ARTICLE

Evidence for a sex-specific contribution of polygenic load for anorexia nervosa to body weight and prefrontal brain structure in nonclinical individuals

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Genetic predisposition and brain structural abnormalities have been shown to be involved in the biological underpinnings of anorexia nervosa (AN). Prefrontal brain regions are suggested to contribute through behavioral inhibition mechanisms to body weight. However, it is unknown if and to which extent biological correlates for AN might be present in individuals without clinical AN symptomatology. We therefore investigated the contribution of polygenic load for AN on body weight and prefrontal brain structure in a sample of $n = 380$ nonclinical individuals. A polygenic score (PGS) reflecting the individual genetic load for the trait of anorexia nervosa was calculated. Structural MRI data were acquired and preprocessed using the cortical parcellation stream of FreeSurfer. We observed a significant PGS $\times$ sex interaction effect on body mass index (BMI), which was driven by a negative correlation between PGS and BMI in female participants. Imaging analyses revealed significant interaction effects of sex $\times$ PGS on surface area of the lateral orbitofrontal cortex (OFC), the pars orbitalis (PO), the rostral middle frontal gyrus (RMF) and the pars triangularis (PT) of the left frontal cortex. The interaction effects were driven by positive correlations between PGS and prefrontal surface areas in female participants and negative correlations in male participants. We furthermore found sex-specific associations between BMI and left RMF surface area as well as between BMI and left PO and left RMF thickness. Our findings demonstrate a sex-specific association between polygenic load for AN, BMI, and prefrontal brain structure in nonclinical individuals. Hence, this study identifies structural abnormalities associated with polygenic load for AN and BMI in brain regions deeply involved in behavioral inhibition and impulse regulation as candidate brain regions for future research.

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INTRODUCTION

Anorexia nervosa (AN) is among the mental disorders with the highest mortality rates [1–3]. With standardized mortality rates of up to 5.86% [4], and a lifetime prevalence of 1% in women and 0.5% in men AN represents a major problem for mental health care [5]. Prevalence of AN in males might be underestimated [6, 7] and clinical presentation of men with AN differs compared to their female counterpart [7, 8].

Beside psychological (e.g., traits associated with perfectionism) and developmental (e.g., adverse life events) factors, biological factors are relevant in the pathogenesis of AN [1]. More specifically, recent neuroimaging studies have provided first evidence for AN specific brain structural correlates: in AN patients increased volume of the medial orbitofrontal cortex (OFC) and the insular cortex was repeatedly demonstrated and seems to persist even after recovery [9, 10].

Structural MRI findings are furthermore supplemented by fMRI findings showing deviations in the reward-circuitry, including the insula and striatum [9, 10]. Kaye et al. [11] postulated two brain

circuits as relevant in AN: (a) a ventral (limbic) circuit associated with the identification of and reaction to significant emotional stimuli and (b) a dorsal (cognitive) circuit involved in cognitive control functions and regulation of emotions. Accordingly, there is evidence that brain areas involved in these circuits show structural abnormalities [12–16]. Prefrontal brain regions are supposed to be highly relevant in AN and alterations in prefrontal regions are suggested to predispose for the development of an AN through behavioral inhibition of food intake, which is, beside other possible regulations behaviors like excessive exercise, responsible for underweight in AN [15, 17, 18]. The finding that incidence of AN is peaking during puberty, a time when especially prefrontal brain regions are restructured furthermore adds to the relevance of prefrontal brain regions in AN [19–21].

With an estimated heritability between 48 and 74% [22], genetic factors are thought to contribute to the development of AN. Recent genome-wide association studies (GWAS) have identified several genetic variants, including neurodevelopmental genes, that are associated with AN [23]. Based on GWAS findings, others

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[24–27] and we [28–30] could recently show the benefits of applying polygenic scores (PGS) in neuroimaging studies on mental disorders and obesity suggesting that this approach could also be adopted for AN. PGS individually subsume genetic variants of small effects, identified in GWAS and therefore try to qualify cumulative effects of several genes. So far only few studies have applied PGS for AN [31–35]. In this regard, a recent publication of the “Enhancing Neuroimaging Genetics through Meta-Analysis Consortium” (ENIGMA) and the Eating Disorders Working Group of the “Psychiatric Genomics Consortium” (PGC-ED) has focused on the covariation of subcortical brain structure and genetic risk for AN [36] but failed to show significant associations. The authors of the aforementioned study suggested the following limitations of their work: lack of investigation of differential structural neuroimaging phenotypes like cortical thickness and surface, heterogeneity of the sample, and the lack of subgroup analysis. The latter notion particularly the analyses of potential sex-specific associations between genetic load, body mass index (BMI), and brain structure appears highly relevant considering that several previous studies found evidence for a sex-specific genetic contribution to BMI [37, 38] and to AN [39]. Further, there is evidence for sex-specific anthropometric and metabolic genetic determinants of body composition [40].

Therefore, with this study we aimed to investigate the contribution of polygenic load for AN to BMI and brain structure by taking into account potential limitations of previous research. In light of the aforementioned evidence from the literature, we hypothesized sex-specific contributions of polygenic load for AN on body weight and prefrontal brain structure in a middle-aged cohort of nonclinical individuals.

METHODS

Participants

This study comprised genetic and neuroimaging data from a total of 380 nonclinical adults as part of the Münster Neuroimage Cohort (MNC) acquired at the Department of Psychiatry, University of Münster (Table 1). Exclusion criteria comprise any history of neurological (e.g., concussion, stroke, tumor, and neuro-inflammatory diseases) and medical (e.g., cancer, chronic inflammatory or autoimmune diseases, heart diseases, diabetes mellitus, and infections) conditions. All participants were ensured to be free from present or history of psychiatric disorders including Anorexia nervosa according to the Diagnostic and Statistical Manual of Mental Disorders criteria [DSM-IV, [41]] using the Structured Clinical Interview [SCID, [42]].

Information on body height and weight were collected based on self-report from each participant. Psychiatric symptomatology was assessed by means of the Beck Depression Inventory [43, 44], the State-Trait Anxiety Inventory [45], and the NEO-Five-Factors-Inventory [46]. Intelligence quotient was ascertained with the multiple-choice vocabulary intelligence test [47] and BMI values were calculated as body weight in kg/(body height in m)². All participants received a financial compensation. The study was approved by the local institutional review board (IRB), and written informed consent was obtained from all participants before study participation.

sMRI methods

Image acquisition. T1-weighted high-resolution anatomical images were acquired for all participants. Details of the imaging procedures for each cohort have been extensively described elsewhere (see Supplementary Methods) [29, 48, 49].

FreeSurfer. All structural images were preprocessed using the cortical parcellation stream of FreeSurfer (Version 5.3) with default parameters (<https://surfer.nmr.mgh.harvard.edu/>). Segmentation

Table 1. Sociodemographic sample characteristics

	Mean (SD)	Min	Max
Male (n = 184)			
Age	38.28 (11.04)	21.00	59.00
BMI	25.35 (3.74)	18.17	39.55
BDI	1.76 (2.53)	0	14.00
STAI	31.15 (6.41)	20.00	53.00
Verbal IQ	116.04 (12.94)	92.00	145
Education (in years)	15.28 (2.30)	9.00	21.00
Female (n = 196)			
Age	39.78 (11.50)	18.00	59.00
BMI	23.96 (4.21)	18.31	42.21
BDI	2.24 (3.15)	0	26.00
STAI	32.24 (7.30)	20.00	58.00
Verbal IQ	115.81 (12.28)	92	145
Education (in years)	15.04 (2.5)	9.00	24.00
Total (n = 380)			
Age	39.06 (11.29)	18.00	59.00
BMI	24.63 (4.04)	18.17	42.21
BDI	2.01 (2.87)	0	26.00
STAI	31.71 (6.90)	20.00	58.00
Verbal IQ	115.81 (12.28)	92.00	145
Education (in years)	15.16 (2.32)	9.00	24.00
Means, standard deviations (SD), minimal (Min), and maximal (Max) values are presented			
BMI body mass index, BDI Beck Depression Inventory, STAI State-Trait Anxiety Inventory, trait version, IQ intelligence quotient			

quality was assessed by visual inspection and furthermore statistically evaluated for outliers following a standardized protocol provided by the ENIGMA consortium (<http://enigma.ini.usc.edu/protocols/imaging-protocols>). Since cortical surface area scales with overall head size, regional specificity of cortical surface area alterations was ascertained by including total intracranial volume (ICV) as nuisance regressor in all analyses of cortical surface area.

Genetic methods

Genotyping in all participants was performed using previously published protocols (see Supplementary Methods) [29, 48]. Quality-controlled single nucleotide polymorphisms (SNPs) were clumped for linkage disequilibrium based on GWAS association *p*-value informed clumping using $r^2 = 0.1$ within a 250-kb window to create a SNP-set in linkage equilibrium using PLINK software [50] run on Linux (`plink -clump-p1 1 -clump-p2 1 -clump-r2 0.1 -clump-kb 250`). A total of eight PGS for AN were generated and applied for this study using set of SNPs selected based on *p*-value thresholds ranging from 0.001 to 1.0 for each participant (see supplementary Table 1). The PGS were calculated as the sum of independent SNPs (genotype dosage from 0 to 2) of the reference allele in the target samples weighted by GWAS effect sizes for the reference allele obtained from AN GWAS [23]. The PGS were computed using PLINK-1.9 [50]. Standardized PGS values based on *z*-transformation were used for all analyses. To adjust for genetic heterogeneity within our samples four multi-dimensional scaling (MDS) components resulting from the genetic population stratification analyses in PLINK were used.

Statistical analyses

SPSS (IBM) version 25 was used for all statistical analyses. In order to address our hypotheses, the following analyses steps were carried out.

Polygenic score (PGS)—body mass index (BMI). First, in order to select the polygenic score that explained most variance in BMI, separate regression analyses were carried out revealing that PGS with the p -value threshold $p = 0.001$ explained most variance in BMI ($B = -0.305$, $\beta = -0.075$, $t = -1.530$, $p = 0.127$). This PGS score was used for all subsequent analyses. (Results for associations between PGS and BMI for all calculated PGS can be found in the supplementary Table S1.)

In order to explore associations between the PGS and BMI, an analysis of covariance (ANCOVA) including age and MDS components as covariates of no interest, sex, PGS as well as the PGS $\times$ sex interaction as predictors and BMI as dependent variable was carried out. To identify the direction of the observed association, bivariate correlation analyses between the PGS and BMI were carried out for each sex subgroup.

PGS—cortical surface. In line with our hypothesis, we first sought to investigate associations between PGS and prefrontal brain structure. To this end, we assessed associations between cortical surface measures of all 22 frontal cortical regions included in the FreeSurfer cortical processing stream based on the Desikan–Killiany atlas [51]. Associations were investigated by using a similar ANCOVA model as compared to analysis step (1) with sex and PGS as predictor variable and by including age and MDS components as nuisance regressors. ICV was included for analyses of cortical surface area. In line with the aforementioned analysis step main effects of PGS as well as interaction effects of PGS $\times$ sex were assessed. FDR correction for multiple comparisons using the Benjamini–Hochberg correction with a $q < 0.05$ for a total of 22 tests was carried out. In addition, to assess potential associations between PGS and surface area outside the frontal cortex, exploratory analyses of associations

with surface area across the entire cortex were carried out using similar models with all 68 cortical regions as dependent variables.

PGS—cortical thickness. The aforementioned analyses steps under (2) were repeated by including thickness instead of surface measures as dependent variables using an identical statistical model. As thickness does not scale with head size, ICV was not included as nuisance regressor in this analyses step.

Associations between BMI, PGS, and cortical brain structure. To investigate potential associations between BMI and prefrontal brain structure, similar linear models as applied in the aforementioned analyses steps (2) and (3) were conducted by including surface and thickness measures of all 22 frontal cortical regions as dependent variables including BMI as predictor and accounting for age, sex, and for analyses of surface measures for ICV. In addition, to further delineate the association between PGS, prefrontal brain structure, and BMI mediation analyses were applied.

RESULTS

Polygenic score (PGS)—body mass index (BMI)

We observed expected significant main effects of sex ($F_{(1,371)} = 14.402$, $p < 0.001$, $\eta_p^2 = 0.037$), and age ($F_{(1,371)} = 31.678$, $p < 0.001$, $\eta_p^2 = 0.079$) on BMI. A trend for a main effect of PGS ($F_{(1,371)} = 2.825$, $p = 0.094$, $\eta_p^2 = 0.008$) was qualified by a significant PGS $\times$ sex interaction effect on BMI ($F_{(1,371)} = 5.995$, $p = 0.015$, $\eta_p^2 = 0.016$) (Fig. 1).

Bivariate correlations for sex subgroups revealed only for the female subsample a significant negative association of PGS and BMI ($r_p = -0.215$, $p = 0.002$) while no significant associations were found for the male subsample ($r_p < 0.001$, $p = 0.999$).

No significant associations between PGS and further clinical or demographic variables occurred (see Supplementary results for details).

Fig. 1 Plot depicting the association between polygenic load scores (PGS) and BMI. PGS Polygenic load score, BMI Body mass index

Fig. 2 Averaged F value for all participants in cortical FreeSurfer regions projected onto the brain surface. Plot depicting the association between polygenic scores (PGS) and left rostral middle frontal gyrus surface area, PGS Polygenic score

PGS—cortical surface

We observed FDR corrected significant PGS $\times$ sex interaction effects on surface area of the left lateral orbitofrontal cortex ($F_{(1, 369)} = 9.791$, $p = 0.002$, $\eta_p^2 = 0.026$), the pars orbitalis of the left frontal cortex (PO: $F_{(1, 369)} = 10.742$, $p = 0.001$, $\eta_p^2 = 0.028$), the left rostral middle frontal gyrus (RMF: $F_{(1, 369)} = 12.000$, $p = 0.001$, $\eta_p^2 = 0.031$) (Fig. 2) and the left pars triangularis of the left frontal cortex (PT: $F_{(1, 369)} = 8.163$, $p = 0.005$, $\eta_p^2 = 0.022$). The observed interaction effects were driven by negative correlations between PGS and prefrontal surface area in male participants (OFC: $r_p = -0.159$, $p = 0.032$; PO: $r_p = -0.207$, $p = 0.005$; RMF: $r_p = -0.110$, $p = 0.139$; PT: $r_p = -0.179$, $p = 0.015$) and positive correlations in female participants (OFC: $r_p = 0.080$, $p = 0.267$; PO: $r_p = 0.066$, $p = 0.360$; RMF: $r_p = 0.127$, $p = 0.076$; PT: $r_p = 0.071$, $p = 0.324$). No FDR corrected significant main effect of PGS could be observed (Table 2).

At an exploratory threshold of $p < 0.05$ uncorrected, a main effect of PGS on left frontal pole area emerged ($F_{(1, 369)} = 4.437$, $p = 0.035$, $\eta_p^2 = 0.012$). According to the FDR corrected PGS $\times$ sex interaction effects on surface area of the left frontal cortex, sex $\times$ PGS interaction effect equivalents on surface area of the right frontal cortex for PO ($F_{(1, 369)} = 5.369$, $p = 0.021$, $\eta_p^2 = 0.014$) and RMF ($F_{(1, 369)} = 5.971$, $p = 0.015$, $\eta_p^2 = 0.016$) could be observed at this exploratory threshold (see Table 2 for detailed overview). The significant interaction of PGS $\times$ sex on prefrontal surface area could be replicated in analyses in the subsample of normal-weight participants (BMI range 18.5–30) (see Supplementary results for details).

Additional analyses of cortical regions throughout the entire cortex revealed no further FDR corrected significant main effects of PGS nor PGS $\times$ sex interaction effects on any cortical region outside the frontal cortex.

PGS—cortical thickness

No significant main effect of PGS or interaction effect of PGS $\times$ sex on cortical thickness could be detected at the applied FDR corrected thresholds. At an exploratory threshold of $p < 0.05$

uncorrected, an interaction effect of PGS $\times$ sex on thickness of the pars triangularis of the left frontal cortex ($F_{(1, 369)} = 6.138$, $p = 0.014$, $\eta_p^2 = 0.016$) was evident (see supplementary Table S2). Additional analyses of cortical regions throughout the entire cortex revealed no FDR corrected significant main effects of PGS nor PGS $\times$ sex interaction effects on any cortical region outside the frontal cortex.

Associations between BMI, PGS, and cortical brain structure

Analyses of potential main effects of BMI and BMI $\times$ sex interaction effects on frontal cortical surface area yielded no significant main effect of BMI, while a BMI $\times$ sex interaction effect on left rostral middle frontal surface area was observed ($F_{(1, 369)} = 8.789$, $p = 0.003$, $\eta_p^2 = 0.023$) of comparable effect size compared to PGS $\times$ sex interaction effects observed in analyses step (2) in the same cortical region but however marginally failed to reach FDR significance (see supplementary Table S3). The interaction effect of BMI $\times$ sex on frontal cortical surface area was driven by a more pronounced negative association between BMI and surface area in male compared to female participants (Fig. S1).

Analyses of main effects of BMI and BMI $\times$ sex interaction effects on frontal cortical thickness yielded several FDR corrected significant main and interaction effects with most pronounced interaction effects on thickness of the left pars opercularis and the left RMF (see supplementary Table S4). Again, interaction effects of BMI $\times$ sex on frontal cortical thickness were driven by a more pronounced negative association between BMI and thickness in male compared to female participants (Figs. S2 and S3).

Additional mediation analyses revealed no significant indirect (mediation) effect of PGS on BMI through prefrontal surface area (see Supplementary results for details).

DISCUSSION

With this study we provide evidence for a sex-specific contribution of polygenic load for AN to BMI and prefrontal brain structure in nonclinical individuals.

Table 2. ANCOVA results for main effects of PGS and PGS × sex interaction effects on cortical surface area including age, sex, total intracranial volume and MDS components as nuisance covariates

	Main effect PGS						Interaction effect PGS × sex					
	Hemisphere	F	p	η^2	Hemisphere	F	p	η^2	Hemisphere	F	p	η^2
Caudal middle frontal gyrus	Left	0.774	0.379	0.002	Right	0.024	0.877	0.000	Left	0.000	0.998	0.000
Lateral orbitofrontal cortex	Left	0.876	0.350	0.002	Right	0.277	0.599	0.001	Left	9.791	0.002*	0.026
Medial orbitofrontal cortex	Left	0.053	0.817	0.000	Right	0.075	0.784	0.000	Left	0.086	0.770	0.000
Paracentral lobule	Left	1.508	0.220	0.004	Right	0.170	0.681	0.000	Left	0.554	0.457	0.001
Pars opercularis	Left	3.694	0.055	0.010	Right	0.363	0.547	0.001	Left	0.603	0.438	0.002
Pars orbitalis	Left	2.360	0.125	0.006	Right	0.411	0.522	0.001	Left	10.742	0.001*	0.028
Pars triangularis	Left	2.760	0.097	0.007	Right	1.087	0.298	0.003	Left	8.163	0.005*	0.022
Precentral gyrus	Left	0.265	0.607	0.001	Right	0.565	0.453	0.002	Left	2.737	0.099	0.007
Rostral middle frontal gyrus	Left	0.104	0.748	0.000	Right	0.051	0.821	0.000	Left	12.00	0.001*	0.031
Superior frontal gyrus	Left	0.982	0.322	0.003	Right	1.973	0.161	0.005	Left	2.652	0.104	0.007
Frontal pole	Left	4.473	0.035	0.012	Right	2.414	0.121	0.006	Left	0.286	0.593	0.001

Hemisphere, F-values (F), uncorrected p-values (p), and partial eta squared (η^2) values are presented. The asterisk indicates FDR corrected significance at $p < 0.05$

Our findings demonstrate a sex-specific negative association between polygenic load for AN and BMI in female participants, whereas this association was absent in males. This finding holds several important implications for future clinical and biological research. Since all participants of our study were ensured to be free from present or any history of eating disorders including AN, this observation might point to a sex-specific contribution of polygenic load for AN on BMI independent of AN diagnosis. This notion is furthermore supported by the fact that our analyses controlled for age and by the fact that the mean age of our sample (mean age = 39.06, SD = 11.29) was above the typical age range in which AN is diagnosed making it unlikely that findings were biased by individuals with a high probability of developing AN in the future. Instead, we demonstrate that the influence of polygenic load for AN on BMI does not seem to depend on AN diagnosis in nonclinical participants. Polygenic load for AN might play a relevant role for body weight regulation in nonclinical individuals. This goes in hand with the fact that apart from clinical manifest AN, symptoms like body and/or weight dissatisfaction are highly prevalent in the general population [52–55] and might result in co-occurrence with disordered eating behavior like extreme dieting [56–58]. The fact that the negative association between PGS and BMI was restricted to female participants is in accordance with the higher prevalence of AN as well as AN-specific eating disorder related symptoms (weight dissatisfaction, dieting, weight control, and use of purging) in general among women compared to men [59]. Based on our observation, it appears likely that higher polygenic load for AN is associated with lower BMI in female individuals, which might be due to alterations in eating and weight regulation behavior. Still, alternative explanations for the association of PGS for AN and low BMI in nonclinical participants like differences in the tolerance or the function of starvation might be possible [60, 61].

Interestingly, the assumption of an aberrant eating and weight regulation behavior appears to correspond to the observed imaging results. We found higher polygenic load for AN to be associated with higher left sided prefrontal surface area in the OFC, PO, RMF, and PT in female participants, with similar sex-specific effects in the right hemisphere for PO and RMF at an uncorrected level. These findings are of particular interest considering the crucial role of prefrontal cortical regions in the evaluation of stimuli valence and executive inhibitory control [62, 63]. Moreover, prefrontal brain regions have frequently been demonstrated to be involved in eating disorders and weight regulation [64, 65]. The left orbitofrontal gyrus rectus gray matter volume has been shown to be increased in patients with acute AN as well as in recovered patients with AN and therefore alterations in this region might constitute a trait marker for AN [64]. Furthermore, alterations in inhibitory control are widely discussed as an explanation factor for altered eating behavior [66–68] and high inhibitory control abilities have been shown in patients with AN [66, 69, 70]. In addition, the frequent finding of decreased prefrontal gray matter volume in obesity, overeating and decreased impulse control, weight regulation, and reward sensitivity might further support this line of argumentation [71–73]. The fact, that we observed an influence of polygenic load for AN exclusively on cortical surface area corresponds to the fact that cortical surface area and thickness have been shown to be genetically independent [74–76].

Finally, we found a sex-specific association between BMI and left RMF surface area as well as between BMI and left PO and left RMF thickness. This association between BMI and lower prefrontal brain surface area and thickness was consistently more pronounced in men compared to women. We did not find evidence for a mediation of polygenic load for AN on BMI through prefrontal brain structure. This finding is in contrast with previous imaging genetic findings in obesity [29] and might

be explained by the presence of further undiscovered variables (e.g., environmental factors) that are known to contribute to body weight.

The finding of sex-specific associations between both BMI and PGS with brain structure in prefrontal regions is supported by various studies including findings from different levels of biological abstraction: several studies show mutual as well as sex-specific associations of BMI and gray matter volume [77, 78]. High BMI has been shown to affect the executive and reward system of the brain in elderly women [79], as well as neurodegeneration in women with Alzheimer's Dementia [80]. Some studies suggest common as well as sex-specific alterations regarding diffusion tensor imaging measures [81, 82]. A recent study found sex differences in metabolic brain age with lower metabolic brain age in women compared to men [83]. Sex-differences have also frequently been reported in gene expression patterns of high relevance for brain structural development [84, 85].

It appears important to note that the sex-specific effect of PGS for AN occurred only on prefrontal surface area, whereas the sex-specific effect of BMI showed up mainly in prefrontal thickness. This fact strengthens the argumentation of further underlying contributors to the association between body weight and brain structure beyond genetic influence.

The precise mechanisms underlying mutual sex-specific associations between polygenic risk for AN, BMI, and prefrontal structure currently remain unclear and should be targeted by future research. Future studies should take into account sex-specific gene expression that might help to unravel the complex picture of genes, BMI, and brain structure in body weight regulation.

Strengths of our work comprise the relatively large sample size in comparison with the previous studies on AN that enabled us to detect associations of small effect size as commonly observed in imaging genetic research. We accounted for multiple testing using the FDR correction for each analysis as it is standard in the field [e.g., [86]]. The inclusion of clinical, genetic, and neuroimaging data furthermore allows for abstraction on different levels. Since biological and imaging research on AN usually suffers from small sample sizes, a strong bias due to malnutrition and somatic as well as psychiatric comorbidities, the application of a PGS for AN and the successful application of the latter in imaging research in this study might prove as a useful approach for future research on AN. The application of a genetic score furthermore allowed us to disentangle between the temporal precedence of the predictor variable (PGS) and the studied outcome variables. Still, the cross-sectional design of our study represents a major limitation since temporal precedence between all other studied variables remains unclear and thus prevents us from drawing causal relationships. We furthermore cannot rule out that other variables (first and foremost environmental factors) have contributed to the detected associations. Moreover, the lack of any eating disorder related psychometric data apart from the SCID interview represents another limitation of the present study that must be acknowledged. As we included only nonclinical individuals, we cannot generalize results to individuals with diagnosed eating disorder.

To conclude our results suggest a sex-specific contribution of polygenic load on body weight and prefrontal brain structure, as well as a sex-specific association between BMI and prefrontal brain structure. These findings highlight a sex-specific role of AN related biological traits in nonclinical individuals. Future studies should aim to clarify to which extent similar sex-specific effects might be present in further domains of AN relevant neurobiology and to disentangle the complexity of these neurobiological mechanisms. Moreover, our results might point to the potential of sex-specific biologically informed prevention of disordered eating behavior in the general population that should be addressed in future research.

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ADDITIONAL INFORMATION

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