Development of disordered eating behaviors and comorbid depressive symptoms in adolescence: neural and psychopathological predictors

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Abstract

BACKGROUND:

Eating disorders are common in adolescence, devastating and strongly comorbid with other psychiatric disorders. Yet, little is known about their etiology to develop effective preventive measures.

METHODS:

Longitudinal assessments of disordered eating behaviors (DEBs; binge-eating, purging and dieting) and comorbid psychopathology were measured in 1,386 adolescents from the IMAGEN study. Development of DEBs and associated mental health problems were investigated by comparing participants who reported symptoms at ages 16 or 19, but not at age 14 to asymptomatic controls. Voxel-based morphometry and psychopathological differences at age 14 were investigated to identify risk factors for the development of DEBs and associated mental health problems.

RESULTS:

DEBs and depressive symptoms developed together. Emotional and behavioral problems, including symptoms of attention deficit hyperactivity disorder (ADHD) and conduct disorder (CD), predated their development. Alterations in fronto-striatal brain areas also predated the development of DEBs and depressive symptoms. Specifically, development of binge-eating was predicted by higher grey matter volumes in the right putamen/globus pallidus at age 14. Conversely, development of purging and depressive symptoms was predicted by lower

volumes in the medial orbitofrontal, dorsomedial and dorsolateral prefrontal cortices. Lower grey matter volumes in the orbitofrontal and anterior cingulate cortices mediated the relationship between ADHD and CD symptoms and future purging and depressive symptoms.

CONCLUSIONS:

These findings suggest that alterations in frontal brain circuits are part of the shared etiology between eating disorders, ADHD, CD and depression and highlight the importance of a transdiagnostic approach to treating these conditions.

Introduction

Eating disorders (EDs), including anorexia nervosa (AN), bulimia nervosa (BN) and binge eating disorder (BED), are severe psychiatric disorders that affect up to 15% of young women and 3% of young men (1). The peak age of onset is from mid adolescence into emerging adulthood (age 15 to 19), i.e. at a developmentally sensitive time (2). EDs are characterized by disordered eating behaviors (DEBs), including dietary restriction, binge-eating and purging. Varying combinations of these DEBs occur in different EDs and across the weight spectrum from severely underweight to obese. Crucially, subclinical DEBs whose prevalence is particularly high (14%-22%) (3, 4) in children and adolescents predict development of full-syndrome EDs in later life (5, 6). Thus, identifying causal risk factors of DEBs and understanding their development is key to identifying high-risk groups and developing prevention strategies.

Comorbid disorders are common in EDs. These include mood, anxiety and substance use disorders, which are common across all EDs (7) and impulse-control disorders like Attention Deficit Hyperactivity Disorder (ADHD), oppositional-defiant and conduct disorder (CD), which are prevalent in BN and BED (7, 8). Longitudinal studies have demonstrated that emotional and behavioral problems, including ADHD (9, 10) and CD symptoms (11) are risk factors of developing EDs. ADHD in childhood also confers higher risk of developing depression in adolescence/young adulthood (12, 13), suggesting that EDs and comorbid depression have shared psychopathological risk factors.

EDs are widely accepted as brain-based disorders and neurobiological overlaps between EDs and addictions have been suggested (14). Neuroimaging studies have revealed structural and functional brain differences in ED patients compared with recovered patients and healthy controls. For example, meta-analyses combining adolescent and adult patients' data revealed reduced grey and white matter and increased cerebrospinal fluid (CSF) in AN patients compared with healthy individuals, such differences becoming less pronounced in recovered patients (15). However, most of these neuroimaging findings focus on AN or are based on small cross-sectional studies. The few studies comparing BN or BED patients to healthy individuals found regional volumetric or cortical thickness differences in the orbitofrontal cortex (OFC), insula, cingulate cortex and several other regions (16-20). Subcortical shape deformations (21) and white matter microstructure abnormality (22) were also found in BN patients and were associated with symptom severity.

Critical questions remain as to whether any abnormalities displayed reflect predisposing risk factors or a consequence of prolonged eating disturbances. Should predisposing brain differences exist, it remains to be answered whether EDs and comorbid mental health problems have common neural underpinnings, and which neural mechanisms mediate the relationship between psychopathological risk factors and the development of EDs and comorbid mental health problems. We have recently demonstrated the value of longitudinal neuroimaging methods by showing that differences in neural responses to inhibitory control

can be detected 2 years before the onset of binge-eating or purging behaviors (23). Altogether, these findings suggest that advances in understanding and prevention of EDs are likely to benefit from an approach using dimensional and longitudinal assessments of DEBs, focusing on underlying neurobiological substrates (24).

Building up on this, here we use the longitudinal design of IMAGEN, a large, prospective cohort of European adolescents, to investigate early psychopathological and neuroanatomical risk factors for the development of DEBs and comorbid mental health problems. Hypothesizing that structural brain alterations underlie shared risk for developing DEBs and comorbid mental health problems, we performed longitudinal and mediation analyses to lend insight into the etiology of EDs and evaluate underlying neural mechanisms through which psychopathological risk factors relate to the development of DEBs and comorbid mental health symptoms.

Methods and Materials

Participants

Questionnaire and neuroimaging data were obtained from IMAGEN – a longitudinal cohort acquired from 8 study sites in Europe. Each site received approval from their local research ethics committee. Written assent from the adolescents and written consent from the parents were obtained prior to participation. See (25) for details of the recruitment and assessment methods. In this study, we used questionnaire data acquired at ages 14, 16 and 19, and neuroimaging data acquired at age 14.

Psychopathological assessments

Eating disorder symptoms: Binge-eating, purging and dieting behaviors were assessed using the self-reports from the Development and Wellbeing Assessment (DAWBA) (26, 27). We used binary variables to indicate the presence or absence of binge-eating, purging and dieting symptoms at each age. A positive response to question 15, related to eating a large amount of food and losing control over eating was used to indicate the presence of binge-eating. A positive response to any of 3 questions (1c, 18f and 18g) related to self-induced vomiting or taking pills/medicines to lose weight was used to indicate the presence of purging behavior. A score of 3 (answer for 'a lot') for any of the 3 questions (question 18a, 18b and 18c) related to eating less at meals, skipping meals and fasting was used to indicate the presence of dieting

behavior. Dieting behaviors were also defined with more relaxed criteria (score ≥ 2), detailed in the Supplemental Information.

We categorized participants into groups who developed DEBs over time and those who remained asymptomatic based on each of the 3 DEBs. The “binge-eating developers” did not report binge-eating symptoms at age 14 but developed binge-eating symptoms at age 16 or 19. The “non-bingers” did not report binge-eating at any of the 3 ages. In the same manner we defined “purging developers”, “non-purgers”, “dieting developers” and “non-dieters”. Besides these, we compared individuals who did not report any DEB at age 14 but reported at least one DEB at ages 16 or 19 (“any DEB developers”) to individuals without any DEB at any age (“non-DEB” group). We also defined groups based on Bartholdy et al. (2019) (23) who combined binge-eating and purging symptoms together. We report these as “binge-eating or purging (BoP)”, defining developers, maintainers and recoverers based on their longitudinal development (See Supplemental Methods).

As expected, these DEB developers and their asymptomatic controls showed significant sex differences (Supplemental Table S1). To obtain sex-balanced groups of cases and controls, each developer group and the corresponding asymptomatic group were matched for sex and acquisition site, by using the propensity score matching method implemented in the Matchit toolbox (28). Details are provided in the Supplemental Information.

Emotional and behavioral problems: The Strengths and Difficulties Questionnaire (SDQ) (29) was used to measure participants' emotional and behavioral symptoms. We used self-report scores at age 14 for the following 4 subscales: emotional symptoms, conduct problems (i.e., CD symptoms), hyperactivity/inattention (i.e., ADHD symptoms) and peer relationship problems.

Mental health symptoms: Computer-generated DAWBA diagnoses (DAWBA bands) (30) derived from the self-report questionnaire were used to measure the severity of psychopathology-related symptoms at the 3 ages. DAWBA bands comprised up to 6 levels (from 0 to 5) and indicated the probability of having a disorder (from <0.1% to >70% probability of DSM-IV based diagnoses). IMAGEN being a normative cohort, we focused on common mental health problems in our cohort, as defined by prevalence ≥ 5% at age 19 for participants scoring 3 and above (15%+ risk according to the DAWBA bands) for the disorder. DAWBA bands for depression and generalized anxiety disorder (GAD) passed this threshold and their associations with DEBs were investigated. We defined a group of "depression developers" (N=290) whose depression scores were below 3 at age 14, and above or equal to 3 at ages 16 or 19. This was compared to controls (labeled as "non-depression", N=857) whose depression scores were below 3 across the 3 ages. Similarly, we defined "anxiety developers" (N=203) and "non-anxiety" (N=1107).

Body mass index (BMI) and medication: BMI (kg/m^2) at age 14 was derived from height and weight measurements and transformed to age- and sex-adjusted z-scores based on the Centre for Disease Control and Prevention Growth Chart (31). A binary variable was created to indicate whether participants took any prescription medicine in the past 30 days based on the Timeline Followback Interview (32).

Structural Magnetic resonance imaging (MRI) acquisition and processing

MRI images were acquired with 3T MRI scanners (Siemens, Philips, General Electric) across all IMAGEN sites. A 3D magnetization scan based on the ADNI protocols (http://adni.loni.usc.edu/methods/documents/mri-protocols/) was used to acquire T1-weighted structural images. Quality control was performed through visual inspection to exclude images with movement artefacts, brace artefacts or field inhomogeneities. Voxel-based morphometry (VBM) analyses were conducted using the VBM8 toolbox (http://www.neuro.uni-jena.de/vbm/) in SPM8 (https://www.fil.ion.ucl.ac.uk/spm/) to obtain grey matter volumes (GMVs), as detailed in the Supplemental Information. Intracranial volume (ICV), estimated in VBM8 by summing up grey matter, white matter and CSF volumes, was used as a covariate in all the analyses involving GMVs (33).

Statistical Analyses

DEB development and comorbid mental health symptoms. To investigate if DEBs and mental health symptoms co-developed, we tested for associations between the development of DEBs

and the development of depression and anxiety symptoms while controlling for sex, acquisition site and depression or anxiety symptoms at age 14. These analyses were performed with the whole sample (i.e., without matching for sex and acquisition site).

Emotional and behavioral problems as predictors of DEBs. We investigated whether SDQ subscales at age 14 could predict DEB development using Firth logistic regression models (34) controlling for sex and acquisition site. Potentially confounding effects of BMI were tested by further controlling significant associations for BMI at age 14. The *p* values were corrected using the Holm-Bonferroni method. We also investigated whether emotional and behavioral problems that predicted DEBs also predicted the development of depression and anxiety symptoms, controlling for depression or anxiety symptoms at age 14, sex and acquisition site.

Voxel-wise GMV analyses. We investigated whether structural brain differences at age 14 predated the development of DEBs. Generalized linear models (GLM) in SPM12 involved GMVs as the dependent variable, and the DEB group (developers vs. controls) as an independent variable. We tested whether shared anatomical differences underlay the development of DEBs and comorbid mental health problems as follows. First, we investigated voxel-wise GMV associations with development of depression and anxiety symptoms. We then tested if the associated brain regions overlapped with those associated with DEB development. We also investigated voxel-wise GMV associations with each of the 4 SDQ subscales at age 14. Control variables included in all analyses were sex, acquisition sites and total intracranial volumes (ICV).

Depression or anxiety symptoms at age 14 were also included as covariates in analyses involving development of depression and anxiety. The threshold for all the neuroimaging analyses was $p<0.001$ uncorrected at the voxel level, and $p<0.05$ corrected for family wise error (FWE) at the cluster level.

Mediation analyses. We tested whether the brain regions associated with SDQ subscales mediated the associations between SDQ subscales at age 14 and development of DEBs and comorbid depression/anxiety symptoms. The brain regions associated with SDQ subscales were used as ROIs. Control variables included sex, acquisition site and ICV. The mental health symptom at age 14 was controlled for when investigating the development of depression/anxiety. The continuous variables were transformed to *z*-scores. Confidence intervals for the mediation effect were estimated from 5000 bootstrap samples by using the PROCESS macro (v3.2, http://processmacro.org) in SPSS (v25, IBM Corporation).

Results

A total of 1594 participants had non-missingness for the SDQ, DEB variables, BMI and neuroimaging data at age 14. Out of these, 1386 participants had DEB data at age 16 or 19 and were used to create DEB developer groups. Among the developers for binge-eating (n=115), purging (n=155), dieting (n=60), BoP (n=204) and any DEB (n = 138), between 60.9% and 79.1% were female. Taking this into account, case and control groups were matched based on sex and recruitment site (Supplemental Table S1 & Figure S1) for the analyses. Descriptive statistics for BMI and psychopathology scores are provided in Supplemental Table S2.

DEBs co-develop with depression and anxiety symptoms

We first established that DEBs co-developed with depression and anxiety by testing for associations between the development of DEBs and depression and anxiety symptoms. Development of DEBs was significantly associated with higher risk of developing depression and anxiety, after controlling for their levels at age 14 (Supplemental Table S3 and Figure S2).

Emotional and behavioral problems predict the development of DEBs, depression and anxiety symptoms

As emotional and behavioral problems are known predictors of eating disorders (9-11), we analyzed their associations with DEBs. Emotional problems at age 14 were significant predictors for the development of binge-eating (OR = 1.35, p = 4.4E-03). ADHD symptoms and

CD symptoms at age 14 predicted the development of purging (OR = 1.35, *p* = 1.6E-03 for ADHD symptoms; OR = 1.43, *p* = 8.5E-05 for CD symptoms; Table 1) and BoP behaviors (OR = 1.28, *p* = 4.7E-03 for ADHD symptoms; OR = 1.40, *p* = 1.0E-04 for CD symptoms; Supplemental Table S4). CD symptoms at age 14 also predicted the maintenance of BoP (OR = 1.69, *p* = 5.8E-04, Supplemental Table S4) and the development of "any DEB" (OR = 1.36, *p* = 3.9E-03, Supplemental Table S5). These associations remained significant after controlling for BMI. Further analyses of the association with ADHD symptoms indicated that both the hyperactivity-impulsivity and inattention components contributed to the association with future purging behaviors (OR = 1.33, *p* = 2.5E-03 and OR = 1.23, *p*= 0.028 for hyperactivity-impulsivity and inattention, respectively). A significant predictor for dieting development was found only by using a more relaxed criterion for dieting (CD symptoms, OR = 1.27, *p* = 0.013, Supplemental Results).

Emotional and behavioral problems at age 14 also predicted the development of depression and anxiety at later ages (Table 2). More specifically, emotional problems (OR = 1.56, *p*= 3.7E-04) and ADHD symptoms (OR = 1.24, *p* = 0.045) predicted the development of anxiety symptoms (controlling for depressive symptoms at ages 14, 16 and 19), while CD symptoms specifically predicted the development of depressive symptoms (OR = 1.22, *p* = 0.025, controlling for anxiety symptoms at ages 14, 16 and 19).

Structural brain differences at age 14 predate the development of DEBs and depressive symptoms

Whole brain VBM analyses demonstrated that binge-eating developers had higher GMVs in a subcortical cluster comprising the right putamen and globus pallidus at age 14 (Figure 1A & Supplemental Table S6). Conversely, purging developers had lower GMVs in a cluster encompassing the medial OFC (mOFC), the gyrus rectus, the anterior and middle cingulate cortex (ACC and MCC), the left dorsomedial and dorsolateral prefrontal cortex (Figure 1B). Similarly, BoP developers had smaller GMVs at age 14 in the mOFC, gyrus rectus, ACC and MCC (Figure 1C). No significant GMV differences were associated with dieting developers, "any DEB" developers, BoP maintainers or BoP recoverers. Repeating analyses by controlling for BMI at age 14, or removing participants who took any medication in the past 30 days, or removing individuals reporting other DEBs at age 14 did not substantially change main associations (see Supplemental Results, Tables S6-S7 & Figures S3-S4). However, repeating the VBM analyses in girls only did not yield significant results on the whole brain level.

We tested if brain regions associated with DEB development were also associated with developing symptoms of depression or generalized anxiety. Whole brain VBM analyses demonstrated that depression developers had lower GMVs in two clusters comprising the medial and left lateral OFC, ACC, MCC, the supplementary motor area, the dorsomedial PFC and left dorsolateral PFC (Figure 1D & Supplemental Table S8). These clusters overlapped with those associated with purging development in the ACC, MCC, mOFC, dorsomedial and left

dorsolateral PFC (Figure 1E). Similar overlaps were found for brain regions associated with development of BoP and depressive symptoms (Figure 1F). No significant results were found for the development of anxiety on the whole-brain level.

Brain structure underlying CD and ADHD symptoms mediate the development of purging and comorbid depressive symptoms

The analyses presented above suggested that neural correlates of SDQ traits – should they be detected – may serve as potential brain-based mediators for DEBs. To test this, we first analyzed associations between GMVs and DEB-associated SDQ measures at age 14, using the whole sample of 1594 participants. Higher CD symptoms were associated with lower grey matter volumes in the ACC, mOFC and the superior and middle frontal gyrus (Figure 2A & Supplemental Table S6). The ACC/mOFC region partly overlapped with those associated with purging development (262 voxels), BoP development (59 voxels) and depression development (74 voxels, Figure 2A). In contrast, higher ADHD symptoms were significantly associated with lower GMVs in a cluster encompassing the mOFC, gyrus rectus and anterior orbital gyrus (Figure 2B & Supplemental Table S6). These regions overlapped with those associated with purging development (461 voxels), BoP development (853 voxels) and depression development (148 voxels, Figure 2B). No significant GMV associations were observed for emotional problems.

Next, we investigated whether the GMV differences identified above mediated the relationship between CD or ADHD symptoms at age 14 and the development of purging, BoP and depression. Brain regions associated with CD symptoms (ACC/mOFC) and ADHD symptoms (labelled as OFC) were used as ROIs. Lower GMVs in the ACC/mOFC mediated the relationship between CD symptoms and the development of purging (indirect effect = 0.021, bootstrap 95% CI = 7.3E-04-0.056) and depression (indirect effect = 0.021, bootstrap 95% CI = 0.0023-0.050, Figure 3A). Likewise, lower GMVs in the OFC mediated the association between ADHD symptoms and the development of purging (indirect effect = 0.024, bootstrap 95% CI = 0.0016-0.058) and depression (indirect effect = 0.025, bootstrap 95% CI = 0.0039-0.053, Figure 3B). Similarly, these ROIs significantly mediated the effects of CD and ADHD symptoms on the development of BoP (Supplemental Figure S5). No significant mediation effects were found for the development of anxiety symptoms.

Discussion

Our longitudinal analyses, aimed at identifying early predictors of the development of DEBs and comorbid depression/anxiety symptoms in adolescence, identified shared neural substrates underlying the psychopathological risk for the development of DEBs and depression. We show that higher GMVs in the putamen and globus pallidus and emotional difficulties predate the development of binge-eating. We similarly demonstrated that lower GMVs in frontal and cingulate cortices, and ADHD and CD symptoms were associated with development of purging, BoP and depression. Importantly, the lower GMVs associated with ADHD and CD symptoms mediated the relationships between these symptoms and future purging, BoP and depression. These results support previous research showing high prevalence of ADHD, CD, depression and GAD in EDs, particularly in bulimia nervosa (7, 8), and extend our knowledge of the neural underpinning of these disorders.

We have identified several neural substrates as early markers for the development of DEBs. Lower GMVs across the prefrontal cortex, including the mOFC, ACC, MCC, the dorsomedial and dorsolateral PFC are early indicators for the development of purging and BoP behaviors. Our mediation analyses also implicate the OFC and ACC/mOFC in the neural mechanisms underlying the associations between ADHD and CD symptoms and future purging and BoP behaviors. These results are consistent with previous suggestions of overlapping neural circuits involved in cognitive control and reward systems between ADHD and EDs (35). For example,

reduced GMVs in the OFC are consistently found in ADHD patients (36), which correlate with their functional impairments in emotion regulation, reward-related decision making and control of motivation (37). Shared neurobiological mechanisms (35) are further supported by observations of overlapping treatment responses to psychostimulant medications in ADHD and BN/BED patients (38, 39).

Youths with ADHD are at higher risk of developing depression (40), and their common neurobiological mechanisms have been suggested (41). For example, resting-state functional connectivity between the left OFC and left hippocampus is reduced in children with ADHD; furthermore, this connectivity is also negatively associated with depressive symptom severity in children with ADHD (41). However, research on neurobiological mechanisms of ADHD and depression has been largely separate, and the neural mediators between the two have been unclear until now. Our results highlight structural differences in the OFC to be a neural substrate that confers higher risk for depression in youths with greater ADHD symptoms. As the OFC plays important roles in emotion regulation (42), our result concurs with the finding that emotion regulation deficiencies mediate the association between ADHD and depressive symptoms (43, 44). By demonstrating that reduced GMVs in the OFC mediate the effect of ADHD symptoms on both future purging and depressive symptoms, our results further suggest that ADHD, depression and EDs may have a common neurobiological basis.

The observed reduced GMVs in the ACC/mOFC was consistent with recent neuroimaging findings in CDs (45). Both the ACC and mOFC are involved in reward-based decision making by encoding action-reward associations (46, 47) and also in top-down emotion regulation (48). Our results suggest that impairments in reward processing and/or emotion regulation may underlie the link between conduct problems and future purging behaviors and depression.

Other brain regions associated with purging/BoP symptoms, i.e., the dorso-lateral, dorso-medial PFC and ACC, are part of the inhibition control system responsible for regulatory control and response inhibition (49). Hypoactivation of these regions has been associated with substance use and behavioral addictions (49). In line with our findings, a cluster in the ACC was also found by Bartholdy *et al.* (2019) to be hypo-activated in BoP developers during successful (vs. failed) response inhibition (23). Conversely, activating the dorsolateral PFC with high-frequency repetitive transcranial magnetic stimulation (rTMS) can reduce food craving and binge-eating frequencies in bulimic disorders (50). Based on these findings, lower GMVs in the dorsolateral and dorsomedial PFC in purging developers suggest weakened functions in inhibition control, which may underlie their vulnerability to impulsive behaviors like purging.

The neural substrates associated with development of binge-eating encompassed the right putamen and globus pallidus, with greater GMVs implicating higher risk. Previous studies of ED patients found reduced GMVs in the bilateral striatum in BN (18) and BED (51, 52) and increased GMVs in the OFC for BN (18), which is at odds with our findings. The differences may

be due to sample characteristics and the study design, previous neuroimaging studies being cross-sectional and involving adult patients with EDs. In comparison, the present study investigated onset of DEBs symptoms in a longitudinal cohort of healthy adolescents. It is possible that higher putamen volumes confer risk for future binge-eating, while reduced volumes ensue from suffering these conditions over the years. Clearly, more longitudinal developmental research is needed to study abnormal developmental patterns associated with DEBs and depression.

Strengths and Limitations

Our study has several strengths. First, it is one of the only two longitudinal studies (23) to examine the neurobiological predictors of DEBs in a well-characterized population-based adolescent cohort. The sample size and multi-modality of the data (questionnaires and neuroimaging) were other strengths of our study. Matching sex and acquisition sites between case and control groups removed confounding effects from these variables.

There are also several weaknesses to consider. First, the very limited number of males in the case groups did not enable us to investigate sex-specific effects. Second, the effects of other confounding factors (e.g., parental and social) were not ruled out. Thirdly, DEBs were assessed through self-reports only. Fourthly, it cannot be concluded that the risk factors identified here are associated exclusively with a single DEB as our analyses did not exclude coexisting DEBs. Fifth, the mediation analysis included two variables (SDQ symptoms and brain structure)

assessed at one time point and a third variable (development of DEB or depression) assessed at another, rather than all variables assessed at separate time points. Lastly, as we we did not find significant structural brain risk factors for dieting, the neurobiological risk factors for restrictive eating behaviors remain unclear (53).

Overall, our study highlights psychopathological traits that may be causal risk factors of DEBs, including emotional problems, ADHD and CD symptoms, which can help identify high-risk groups for targeted prevention. The identification of neurobiological substrates of DEBs and comorbid depression, specifically in the OFC and ACC, provides promising therapeutic strategies for EDs and comorbid conditions (54, 55).

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Disclosures

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Figure Legends

FIGURE 1. Structural brain associations with the development of binge-eating (A), purging (B), binge-eating or purging (BoP, C) and depressive symptoms (D). The bar plots show the regional means of GMVs, adjusted by sex, acquisition site and total intracranial volumes. Error bars represent standard errors. Statistical parametric maps were thresholded at voxel-level $p<0.001$ (uncorrected) and cluster-level $p<0.05$ (FWE corrected). Overlapping brain regions associated with the development of purging and depressive symptoms are presented in E. Overlapping brain regions for the development of BoP and depressive symptoms are presented in F. The 3D rendered views are generated by MRIcroGL (https://www.mccauslandcenter.sc.edu/mricrogl/).

FIGURE 2. Grey matter volume associations with CD symptoms (A, negative association) and ADHD symptoms (B, negative association) at age 14. Statistical parametric maps were thresholded at voxel-level $p<0.001$ (uncorrected) and cluster-level $p<0.05$ (FWE corrected). The columns to the right show overlapping brain regions associated with the development of purging, BoP and depressive symptoms.

FIGURE 3. Results for the mediation analysis, using the ACC/mOFC ROI linked to CD symptoms (A) and the OFC ROI linked to ADHD symptoms (B) as mediators. For analyses on the development of purging, control variables included sex, acquisition sites and the total

intracranial volume. For analyses on the development of depression (blue dashed lines), the depression symptom at age 14 was involved as an additional control variable. ROI: region of interest; CI: confidence interval; ACC: anterior cingulate cortex; OFC: orbitofrontal cortex.

Tables

Table 1. Psychopathological predictors of DEB symptoms

developers of DEBs	SDQ symptoms at age 14	Without controlling for BMI			After controlling for BMI		
		OR	95% CI	P	OR	95% CI	P
binge-eating developers vs. non-bingers	conduct problems	1.29	1.06-1.57	1.1E-02			
	emotional symptoms	**1.35**	**1.10-1.66**	**4.4E-03**	1.34	1.09-1.65	5.7-03
	hyperactivity/ inattention	1.27	1.03-1.57	2.4E-02			
	peer problems	1.24	1.01-1.51	3.7E-02			
purging developers vs. non-purgers	conduct problems	**1.43**	**1.20-1.71**	**8.5E-05**	1.41	1.18-1.70	1.5E-04
	emotional symptoms	1.24	1.03-1.49	2.5E-02			
	hyperactivity/inattention	**1.35**	**1.12-1.64**	**1.6E-03**	1.37	1.13-1.66	1.2E-03
	peer problems	0.98	0.81-1.18	8.6E-01			
dieting developers vs. non-dieters	conduct problems	1.22	0.92-1.59	1.6E-01			
	emotional symptoms	1.22	0.91-1.63	1.8E-01			
	hyperactivity/inattention	1.17	0.88-1.57	2.7E-01			
	peer problems	1.23	0.94-1.59	1.2E-01			

The p values shown in bold survived the Holm-Bonferroni correction, correcting for 12 tests (3 DEBs × 4 SDQ subscales). Significant associations were further controlled for BMI. DEB: disordered eating behavior.

Table 2. Psychopathological predictors for the development of depression and generalized anxiety symptoms

Development of mental health symptoms	SDQ symptoms at age 14	Controlling for the corresponding mental health symptom at age 14			Additionally controlling for the other mental health symptom at all ages		
		OR	95% CI	P	OR	95% CI	P
Depression	hyperactivity/ inattention	1.25	1.08-1.44	**2.5E-03**	1.10	0.93-1.29	0.27
	conduct problems	1.32	1.13-1.54	**4.6E-04**	1.22	1.03-1.46	0.025
	emotional symptoms	1.39	1.19-1.62	**2.8E-05**	0.98	0.79-1.20	0.82
Generalized anxiety	hyperactivity/ inattention	1.33	1.13-1.57	**5.4E-04**	1.24	1.00-1.53	0.045
	conduct problems	1.26	1.06-1.49	**9.3E-03**	0.97	0.77-1.22	0.79
	emotional symptoms	1.79	1.46-2.19	**1.0E-08**	1.56	1.22-2.00	3.7E-04

The p values shown in bold survived the Holm-Bonferroni correction, correcting for 6 tests (2 mental health symptoms × 3 SDQ subscales). Significant associations were further controlled for the other mental health symptom at ages 14, 16 and 19 (i.e., controlling depression development for anxiety symptoms at all ages, and vice-versa).