The relationship between BMI, eating habits and executive functioning in female adolescents with Anorexia Nervosa

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The relationship between BMI, eating habits and executive functioning in female adolescents with Anorexia Nervosa

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Abstract

Background: Previous studies found that patients with anorexia nervosa (AN) perform worse on executive functioning (EF) compared to healthy controls (HC's). EF plays an important role in the regulation of behaviour in daily life. EF impairment can therefore lead to problems with functioning in daily life.

Aims: The aim of this study was to investigate whether there is a difference between AN patients and HC's in EF. In addition, it was investigated whether there is a correlation between EF, eating habits and BMI-SDS. The final aim of this study was to investigate whether EF improves in patients with AN after a one-year follow-up. In each case, the total EF scores and the scores on the 12 subscales of EF were examined.

Methods: The study population consisted of 126 girls aged 12-22 years (M= 18.42; SD=2.35), 57 girls belonged to the AN group and 69 to the HC group (M age AN=17.98; M age HC= 18.84). The participants completed the Behaviour Rating Inventory of Executive Function (BRIEF), the Eating Disorder Examination (EDE) and the Body Mass Index (BMI) was calculated for the baseline measurements and for the follow-up one year later. Several independent-samples t-tests, linear regression analyses and a linear mixed model analysis were performed as analyses for the results.

Results: No differences were found between the AN group and the HC's with regard to total score of EF, but the AN group did show significantly lower flexibility (p< .001), emotion regulation (p< .001) and taking initiative (p= .001) compared to the HC. However, the AN group did report significantly more orderliness and neatness (p< .001) than the HC. BMI-SDS and eating habits were not associated with the total score of EF, even after adjusting for the confounders depression and age of onset. The subscales taking initiative (p= .029, inhibition (p= .006) and working memory (p= .010) turned out to be negatively associated with BMI-SDS and eating habits. Finally, there appeared to be no significant change in the total score of EF between the baseline measurement and the follow-up after one year for patients with AN. No significant change was found for the subscales either.

Conclusion: AN patients showed impairment on certain subscales of EF, but the overall EF score was not different from the HC's. The impairment found in subscales of EF did not change from baseline measurement after one year of follow-up. However, the participants in this study were all diagnosed with AN less than a year ago. Further research with a longer follow-up time is needed to find out whether this conclusion is the same for patients with chronic AN or patients who have recovered.

Layman's abstract

Anorexia Nervosa (AN) is een eetstoornis met het hoogste aantal sterfgevallen van alle psychiatrische stoornissen. Uit onderzoek blijkt dat patiënten met AN problemen ervaren met het executief functioneren (EF). EF verwijst naar het uitvoeren van taken en alles wat daarbij komt kijken, zoals plannen en inhibitie. EF zijn vereist bij alle dagelijkse activiteiten. Schade aan EF kan daarom het dagelijks leven beïnvloeden. Het doel van deze studie was om het verschil in EF tussen jongeren met AN en een gezonde controlegroep (HC) te onderzoeken. Daarnaast is er onderzoek gedaan naar het verband tussen EF, eetgewoonten en de body mass index (BMI). Tot slot is er onderzocht of EF bij patiënten met AN verbetert na een follow-up van een jaar. De onderzoekspopulatie bestond uit 126 vrouwelijke adolescenten tussen de 12-22 jaar oud, waarvan 57 AN en 69 HC. Alle deelneemsters hebben twee vragenlijsten ingevuld, één over hun dagelijkse eetgedrag (EDE) en één over EF (BRIEF). Om te onderzoeken of EF verbeterde bij patiënten met AN, werden deze vragenlijsten een jaar later opnieuw ingevuld. Uit de resultaten bleek er geen verschil te zijn in EF tussen de AN-patiënten en de HC's op het eerste meetmoment. Er werden echter wel verschillen gevonden voor afzonderlijke delen van EF, namelijk voor flexibiliteit, emotie regulatie, ordelijkheid en netheid, initiatief nemen, werkgeheugen, inhibitie. Ten slotte bleek dat het EF een jaar later niet verbeterd was bij de patiënten met AN. Alle AN-patiënten die deelnamen aan deze studie werden minder dan een jaar geleden gediagnosticeerd, waardoor de ernst van de symptomen nog licht kunnen zijn. Toekomstig onderzoek zou zich kunnen richten op de vraag of er een verschil in EF is tussen patiënten met een diagnose van een jaar geleden of korter, patiënten die lijden aan chronische AN en adolescenten die zijn hersteld van AN door middel van een langere follow-up tijd te gebruiken.

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Introduction

Today obesity is a very common phenomenon. However, dieting in extreme forms, resulting in anorexia or bulimia is also increasing, in particular in female adolescents (Faje et al., 2014). Although anorexia nervosa (AN) has a long history, the disease has changed a lot over the years. In the ancient times, self-starvation was a form of holiness, while self-starvation is now a means of fulfilling the beauty ideals of thinness (Bemporad, 1996). In addition, it has been shown that the media nowadays has gained more influence on the body image of women. In some cases, the media is even held responsible for creating or perpetuating this disease (Griffin & Berry, 2003). Through all the media, the age-old disease AN is perhaps more well-known nowadays under female adolescents than it was before.

AN is a psychiatric disorder with the highest mortality of all psychiatric disorders (Papadopoulos, Ekbom, Brandt & Ekselius, 2009). The incidence of AN is around 8 per 100.000 persons per year, this means that approximately 1,300 people are diagnosed with AN in the Netherlands every year (Hoek, 2006). Characteristics of AN are low body weight, disturbed body image, intense fear of gaining weight and weight loss behaviours. According to the DSM-5, a person is diagnosed with AN when the following criteria are met: A. Energy intake is restricted concerning energy requirement, resulting in significant underweight for age, sex, growth curve and physical health. B. There is an intense fear of gaining weight or getting fat, or persistent behaviour that prevents weight gain, even if the subject is significantly underweight. C. A disturbance in the individual's way of perceiving his or her body weight or shape, a disproportionate influence of body weight or body shape on self-judgment, or persistence in not recognizing the severity of the current low body weight (American Psychiatric Association, 2013). The severity of the disorder can best be determined by the current Body Mass Index (BMI). The DSM-5 distinguishes two subtypes in the diagnosis of AN. First, the restrictive type, when weight loss is mainly achieved through dieting and / or excessive exercise. Second, the binge-eating/purging type, where the individual experiences recurrent episodes of binge eating or purging behaviour during the last three months, through vomiting, or the misuse of laxatives, diuretics, or enemas (American Psychiatric Association, 2013).

The prognosis of AN can be considered as poor. Mortality rates are high, about 5% of patients with AN die from direct or indirect consequences of AN. In addition, less than half (46%) of patients with AN fully recover. One third of the patients partially recover and 20% will remain chronically ill (Steinhausen, 2002). In addition to the poor prognosis of AN, many patients have comorbid disorders such as anxiety disorders, affective disorders, depression,

obsessive-compulsive disorders, and substance misuse. There is evidence that these comorbidities contribute to a worse outcome of AN (Steinhausen, 2002). As mentioned earlier, the fatal outcome of AN is not always a direct result of the eating disorder. In 27% of cases, patients commit suicide as a result of a comorbid depression (Hoek, 2006). Another influential factor in the course of AN is the age of onset. Several studies show that an earlier age of onset is associated with a lower mortality rate compared to the onset of AN at a later age (Steinhausen, 2002; Wentz, 2009). Currently, there is still a lot of uncertainty about the etiology of the disease, making it difficult to predict the differential course.

In eating disorders, like AN, disturbed behaviour in the form of lack or excess of inhibition is frequently noticed (Spinella & Lyke, 2004). Functional neuroimaging studies show that the activity in prefrontal-subcortical systems is impaired in patients with an eating disorder compared to healthy controls (HC's). Eating behaviour is often disturbed by illnesses and injuries affecting the prefrontal-subcortical systems (Spinella & Lyke, 2004). The executive functions (EFs) play an important role in regulating behaviour, also in eating behaviour. Prefrontal-subcortical systems are structures critical to mediating EFs (Spinella & Lyke, 2004).

According to recent literature EFs refer to high-level cognitive processes that, by operating on lower-level mental processes, flexibly regulate and control our thoughts and goal-directed behaviour (Ambrosini, Arbula, Rossato, Pacella & Vallesi, 2019). According to Huizinga and Smidts (2012) EFs can be divided into different subscales: inhibition, flexibility, emotion regulation, working memory, planning and organizing, orderliness and neatness, orderliness, behavioural evaluation, self-evaluation, finishing tasks, task evaluation and finally taking initiative.

EFs are required in all daily activities. EF problems can therefore affect your daily life. Of the EFs, 2 subscales are specifically associated with impairment in adolescents with AN. These are a weak central coherence, which means that more attention is paid to the small details instead of the bigger picture. Also, set-shifting difficulties, or cognitive inflexibility were impaired, which means patients have difficulty to switch efficiently between different tasks (Allen et al., 2013). Several studies have investigated the association between EFs and AN, which showed that patients with AN performed worse on EF, measured with several neuropsychological tests compared to HC's (Tchanturia et al., 2004). This can be explained by impaired activity in prefrontal-subcortical systems, which is necessary for regulating food behaviour (Spinella & Lyke, 2004). Previous research showed that these deficits in EF in patients with AN seem to be independent of the current BMI, current symptoms of the eating

disorder, or the length of the eating disorder. This indicates that problems with EF remain even after weight recovery in AN (Gillberg et al., 2010).

In contrast, other studies such as the study by Scharnel & Stengel (2019) showed that the loss of the volume of white and grey matter in the brain, which occurs with AN, is reversible. The grey matter loss appears to be correlated with cognitive deficits such as cognitive flexibility, but also with memory and the ability to learn, which are aspects of EF (Seitz, Herpertz-Dahlmann & Konrad, 2016). This implicates that EF would improve if the volume of the grey matter is restored to normal levels. Hatch et al. (2010) also showed that EFs are impaired in adolescents with AN. However, they found reversibility of this damage. Due to weight recovery, these adolescents with AN not only improved in terms of EF, but also outperformed the matched HC's. In conclusion, results on the reversibility of the impairment of EFs are contradictory in the current literature.

In this research the study population consists of female patients with the diagnosis of AN between 12 and 22 years old and female HC's in the same age group. The aim of this study is to compare EFs among both of these groups. In addition, this study aims to measure the relationship between on the one hand EFs, measured on the basis of a self-report, and on the other hand BMI and eating habits in the AN group. A year later, the measurements are administered again in the same participants, in order to examine whether EFs will improve after one year follow-up. Firstly, the overall EF scores are looked at for each aim. This is followed by an interpretation of the different subscales of EF to provide a complete overview of the problems AN patients experience with EF.

The data in this study will be corrected for the confounders depression and age at onset. Research shows that many AN patients suffer from a comorbid depressive disorder. Deficits in EF can also be caused by the symptoms of this depressive disorder (Jáuregui-Lobera, 2014). In addition to the comorbid depression disorder, the age at which AN starts can also influence EF. Although an early age of onset provides a better prognosis, an early age of onset seems to be associated with a reduction in white and grey matter volume in the brain for both adults and adolescents. In adolescents with AN, it is unclear how the age of onset of AN affects the severity of EF damage. This is in contrast to adults where full recovery of these reduction seems possible (Seitz, Herpertz-Dahlmann & Konrad, 2016). Both depression and age at onset could affect the impairment of EF, therefore an adjustment is made for both variables.

As a previous study found EF deficits in patients with AN (Tchanturia et al., 2004), it is expected that the patients with AN will show worse self-reported EF than the HC's. It is

hypothesized that lower BMI and poorer eating habits will be related to worse self-reported EF (Hirst et al., 2017). In addition, it is expected that weight recovery does not lead to improved EF (Gillberg, 2010). The AN group is therefore expected to show no difference in the results of the self-reported EF after one year as compared to baseline, although weight recovery may have occurred through treatment. An alternative hypothesis could be based on the results of Scharnel & Stengel (2019) and Hatch et al. (2010) with regard to the recovery of the grey and white matter in the brain in patients with weight recovery. In that case, EF will be improved at the follow-up measurement compared to the baseline measurement.

AN is called a welfare disease and has become an increasingly well-known phenomenon in recent years. AN has been shown to be a psychiatric disorder with the highest mortality and many comorbidities. This study provides more information about the relationship between AN and EF in order to improve treatments for AN wherefore adolescents receive the appropriate help they need.

Methods

Design

This study will use a longitudinal case-control repeated measures design, with measurements at baseline (T1) and after one year (T2). The independent variables are BMI and eating habits. The dependent variable is EF. This project is part of the BRAVE study conducted at Erasmus Medical Centre (Erasmus MC) – Sophia children's hospital. The aim of the BRAVE study is to examine brain functions and attention processes in 90 female adolescents with AN and compare these with 90 HC's, with the purpose to identify predictors of one-year treatment response after initial diagnosis. It investigates whether the brain functions and attention processes of young people with AN are different from those of healthy young people. In addition, it is investigated whether the brain functions and attention processes of young patients with AN have changed after one year of treatment. For the current study, baseline and follow-up measurements of self-reported EF , BMI and eating habits will be used.

Ethics

This study is conducted in accordance with the Helsinki Convention and the Medical Scientific Research with humans (World Medical Association, 2013). Ethical approval from the committee for medical ethics (METC) has been obtained for this study on 9 December 2016, protocol number: 1530611.

Participants

The study included 57 AN patients and 69 HC's, who were recruited via different means. Patients with AN were mostly referred to the study via their health care provider in the Erasmus MC-Sophia and HC's were mostly recruited via social media. Besides, we collaborate with 12 outlying institutions in the neighbourhood of Rotterdam. All participants were from the Netherlands. To ensure eligibility, participants underwent a screening procedure, which consisted of several questionnaires. The following inclusion criteria applied to the AN group: The girls are between 12 and 22 years old, meet the DSM 5 criteria for AN, first-onset AN and the diagnosis should be less than a year ago. The HC's consisted of girls aged between 12 and 22 years old, with a normal BMI (BMI value corrected with the mean standard deviation score (SDS)> -2 SD and BMI-SDS <+2 SD). Exclusion criteria were for both

groups: Schizophrenia or other psychotic disorders, claustrophobia, severe visual or motor impairment, inability to independently complete questionnaires, IQ <70, poor command of the Dutch language.

Measures

BRIEF

EFs are operationalized by the Behaviour Rating Inventory of Executive Function (BRIEF). The BRIEF consists of a parent version for children aged 5 to 17 years. This is a 75-item questionnaire about various behaviours related to EF. In addition, the BRIEF consists of a self-report of 68 items for children aged 11 to 17 years. By the age of 18 years and older the BRIEF-A is used, and parents fill in the BRIEF-A informant report. The BRIEF can be used in diagnosing EF deficits in children with a variety of psychological, psychiatric, and medical conditions. The BRIEF consists of twelve clinical scales: inhibition, flexibility, emotion regulation, working memory, planning and organizing, orderliness and neatness, orderliness, behavioural evaluation, self-evaluation, finishing tasks, task evaluation and taking initiative. The scores are summarized in two general indexes and a total score. The two validity scales (negativity and inconsistency) provide insight into the way in which the questionnaire was completed. The items are statements about the behaviour of young people over the past six months. The items are rated on a three- point Likert-type scale (Huizinga & Smidts, 2012). A high raw score on this questionnaire is an indicator of EF problems. The BRIEF is found to show a high internal consistency (α = .96). The convergent validity shows a high positive relationship between the self-report and informant-report versions. The BRIEF is a reliable and valid tool for measuring EF (Ciszewski et al., 2014).

EDE

Eating habits are operationalized by the Eating Disorder Examination (EDE). The EDE is conducted in the form of an interview with a participant performed by an employee of the BRAVE team. The Dutch version was used for this research (Jansen, 2002). The EDE consists of 35 items concerning eating disorder behaviours and attitudes during the previous 4 weeks. The items are scored on a seven-point Likert-type scale. The following four subscales are measured in the EDE: dieting, eating concern, concerns about body shape, and weight concern (Fairburn, Cooper & O'Connor, 1993). Higher scores indicate problematic eating behaviour. The internal consistency of the global score is 0.92 (De Vos, Radstaak, Bohlmeijer and Westerhof, 2018).

BMI-SDS

The BMI of the participants was measured with the formula weight/height^2. The BMI was then adjusted for age and gender using the TNO online growth calculator, whereby the BMI-SDS is calculated (TNO, n.d.).

Procedure

After informing participants via patient information letters and verbal explanation, written informed consent was acquired from all subjects. First, the consent forms were checked during the consent meeting. These needed to be signed by the adolescent and, if the participant was younger than 16 years, by both parents. After the consent forms were checked, the inclusion and exclusion criteria were checked by using the DSM-V checklist criteria for AN. Height and weight were surveyed for HC's to check if they have a healthy BMI. Finally, The Mini International Neuropsychiatric Interview (MINI-KID/PLUS) was administered to check whether someone was suffering from a psychotic disorder. If the inclusion and exclusion criteria were met, the Eating Disorder Examination (EDE), the Readiness and Motivation Questionnaire (RMQ), and (Children's) Yale–Brown Obsessive Compulsive Scales (CY-BOCS/Y-BOCS) were administered in both groups to gather data about the eating disorder and comorbid psychiatric disorders. During the consent meeting also two other appointments were made for administration of cognitive tasks, biological measurements and functional and structural MRI scans of the brain.

Participants who were included received an invitation via mail to fill out nine online questionnaires, including the BRIEF questionnaire. Participants filled in the questionnaires at any convenient moment, before their last appointment of the baseline measurement.

Besides the completion of questionnaires digitally, the baseline measurement included: neurophysiological assessments, anthropometrics, MRI and an eye-tracking task, which were measured during two different appointments at Erasmus MC.

During the first appointment at Erasmus MC, the neurophysiological assessments were administered. All adolescents performed the Rey Complex Figure Test (RCFT), the Wechsler Abbreviated Scale of Intelligence-II (WASI-II) and the Motor Free Visual Perception test (MVPT) to obtain a profile of verbal and non-verbal cognitive functioning. After the administration of these tests, the participants performed tests on a computer to obtain data about visual spatial abilities, memory, inhibition, set-shifting abilities and decision making. At the end of the appointment, blood samples were taken by a venapuncture, if the participant agreed. In addition, materials for a stool sample were given.

During the second appointment, anthropometrics, MRI and an eye-tracking tasks were performed. First, all adolescents completed the hunger scale questionnaire, contra-indication MRI-scanning for adolescents and course of health care questionnaire. Parents completed the questionnaire 'contra indications MRI-scanning for parents' if the participant was under the age of 16. Next, a small tuft of hair was cut to estimate the participants' previous stress levels and anthropometry was measured by the BODPOD®, arm circumference, height and muscle strength measurement (measured by the JAMAR Plus®). This was followed by the MRI scan, which was used to measure brain structures and activity. Finally, the eye tracking tasks were performed. The participant performed a dot probe task, while eyetracking was applied. Furthermore, participants performed tasks that measure executive functioning.

A year later, T2 took place, where the same questionnaires were administered, and measurements were performed. Between T1 and T2 there was no extra burden for the participants. Patients with AN received treatment as usual and controls did not receive any form of intervention.

Statistical analyses

To investigate whether there is a difference between the AN group and the control group regarding to EF, an independent-samples t-test was performed. The independent variable was a dummy variable group (AN or HC) and the dependent variable was EF. Independent-samples t-tests were also performed for the 12 subscales of EF. Due to the amount of tests, a Bonferroni correction has been used, the p-value for the independent-samples t-tests therefore was .05/12=.004.

The second analysis concerned a linear regression analysis to examine the relationship between BMI and eating habits on the one hand and EF on the other hand in the AN group. In this analysis BMI and eating habits were the independent variables, the dependent variable was EF. Data was corrected for the confounders depression and age at onset. These variables were added in a second block to the regression. A significance level of $p<0.05$ was used. The subscales of EF were examined on an exploratory basis by means of separate linear regression analyses. Also in these analyses, the confounders were added in a second block to the regression. Because the analyzes were performed on an exploratory basis, significance level of $p<.05$ was used.

Finally, a linear mixed model analysis was performed to compare self-reported EF at T1 and T2 within the AN group, relative to changes in BMI and eating habits from T1 to T2. The fixed effects were BMI and eating habits, the dependent variable was EF, the factor

variable was time. The interaction between BMI and time and eating habits and time was also included in the analysis. Separate linear mixed model analyses were performed for the subscales of EF on exploratory basis. The p-value used for these analyses was $p<.05$. The computer program IBM SPSS Statistics version 26 was used for the statistical analyses.

Results

Data of 126 participants, all females between 12 and 22 years old, was analyzed. 57 participants belong to the AN group and 69 to the HC group. Of the 126 participants, 60 participants have already participated in the second measurement. 95 participants completed the EDE and 112 the BRIEF at T1. For T2, there were 37 participants who completed the EDE and 54 the BRIEF. The other participants were not interested in participating in the follow-up or were not yet able to participate because the baseline measurement had taken place less than a year ago, so they were coded as missing. For the linear mixed model analysis, only those participants who have completed both T1 and T2 and have AN were included (N=31). An overview has been obtained for the baseline characteristics of the study population, these data are shown in *table 1*.

Table 1

Baseline characteristics of the study population

	AN (N=57)	HC (N=69)	Total (N=126)
Age	17.98 ± 2.31	18.84 ± 2.33	18.42 ± 2.35
BMI-SDS	-1.31 ± 1.20	.48 ± .99	-.40 ± 1.41
EDE total	3.42 ± 1.29	.30 ± .46	1.67 ± 1.80
BRIEF total (t-scores)	45.46 ± 10.28	43.59 ± 8.22	44.45 ± 9.24
Subscales of EF			
Inhibition	42.59 ± 9.62	44.86 ± 8.65	43.80 ± 9.16
Flexibility	54.89 ± 12.50	44.87 ± 8.75	49.54 ± 11.75
Behavioral evaluation	44.66 ± 8.54	45.11 ± 7.14	44.88 ± 7.87
Self-evaluation	47.69 ± 12.61	43.81 ± 6.01	45.10 ± 8.83
Emotion regulation	52.32 ± 9.85	46.23 ± 9.90	49.07 ± 10.30
Working memory	48.17 ± 12.48	46.36 ± 9.12	47.21 ± 10.81
Orderliness and neatness	39.88 ± 6.72	48.09 ± 7.68	43.81 ± 8.26
Orderliness	47.88 ± 11.03	47.91 ± 10.65	47.90 ± 10.66
Finishing tasks	43.53 ± 9.47	43.30 ± 9.07	43.42 ± 9.24
Task evaluation	51.81 ± 10.92	46.22 ± 7.96	48.08 ± 9.32
Taking initiative	56.44 ± 11.07	47.00 ± 7.78	50.15 ± 9.96
Planning and organizing	43.04 ± 9.34	45.00 ± 7.79	44.09 ± 8.57

** Values are expressed as mean ± Standard Deviation. AN = Anorexia Nervosa. HC = Healthy Control. BMI-SDS = Standardized Body Mass Index. EDE = Eating Disorder Examination. BRIEF= Behaviour Rating Inventory of Executive Function. EF = Executive Functioning*

To gain an overview of the difference in EF, *Figure 1* shows a distribution of the mean t-scores per group.

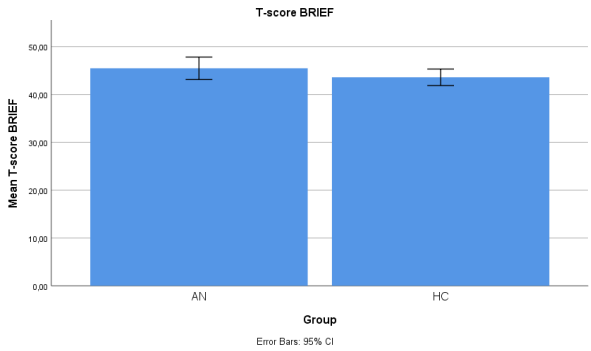

Figure 1. Distribution of the mean t-scores of the BRIEF for the HC - and AN group

Hypothesis 1:

For the first hypothesis, an independent-samples t-test was performed to investigate whether there is a difference between the HC's and the AN group regard to EF.

Assumptions

The dependent variable is interval ratio. The residues are normally distributed and the scores are independent. There does not appear to be any heteroscedasticity and the variance of the dependent variable is homogeneous.

The results in *table 2* show no significant effect for group, meaning that the AN and HC group did not differ in EF (t(164)= -1.30, *p*= .19).

Subscales of EF

Independent-samples t-tests were performed for the subscales of EF. Due to the low power, a Bonferroni correction has been applied, *p*= .05/12= .004. The variable group had a significant effect on the subscales flexibility (t= -5.95, *p*< .001), emotion regulation (t= -3.90, *p*< .001), orderliness and neatness (t= 6.06, *p*< .001) and taking initiative (t= -3.43, *p*= .001). This means that the AN group performed significantly worse than the HC group on these subscales. Except for the orderliness and neatness subscale, the AN group scored significantly better than the HC's. For other subscales no significant effects were found. An overview of these results can be found in the appendix in *table 6*.

Table 2

Independent samples t-test analysis for EF total score

Variable	t	df	95% CI	p
BRIEF total (t-scores)	-1.30	164	[-4.71, .96]	.19

*Note. *p <.05. **p<.01 ***p<.001. df= degrees of freedom. CI= Confidence interval. BRIEF= Behaviour Rating Inventory of Executive Function.*

Hypothesis 2:

For the second hypothesis, a linear regression analysis was performed to examine the relationship between BMI and eating habits on the one hand and EF on the other hand. The analysis, was corrected for the variables age of onset and depression by adding these variables in the second block.

Assumptions

The independent variables are continuous or have only two categories. The dependent variable is continuous and unlimited. The sample was obtained randomly. The residues are normally distributed and uncorrelated, Durbin-Watson Test = 1,816. There does not appear to be any heteroscedasticity.

The results in *table 3* show no significant effects of the variables. The model explained 9.7% of the variance, F (2, 24) = 1.28, *p*=.30. When adding age of onset and depression in the second block, the explained variance of the model changed to 15.6%, but the model was still non-significant, F (4,22) = 1.02, *p*=.42.

Subscales of EF

Separate linear regression analyses were performed for the EF subscales on exploratory basis. Eating habits had a significant effect on the subscale taking initiative, F(2,4)= 9.98, *p= .028, R^2= .83;* B= 9.37, *p*= .029. More problematic eating behaviour was associated with worse performance on this EF subscale. The second model, adding the variables depression and age of onset did not significantly add to taking initiative ΔR2= .03, *p*=.85. The confounder age of onset had in the second block a significant effect on inhibition, F(4,22)= 3.34, ΔR2= *.37, p= .028, (*B= 1.75, *p*= .006) and working memory, F(4,22)= 3.43,

ΔR2= .23, *p= .025, (*B=2.37, *p*= .010). In both cases the R square changed was significant, so model 2 adds significantly more. A higher age of onset results in poorer inhibition and working memory. For the other subscales the models were not significant. An overview of these results can be found in the appendix in *table 7 to 18*.

Table 3

Linear regression analysis for EF total score, with confounders depression and age of onset

Model	Variable	B	SE	95% CI
1	(Constant)	36.18***	6.44	[22.89, 49.47]
	BMI_SDS	.16	1.23	[-2.38, 2.70]
	Eating Habits (EDE)	2.37	1.53	[-.79, 5.52]
	R^2	.10		
	F	1.28		
2	(Constant)	25.47	11.08	[22.89, 49.47]
	BMI-SDS	.27	1.25	[-2.38, 2.70]
	Eating Habits (EDE)	1.46	1.75	[-2.16, 5.08]
	Depression	.23	2.22	[-4.38, 4.84]
	Age of onset	.89	.71	[-.59, 2.36]
	R^2	.16		
	F	1.02		

*Note. *p <.05. **p<.01 ***p<.001. B=unstandardized regression coefficient. SE=standard error of the coefficient. CI= Confidence interval. BMI-SDS = Standardized Body Mass Index. EDE = Eating Disorder Examination. R^2= coefficient of determination.*

Hypothesis 3:

A linear mixed model analysis was performed to compare EF at T1 and T2 within the AN group, relative to changes in BMI and eating habits from T1 to T2. The dependent variable is EF, the fixed effects are BMI and eating habits and the factor variable is time. As interaction variables, BMI-SDS*time and eating habits*time were included in the analysis.

Assumptions

The residuals are normally distributed and there is linearity between the dependent and independent variables. The observations are independent and there is homoscedasticity of the residuals.

Table 4 shows the mean scores and standard deviations of the AN patients from T1 and T2 for BMI-SDS, eating habits and EF. The EF total score did not differ significantly between the T1 and T2 measurements, which is shown in *table 5*. No significant results were found within the subdomains of EF either, therefore the results are not included in the appendix.

Table 4

Development of BMI-SDS, eating habits and EF over time

	T1	T2
BMI-SDS	-1.18 ± 1.25	-1.69 ± .98
EDE total	3.81 ± 1.08	2.43 ± 1.28
BRIEF total (t-scores)	46.52 ± 10.36	43.42 ± 10.00

** Values are expressed as mean ± Standard Deviation. T1= first measurement. T2= second measurement, follow-up one year later. BMI-SDS = Standardized Body Mass Index. EDE = Eating Disorder Examination. BRIEF = Behaviour Rating Inventory of Executive Function.*

Table 5

Mixed Model Analysis, comparison EF total score between baseline and follow-up in patients with Anorexia Nervosa

Variable	estimate	SE	95% CI
Intercept	36.92***	6.93	[22.68, 51.16]
BMI-SDS	-1.44	2.99	[-7.58, 4.70]
Eating Habits (EDE)	1.03	2.45	[-4.02, 6.07]
BMI-SDS*Time	.76	3.25	[-3.16, 4.68]
Eating habits*Time	1.12	1.91	[-5.57, 7.80]

*Note. *p <.05. **p<.01 ***p<.001. SE=standard error of the coefficient. CI= Confidence interval. BMI-SDS = Standardized Body Mass Index. EDE= Eating Disorder Examination.*

Discussion

Previous research has found EF impairment in patients with AN and conflicting results on the irreversibility of this impairment (Gillberg et al., 2010; Hatch et al. 2010). The aim of this study was to investigate whether there is a difference between AN patients and HC's in EF. In addition, it was investigated whether there is a correlation between EF, eating habits and BMI-SDS. Finally, it was examined whether EF improves in patients with AN after one year, a year during which treatment as usual was provided.

Differences in EF between patients with AN and HC's

This study examined differences in EF in 57 female adolescents with recently diagnosed AN and 69 HC's from 12 to 22 years old. It was hypothesized that the AN group would perform worse than the HC's on self-reported EF. The results showed no differences in the overall score for self-reported EF between patients with AN and HCs. This is notable because it does not correspond with results from previous research (Tchanturia et al., 2004). Further investigation into the separate subscales of EF did show significantly lower flexibility, emotion regulation and taking initiative in the AN group as compared to the HC. However, the AN group did report significantly more orderliness and neatness than the HC. Although evidence has been found in previous studies for poorer functioning in EF for patients with AN (Spinella & Lyke, 2004), this study only found evidence for some subscales of EF. The subscales of EF that functioned differently in patients with AN compared to HC's were consistent with previous research (Tchanturia et al., 2004). The better functioning on the subscale orderliness and neatness of the AN group has been explained in previous studies by considering an eating disorder as a modern obsessive-compulsive syndrome (Rothenberg, 1986). There are some similarities between obsessive-compulsive disorder and AN, such as cleanliness, orderliness, and perfectionism (Rothenberg, 1986). This is a possible explanation for why the AN group is more orderly and neat than the HC.

Association between BMI-SDS, eating habits and EF

It was hypothesized that lower mean BMI-SDS scores and poorer eating habits would be related to worse self-reported EF. The results showed that BMI-SDS and eating habits were not associated with the overall EF score, even after adjusting for the confounders depression and age of onset. Interestingly, on the separate EF subscales eating habits and age of onset were significantly associated with EF. We observed that more problematic eating behaviour is

associated with poorer performance on the subscale taking initiative. Age of onset was significantly associated with the subscales inhibition and working memory. The older the age of the diagnosis of AN, the more impact this had on the poorer functioning of inhibition and working memory. Earlier research had shown that AN patients have an impaired response inhibition and deficits in working memory (Collantoni et al., 2016; Kemps, Tiggemann, Wade, Ben-Tovim & Breyer, 2006). However, the effect of age of onset has never been studied for these subscales before.

Because the severity of AN is determined by BMI, BMI was included in the analysis to see if it had an effect on EF. It was expected that a lower BMI would be associated with worse self-reported EF. However, in line with a previous study, BMI was found to have no influence on EF (Guillaume et al., 2015). In our study, there was also no influence of BMI on the subscales of EF. BMI negatively was associated with another important criterion for the diagnosis of AN, the low energy intake resulting in underweight. This low energy intake is reflected in a patient's eating habits, hence the expectation was that higher scores on the EDE would be associated with worse EF (Dahlgren, Lask, Landrø & Rø, 2014). Although this effect did not follow from the results, the subscale taking initiative was found to be impaired by high scores on the EDE.

Regarding the influence of age of onset, previous research has hypothesized that an earlier age of onset could mitigate problems in EF (Hirst et al., 2017). In our study we found a positive correlation between age of onset and the subscales inhibition and working memory, which means that a higher age of onset was indeed related to lower EF. Studies focusing on the development of working memory and inhibition indicated a gradual development during childhood, and this development continued into adolescence (Huizinga, 2007). With an earlier recovery at a young age, this development of the EF subdomains could continue.

The comorbidity of depression even turned out to have no effect at all. Although the comorbidity between AN and depression is high, depression does not affect EF in our study.

Changes in EF after one year follow-up within the AN group

It was expected that weight recovery would not lead to improved EF, meaning that despite one year of treatment, the AN group will show no difference self-reported EF at the measurement after one year as compared to baseline. We found no significant change in the total score of EF between the baseline measurement and the follow-up after one year for patients with AN. Thus, EF does not change after one year despite standard treatment for AN focused on weight recovery. This result is consistent with previous

research showing that deficits in EF in patients with AN after 18 years of follow-up were found to be independent of current BMI, current eating disorder symptoms, or eating disorder duration (Gillberg et al., 2010). Thus, the results of our one year follow-up study might be in line with the findings of the 18-year follow-up study by Gillberg et al (2010). Future research could determine whether a longer follow-up time confirms this.

Strengths and limitations

Our study has a number of strengths that make the results reliable. The size of the study population is large, which means that a good reflection can be made for the entire population. Both groups were about the same size and equally divided in age. Studying the separate subscales of EF has been done infrequently, which makes this study unique. Moreover, the confounders included in the analyses make the results more accurate and prevents false associations.

A recommendation for future research is to do a longer follow-up study. The participants with AN in our study were diagnosed less than a year ago before their participation. This means that the participants' symptoms were not as severe as AN patients who are chronically ill. Future research with a longer follow-up time could examine the difference in EF between patients who recover relatively quickly and patients suffering from chronic AN. In addition to the difference in the time of diagnosis, this study only included the BRIEF as a measure of self-reported EF. To make the results of this study more reliable, objective EF tests should be used in future research. Well-known tests that are regularly used to measure EF are the Trail Making Test (TMT), Verbal Fluency Test (VFT), Clock Drawing Test (CDT), Digits Forward and Backward subtests (WAIS-R or WAIS- III), Stroop Test and Wisconsin Card Sorting Test (WCST) (Faria, Alves & Charchat-Fichman, 2015).

In conclusion, we observed that AN patients did not differ in overall self-reported EF as compared to the HC. However, significant differences were found on the subscales flexibility, emotion regulation, orderliness and neatness and taking initiative. Functioning was worse for almost all of these subscales in the AN group as compared to the HC. Only for orderliness and neatness did the AN group report significantly better than the HC's. Poor eating habits and an a relatively late age of onset were also found to have negative effects on the functioning of the subscales taking initiative, inhibition and working memory. Based on the results, the damage found in the subscales mentioned above in the participants with AN appears to be irreversible over the course of one year independent of weight recovery. More research is needed to find out whether the impairment of the EF subscales is different in

patients with chronic AN as compared with AN patients diagnosed less than a year ago and patients who have recovered, because the damage can worsen with a longer duration of the disease. In addition, it would be an addition to use objective instruments that measure EF. The results in our study are only based on the BRIEF, which is a self-reported measurement of EF. Objective tests could be used in addition to self-reported version of the BRIEF.

If the duration of the disease appears to have an effect on the severity of the EF impairment, this would be a good incentive to detect early symptoms of AN earlier to prevent further development of impaired EF. Identifying symptoms of AN earlier, in combination with appropriate treatment, will improve the speed of recovery and increase the likelihood of disease development (Ramírez-Cifuentes, Mayans & Freire, 2018).

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Appendices

Appendix A

This appendix provides an overview of the independent-samples t-tests of the subscales of EF.

Table 6

Independent-samples t-test for the variable group and the subscales of EF

Subscale	t	df	p	95% CI
Inhibition	1.58	159	.12	[-.57, 5.12]
Flexibility	-5.95	159	**.00**	[-13.35, -6.69]
Behavioral evaluation	.30	111	.76	[-2.50, 3.40]
self-evaluation	-1.45	46	.15	[-9.26, 1.51]
Emotion regulation	-3.90	159	**.00**	[-9.17, -3.01]
Working memory	-1.06	159	.29	[-5.19, 1.56]
Orderliness and neatness	6.06	111	**.00**	[5.53, 10.90]
Orderliness	.01	46	.99	[-6.61, 6.67]
Finishing tasks	-.13	110	.90	[-3.71, 3.26]
Task evaluation	-2.02	46	.049	[-11.16, -.03]
Taking initiative	-3.43	46	**.001**	[-14.97, -3.90]
Planning and organizing	1.45	159	.15	[-.71, 4.63]

Note. Significant = .004; t= t-score; df= degrees of freedom. CI= Confidence interval

Appendix B

This appendix provides an overview of the the regression analyses of the subscales of EF.

Table 7

Linear regression analysis for inhibition, with confounders depression and age of onset

Model	Variable	B	SE	95% CI
1	(Constant)	43.63***	6.35	[30.53 ,56.74]
	BMI_SDS	-.41	1.21	[-2.91, 2.10]
	Eating Habits (EDE)	-.55	1.51	[-3.66, 2.57]
	R^2	.01		
	F	.15		
2	(Constant)	26.61**	9.00	[8.00, 45.23]
	BMI-SDS	-.22	1.01	[-3.32, 1.87]
	Eating Habits (EDE)	-1.79	1.41	[-4.72, 1.15]
	Depression	-2.98	1.80	[-6.71, .76]
	Age of onset	1.75**	.58	[.56, 2.95]
	R^2	.38		
	F	3.34*		

*Note. *p <.05. **p<.01 ***p<.001. B=unstandardized regression coefficient. SE=standard error of the coefficient. CI= Confidence interval. BMI-SDS = Standardized Body Mass Index. EDE = Eating Disorder Examination.* R^2*= coefficient of determination.*

Table 8

Linear regression analysis for flexibility, with confounders depression and age of onset

Model	Variable	B	SE	95% CI
1	(Constant)	42.81***	9.11	[24.01, 61.62]
	BMI_SDS	1.39	1.74	[-2.20, 4.98]
	Eating Habits (EDE)	3.79	2.16	[-.68, 8.25]
	R^2	.15		
	F	2.16		
2	(Constant)	38.61*	15.76	[5.92, 71.29]
	BMI-SDS	1.42	1.77	[-2.26, 5.09]
	Eating Habits (EDE)	3.21	2.48	[-1.94, 8.36]
	Depression	3.61	3.16	[-2.95, 10.17]
	Age of onset	-.01	1.01	[-2.11, 2.09]
	R^2	.20		
	F	1.38		

*Note. *p <.05. **p<.01 ***p<.001. B=unstandardized regression coefficient. SE=standard error of the coefficient. CI= Confidence interval. BMI-SDS = Standardized Body Mass Index. EDE = Eating Disorder Examination.* R^2*= coefficient of determination.*

Table 9

Linear regression analysis for behavioral evaluation, with confounders depression and age of onset

Model	Variable	B	SE	95% CI
1	(Constant)	45.60***	5.23	[34.57, 56.63]
	BMI_SDS	-.49	1.03	[-2.66, 1.69]
	Eating Habits (EDE)	-1.19	1.30	[-3.93, 1.56]
	R^2	.07		
	F	.59		
2	(Constant)	54.19**	17.91	[16.02, 92.37]
	BMI-SDS	-.44	1.05	[-2.67, 1.80]
	Eating Habits (EDE)	-.64	1.58	[-4.00, 2.71]
	Depression	-1.97	1.78	[-5.75, 1.82]
	Age of onset	-.47	1.41	[-3.49, 2.54]
	R^2	.15		
	F	.65		

*Note. *p <.05. **p<.01 ***p<.001. B=unstandardized regression coefficient. SE=standard error of the coefficient. CI= Confidence interval. BMI-SDS = Standardized Body Mass Index. EDE = Eating Disorder Examination.* R^2*= coefficient of determination.*

Table 10

Linear regression analysis for self-evaluation, with confounders depression and age of onset

Model	Variable	B	SE	95% CI
1	(Constant)	-.29	30.96	[-86.25, 85.67]
	BMI_SDS	1.83	4.88	[-11.71, 15.37]
	Eating Habits (EDE)	11.43	6.73	[-7.27, 30.12]
	R^2	.49		
	F	1.89		
2	(Constant)	-13.50	158.93	[-697.32, 670,32]
	BMI-SDS	-2.29	9.50	[-43.15, 38.58]
	Eating Habits (EDE)	22.88	16.68	[-48.88, 94.63]
	Depression	-21.88	27.75	[-141,27, 97.51]
	Age of onset	-.12	8.40	[-36.25, 36.02]
	R^2	.61		
	F	.80		

*Note. *p <.05. **p<.01 ***p<.001. B=unstandardized regression coefficient. SE=standard error of the coefficient. CI= Confidence interval. BMI-SDS = Standardized Body Mass Index. EDE = Eating Disorder Examination.* R^2*= coefficient of determination.*

Table 11

Linear regression analysis for emotion regulation, with confounders depression and age of onset

Model	Variable	B	SE	95% CI
1	(Constant)	51.47***	5.57	[39.97, 62.96]
	BMI_SDS	-2.32*	1.06	[-4.52, -.12]
	Eating Habits (EDE)	-.90	1.32	[-3.63, 1.83]
	R^2	.20		
	F	2.96		
2	(Constant)	61.90***	9.48	[42.24, 81.56]
	BMI-SDS	-2.42*	1.07	[-4.63, -.21]
	Eating Habits (EDE)	.09	1.49	[-3.01, 3.19]
	Depression	-1.86	1.90	[-5.80, 2.09]
	Age of onset	-.70	.61	[-1.96, .56]
	R^2	.27		
	F	2.01		

*Note. *p <.05. **p<.01 ***p<.001. B=unstandardized regression coefficient. SE=standard error of the coefficient. CI= Confidence interval. BMI-SDS = Standardized Body Mass Index. EDE = Eating Disorder Examination.* R^2*= coefficient of determination.*

Table 12

Linear regression analysis for working memory, with confounders depression and age of onset

Model	Variable	B	SE	95% CI
1	(Constant)	32.84**	8.65	[14.99, 50.68]
	BMI_SDS	.06	1.65	[-3.35, 3.47]
	Eating Habits (EDE)	4.18	2.05	[.06, 8.42]
	R^2	.15		
	F	2.15		
2	(Constant)	2.33	13.12	[-24.88, 29.55]
	BMI-SDS	.36	1.47	[-2.70, 3.42]
	Eating Habits (EDE)	1.48	2.07	[-2.80, 5.77]
	Depression	2.22	2.63	[-3.24, 7.69]
	Age of onset	2.37*	.84	[.62, 4.12]
	R^2	.38		
	F	3.43*		

*Note. *p <.05. **p<.01 ***p<.001. B=unstandardized regression coefficient. SE=standard error of the coefficient. CI= Confidence interval. BMI-SDS = Standardized Body Mass Index. EDE = Eating Disorder Examination.* R^2*= coefficient of determination.*

Table 13

Linear regression analysis for planning and organizing, with confounders depression and age of onset

Model	Variable	B	SE	95% CI
1	(Constant)	36.29***	6.56	[22.76, 49.82]
	BMI_SDS	.-36	1.25	[-2.94, 2.23]
	Eating Habits (EDE)	1.40	1.56	[-1.81, 4.62]
	R^2	.03		
	F	.42		
2	(Constant)	21.15	10.96	[-1.58, 43.88]
	BMI-SDS	-.21	1.23	[-2.76, 2.35]
	Eating Habits (EDE)	.08	1.73	[-3.50, 3.66]
	Depression	.92	2.20	[-3.65, 5.48]
	Age of onset	1.20	.70	[-.26, 2.65]
	R^2	.15		
	F	.96		

*Note. *p <.05. **p<.01 ***p<.001. B=unstandardized regression coefficient. SE=standard error of the coefficient. CI= Confidence interval. BMI-SDS = Standardized Body Mass Index. EDE = Eating Disorder Examination.* R^2*= coefficient of determination.*

Table 14

Linear regression analysis for orderliness and neatness, with confounders depression and age of onset

Model	Variable	B	SE	95% CI
1	(Constant)	28.88***	4.98	[18.38, 39.39]
	BMI_SDS	-1.03	.98	[-3.10, 1.04]
	Eating Habits (EDE)	2.42	1.24	[-.19, 5.04]
	R^2	.21		
	F	2.26		
2	(Constant)	17.78	16.99	[-18.42, 53.99]
	BMI-SDS	-.95	1.00	[-3.07, 1.17]
	Eating Habits (EDE)	1.98	1.49	[-1.21, 5.16]
	Depression	-1.79	1.68	[-5.38, 1.81]
	Age of onset	1.12	1.34	[-1.74, 3.98]
	R^2	.29		
	F	1.51		

*Note. *p <.05. **p<.01 ***p<.001. B=unstandardized regression coefficient. SE=standard error of the coefficient. CI= Confidence interval. BMI-SDS = Standardized Body Mass Index. EDE = Eating Disorder Examination.* R^2*= coefficient of determination.*

Table 15

Linear regression analysis for orderliness, with confounders depression and age of onset

Model	Variable	B	SE	95% CI
1	(Constant)	35.73	26.99	[-39.22, 110.68]
	BMI_SDS	3.22	4.25	[-8.58, 15.03]
	Eating Habits (EDE)	2.88	5.87	[13.42, 19.18]
	R^2	.23		
	F	.58		
2	(Constant)	-106.69	117.51	[-612.30, 398.92]
	BMI-SDS	9.24	7.02	[-20.70, 39.46]
	Eating Habits (EDE)	3.62	12.33	[-49.44, 56.68]
	Depression	-1.61	20.52	[-89.89, 86.67]
	Age of onset	7.98	6.21	[-18.74, 34.70]
	R^2	.58		
	F	.69		

*Note. *p <.05. **p<.01 ***p<.001. B=unstandardized regression coefficient. SE=standard error of the coefficient. CI= Confidence interval. BMI-SDS = Standardized Body Mass Index. EDE = Eating Disorder Examination.* R^2*= coefficient of determination.*

Table 16

Linear regression analysis for finishing tasks, with confounders depression and age of onset

Model	Variable	B	SE	95% CI
1	(Constant)	44.49***	9.00	[25.51, 63.47]
	BMI_SDS	1.76	1.77	[-1.98, 5.50]
	Eating Habits (EDE)	.43	2.24	[-4.29, 5.15]
	R^2	.06		
	F	.54		
2	(Constant)	76.94*	30.20	[12.57, 141.32]
	BMI-SDS	1.61	1.77	[-2.16, 5.38]
	Eating Habits (EDE)	1.88	2.66	[-3.78, 7.55]
	Depression	2.76	3.00	[-3.62, 9.15]
	Age of onset	-2.98	2.38	[-8.06, 2.10]
	R^2	.18		
	F	.81		

*Note. *p <.05. **p<.01 ***p<.001. B=unstandardized regression coefficient. SE=standard error of the coefficient. CI= Confidence interval. BMI-SDS = Standardized Body Mass Index. EDE = Eating Disorder Examination.* R^2*= coefficient of determination.*

Table 17

Linear regression analysis for task evaluation, with confounders depression and age of onset

Model	Variable	B	SE	95% CI
1	(Constant)	2.58	15.03	[-39.16, 44.32]
	BMI_SDS	-.52	2.37	[-7.10, 6.05]
	Eating Habits (EDE)	11.12*	3.27	[2.04, 20.19]
	R^2	.76		
	F	6.17		
2	(Constant)	54.75	77.47	[-278.58, 388,07]
	BMI-SDS	-1.05	4.63	[-20.70, 18.87]
	Eating Habits (EDE)	6.77	8.13	[-28.21, 41.75]
	Depression	8.38	13.53	[-49.82, 66.57]
	Age of onset	-2.61	4.09	[-20.23, 15.00]
	R^2	.82		
	F	2.20		

*Note. *p <.05. **p<.01 ***p<.001. B=unstandardized regression coefficient. SE=standard error of the coefficient. CI= Confidence interval. BMI-SDS = Standardized Body Mass Index. EDE = Eating Disorder Examination.* R^2*= coefficient of determination.*

Table 18

Linear regression analysis for taking initiative, with confounders depression and age of onset

Model	Variable	B	SE	95% CI
1	(Constant)	21.88	12.95	[-14.09, 57.84]
	BMI_SDS	3.67	2.04	[-2.00, 9.33]
	Eating Habits (EDE)	9.37*	2.82	[1.55, 17.19]
	R^2	.83		
	F	9.98*		
2	(Constant)	49.32	70.55	[-254.22, 352.86]
	BMI-SDS	1.69	4.22	[-16.45, 19.83]
	Eating Habits (EDE)	11.23	7.40	[-20.63, 43.08]
	Depression	-3.51	13.32	[-56.50, 49.49]
	Age of onset	-1.69	3.73	[-17.73, 14.35]
	R^2	.86		
	F	3.04		

*Note. *p <.05. **p<.01 ***p<.001. B=unstandardized regression coefficient. SE=standard error of the coefficient. CI= Confidence interval. BMI-SDS = Standardized Body Mass Index. EDE = Eating Disorder Examination.* R^2*= coefficient of determination.*