AQ Dutch. Future research into this topic would benefit from reliable regional data based on the 1 to 4-point scoring system.

Strengths of this study were the prospective, longitudinal design, the focus on adolescents specifically and the spread over different regional treatment settings resulting in the inclusion of patients from all over the Flemish region and with all treatment intensities. Taking into account the limited available longitudinal research into this topic, the results of this report remain relevant, despite the small study cohort.

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