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ORIGINAL ARTICLE

High levels of physical activity in female adolescents with anorexia nervosa: medical and psychopathological correlates

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Abstract

Purpose While overexercise is commonly described in patients who experience anorexia nervosa (AN), it represents a condition still underestimated, especially in the paediatric population.

Method The present study aims at assessing the possible associations between levels of physical activity (PA) and clinical features, endocrinological data and psychopathological traits in a sample of 244 female adolescents hospitalised for AN subdivided into two groups according to PA levels (high PA vs. no/low PA). The two groups were compared through multivariate analyses, while multiple regression analysis was conducted to determine whether physical activity predict specific outcomes.

Results No significant differences were found between the two groups in terms of last Body Mass Index (BMI) before illness, BMI at admission and disease duration, while a difference emerged in delta BMI(rapidity of weight loss), significantly higher in high-PA group ($p=0.021$). Significant differences were observed in Free triiodothyronine- ($p<0.001$), Free thyroxine ($p=0.046$), Follicle-stimulating hormone ($p=0.019$), Luteinising hormone ($p=0.002$) levels, with values remarkably lower in high-PA group. Concerning psychopathological scales, the high-PA group showed worst Children's Global Assessment Scale (CGAS) scores ($p=0.035$). Regression analyses revealed that higher PA predicts higher delta BMI ($p=0.021$), presence of amenorrhea ($p=0.003$), lower heart rate ($p=0.012$), lower thyroid (Free triiodothyronine $p<0.001$, Free thyroxine $p=0.029$) and gynaecological hormones' levels (Follicle-stimulating hormone $p=0.023$, Luteinising hormone $p=0.003$, 17-Beta estradiol $p=0.041$). Concerning psychiatric measures, HPA predicts worst scores at CGAS ($p=0.019$), and at scales for evaluation of alexithymia ($p=0.028$) and depression ($p=0.004$).

Conclusions Results suggest that high levels of physical activity in acute AN associate with worst clinical conditions at admission, especially in terms of endocrinological and medical features.

Level of evidence Level III.

Keywords Anorexia nervosa · Adolescents · Physical activity · Endocrinological data · Psychopathology

Introduction

Anorexia Nervosa (AN) is a psychiatric condition with substantial medical and psychiatric morbidity that generally affects adolescent females in Western countries. In this condition, self-evaluation is predominantly based on the perception of one's own body, and everyday life is unduly influenced by weight-control practices [1]. The worldwide prevalence of AN in females is estimated at 0.3–1%, with a yearly incidence of 8 cases/100,000 [2], while it is tenfold lower in males [2]. The mortality rate for medical complications and suicide is about 6%, the highest among all the psychiatric diseases [3]. Comorbidities in AN involving psychiatric, cardiac, gastrointestinal, immunological, and endocrine systems, are well established. Dysfunction

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of the hypothalamic–pituitary axis includes hypogonadotropic hypogonadism with relative oestrogen and androgen deficiency, hypoleptinemia, low insulin-like growth factor-1 (IGF-1) and growth hormone resistance, hypercortisolaemia, non-thyroidal illness syndrome, hypooxytocinaemia and hyponatraemia. Though amenorrhea is no longer included among the DSM-5 diagnostic criteria, menstrual dysfunction remains common: psychological stress, disordered eating, excessive exercise or a combination of these factors often result in suppression of the hypothalamic–pituitary–ovarian axis and subsequent functional hypothalamic oligo-amenorrhea (FHA). Hypoestrogenism plays a detrimental role on cardiovascular, skeletal, psychological, and reproductive systems. It has been demonstrated that women with FHA can begin to experience bone loss in as little as 6 months after the onset of amenorrhea, leading to premature osteoporosis; additionally, they present with additional susceptibility to anxiety and depressive traits [4]. Although most, but not all, of these endocrine disturbances are adaptive responses to the chronic starvation state and are reversible, many of them contribute to neuropsychiatric comorbidities and adverse medical outcomes [5].

As widely described, in AN, weight loss is caused primarily by a restriction in food intake, but additional behaviours that increase energy expenditure such as overexercising can play a contributory role [3, 6]. Abnormally high levels of physical activity (HPA) have been reported since the earliest clinical description of eating disorders (ED), especially in AN [7]. Overexercising negatively affects the course of AN, given the demonstrated association between PA and longer length of hospital stay [8], poor treatment outcome [9], interferences with refeeding strategies and body weight stabilisation [10] and increased risk of relapse and chronicity [11, 12]. Exercise is sometimes voluntarily increased as a conscious strategy to optimise weight loss and often becomes a coping strategy to compensate, suppress, and/or alleviate both negative affective states, anxiety [13, 14], depression [13] stress and ED symptoms [15], including weight preoccupation [12, 16]. As the ED progresses, involuntary PA could appear, with automation of the behaviour as a compulsive component not under voluntary cognitive control (maintaining muscles contracted without even thinking about it, running instead of walking and/or standing up when one normally should be sitting down), adding to voluntary exercise. In the advanced stages of the illness, with a subconscious biological drive, a part of this activity becomes totally automatic and largely triggered by hypoleptinemia [17, 18] and other metabolic changes [3, 19].

While overexercise has often been described in patients with AN, the underlying mechanisms are not fully understood. Previous research has focused on the neurobiological regulation of increased physical activity (PA) during severe energy restriction [20]. Research investigating the linkage between PA levels and age at AN onset showed that the levels of PA tend to increase with age [3, 12, 21]. Studies assessing the potential linkage between PA levels and weight, body mass index (BMI) or body composition provided conflicting results [12], with half of them ruling out any correlations, and the other half showing a significant association between PA and body weight [22, 23], BMI [23–26], percentage of body fat [23, 24] and resumption of menses [27]. Several studies also suggest the association between high PA levels and eating disorder-specific psychological factors, such as eating disorder severity [5, 28], depression, obsessive–compulsiveness and symptoms of anxiety disorders [8, 15, 28, 29].

Nevertheless, most of these analyses have been conducted in small samples of adolescents and/or in adults with AN. Furthermore, exercise behaviours are relatively understudied among adolescents with AN in relation to medical aspects of AN. To date, only one research recently held by Nagata and colleagues focused on the association between exercise behaviours and vital sign abnormalities (such as bradycardia) in a cohort of adolescents ED [30].

Overall, to the best of our knowledge, no systematical research on a large sample of AN patients who have low to no PA levels in comparison with those having high PA have been published, especially in the paediatric population. In addition, the relationships between high PA levels in patients with acute AN on the one side and their medical and psychopathological features on the other side have not been studied so far. The present study aims at comparing (1) clinical features, endocrinological data and psychopathological traits in a large cohort of female adolescents with AN with or without High PA; (2) to assess the possible relationships between HPA and clinical, endocrinological and psychological/psychiatric outcomes, and (3) to verify the hypothesis of a more severe clinical presentation of acute AN for HPA group. The purpose of this research is to improve knowledge of physio-pathological underlying mechanisms and to allow more individualised, efficient and early medical treatments.

Methods

We performed a single-center, retrospective and cross-sectional study conducted on a sample of 244 female adolescents hospitalised at Child and Adolescent mental health Department-ASST Monza, University of Milano-Bicocca (Monza, Italy) from 2016 to 2019 for severe malnutrition due to AN, diagnosed according to DSM-5 criteria.

Considering the low percentage of males with AN admitted to our center, as consistent with published data that report a frequency of AN 10 times lower in males than in females [2], we decided to exclude males from our research, to get a more homogeneous sample and to study the linkage

between physical activity and clinical features, with particular regards to endocrinological data, included sexual hormones. Other exclusion criteria included severe intellectual disabilities, severe psychosis, alcohol or drug addictions and any somatic comorbidities with a strong influence on physical activity (e.g., multiple sclerosis or severe anaemia).

Ethical approval was waived by the local Ethics Committee of ASST Monza in view of the retrospective nature of the study and all the procedures being performed were part of the routine care. Data were collected from patients' medical records and included:

a. anthropometric and clinical data upon admission, i.e., age, height, weight, BMI (calculated as kg/m^2), heart rate, current medications;
b. information related to family history (family history consistent with eating disorders or different psychiatric conditions, socioeconomic level);
c. information related to individuals' anamnestic history (psychiatric and medical comorbidities);
d. clinical information related to the course and severity of AN, including BMI recorded prior to the onset of AN, BMI at the time of diagnosis, the last BMI recorded, rapidity of weight loss (delta BMI) and duration of disease (months);
e. menstrual history including age at menarche (years), menstrual cycle features at admission, presence of amenorrhea upon admission, duration of amenorrhea (months),
f. endocrinological analysis for hormonal serum levels: thyroid-stimulating hormone (TSH), free thyroxine (FT4), free triiodothyronine (FT3), follicle-stimulating hormone (FSH), luteinising hormone (LH), 17-beta estradiol.

Psychopathological traits were assessed by the following psychiatric measures at admission:

EDI-3 (Eating Disorders Inventory): a 91-item self-reporting questionnaire intended to provide a psychological profile of symptoms related to eating disorders and a quantitative measure of their presence and intensity. The Italian version of the EDI-3 [31] provides six composite scales: Eating Disorder Risk Composite (EDRC), Ineffectiveness Composite (IC), Interpersonal Problems Composite (IPC), Affective Problems Composite (APC), Overcontrol Composite (OC), and General Psychological Maladjustment Composite (GPMC). For each composite scale, higher scores reflect worse symptomatology [32].

SCL-90R (Symptom Checklist-90-Revised): a self-report questionnaire designed to assess psychological problems and psychopathological symptoms on individuals aged 13 years and older. This original measure, and the validated Italian version [33], consists of 90 items rated on a five-point Likert scale that assesses nine symptom dimensions [somatisation (SOM), obsessive–compulsive (OC), interpersonal sensitivity (INT), depression (DEPR), anxiety (ANX), hostility (HOS), phobic anxiety (PHOB), paranoid ideation (PAR), psychoticism (PSY)].

TAS-20 (Toronto Alexithymia Scale) [34]: a 5-point Likert-type self-report 20-item questionnaire to assess the alexithymia in the total level and three factors: difficulties in identifying feelings (DIF), difficulties in describing feelings (DDF), and lack of focus on internal emotional experiences (EOT). The presence of alexithymia tract is related to a score > 61 at the scale.

CDI (Children's Depression Inventory): a brief self-rated test that helps to evaluate the presence and severity of specific depressive symptoms in children. The test contains 27 items, each consisting of three statements. For each item, the individual had to select the statement that best describes his or her feelings over the past two weeks. Every item is scored from zero to two depending on the answer. The total CDI score is the sum of the responses to all 27 items. The CDI uses cut-off scoring: equal to or less than 16 = no depression trait, equal to or greater than 19 = presence of a depression trait. Score of 17 or 18 = border trait [35, 36].

C-GAS (Children's Global Assessment Scale): a scale for the assessment of the global social adjustment of the patients. The Italian version has been used in previous samples of adolescents with psychiatric morbidities. The scale is separated into 10-point sections that are headed with a description of the level of global functioning and followed by examples matching the given interval. The final score ranges from 1 (the most impaired level of global functioning) to 100 (the superior level of global functioning) [37, 38].

Assessment of physical activity for each subject was obtained by the administration of the semi-structured Interview SIAB-EX. (Structured Interview for Anorexic and Bulimic Disorders-Expert form) [39].For the SIAB-EX test, we used the module 40 for assessment of questions that pertain to physical activity of the previous 3 months.

The SIAB-EX distinguishes five levels of physical activity: first level, no excessive physical activity; second level, slight and/or rare excessive physical activity: a person rarely exercises (for example, on weekends or in the evenings) to burn calories or to reduce weight, but can just as well turn to other activities, if they are interesting or appear more important; third level, marked and/or occasional excessive physical activity: a person exercises sometimes (up to twice weekly) or with marked vigour, the person may report discomfort when prevented from physical activity, and distraction is possible but is associated with some discomfort; fourth level, strong and/or frequent excessive physical activity: the person objectively exercises very much (every day for 1 h or three–four times a week for 2 h or more), and also

experiences discomfort when prevented from physical activity; fifth level, very strong excessive physical activity: excessive physical activity occurs more than once a day or for longer periods (1.5 h/day), and the physical activity occurs irrespective of physical weakness and pain. This interview evaluates both quantitative (frequency, duration, intensity) and qualitative (compulsion to exercise) dimensions of physical activity in the previous 3 months and classify it in five different levels for frequency and intensity basing on parents' observation and clinician's evaluation. This tool has been widely used in previous studies to give an evaluation of the PA levels in subjects with AN [14, 17, 40–42, 53]. Recent literature on this topic and previous studies conducted with this questionnaire (SIAB-EX) [42, 53, 55] usually propose a partition into high (or moderate–vigorous) and low PA [15, 18, 26, 43]. Our research follows this practice, which was further corroborated by the distribution of our data: most of our subjects placed themselves at extreme levels in the SIAB-EX test, thus effectively splitting into two sub-groups which coincided with our clinical groups.

Group 1—High PA (HPA) = levels 4–5.

Group 2—No/low PA (N/LPA) = levels 1–2–3.

Statistical analysis

The continuous variables were expressed through mean ± standard deviation of the corresponding distribution; the categorical variables were expressed as absolute or percentage frequencies. Comparisons for age across the two groups subdivided for PA levels were performed using analysis of variance for continuous variables. Comparison for clinical features, physical examination (heart rate), endocrinological findings and psychiatric measures at admission in the two groups were conducted through multivariate analyses (MANCOVA) using age as covariate. Multiple regression analyses entering clinical, physical, endocrinological and psychological/psychiatric outcomes as dependent variables and physical activity (HPA/NLPA) as independent variable were conducted to determine whether physical activity predict specific outcomes. Chi-squared or Fisher's exact tests were performed to compare categorical variables. The level of significance was set at $p < 0.05$.

Statistical analysis was performed using the SPSS 24.0 package.

Results

102 patients out of the 244 enrolled (41.8%) were included in Group 1, while 142 (58.2%) in Group 2. Mean age at admission was statistically different between the two groups [$F(1, 242) = 18.99$, $p = 0.024$], with older subjects belonging to Group 1—High PA (*M* 15.06, SD 1.58 vs. *M* 14.5, SD 2.13 years). The two groups did not differ in terms of socio-demographic data and anamnestic histories (Tables 1, 2), except for the percentage of patients with a family history positive for psychiatric disorders, statistically higher in Group 1 than in Group 2 (34.3% vs. 19.7%; $X^2(1) = 0.644$, $p = 0.009$).

Taking into account the clinical features (Table 3), the two groups showed a superimposable distribution of AN subtypes diagnosed according to DSM-V [$X^2(1) = 1.217$, $p = 0.360$], with most subjects being classified as restrictive type (Group 1 = 77.45%, Group 2 = 83.09%). The MANCOVA, conducted to evaluate differences in clinical and endocrinological features in the two groups (Table 3), showed a significant multivariate effect of Group, $F(13, 112) = 1.762$, $p = 0.05$, $\eta^2 = 0.170$. No significant differences were found when comparing the two Groups in terms of last BMI before illness, BMI at admission and disease duration. On the other hand, the two groups differed for delta BMI (index of body weight loss which expresses the variation of the BMI between the onset of the disorder and the

Table 1 Differences in socio-demographic features

	Group 1 HPA[a] N.102	Group 2 N/LPA[a] N.142	ANOVA (*F*) *p*	Chi square (X^2) *p*
Age Mean (S.D)	15.06 (1.58)	14.5 (2.13)	(18.99) 0.024*	
SES[b] *N* (%)				
< 19.5	17 (17.5)	24 (18.3)		(3.152) 0.533
20 < SES < 29.5	20 (20.6)	30 (22.9)		
30 < SES < 39.5	19 (19.6)	35 (26.7)		
40 < SES < 54.5	32 (33)	31 (23.6)		
> 55	9 (9.3)	11 (8.4)		

*$p < 0.05$, **$p < 0.01$

[a]HPA = high physical activity; N/LPA = no to low physical activity

[b]SES = socio-economic state

Table 2 Differences in anamnestic histories

	Group 1 HPA[a] N.102	Group 2 N/LPA[a] N.142	Chi square (X^2) p
Psychiatric familiarity *N (%)*			
No	67 (65.7)	114 (80.28)	(0.644) 0.009**
Yes	35 (34.3)	28 (19.72)	
Eating Disorder familiarity *N (%)*			
No	94 (92.15)	136 (95.78)	(2.11) 0.122
Yes	8 (7.85)	6 (4.22)	
Medical comorbidities *N (%)*			
No	96 (94.1)	135 (95.07)	(0.393) 0.360
Yes	6 (5.9)	7 (4.93)	
Endocrine conditions	2	1	
Conditions involving malabsorption	3	4	
Metabolic disorders	0	1	
Endocrine + malabsorption pathologies	0	1	
Other	1	0	
Pharmacological therapy *N (%)*			
No	86 (84.3)	121 (85.2)	(0.029) 0.859
Yes	16 (15.7)	21 (14.8)	
Antipsychotic	3	4	
Antidepressant	4	6	
Ansiolitic	3	4	
Antipsychotic + Antidepressant	2	1	
Antipsychotic + Ansiolitic	0	1	
Antidepressant + Ansiolitic	1	2	
Antipsyc + Antidepress + Ansiolitic	3	3	
Psychiatric comorbidities *N (%)*			
No	67 (65.7)	88 (61.8)	(0.458) 0.294
Yes	35(34.3)	54 (38.2)	
Obsessive–compulsive disorder	6 (16.21)	5 (8.77)	
Mood disorders	4 (10.81)	13 (22.80)	
Psychotic disorders	10 (27.03)	8 (14.03)	
Personality disorders	9 (24.32)	9 (15.79)	
Anxiety disorders	3 (8.11)	12 (21.05)	
Other	3 (8.11)	7 (12.3)	

*$p < 0.05$, **$p < 0.01$

[a]HPA = high physical activity; N/LPA = no to low physical activity

admission), significantly higher in Group 1 than in Group 2 ($F = 7.13$, $p = 0.009$).

Age of menarche (*M* 11.73, SD 1.24 in Group 1 vs. *M* 11.90, SD 1.22 years in Group 2), was not significantly different between groups. A significantly higher percentage of amenorrhoeic patients was reported in Group 1 [$X^2(1) = 8.96$, $p = 0.003$], with a higher frequency of secondary amenorrhea (68.6% vs. 52.8%) and fewer patients reporting regular menses (7% vs. 16.2%) at admission than in Group 2 [$X^2(5) = 11.64$, $p = 0.040$]. No differences in the two groups concerning duration of amenorrhea were reported. Considering clinical and endocrinological features (Table 3), statistically significant differences were observed in mean FT3 ($F = 10.70$, $p = 0.001$), FT4 ($F = 4.072$, $p = 0.046$), FSH ($F = 4.939$, $p = 0.028$), LH ($F = 7.56$, $p = 0.007$) levels, with lower values in Group 1 than in Group 2. No statistically significant differences were observed in heart rate, TSH, and 17-Beta Estradiol levels. The MANCOVA, conducted to evaluate differences in psychological/psychiatric traits (Table 4), showed a significant multivariate effect of Group, $F(12, 150) = 1.814$, $p = 0.05$, $\eta^2 = 0.127$. The two groups did not differ in EDI-3, SCL-90, TAS-20 and CDI mean scores. Significant differences were otherwise observed in C-GAS

Table 3 Differences in clinical features, physical examination (heart rate) and endocrinological findings at admission

	Group 1 HPA[a] N.102	Group 2 N/LPA[a] N.142	MANOVA corrected for age (*F*) *p*	Chi square (X^2) *p*
Last BMI before illness Mean (S.D)	21.45 (3.44)	20.60 (2.89)	(2.29) 0.133	
Delta BMI[c] Mean (S.D)	5.21 (3.09)	3.87 (2.63)	(7.13) 0.009**	
Duration of disease (months) Mean (S.D)	10.56 (9.58)	9.17 (7.59)	(8.17) 0.368	
BMI at admission[b] Mean (S.D)	15.62 (2.39)	16.72 (2.17)	(1.454) 0.230	
Type of eating disorder *N* (%)				
R-AN[d]	79 (77.45)	118 (83.09)		(1.217) 0.324
BP-AN[d]	23 (22.55)	24 (16.91)		
Age at menarche (years) Mean (S.D)	11.73 (1.24)	11.90 (1.22)	(2.407) 0.123	
Menstrual cycle features at admission *N* (%)				
Regular	7 (7)	23 (16.2)		(11.64) 0.040*
Primary amenorrhea	19 (18.6)	26 (18.3)		
Secundary amenorrhea	70 (68.6)	75 (52.8)		
Premenarcheal	1 (1)	9 (6.3)		
Irregular	5	8		
Not relevant[e]	0	1		
Amenorrhea at admission *N* (%)				
No	13 (12.74)	41 (28.88)		(8.96) 0.003**
Yes	89 (87.26)	101 (71.12)		
Duration of amenorrhea at admission (months) Mean (S.D)	5.35 (5.20)	4.10 (4.88)	(1.91) 0.169	
Heart Rate (bpm[f]) Mean (S.D)	56.95 (14.59)	60.84 (15.29)	(2.095) 0.150	
TSH[g] microU/mL Mean (S.D)	1.94 (1.01)	2.33 (1.56)	(2.54) 0.114	
FT3[h] pg/mL Mean (S.D)	2.00 (0.72)	2.45 (0.79)	(10.70) 0.001**	
FT4[i] pg/mL Mean (S.D)	10.79 (1.97)	11.42 (1.61)	(4.072) 0.046*	
FSH[l] mUI/mL Mean (S.D)	3.02 (2.97)	4.20 (3.02)	(4.939) 0.028*	
LH[m] mUI/mL Mean (S.D)	1.25 (3.32)	3.36 (4.92)	(7.56) 0.007**	
17- Beta Estradiol pg/mL Mean (S.D)	14.15 (34.64)	27.41 (43.46)	(3.51) 0.063	

*$p < 0.05$, **$p < 0.01$

[a]HPA = high physical activity; N/LPA = no to low physical activity

[b]BMI = Body Mass Index

[c]Delta BMI = index of body weight loss which expresses the variation of the BMI between the onset of the disorder and the admission

[d]R-AN: restrictive type anorexia nervosa; BP-AN: bingeing/purging type anorexia nervosa

[e]Not relevant = subjects with HRT(Hormone Replacement Therapy)

[f]bpm = beats per minute

[g]TSH = Thyroid-stimulating hormone

[h]FT3 = Free triiodothyronine

[i]FT4 = Free thyroxine

[l]FSH = Follicle-stimulating hormone

[m]LH = Luteinising hormone

($F = 6.151$, $p = 0.014$) scores, with worst results found for Group 1 compared to Group 2.

Regression analyses (Table 5), conducted to determine whether PA predicts specific outcomes, revealed that HPA predicts higher delta BMI ($R^2 = 0.024$, $b = 0.154$, $p = 0.021$) and presence of amenorrhea at admission ($R^2 = 0.037$, b = 0.192, $p = 0.003$), while HPA predicts lower heart rate ($R^2 = 0.026$, $b = -0.161$, $p = 0.012$) and FT3 ($R^2 = 0.070$, $b = -0.265$, $p < 0.001$), FT4 ($R^2 = 0.021$, $b = -0.146$, $p = 0.029$), FSH ($R^2 = 0.023$, $b = -0.153$, $p = 0.023$), LH ($R^2 = 0.039$, $b = -0.197$, $p = 0.003$), 17-Beta estradiol ($R^2 = 0.019$, $b = -0.137$, $p = 0.041$) levels. Concerning psychological/

Table 4 Main differences in psychopathological traits by psychological/psychiatric measures at admission

	Group 1	Group 2	MANOVA corrected for age
	HPA[a]	N/LPA[a]	(*F*) *p*
	N.102	N.142	
EDI-3 (Eating Disorders Inventory) Mean (S.D)			
EDRC[b]	61.66 (28.16)	57.21 (33.08)	(0.380) 0.538
IC[c]	68.24 (28.29)	64.01 (28.94)	(0.439) 0.509
IPC[d]	64.52 (30.06)	63.53 (29.92)	(0.005) 0.943
APC[e]	59.81 (34.87)	64.85 (30.70)	(1.370) 0.243
OC[f]	57.90 (33.81)	52.99 (33.69)	(0.523) 0.470
GPMC[g]	59.27 (35.86)	55.41 (36.34)	(0.158) 0.691
SCL-90 R (Symptoms Check List-90 Revised) Mean (S.D)			
GSI[h]	54.81 (12.88)	53.38 (12.57)	(0.337) 0.562
PST[i]	54.64 (12.65)	52.74 (12.56)	(0.694) 0.406
PSDI[l]	52.58 (11.29)	52.36 (11.16)	(0.002) 0.962
C-GAS (Children's Global Assessment Scale) Mean (S.D)	55.32 (12.99)	60.49 (12.58)	(6.151) 0.014*
TAS-20 (Toronto Alexithymia Scale) Mean (S.D)	60.27 (12.01)	58.28 (15.61)	(0.598) 0.441
CDI (Children's Depression Inventory) Mean (S.D)	20.77 (8.99)	18.54 (9.30)	(2.194) 0.149

*$p < 0.05$, **$p < 0.01$

[a]HPA = high physical activity; N/LPA = no to low physical activity

[b]EDRC = Eating Disorder Risk Composite

[c]IC = Ineffectiveness Composite

[d]IPC = Interpersonal Problems Composite

[e]APC = Affective Problems Composite

[f]OC = Overcontrol Composite

[g]GPMC = General Psychological Maladjustment Composite

[h]GSI = Symptoms Check List-90 Revised -Global Severity Index

[i]PST = Symptoms Check List-90 Revised -Positive Symptoms Total

[l]PSDI = Symptoms Check List-90 Revised -Positive Symptom Distress Index

psychiatric measures, HPA predicts higher and worst CGAS ($R^2 = 0.026$, $b = -0.161$, $p = 0.019$), TAS-20 ($R^2 = 0.021$, $b = 0.145$, $p = 0.028$) and CDI ($R^2 = 0.035$, $b = 0.187$, $p = 0.004$) scores.

Discussion

High-level PA is a frequent symptom in patients with AN, influencing the development, maintenance, complications, treatment success, relapse rate and severity of the disease.

The first purpose of this study was to compare clinical, physical, endocrinological and psychological/psychiatric features in two groups of AN adolescents split for PA levels: HPA and N/LHPA.

Results of our study confirm, in line with literature, a prevalence of 41.81% of HPA in patients with AN [26], and a mean age higher for patients with HPA than for patients with N/LPA [21]. By systematically assessing the differences between the two groups of patients, we outlined that HPA was neither associated with a worse BMI at the time of admission, as already described [18, 44–47], nor with a worse BMI recorded before illness onset and or to a longer duration of disease. On the other hand, the differences demonstrated in delta BMI suggested that patients engaged in high-level PA presented with a statistically greater weight loss in the same amount of time. These data support the well-known hypothesis that PA is usually used by patients who experience anorexia to optimise weight loss.

Concerning heart rate at admission, the whole sample showed signs of bradycardia, a common finding in subjects with AN [48–50], but no differences emerged in the two groups even though the HPA group show lower heart rate values than N/LPA one. This result is in contrast with the only published study to our knowledge by Nagata et al. (2017), that investigating the effect of physical exercise on bradycardia among adolescents associated higher PA with

Table 5 Regression analyses entering clinical, physical, endocrinological and psychological/psychiatric outcomes as dependent variables and physical activity (HPA/NLPA) as independent variable

	R^2	Beta	95% CI[a]		*P*
			LL[a]	UL[a]	
BMI[b]	0.004	− 0.064	− 0.901	0.294	0.318
Delta BMI[c]	0.024	0.154	0.146	1.738	0.021*
Amenorrhea at admission	0.037	0.192	0.057	0.266	0.003**
Duration of amenorrhea at admission	0.019	0.138	− 0.116	3.288	0.680
Heart rate	0.026	− 0.161	− 8.552	− 1.046	0.012*
TSH[d]	0.015	− 0.122	− 0.653	0.022	0.067
FT3[e]	0.070	− 0.265	− 0.680	− 0.239	< 0.001**
FT4[f]	0.021	− 0.146	− 1.084	− 0.060	0.029*
FSH[g]	0.023	− 0.153	− 1.762	− 0.133	0.023*
LH[h]	0.039	− 0.197	− 2.493	− 0.507	0.003**
17- Beta Estradiol	0.019	− 0.137	− 19.536	− 0.412	0.041*
EDI-3 EDRC[i]	0.003	0.059	− 5.252	12.370	0.427
EDI-3 IC[l]	0.000	0.014	− 7.388	9.010	0.845
EDI-3 IPC[m]	0.001	− 0.030	− 10.524	6.951	0.687
EDI-3 APC[n]	0.009	− 0.095	− 15.312	3.230	0.200
EDI-3 OC[o]	0.002	0.048	− 6.509	12.809	0.521
EDI-3 GPMC[p]	0.000	0.005	− 9.860	10.561	0.946
SCL90-R GSI[q]	0.004	0.060	− 2.321	5.363	0.435
SCL90-R PST[r]	0.007	0.084	− 1.697	5.900	0.276
SCL90-R PSDI[s]	0.000	0.003	0.968	− 3.327	3.466
CGAS (Children's Global Assessment Scale)	0.026	− 0.161	− 7.724	− 0.698	0.019
TAS-20 (Toronto Alexithymia Scale)	0.021	0.145	0.842	14.445	0.028*
CDI (Children's Depression Inventory)	0.035	0.187	1.338	7.050	0.004**

*$p < 0.05$. **$p < 0.01$

[a]CI = confidence interval; LL = lower limit; UL = upper limit

[b]BMI = Body Mass Index

[c]Delta BMI = index of body weight loss which expresses the variation of the BMI between the onset of the disorder and the admission

[d]TSH = Thyroid-stimulating hormone

[e]FT3 = Free triiodothyronine

[f]FT4 = Free thyroxine

[g]FSH = Follicle-stimulating hormone

[h]LH = Luteinising hormone

[i]EDI-3 EDRC = Eating Disorders Inventory Eating Disorder Risk Composite

[l]EDI-3 IC = Eating Disorders Inventory Ineffectiveness Composite

[m]EDI-3 IPC = Eating Disorders Inventory Interpersonal Problems Composite

[n]EDI-3 APC = Eating Disorders Inventory Affective Problems Composite

[o]EDI-3 OC = Eating Disorders Inventory Overcontrol Composite

[p]EDI-3 GPMC = Eating Disorders Inventory General Psychological Maladjustment Composite

[q]SCL90-R GSI = Symptoms Check List-90 Revised -Global Severity Index

[r]SCL90-R PST = Symptoms Check List-90 Revised -Positive Symptoms Total

[s]SCL90-R PSDI = Symptoms Check List-90 Revised -Positive Symptom Distress Index

severe bradycardia. However, this research [30] is not easily comparable to ours, as it included both female and male adolescents affected by either Anorexia Nervosa or Bulimia Nervosa.

In addition, we demonstrated significative differences for endocrinological data recorded upon admission between the two groups, not attributable to age, BMI, duration of disease, medical comorbidity or pharmacological therapy.

The analysis of endocrinological findings outlined a tendency towards lower plasmatic levels of FreeT3 and gonadotropins in the whole population, as commonly found in AN [2, 51, 52]. From a gynaecological perspective, the endocrinological pattern found reflected a significantly higher percentage of amenorrhoeic patients in the high-level PA group, with most patients presenting with secondary amenorrhea. Only a retrospective Italian work by Maestro et al. (2014) [53] on acute anorexia and hyperactivity in 73 female adolescents outlined similar findings about menstrual history at admission and tendency to worst global hormonal levels in HPA. Nevertheless, to the best of our knowledge, our analysis, performed on a remarkably wider sample, has been the first that allowed to demonstrate a statistically significant difference between HPA and N/LPA groups in terms of gynaecological and endocrinological outcomes. From a psychopathological perspective, our results showed no significant differences between the two groups with reference to AN symptomatology. These data were consistent with other studies [12], that examined general eating disorder pathology with either levels of physical activity [18, 26], actimetry [15] or locomotor activity [54], but in contrast to those works that underlined the presence of greater weight preoccupation, body dissatisfaction and drive for thinness in the high-PA group than in controls [55, 56]. Furthermore, we did not find any significant differences when assessing the presence of symptoms such as compulsivity or anxiety traits, measured by SCL-90, in the two groups. With reference to compulsivity, our results are consistent with several studies in which no direct relationship was found between different levels of physical activity and obsessive–compulsiveness as assessed with the SCL-90-R [13, 14, 57, 58]. Conversely, obsessive–compulsiveness was found to be associated with PA in other studies [16, 55, 58, 59], with a hyperactive behavioural profile representing a phenotype more closely linked to OCD than their non-exercising counterparts [55]. About this result, it is important to point out that we only examined acutely ill patients during semistarvation upon initiation of inpatient treatment. As Holtkamp and colleagues stated (2004) [14], we thought that it may be possible that in the beginning of dieting, body image plays a much more important role in developing excessive exercise; elevated activity levels in patients could have multiple underlying mechanisms whose relative contribution might differ according to the stage of the disorder. Regarding to anxiety traits, our study did not reveal any differences in the compared groups, in line with other studies which failed to demonstrate the impact of anxiety on recorded levels of PA in AN, [18, 46, 54], even when specifically comparing high/non high exercisers [18, 55]. Other studies disagreed to this result, underlining instead that there was an increase in PA in cases of elevated anxiety [14, 54, 60], as an attempt to cope with this negative state. No statistically significant differences emerged in depressive traits between the two groups, though HPA group showed means scores in the pathological range differently from the N/LHPA group that obtained borderline scores. Up to date, discrepant results about the relationship between depression and PA have been reported in literature. While several works that found that depression was not increased in patients with AN classified as excessive exercisers in comparison to those classified as non-excessive exercisers [13, 14, 26, 46, 54], others [56, 60, 61] reported a positive association between depression and exercise status, on both categorical and dimensional approaches. Like for anxiety, this was generally seen as an attempt of this patients to improve their mood and emotional state with physical activity by pursuing the boosting effect of endogenous opioids [62]. Dealing with our results, we should remember that the explored psychopathological areas were mainly assessed by self-report scale as screening tools usually used in the clinical practice. Nevertheless, the state of acute AN is often itself associated with a state of illness denial. In a clinical sample, this could underestimate the global scores found and it could explain both the overall absence of pathological scores in both groups and the absence of differences in the mean scores in the two groups. In our study, the only significant differences were observed in C-GAS mean scores, with worst results found for High-PA group. Thus, consistent with previous studies, an objective evaluation could let greater psychopathological differences emerge between the two groups.

The second aim of our study was to assess possible associations between HPA and AN outcomes. Our regression analyses confirmed that the presence of HPA predicts worse clinical, endocrinological and psychological/psychiatric outcome in patients with AN. In particular, if we look at clinical and hormonal data, HPA predicts higher delta BMI, the presence of amenorrhea, lower heart rate, lower thyroid and gynaecological hormones' levels; while regarding psychological/psychiatric traits, HPA predicts worst scores in Children's Global Assessment Scale and in scales for evaluation of alexithymia and depression.

In conclusion, our results showed that subjects with AN-HPA were more clinically compromised, confirming the hypothesis of a more severe clinical picture of acute AN for this group.

Limitations to this study include the lack of a healthy control group. Moreover, we used a subjective measurement tool to assess physical activity levels (SIAB-EX) and, although we tried to improve reliability through direct interview of the patients and independent confirmation from parents and clinician, an objective measurement of physical activity

(e.g., by accelerometery) would improve the quality of further studies.

Conversely, strengths of this study include a large and homogeneous sample including exclusively girls who experience anorexia in paediatric age, thus improving the quality of the results and reducing possible bias.

Further research should be conducted comparing hyperactive AN girls and female athletes, to better study differences in global physical state and endocrinological asset; it could be useful improve this analysis by evaluating also nutritionals aspects by dual-energy X-ray absorptiometry (DEXA) or bioelectrical impedance analysis (BIA) to improve knowledge of physio-pathological underlying mechanisms and to give more clinical information about possible intercurrent medical risks. Other interesting perspectives for future research include longitudinal studies, to evaluate HPA during the course of the illness, and an enlargement of the sample that could also allow to study HPA in different AN subtypes.

In conclusion, our research confirmed our hypothesis that high levels of physical activity in acute AN are frequently associated with worst clinical conditions at admission, especially in terms of endocrinological and medical features. We believe that our study could help the physician, not only the psychiatrist, in providing patients with a tailored, rapid and necessary multidisciplinary approach. Our results suggest that a systematic investigation of PA should be performed upon admission in all the female adolescents with AN, irrespectively of BMI or disease duration. Indeed, HPA can be regarded as a red flag and should lead to more in-depth biochemical and clinical assessment of endocrinological features. In practice, as HPA suggests a more severe impairment of the endocrine system, it could be considered as a marker for prompting the start of a hormone replacement therapy in case of amenorrhoea and hypoestrogenism.

What is already known on this subject?

Underlying mechanisms of overexercise in AN patients are still unknown. Previous research on small samples focused on associations between physical activity and BMI or vital sign abnormalities.

What your study adds?

Our study show how high levels of physical activity in acute female adolescents with Anorexia Nervosa frequently associate with worst clinical, endocrinological and psychological/psychiatric outcome at admission. An investigation of these aspect in these population should be considered routinely by all the physicians.

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Compliance with ethical standards

Conflict of Interest Nothing to declare for all the authors.

Ethical approval The present research has been approved by Ethics Committee of ASST Monza and it conforms to the provisions of the Declaration of Helsinki.

Informed consent Written informed consent was obtained from all individual participants in the present study.

Consent for publication All the authors approved the manuscript content. This manuscript is not under consideration for publication elsewhere and none of the data presented have ever been published elsewhere.

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