


## ORIGINAL ARTICLE

# Prominent autistic traits and subthreshold bipolar/mixed features of depression in severe anorexia nervosa

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**Objective:** Autistic traits are associated with a burdensome clinical presentation of anorexia nervosa (AN), as is AN with concurrent depression. The aim of the present study was to explore the intertwined association between complex psychopathology combining autistic traits, subthreshold bipolarity, and mixed depression among people with AN.

**Method:** Sixty patients with AN and concurrent major depressive episode (mean age, 22.2±7 years) were cross-sectionally assessed using the Autism-Spectrum Quotient test (AQ-test), the Hamilton depression scales for depression and anxiety, the Young Mania Rating Scale (YMRS), the Hypomania-Checklist-32 (HCL-32), second revision (for subthreshold bipolarity), the Brown Assessment and Beliefs Scale (BABS), the Yale-Brown-Cornell Eating Disorders Scale (YBC-EDS), and the Eating Disorder Examination Questionnaire (EDE-Q). Cases were split into two groups depending on body mass index (BMI): severe AN (AN<sup>+</sup>) if BMI < 16, not severe (AN<sup>-</sup>) if BMI ≥ 16.

**Results:** The “subthreshold bipolarity with prominent autistic traits” pattern correctly classified 83.6% of AN patients (AN<sup>+</sup> = 78.1%; AN<sup>-</sup> = 91.3%, Exp(B) = 1.391). AN<sup>+</sup> cases showed higher rates of positive scores for YMRS items 2 (increased motor activity-energy) and 5 (irritability) compared to AN<sup>-</sup> cases.

**Conclusions:** In our sample, depressed patients with severe AN had more pronounced autistic traits and subtly mixed bipolarity. Further studies with larger samples and prospective follow-up of treatment outcomes are warranted to replicate these findings.

**Keywords:** Anorexia nervosa; autism spectrum; bipolar disorder; mixed depression

## Introduction

Accumulating evidence suggests a relationship between autism spectrum disorders (ASDs) and anorexia nervosa (AN).<sup>1-3</sup>

An underlying genetic vulnerability shared by AN and ASDs has been proposed since the late 1980s, with research pointing out prominent AN features in (pre-) adolescent females and autistic features in infant males, following the interaction of certain environmental factors.<sup>4</sup> Elevated autistic traits have also been reported in females with AN,<sup>5,6</sup> as have morphometric alterations in brain areas linked to social cognition, including the amygdala, the orbitofrontal cortex, the fusiform face area (in the temporal lobe and Brodmann's area 37), and the superior temporal sulcus.<sup>7,8</sup> Overall, the prevalence of ASD in AN has been reported to approximate 23% of cases.<sup>9</sup> This is a compelling finding, taking into account the similarities in cognitive, social, and emotional processing

between AN and ASD.<sup>10,11</sup> These similarities pertain attention-switching tasks, perspective taking and fantasy, lack of emotional introspection, and the theory of mind profile,<sup>12</sup> and have led to the conceptualization of AN as a distinct female autism phenotype.<sup>1</sup> The presence of autistic-spectrum features in AN is associated with a more severe clinical presentation, depression, anxiety, and poorer everyday functioning overall.<sup>13,14</sup> Poorer treatment outcomes of AN have been documented in patients with trait-like (stable) ASD features,<sup>15</sup> possibly leading to multiple treatment-augmentation attempts and polypharmacy.<sup>16</sup>

The impact of ASD on the outcomes of AN treatment deserves research attention, especially considering that ASD is associated with a fourfold increase in lifetime depression rates<sup>17</sup> and that adults with prominent autistic traits have high rates of suicide attempts.<sup>18</sup> Little attention has been given to the impact of depression in this particular population, although clinical practice suggests a high burden of depression (often associated with irritability

and increased motor-activity/energy expenditure, possibly seen as subtle hints of bipolarity) and prominent autistic traits in AN.

To the best of our knowledge, no research has been published concerning the potential impact of concurrent depression (herein including subthreshold bipolar depression) and autistic traits on body mass index (BMI) scores in AN, a parameter otherwise regarded as a hallmark of severity in the DSM-5.<sup>19</sup>

However, we hypothesize that the presence of autistic traits and subthreshold bipolarity with mixed features may be more pronounced among severe AN people with a current major depressive episode (MDE).

Therefore, the present study aims at preliminary assess the impact of depression and autistic traits on the severity of AN, ideally paving the ground for future prospective studies providing a systematic neuropsychological and treatment-outcome assessment.

## Methods

The procedures adopted in the present cross-sectional study are outlined below, following the recommendations of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.<sup>20</sup>

### *Study setting, participants, and eligibility criteria*

In- and outpatients of both sexes, aged 14 years or older, with a primary diagnosis of AN and comorbid MDE, either in the course of major depressive disorder (MDD) or bipolar disorder (BD), were screened for inclusion. Given the non-experimental design of this study, the inclusion criteria were very permissive.

Enrollment took place in January 2017 and October 2018, at the outpatient psychiatric unit of Federico II University of Naples, Italy. Two experienced psychiatrists (TS and IS) were appointed to establish the diagnoses according to the DSM-5 criteria. The exclusion criteria were substance use disorder, lack of valid informed consent, and any condition potentially affecting BMI. Finally, AN subjects were split into two groups: severe (AN<sup>+</sup>) if BMI < 16 or non-severe (AN<sup>-</sup>) if BMI ≥ 16, as per the DSM-5 threshold.

### *Variables, measures, and procedures*

Once demographic and clinical data had been gathered, a broad range of rating tools were administered. The Autism-Spectrum Quotient-test (AQ-test), Italian-language version,<sup>21</sup> has also been validated for use with patients with a primary diagnosis of AN.<sup>10</sup> The AQ-test includes 50 items assessing five areas of functioning: social skill, attention switching, attention to detail, communication, and imagination. The Hamilton Rating Scale for Depression 17-item version (HAM-D-17)<sup>22</sup> and Anxiety (HAM-A)<sup>23</sup> and the Young Mania Rating Scale (YMRS) were administered to all participants. Additionally, the Hypomania Checklist-32-item, second revision (HCL-32-R2, 34-item version), was used to test for presence of subthreshold bipolarity among participants with a DSM-5 diagnosis of unipolar major

depression. The severity and the type of eating disorder were self-reported using the Yale-Brown-Cornell Eating Disorders Scale (YBC-EDS)<sup>24</sup> and the Eating Disorder Examination Questionnaire (EDE-Q).<sup>25</sup> The YBC-EDS assess both current and “worst ever” scores for rituals and preoccupations about a range of habits and somatic features. The EDE-Q comprises three domains: restraint, eating concern, and weight concern. Finally, a multi-purpose scale for the assessment of insight of illness, the Brown Assessment and Beliefs Scale (BABS),<sup>26</sup> was administered.

On all of the aforementioned scales, higher scores indicate a higher symptom burden. Patients' clinical records were anonymized and pooled for the present analysis.

### *Statistical analysis*

All statistical analyses were performed in SPSS version 25.0 for Windows, adopting an alpha error rate of 0.05 (two-tailed) and a conservative statistical power of 95%. Interrater reliability for the analysis was ascertained preliminarily using Cohen's  $\kappa$  statistic, to ensure consistency of clinician-administered ratings among raters and minimize rating bias. The normality of data distribution and the homogeneity of variance were verified using the Kolmogorov-Smirnov and Levene tests, respectively. Parametric comparative analyses for demographic and clinical characteristics of the groups were performed using an independent-samples Student *t*-test for continuous variables where appropriate (with the Wilcoxon rank-sum test planned for nonparametric distributions) and chi-square analysis for categorical variables (again, nonparametric as appropriate). Pearson's or Spearman's rho correlations were calculated for selected clinical variables as appropriate. Binary logistic regression (dependent variable = AN<sup>+</sup>/AN<sup>-</sup>) was carried out using the conditional backward logistic regression method for those variables having a significantly different distribution between the AN<sup>+</sup> vs. AN<sup>-</sup> groups upon descriptive analysis; linear regression analysis using BMI as a dependent variable followed the logistic regression. Finally, missing data were excluded pairwise.

### *Ethics statement*

The participating patients provided a valid, written informed consent after two experienced psychiatrists (TS and IS) had thoroughly explained the study procedures, according to the norms outlined by the local ethics committee.

## Results

Among 72 potentially eligible patients screened, 60 were confirmed eligible for inclusion. Of these, 56 had MDD; three had BD-II (two AN<sup>+</sup> and one AN<sup>-</sup>); and one (AN<sup>+</sup>) had BD-I. Excluded patients either failed to meet the diagnostic criteria of a current MDE (n=10) or refused consent due to privacy concerns (n=2).

The sample included 55 females (F) and five males (M). Overall, 35 patients were rated as AN<sup>+</sup> (F/M = 31/4)

and 25 as AN<sup>-</sup> (F/M = 24/1). The age of the AN<sup>+</sup> patients ranged from 14-46 years (mean  $\pm$  standard deviation [SD] = 22.82 $\pm$ 6.99); 26 were adult (aged 18 years or older). In the AN<sup>-</sup> group, age ranged between 15-45 years (mean  $\pm$  SD = 21.32 $\pm$ 7.16), of whom 18 were adult. Most AN<sup>+</sup> cases were inpatients at the time of assessment (27 of 35, 77.1%), in contrast to the AN<sup>-</sup> cases (6 of 25, or 24% of cases). Additional demographic and clinical features are described in Table 1.

#### *Interrater variability*

The preliminary interrater variability for diagnosis of current MDE (HAM-D-17 total score  $\geq$  7) was  $\kappa = 0.749$  ( $p \leq 0.001$ ), 95% confidence interval (95%CI) -0.0710 to 0.1038, denoting substantial agreement. Additional measures of interrater variability for other non-self-report ratings ranged from 0.72 (substantial agreement) to 0.83 (almost perfect agreement).

#### *Selected correlation measures in the AN<sup>+</sup> group*

Figure 1 provides a pictorial synthesis of the correlation between BMI and YMRS total scores in the AN<sup>+</sup> and AN<sup>-</sup> groups.

Essential correlation metrics in the AN<sup>+</sup> and AN<sup>-</sup> groups are reported in Table 2.

YMRS items 2 (increased motor activity-energy) and 5 (irritability) correlated significantly with AN<sup>+</sup>:  $r_s = 0.452$  ( $p \leq 0.001$ ) and  $r_s = 0.406$  ( $p \leq 0.001$ ), respectively. YMRS item 5 also correlated with AQ-test total score in AN:  $r_s = 0.353$  ( $p \leq 0.001$ ). The strongest and most significant (positive) correlation in the AQ-test subset was found between AQ-test attention switching and EDE-Q shape, in the AN<sup>+</sup> group only ( $r = 0.492$ ,  $p \leq 0.001$ ).

#### *Essential multivariate statistics*

A backward (conditional) stepwise binary logistic regression analysis was conducted to allocate patients to either the AN<sup>+</sup> or the AN<sup>-</sup> group, accounting for autistic traits measured using the AQ-test scale and subthreshold bipolarity scores recorded with the HCL-32-R2, among other predictors.

A test of the full model against a constant-only model was statistically significant, indicating that the predictors as a set reliably discriminated between AN<sup>+/-</sup> cases: ( $\chi^2_{[2]} = 27.409$ ;  $p \leq 0.001$ ). Nagelkerke's  $R^2 = 0.528$  indicated a sound explanatory value of the regression model. Overall AN predictive capacity was 83.6% (AN<sup>+</sup> = 78.1%; AN<sup>-</sup> = 91.3%).

Additional variables were likewise included in the multistep procedure outlined in Table 3, although step 6 of the logistic regression (AQ-test and HCL-32-R2 total scores input as covariates) provided the best fit, possibly due to multicollinearity issues as well. The Wald criterion demonstrated that both AQ-test total ( $p = 0.039$ ) and HCL-32-R2 total ( $p = 0.001$ ) made significant contributions to the prediction, with prominent autistic traits and higher HCL-32-R2 scores providing odd ratios (OR) – (Exp[betas]) – of roughly 1.2 and 1.4, respectively, for

prediction of AN<sup>+</sup> vs. AN<sup>-</sup> categorization. For purposes of convenience and ease of interpretation, an OR = 1 indicates the same propensity of an event belonging to a given AN subgroup.

Linear regression analysis using BMI total score as the dependent variable and AQ-test and HCL-32-R2 total scores as covariates indicated that the model predicted the BMI scores of AN patients (adjusted  $R^2 = 0.383$ ;  $p \leq 0.001$ ). However, only the standardized  $b$  coefficient of AQ-test was significant ( $p \leq 0.001$ ).

## **Discussion**

The primary aim of the present study was to explore severe AN through correlations with complex psychopathology (combining autistic traits, mixed features, and subthreshold bipolarity) among patients presenting with a MDE. As expected, descriptive analyses indicated that AN<sup>+</sup> cases were more frequently inpatients, on pharmacological treatment (especially benzodiazepines or antipsychotics), had higher rates of lifetime psychiatric hospitalization, and had significantly higher scores on all domains of the YBC-EDS and global EDE-Q compared to AN<sup>-</sup>. Consistent with previous research,<sup>10-12</sup> the preliminary results of the present study indicate that severe AN is associated with higher scores on the AQ-test compared to AN<sup>-</sup>, especially in the attention-switching and communication domains.

Multiple lines of research support the connection between ASD and AN, including shared neurobiology<sup>7,8</sup> and genome-wide association studies.<sup>27</sup> Elevated ASD traits are associated with lower BMI scores, suggesting that ASD traits may arise from the starved state of AN<sup>28</sup> and thus warrant follow-up over the natural history and treatment course of AN. The relationship between AN and ASD is nonspecific, so that ASD traits could be over-represented in AN, perhaps even maintaining the associated eating disorder rather than causing it.<sup>13</sup> It has been hypothesized that rigidity, obsessive interest, and social withdrawal/impairments could be the manifestations of an underlying ASD or may be the consequences of highly prevalent conditions in AN, such as starvation, anxiety, depression, and obsessive-compulsive disorder.<sup>29</sup> The label of “severe” AN proposed by the DSM-5 based solely on BMI, as we adopted in the present study, may therefore insufficient to capture the complexity of the phenomenon of AN, especially when combined with prominent autistic traits and depression, both of which may have a pathoplastic effect of AN. Similarly, very low BMI could induce agitation, hyperactivity, problematic physical activity<sup>30</sup> and other bipolar-like symptoms through anaerobic (ketotic) metabolism; thus, we cannot rule out that at least part of the psychopathological features associated with AN<sup>+</sup> could be explained as “soft bipolarity” due to severe metabolic disturbances and malnutrition, which is a condition known to predict inadequate response towards standalone antidepressant drugs<sup>31</sup> (indeed, roughly half of the AN<sup>+</sup> patients in our sample were on antidepressants). If corroborated by prospective follow-up, changes in BMI scores in the AN<sup>+</sup> subgroup may explain at least part of the bipolar-like and autism-spectrum symptoms

**Table 1** Demographic and clinical features of the subjects included in the study

Study subjects (n=60)	Severe AN n=35 (58%)	Non-severe AN n=25 (42%)	t or $\chi^2$ (df)	p-value
<b>Demographics</b>				
Age in years, mean $\pm$ SD (range)	22.82 $\pm$ 6.99 (14-46)	21.32 $\pm$ 7.16 (15-45)	-0.816 <sub>(58)</sub>	ns
Female-to-male ratio, n (%)	31 (88.6)/4 (11.4)	24 (96.0)/1(4.0)	1.054 <sub>(1)</sub>	ns
Education level				
Primary	1 (2.9)	0 (0.0)	5.362 <sub>(3)</sub>	ns
Secondary	16 (45.7)	19 (72.0)		
Higher	16 (45.7)	5 (20.0)		
College or university	2 (5.7)	2 (8.0)		
<b>Clinical features</b>				
BMI	14.07 $\pm$ 1.44	17.12 $\pm$ 0.91	9.334 <sub>(58)</sub>	< <b>0.001</b>
Duration of untreated illness, years (mean $\pm$ SD)	5.68 $\pm$ 4.17	4.08 $\pm$ 6.05	-1.161 <sub>(58)</sub>	ns
Age at onset, years (mean $\pm$ SD)	17.2 $\pm$ 6.22	17.24 $\pm$ 4.78	-0.027 <sub>(58)</sub>	ns
Current MDE	35 (100.0)	25 (100.0)		ns
Current mixed features (DSM-5 defined)	16 (45.7)	4 (16.0)	5.794 <sub>(1)</sub>	<b>0.016</b>
Purging type	9 (25.7)	6 (24.0)	0.023 <sub>(1)</sub>	ns
Lifetime MDD	32 (91.4)	24 (96.0)	0.490 <sub>(1)</sub>	ns
Lifetime BD-II	2 (5.7)	1 (4.0)	0.090 <sub>(1)</sub>	ns
Lifetime BD-I	1 (2.9)	0 (0.0)	0.726 <sub>(1)</sub>	ns
Lifetime OCD	5 (14.3)	2 (8.0)	0.559 <sub>(1)</sub>	ns
Lifetime anxiety disorders other than OCD	10 (28.6)	5 (20.0)	0.571 <sub>(1)</sub>	ns
Lifetime BN	7 (20.0)	5 (20.0)	0.000 <sub>(1)</sub>	ns
Lifetime BED	3 (8.6)	0 (0.0)	2.256 <sub>(1)</sub>	ns
Lifetime suicidal behavior	6 (17.1)	3 (12.0)	0.303 <sub>(1)</sub>	ns
Lifetime hospitalization	17 (48.6)	3 (12.0)	8.777 <sub>(1)</sub>	<b>0.003</b>
Currently on pharmacotherapy (any type)	31 (88.6)	12 (48.0)	11.822 <sub>(1)</sub>	<b>0.001</b>
Currently on antidepressant	16 (45.7)	9 (36.0)	0.566 <sub>(1)</sub>	ns
Currently on benzodiazepines	21 (60.0)	6 (24.0)	7.636 <sub>(1)</sub>	<b>0.006</b>
Currently on second-generation antipsychotic	14 (40.0)	1 (4.0)	10.08 <sub>(1)</sub>	<b>0.001</b>
Currently on lithium	0 (0.0)	1 (4.0)	1.42 <sub>(1)</sub>	ns
Currently on other mood stabilizer	1 (2.9)	4 (16.0)	3.29	ns
Family history of eating disorders	3 (8.6)	1 (4.0)	0.49 <sub>(1)</sub>	ns
Family history of affective disorders	10 (28.6)	8 (32.0)	0.082 <sub>(1)</sub>	ns
Family history of anxiety disorders other than OCD	11 (31.4)	6 (24.0)	0.396 <sub>(1)</sub>	ns
Family history of suicidal behavior	0 (0.0)	0 (0.0)		ns
Family history of OCD	3 (8.6)	1 (4.0)	0.490 <sub>(1)</sub>	ns
Inpatient status	27 (77.1)	6 (24.0)	16.641 <sub>(1)</sub>	< <b>0.001</b>
Number of previous hospitalizations (mean $\pm$ SD)	0.74 $\pm$ 1	0.2 $\pm$ 0.5	-2.416 <sub>(58)</sub>	<b>0.019</b>
<b>AQ-test total score (mean <math>\pm</math> SD)</b>				
AQ-test total score (mean $\pm$ SD)	24.25 $\pm$ 5.29	20.04 $\pm$ 4.46	-3.241 <sub>(58)</sub>	<b>0.002</b>
Attention switching	7.11 $\pm$ 1.07	5.32 $\pm$ 1.51	-5.35 <sub>(58)</sub>	< <b>0.001</b>
Attention to detail	3.48 $\pm$ 1.24	3.40 $\pm$ 1.19	-0.268 <sub>(58)</sub>	ns
Communication	3.94 $\pm$ 1.58	3 $\pm$ 1.08	-2.570 <sub>(58)</sub>	<b>0.013</b>
Imagination	3.08 $\pm$ 1.19	3.94 $\pm$ 1.58	-2.570 <sub>(58)</sub>	ns
Social skills	6.62 $\pm$ 1.68	5.88 $\pm$ 1.3	-1.861 <sub>(58)</sub>	ns
ADHD	2 (5.7)	0 (0.0)	1.478 <sub>(1)</sub>	ns
HCL-32-R2 total score* (mean $\pm$ SD)	7.78 $\pm$ 5.05	4.34 $\pm$ 3.94	-2.714 <sub>(58)</sub>	0.009
<b>Rating scales</b>				
HAM-D-17, total score (mean $\pm$ SD)	17.74 $\pm$ 5.19	13.4 $\pm$ 3.35	-3.663 <sub>(58)</sub>	<b>0.001</b>
YMRS, total score (mean $\pm$ SD)	7.51 $\pm$ 4.04	3.4 $\pm$ 2.56	-4.476 <sub>(58)</sub>	< <b>0.001</b>
YMRS, item 2 (increased motor activity-energy) recoded as yes/no	23 (65.7)	5 (20.0)	12.245 <sub>(1)</sub>	< <b>0.001</b>
YMRS, item 5 (irritability) recoded as yes/no	29 (89.2)	11 (44.0)	9.909 <sub>(1)</sub>	<b>0.002</b>
YMRS, item 7 (language-thought disorder) recoded as yes/no	8 (22.9)	5 (20.0)	0.070 <sub>(1)</sub>	ns
YMRS, item 9 (disruptive-aggressive behavior) recoded as yes/no	8 (22.9)	3 (12.0)	1.148 <sub>(1)</sub>	ns
HAM-A total score (mean $\pm$ SD)	13.34 $\pm$ 4.23	10.88 $\pm$ 3.19	-2.45 <sub>(58)</sub>	<b>0.017</b>
BABS total score (mean $\pm$ SD)	8.51 $\pm$ 4.69	8.12 $\pm$ 5.55	-0.297 <sub>(58)</sub>	ns
<b>YBC-EDS (mean <math>\pm</math> SD)</b>				
Total, current	33.85 $\pm$ 5.32	29.64 $\pm$ 5.16	-3.096 <sub>(58)</sub>	<b>0.003</b>
Total, worst	34.62 $\pm$ 5	30.76 $\pm$ 4.42	-3.06 <sub>(58)</sub>	<b>0.003</b>
Total, current rituals	11.05 $\pm$ 1.89	9.44 $\pm$ 1.70	-3.394 <sub>(58)</sub>	<b>0.001</b>
Total, worst rituals	11.25 $\pm$ 1.8	9.84 $\pm$ 1.65	-3.106 <sub>(58)</sub>	<b>0.003</b>
Total, current preoccupations	11.68 $\pm$ 1.77	9.8 $\pm$ 1.89	-3.94 <sub>(58)</sub>	< <b>0.001</b>
Total, worst preoccupations	11.88 $\pm$ 1.71	10.12 $\pm$ 2.04	-3.63 <sub>(58)</sub>	<b>0.001</b>

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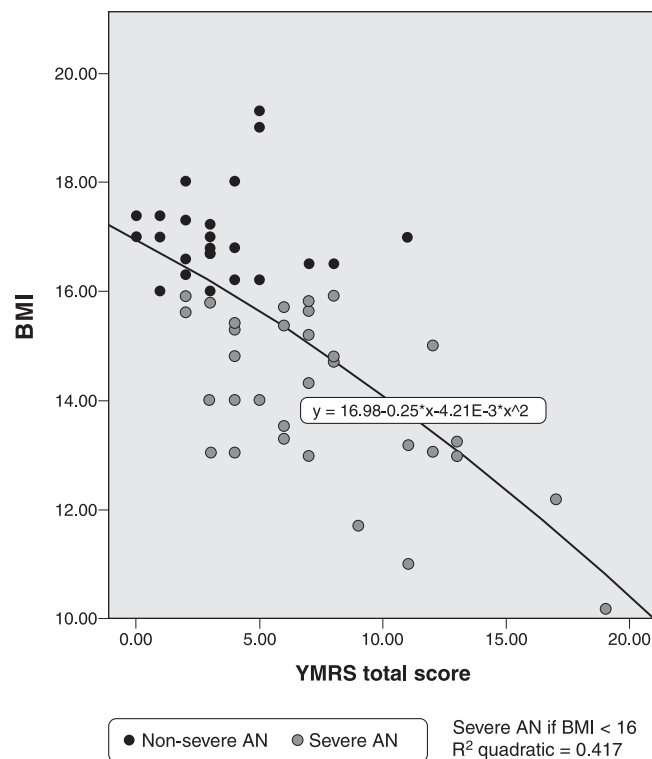
Table 1 (continued)

Study subjects (n=60)	Severe AN n=35 (58%)	Non-severe AN n=25 (42%)	t or $\chi^2$ (df)	p-value
EDE-Q (mean $\pm$ SD)				
Restraint subscale	22.4 $\pm$ 3.79	19.52 $\pm$ 5.5	2.401 <sub>(58)</sub>	<b>0.020</b>
Eating concern subscale	16.65 $\pm$ 4.57	14.48 $\pm$ 3.88	-1.932 <sub>(58)</sub>	ns
Shape concern subscale	28.28 $\pm$ 5.67	27.56 $\pm$ 8.23	-0.373 <sub>(58)</sub>	ns
Weight concern subscale	15.77 $\pm$ 4.62	16.28 $\pm$ 5.67	0.382 <sub>(58)</sub>	ns
Global	78.14 $\pm$ 14.28	75.44 $\pm$ 19.43	-2.405 <sub>(58)</sub>	<b>0.019</b>

Data presented as n (%), unless otherwise specified.

ADHD = attention deficit and hyperactivity disorder; AN = anorexia nervosa; AQ-test = Autism-Spectrum Quotient test; BABS = Brown Assessment and Beliefs Scale; BD = bipolar disorder; BED = binge eating disorder; BMI = body mass index; BN = bulimia nervosa; df = degrees of freedom; EDE-Q = Eating Disorder Examination Questionnaire; HAM-A = Hamilton Anxiety Rating Scale; HAM-D-17 = Hamilton Scale for Depression, 17-item; HCL-32-R2 = Hypomania Checklist, 32-item, second revision, 34-item version; MDD = major depressive disorder; MDE = major depressive episode; ns = nonsignificant; OCD = obsessive-compulsive disorder; SD = standard deviation; YBC-EDS = Yale-Brown-Cornell Eating Disorders Scale; YMRS = Young Mania Rating Scale.

\* 56/60 MDD patients.



**Figure 1** Pearson's correlation of BMI and YMRS total score,  $r^2 = -0.545$ ;  $p \leq 0.001$ . BMI dichotomizes AN as severe ( $< 16$ ) or non-severe ( $\geq 16$ ). This plot provides an estimate of the impact of manic-series symptoms in depression, and should be considered a crude approximation of the impact of the "mixed features" DSM-5 specifier for MDE. AN = anorexia nervosa; BMI = body mass index; MDE = major depressive episode; YMRS = Young Mania Rating Scale.

upon improvement of imbalances due to anaerobic metabolism and vigorous physical exercise. However preliminary, the results of the present study suggest that DSM-5 mixed features of depression were significant more prevalent among AN<sup>+</sup> vs. AN<sup>-</sup> cases, regardless of the putative causes. Furthermore, increased motor-activity/energy and irritability were also more common among those AN individuals with lower BMI scores, although not significantly so. This has major clinical implications, considering that neither "increased motor-activity/energy" nor "irritability" are included by the DSM-5 among the mixed features, despite their discriminant predictive value for bipolarity in the clinical setting.<sup>32</sup>

Likewise, the higher HCL-32-R2 scores detected do not necessarily indicate bipolarity in AN<sup>+</sup> cases, since in most instances the usual cutoff of 14 was not met. As the HCL-32-R2 has not yet been validated for use in patients with DSM-5-defined unipolar depression associated with AN and prominent autistic traits, we submit that even a trend towards higher HCL-32-R2 scores (significantly higher in AN<sup>+</sup> vs. AN<sup>-</sup> cases) may indicate a plausible trend toward subthreshold bipolarity (once again, regardless of putative neuroendocrine causes). This is particularly worth of note considering that the potential presence of "signs of excitement" may account for a specific therapeutic approach, assuming an internal medicine workup

**Table 2** Selected significant correlations for major metrics in the AN<sup>+</sup> (top line) and AN<sup>-</sup> group (bottom line of the cell)

	DUI	AQ-test-attention switching	AQ-test-attention details	AQ-test-communication	AQ-test-imagination	AQ-test-social skills	YBC-EDS total (current habits)	EDE-Q restraint	EDE-Q eating	EDE-Q shape	EDE-Q weight	YMRS total score	HCL-32-R2 total score*	BABS total score
DUI	1	0.015 -0.179	-0.394 <sup>†</sup> -0.015	-0.047 0.325	-0.140 -0.021	0.004 -0.170	-0.013 -0.229	-0.012 -0.458 <sup>†</sup>	-0.075 -0.251	-0.182 -0.311	-0.060 -0.445 <sup>†</sup>	-0.069 0.246	0.277 0.202	-0.112 -0.395
AQ-test-attention switching		1	0.133 0.249	0.278 -0.102	0.348 <sup>†</sup> -0.012	0.705 <sup>‡</sup> 0.568 <sup>‡</sup>	0.300 0.042	0.255 0.263	0.133 0.022	0.492 <sup>†</sup> 0.158	0.241 -0.020	0.195 0.083	-0.107 0.076	0.348 <sup>†</sup> 0.316
AQ-test-attention to details			1	0.445 <sup>‡</sup> 0.583 <sup>‡</sup>	0.412 <sup>†</sup> 0.692 <sup>‡</sup>	0.341 <sup>†</sup> 0.382	0.286 -0.023	0.001 0.050	0.020 -0.034	-0.145 -0.037	-0.052 0.014	0.264 0.273	0.314 -0.135	0.248 0.207
AQ-test-communication				1	0.837 <sup>‡</sup> 0.776 <sup>‡</sup>	0.377 <sup>†</sup> 0.445 <sup>†</sup>	0.270 -0.090	-0.030 -0.259	0.001 -0.040	-0.270 -0.276	-0.162 -0.136	-0.046 0.301	-0.176 -0.077	0.150 -0.097
AQ-test imagination					1	0.456 <sup>‡</sup> 0.411 <sup>†</sup>	0.149 -0.068	-0.017 -0.087	-0.031 -0.200	-0.073 -0.119	-0.188 -0.031	-0.117 0.117	-0.177 -0.061	0.075 0.174
AQ-test social skills						1	0.299 -0.019	0.116 0.131	0.079 -0.095	0.330 -0.087	0.019 -0.069	0.137 0.202	-0.067 0.144	0.167 0.089
YBC-EDS total (current habits)							1	0.417 <sup>†</sup> 0.042	0.174 0.410 <sup>†</sup>	0.089 0.349	0.184 0.400 <sup>†</sup>	0.498 <sup>‡</sup> 0.360	0.311 0.065	0.594 <sup>‡</sup> 0.477 <sup>‡</sup>
EDE-Q restraint								1	0.397 <sup>†</sup> 0.471 <sup>†</sup>	0.347 <sup>†</sup> 0.695 <sup>‡</sup>	0.404 <sup>†</sup> 0.567 <sup>‡</sup>	0.360 <sup>†</sup> -0.119	0.313 -0.008	0.153 0.031
EDE-Q eating									1	0.371 <sup>†</sup> 0.524 <sup>‡</sup>	0.568 <sup>‡</sup> 0.772 <sup>‡</sup>	0.351 <sup>†</sup> 0.139	0.406 <sup>†</sup> 0.247	0.380 <sup>†</sup> 0.076
EDE-Q shape										1	0.521 <sup>†</sup> 0.754 <sup>‡</sup>	0.318 -0.159	0.113 -0.118	0.304 0.278
EDE-Q weight											1	0.368 <sup>†</sup> -0.051	0.204 0.131	0.550 <sup>‡</sup> 0.205
YMRS total score												1	0.690 <sup>‡</sup>	0.474 <sup>‡</sup> 0.067
HCL-32-R2 total score*													1	0.346 -0.207
BABS total score														1

AQ-test = Autism-Spectrum Quotient; AQ-test-attention details = attention to details area of the AQ-test; AQ-test-attention switching = attention switching area of the AQ-test; AQ-test-communication = communication area of the AQ-test; AQ-test-imagination = imagination area of the AQ-test; AQ-test-social skills = social skills area of the AQ-test; BABS = Brown Assessment of Beliefs Scale; DUI = duration of untreated illness; EDE-Q = Eating Disorder Examination Questionnaire; EDE-Q eating = eating concern subscale of the EDE-Q; EDE-Q restraint = restraint subscale of the EDE-Q; EDE-Q shape = shape concern subscale of the EDE-Q; EDE-Q weight = weight concern subscale of the EDE-Q; HCL-32-R2 = Hypomania Checklist-32-item, second revision, 34-item version; YMRS = Young Mania Rating Scale.

\* Refers to 56 out of 60 patients with unipolar depression. † Refers to 56 out of 60 patients with unipolar depression. ‡ Refers to 56 out of 60 patients with unipolar depression.

Not flagged = not significant (for p ≥ 0.05); † p ≤ 0.05 (two-tailed); ‡ p ≤ 0.01 (two-tailed).

**Table 3** Multistep logistic regression

Variables in the equation	B	p-value	Exp(B)	95%CI for Exp(B)	
				Lower bound	Upper bound
<b>Step 1</b>					
AQ-test total score	0.198	0.027	1.219	1.023	1.454
HCL-32 total score	0.366	0.016	1.442	1.071	1.940
YMRS					
Item 2	1.637	0.095	5.137	0.754	35.002
Item 5	0.267	0.780	1.306	0.201	8.497
Item 7	-1.779	0.153	0.169	0.015	1.937
Item 9	-0.743	0.595	0.476	0.031	7.386
BABS total score	-0.119	0.189	0.888	0.744	1.060
Constant	-5.584	0.004	0.004		
<b>Step 2</b>					
AQ-test total score	0.202	0.023	1.224	1.028	1.456
HCL-32 total score	0.377	0.012	1.458	1.086	1.956
YMRS					
Item 2	1.705	0.071	5.503	0.865	35.008
Item 7	-1.754	0.156	0.173	0.015	1.958
Item 9	-0.850	0.529	0.427	0.030	6.045
BABS total score	-0.117	0.192	0.889	0.745	1.061
Constant	-5.557	0.004	0.004		
<b>Step 3</b>					
AQ-test total score	0.207	0.019	1.230	1.035	1.461
HCL-32 total score	0.330	0.007	1.392	1.094	1.770
YMRS					
Item 2	1.748	0.064	5.745	0.905	36.487
Item 7	-1.682	0.171	0.186	0.017	2.071
BABS total score	-0.123	0.173	0.885	0.741	1.055
Constant	-5.543	0.004	0.004		
<b>Step 4</b>					
AQ-test total score	0.166	0.041	1.180	1.007	1.383
HCL-32 total score	0.294	0.009	1.342	1.077	1.673
YMRS					
Item 2	1.656	0.075	5.238	0.845	32.478
Item 7	-1.441	0.235	0.237	0.022	2.551
Constant	-5.375	0.004	0.005		
<b>Step 5</b>					
AQ-test total score	0.172	0.031	1.188	1.016	1.390
HCL-32 total score	0.287	0.011	1.332	1.067	1.663
YMRS item 2	1.242	0.128	3.463	0.698	17.177
Constant	-5.558	0.003	0.004		
<b>Step 6</b>					
AQ-test total score	0.165	0.039	1.179	1.008	1.380
HCL-32 total score	0.347	0.001	1.415	1.146	1.748
Constant	-5.228	0.004	0.005		

Step 6 provided the best fit, correctly classifying up to 78.1% of AN<sup>+</sup> cases.

The HCL-32-R2 scores refer to 56/60 unipolar depression patients.

95%CI = 95% confidence interval; AN = anorexia nervosa; AQ-test = Autism-Spectrum Quotient-test; BABS = Brown Assessment of Beliefs Scale; HCL-32 = Hypomania Checklist-32-item, second revision, 34-item version; YMRS = Young Mania Rating Scale.

has already ruled out any underlying organic condition which might affect attitudes toward eating. We hypothesize that, at least in a proportion of severe cases of AN, the combination of prominent autistic traits and depression with irritability and increased motor-activity/energy, alongside obsessive interests (i.e., a focus on shape concerns) and an inability to divert attention switching toward objects/goals other than eating and weight concerns, may represent an atypical mixed state. According to Emil Kraepelin and his pupil Wilhelm Weygandt, depression may accompany “psychomotor activity” and “formal reasoning” in different ways, leading to multiple mixed

configurations.<sup>33</sup> Possibly, at least some depressed AN<sup>+</sup> patients may thus present with atypical manifestations of two Kraepelinian mixed states, namely “depressive-anxious mania” (low mood, increased psychomotor activity, and increased formal reasoning) and “aroused depression” (low mood, increased psychomotor activity, and reduced formal reasoning). Alternatively, very severe AN with prominent autistic traits may resemble Esquirol’s monomania, a sort of “partial insanity” conceived as “single pathological preoccupation in an otherwise sound mind”<sup>34</sup> (herein, the goal-directed activity/hyperactivity is focused on shape and diet). On the other hand, at least a proportion of

patients with overt BD may experience lifetime weight cycling (possibly alternating bulimic and anorexic phases) which resemble manic-depressive excitement (vigorous physical exercise and starvation, or intense bingeing/purging), alternating with apparent remission of this excitement, resulting in less disabling – yet transient – eating disturbances.<sup>35,36</sup>

Ideally, future controlled trials should consider low-dose lithium (upon careful evaluation of cardiac and renal function) and/or antipsychotics (preferably agents with a low propensity to cause cardiac arrhythmias and weight gain, so as to minimize the subsequent risk of refeeding syndrome) for the most severe cases of AN with sub-threshold bipolar depression and/or psychotic features, such as lack of insight of illness corroborated by high BABS scores. If confirmed in replication studies including prospective assessment of different treatment modalities, the potential impact of subtle features associated with some of the most severe cases of AN should affect treatment response, as postulated for some MDD cases which are devoid of AN comorbidity yet respond inadequately to medication due to subthreshold bipolarity.<sup>37-39</sup> Nevertheless, these considerations should be made only after first-line evidence-based treatments,<sup>40</sup> including intensive medical and psychological care,<sup>41,42</sup> prove to be ineffective.

Limitations of this study include the small sample size, lack of neuropsychological/IQ testing, and absence of recording of treatment outcomes, energy expenditure, and exercise activity across different treatment interventions. In addition, besides the statistical significance of the corresponding p-values, the ORs for the pivotal predictors “autistic traits” (OR = 1.18) and “sub-threshold bipolar depression” (OR = 1.34) only slightly exceed 1, meaning that the association between such predictors and AN<sup>+</sup> is not definitive (refer to the last step of the regression model in Table 3). The severity of AN was defined solely by BMI threshold, as in the DSM-5. Frail patients with AN may have presented with medical symptoms resembling depression, and no AN control without depression was included in the present study. Female cases were overrepresented, although this reflects the natural history of the condition itself. On the other hand, the “real-world” setting of the present study may have reduced the chances of Berkson’s bias.

In conclusion, the findings of the present study must be considered as explorative. No recommendation whatsoever about therapeutic choices can be inferred at this time; any potential implications for treatment must be viewed as a critical, yet theoretical, appraisal, relevant only for forthcoming research on the topic. However, considering the burden related to the complex clinical phenotype of severe AN with comorbid depression and prominent autistic traits and the absence of evidence on the matter, even results warranting replication – such as ours – should be reported in such a hard-to-capture special population.<sup>43</sup>

## Disclosure

The authors report no conflicts of interest.

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