Relationships between eating behaviours, psychopathology, brain maturation and genetic risk for obesity in a longitudinal adolescent cohort study

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Abstract

Unhealthy eating, a risk factor for eating disorders (EDs) and obesity, often co-exist with emotional and behavioural problems, but the underlying neurobiological mechanisms are poorly understood. Analysing data from the longitudinal IMAGEN adolescent cohort, we investigated associations between eating behaviours, genetic predispositions for high BMI (BMI PGS), and trajectories (ages 14y to 23y) of ED-related psychopathology and brain maturation. Clustering analyses at age 23y (N = 996) identified three eating groups: restrictive, emotional/uncontrolled, and healthy eaters. BMI PGS, trajectories of ED symptoms, internalising and externalising problems, and brain maturation distinguished these groups. Decreasing volumes and thickness in several brain regions were less pronounced in restrictive and emotional/uncontrolled eaters. Smaller cerebellar volume reductions uniquely mediated the effects of BMI PGS on restrictive eating. Smaller volumetric reductions across multiple brain regions mediated the relationship between elevated externalising problems and emotional/uncontrolled eating, independently of BMI. These findings shed light on distinct contributions of genetic risk, protracted brain maturation and behaviour in ED symptomatology.

Main

Eating disorders (EDs) are serious psychiatric disorders with high mortality rates, substantial impacts on quality of life, and economic burdens[1,2]. Their increasing prevalence[3,4] particularly during mid-adolescence[5] highlights the need for early detection and effective interventions.

Key risk factors for EDs include eating behaviours such as dietary restraint and overeating, which increase the risk for unhealthy weight control behaviours and EDs like bulimia nervosa and binge eating disorder[6]. Assessments of eating behaviours in various population groups[7,8] indicated that cognitive restraint (CR), the conscious restriction of food intake to control body weight and shape, can lead to episodic overeating and is a strong predictor of disordered eating and negative body image. Conversely, uncontrolled eating (UE) –which refers to eating in response to food palatability, social cues and hunger, resulting in eating episodes– and emotional eating (EE) –eating episodes elicited by negative affect– is associated with higher susceptibility to EDs, hedonically driven food choices, higher BMI, and obesity. Genetic studies indicate that these behaviours may be partially genetically determined, with obesity-associated variants linked to CR, UE and EE[9], and eating behaviour trajectories in childhood[10] and adolescence[11].

Neural factors also play a role in EDs[12], with neurobiological differences observed in clinical samples[13–17]. Neurobehavioural correlates suggest that the hypothalamic, emotion/memory, and executive systems are involved in eating control[18,19]. Neural activation of lateral prefrontal structures underpinning self-control and decision-making and striatal reward regions have been shown to underly individual differences in CR[20]. Longitudinal studies have revealed volumetric brain differences, particularly in striatal and prefrontal regions,

suggesting differences in brain maturation as etiological factors for disordered eating behaviours and comorbid depressive symptoms[21].

Internalising and externalising psychopathology symptoms may serve as premorbid risk factors for eating disorders[22–24]. Externalising problems in early adolescence predict the onset[11] and persistence of eating pathology[25], while generalized anxiety symptoms predict adolescent-onset ED[26]. Negative affect and functional impairment are found to predict the onset of all eating disorders[6,27]. However, how trajectories of adolescent maladjustment, as evidenced by internalising and externalising problems, relate to eating behaviours, genetic liability and brain maturation, is not well understood.

This study aimed to advance our understanding of eating behaviours by analysing longitudinal data from the IMAGEN adolescents' cohort. Applying a multivariate analytical framework, the study identified eating profiles at age 23, characterized by associations with polygenic scores for higher BMI (BMI PGS), and differences in earlier trajectories of disordered eating, internalising and externalising problems, and brain maturation. The mediating roles of brain maturation and BMI PGS were also investigated using multivariate models. The analytical workflow is illustrated in **Fig. 1**.

Results

Identification of groups with distinct eating profiles

A total of 996 participants (478 males and 518 females) with completed Three-Factor Eating Questionnaire (TFEQ) scores at age 23 and had at least one measure from the Strengths and Difficulties Questionnaire (SDQ) available at ages 14, 16, 19 and 23 were included in the current study (**Methods**). Three groups were identified from K-means clustering analysis with distinct eating behaviours (**Table 1** and **Fig. 2a**). Group distribution and the within-group sum of squares are detailed in **Supplementary Fig. S1**. Validity and stability analyses confirmed the three-group solution with Jaccard similarities of 0.83, 0.77, and 0.75, respectively. One group (N = 423) scored low on all eating behaviours, indicating healthy eaters (HEs). Another group (N = 324) exhibited the highest cognitive restraint, indicating restrictive eaters (REs). Behaviours that differentiated REs most from HEs (Odds Ratios > 5) included consciously eating less to control weight and weight gain, the intensity of restrained eating, consciously eating less than wanted, and not eating foods that made them fat (**Supplementary Information**). This group also scored significantly higher than HEs on uncontrolled eating. The third group (N = 249) showed the highest emotional and uncontrolled eating, indicating emotional and uncontrolled eaters (E/UEs). Behaviours that distinguished E/UEs most from HEs included eating/overeating when feeling blue, lonely or anxious (all EE items), inability to stop eating, and frequency of binge eating episodes (UE items). This group also reported significantly higher cognitive restraint than HEs. REs and E/UEs comprised predominantly female participants, contrasting with HEs, which had a higher proportion of males. Consistent with differences in BMI, the BMI PGSs were higher in REs and E/UEs than in HEs (**Table 1**).

Group differences in trajectories of eating disorder symptoms across adolescence

Linear mixed models were applied to investigate group differences in trajectories of ED symptoms (dieting, binge eating and purging) from ages 14 to 23. Analyses of age-by-group interactions were used to identify symptom trajectories that differed in the REs or E/UEs groups compared to HEs (**Fig. 2b and Supplementary Tables S1 and S2**). REs were characterised by significantly ($p = 6.29 \times 10^{-3}$) higher overall levels of dieting compared to HEs, with no significant age-by-group interactions. Trends towards increased dieting from ages 14 to 16 and increased binge eating from ages 14 to 19 were observed in this group. In E/UEs, significant age-by-group interactions were observed when compared to HEs, with significantly increased dieting from ages 14 to 16 ($p_{Bonferroni} = 0.026$), and increased binge eating from ages 14 to 19 ($p_{Bonferroni} = 0.028$) and 14 to 23 ($p_{Bonferroni} = 3.024 \times 10^{-7}$). Nominal increases in purging were observed from age 14 to 16, 19 and 23.

Group differences in trajectories of internalising and externalising problems

We explored behavioural group differences further, using latent growth curve models (LGCM) to measure trajectories of internalising and externalising problems across (**Fig. 3a**) and within groups (**Fig. 3d**). Between groups univariate analyses revealed that compared to HEs, unhealthy eaters (REs and E/UEs) exhibited significant differences in how their internalising problems developed over time. Both REs ($b = 0.073$, 95% CI = 0.019-0.126, $p = 0.008$; **Fig. 3b**) and E/UEs ($b = 0.110$, 95% CI = 0.051-0.169, $p < 0.001$) reported a significant increase (i.e., the slopes of their trajectories; **Supplementary Tables S3** and **S4**) in internalising problems with age. Intercepts of internalising problems also differed, with E/UEs already reporting higher levels of internalising problems at age 14 than HEs ($b = 0.712$, 95% CI = 0.281-1.144, $p = 0.001$). Regarding externalising problem trajectories, all

three groups showed a decrease in these problems over time, but the rate of decrease did not significantly differ between groups (**Fig. 3c**). Nevertheless, the externalising problems reported at age 14 were higher in E/UEs compared to HEs (b = 0.855, 95% CI = 0.418-1.292, $p < 0.001$) and REs (b = 0.743, 95% CI = 0.278-1.209, p = 0.002).

Within-group multivariate LGCM analyses, which included internalising and externalising problems in the same model (**Fig. 3d**), revealed significant within- and between-constructs correlations (**Fig. 3e**). Within-construct correlations revealed that in all groups, higher levels of externalising problems at age 14 were significantly correlated with smaller decreases in these problems over time. This association was especially strong in unhealthy eaters (REs and E/UEs), indicating that higher initial levels of externalising problems were linked to less improvement over time. Similarly, in REs and HEs, higher initial levels of internalising problems were associated with smaller decreases in these problems over time, but this pattern was not observed in E/UEs. Interestingly, our models highlighted notable connections between internalising and externalising problems. Specifically, we found that these problems tended to co-occur, especially in unhealthy eaters (REs and E/UEs), suggesting that individuals who started with higher levels of one type of problem were more likely to have higher levels of the other as well. In healthy eaters, changes in internalising and externalising problems were positively correlated, indicating that as one type of problem decreased, the other tended to decrease as well. Additionally, in contrast to the other groups, in REs, there was a significant positive correlation between the initial levels of internalising problems and the changes in externalising problems over time, suggesting that higher initial levels of internalising problems were related to more subsequent changes in externalising problems. No other significant relationships between internalising and externalising problems were found in these analyses.

Group differences in brain maturation across adolescence

Longitudinal analyses were conducted to investigate between-groups differences in brain maturation during adolescence, comparing changes in grey matter volumes (GMV), cortical thickness (CT), and sulcal depth (SD) from age 14 to 23. All primary analyses included sex, recruitment sites, and total intracranial volume (TIV) as covariates.

For GMV (**Supplementary Table S6** and **Fig. 4a**), longitudinal VBM analyses were conducted, which revealed significant age-by-group interactions. Compared to HEs, REs showed smaller GMV reductions in the left cerebellum. E/UEs had smaller GMV reductions in 2 subclusters in the left cerebellum and 5 subclusters in the right hemisphere, including the middle frontal gyrus (MFG), putamen, medial superior frontal gyrus (SFGmedial) and postcentral gyrus. Lower GMV increase in the right parahippocampal gyrus was also observed. Differences remained similar after controlling for the joint effects of pubertal status, IQ, educational attainment and age- and sex-adjusted BMI (**Supplementary Table S7**). No significant differences in GMV trajectory were observed between REs and E/UEs.

For CT (**Supplementary Table S8** and **Fig. 4b**), mixed linear analyses revealed significant age-by-group interactions in the right frontal pole when comparing E/UEs to REs, with REs experiencing more pronounced CT reduction. In contrast, comparing E/UEs to HEs revealed significant interactions across 9 brain regions. These included the left lingual gyrus, bilateral frontal pole, bilateral rostral MFG, left pericalcarine, left cuneus, right caudal MFG and right caudal anterior cingulate gyrus, with E/UEs displaying less CT reduction than HEs. Most differences remained significant after controlling for the joint effects of pubertal status, IQ, educational attainment (EA), age- and sex-adjusted BMI, Euler's number, and their joint effects (**Supplementary Table S9**).

Regarding SD (**Supplementary Table S10** and **Fig. 4c**), REs had a less pronounced reduction in the left frontal pole compared to E/UEs. Moreover, E/UEs displayed larger SD reductions across 9 regions compared to HEs, including the bilateral rostral MFG, left frontal pole, bilateral SFG, right caudal MFG, right pars orbitalis, right pars opercularis, and right pars triangularis gyrus. Most differences remained significant after controlling for all covariates (**Supplementary Table S11**).

No significant age-by-group interactions in CT and SD were found when comparing REs to HEs.

Brain maturation mediates relationships between adolescent psychopathology and eating behaviours

We conducted mediation analyses to examine whether the brain differences identified above mediated the relationships between variations in internalising (IP) and externalising problem (EP) trajectories during adolescence and eating behaviours in young adulthood, as determined by the k-means derived clusters (the "psychopathology-brain maturation-eating behaviours" models). Brain regions with significant group differences in their GMV, CT or SD trajectories were identified as regions of interest (ROIs) and tested for their mediating effects on behavioural group differences between RE or E/UEs compared to HEs. For REs, the cluster in the left cerebellum was used as the ROI. For E/UEs, differences across E/UE-related clusters were combined into a single ROI for each structural brain measure. All primary mediation analyses were adjusted for sex, recruitment sites, and TIV differences to account for overall brain size variations across ages.

For REs, who differed from HEs during adolescence by their increasing trajectories of internalising problems (IP slope) and less pronounced GMV reductions in the left cerebellum,

differences in cerebellar volume reductions partially mediated the relationship between increased internalising problems and being classified as an RE at age 23 (**Fig. 5a**). This mediation was no longer significant after adjustments for BMI, IQ and pubertal status.

Behaviourally, E/UEs differed from HEs in adolescence by their higher levels of internalising and externalising problems (EP and IP intercepts) and increasing trajectory of internalising problems (IP slope). Nominal significance was found when testing the mediation effects of GMV (**Fig. 5b**) and CT (**Fig. 5c**) differences on the relationship between IP slope and being classified as an E/UE at age 23. Mediation in the "IP slope-GMV-E/UE" model remained significant after controlling for covariates, while for the "IP slope-CT-E/UE" model, the mediation remained significant after adjusting for BMI or EA, but no longer when adjusting for pubertal status or IQ. GMV differences in E/UE-related ROIs significantly ($p < .001$) also mediated the associations between EP intercept and E/UEs (**Fig. 5d**). This was unaffected by BMI, IQ, EA or pubertal status. No significant mediating effects were found for SD differences.

Altogether, these findings suggest that altered neurodevelopment in the restrictive and emotional/uncontrolled eating groups, as evidenced by protracted GMV and CT reductions, may contribute to ED symptoms, partly by mediating the effects of internalising and externalising problems.

Relationships between genetic predispositions, brain maturation, psychopathology and eating behaviours

Considering the effects of covarying BMI in the mediation analyses above, we explored the potential contributions of polygenic risk for higher BMI. Simple "genetics-brain maturation-eating behaviours" mediation models indicated that smaller GMV reductions in the RE and

E/UE groups (compared to HEs) mediated the effects of BMI PGS on eating behaviour profiles at age 23 in these groups (REs vs. HEs: indirect effect = 0.042, $p = 0.002$, 13.5% mediated; E/UEs vs. HEs: indirect effect = 0.043, $p = 0.026$, 11.7% mediated). For REs, this remained significant after adjusting for IQ, EA or pubertal status, not BMI. For E/UEs, this only remained significant after controlling for IQ or EA. No significant association was found between BMI PGS and CT reductions related to E/UEs. These analyses suggest that genetic predispositions to higher BMI influence BMI and restrictive and emotional/uncontrolled eating partly through their effects on protracted GMV reductions during adolescence.

Multivariate mediation analyses including internalising or externalising problems in these models revealed the unique contribution of smaller cerebellar GMV reductions in mediating the effects of BMI PGS on REs, when changes in internalising problems were also considered (**Fig. 5e)**. In contrast, smaller GMV reductions in E/UEs mediated the effects of early externalising problems (at age 14) in this group, beyond the effects of BMI PGS (**Fig. 5f)**. These findings suggest a specific role for cerebellar maturation in the control of BMI and restrictive eating, and additional roles for cortical and putamen maturations in mediating the effects of behavioural problems on emotional/uncontrolled eating.

Discussion

In this study, we used a longitudinal, multivariate analytical framework to explore the interplay among eating behaviours, genetic factors, ED-related psychopathology, and brain maturation during adolescence. Our analyses revealed a high prevalence of unhealthy eating behaviours (restrictive and emotional/uncontrolled eaters) associated with higher BMI and BMI PGS. Unhealthy eaters exhibited higher levels of externalising problems (emotional/uncontrolled eaters) and increasing trajectories of dieting (restrictive and emotional/uncontrolled eaters), binge eating (emotional/uncontrolled eaters) and internalising problems (restrictive and emotional/uncontrolled eaters). Age-related decreases in volumes and thickness in several brain regions, particularly in the cerebellum and prefrontal cortex, were less pronounced in restrictive and emotional/uncontrolled eaters compared to healthy eaters, suggesting protracted brain maturation. Smaller volumetric reductions in the left cerebellum mediated the effects of BMI PGS on restrictive eating, even after accounting for internalising problems. Reductions within additional brain regions of the right hemisphere uniquely mediated the relationship between externalising problems and emotional/uncontrolled eating, even after accounting for BMI PGS. These findings enhance our understanding of adolescent neurodevelopment related to eating disorder symptomatology.

Unhealthy eaters were characterised by differing trajectories of ED symptoms during adolescence, with increasing rates of binge eating, dieting and purging in emotional/uncontrolled eaters, suggesting a greater risk for BN, in line with previous research[6]. Unsurprisingly[11,28], higher levels of externalising problems in this group also indicated that adolescents with ADHD and conduct disorder symptoms may be more likely to

engage in emotional/uncontrolled eating. Internalising problems also increased during adolescence in unhealthy eaters, notably in emotional/uncontrolled eaters, highlighting the close relationships between emotional eating and psychological well-being[29]. While the decreasing levels of internalising and externalising problems in healthy eaters replicate previous findings[30], differing trajectories in unhealthy eaters, already evidenced at age 14, indicate that internalising and externalising problems predate the development of ED symptoms.

Consistent with cortical development trajectories[31,32], declines in structural brain measures (except for increases in sulcal depth) were observed in all eating groups, with evidence of protracted brain maturation in unhealthy eaters. Protracted brain maturation was also related to internalising and externalising problems, corroborating findings from children[33], and findings of delayed trajectories of cortical thinning in children and adolescents with ADHD[34]. The smaller volumetric reductions in the cerebellum observed in unhealthy eaters support its role in eating pathology. Findings from anatomical, functional, and behavioural studies indicate that the cerebellum is involved in the regulation of feeding behaviours and appetite control[35,36,37,38]. Disruption of a cerebellum-driven satiety network contributes to excessive eating, difficulties in stopping eating, and weight gain[38]. Our finding of protracted cerebellar maturation in unhealthy eaters suggests disrupted development of such satiety network, and engagement in restrictive eating as a compensatory mechanism to consciously control weight gain. Additional alterations in reward (right putamen) and prefrontal (e.g., right PFC) circuitry might lead emotional/uncontrolled eaters to also engage in disinhibited eating due to impairments in self-regulation[39] and impulsive action control[40], making them more susceptible to emotional and uncontrolled eating behaviours.

Genetic and environmental factors[41] contribute to changes in developmental brain trajectories related to eating. Genetic risk for obesity was previously found to correlate with disordered eating and weight control behaviours in adolescents[42,43]. High BMI was also found to be associated with reduced cortical thinning in adolescence[44,45]. Our findings extend these analyses, indicating that genetic risk for obesity may influence eating-related weight control behaviours partially via effects on cerebellar maturation, in a BMI-dependant manner.

Environmental stressors, such as adverse social environments and peer interactions, also modulate brain development[46]. Smaller GMV decreases in the cerebellum, PFC and anterior cingulate, are observed in adolescents disliked by their peers, correlating with callous-unemotional traits found in externalising disorders[47]. This altered brain development may underlie these adolescent adjustment problems and hypersensitivity to peer rejection[48]. Our findings suggest that adjustment problems influence brain maturation beyond genetic predispositions for high BMI, increasing the risk for emotional/uncontrolled eating.

Our study's key strengths include a well-characterized, deeply phenotyped longitudinal adolescent cohort and an innovative multivariate analytical approach. However, some limitations exist. First, the analysis is based on participants of European ancestry, necessitating future research with more ethnically diverse samples for broader applicability. Second, the use of summary scores to assess eating behaviours may oversimplify complex interactions and variations. Third, some analyses rely on VBM, which can impact GMV estimates[49]. Additionally, while we considered cortical thickness and sulcal depth, we did not

analyse surface area, a key volume component with distinct genetic architecture, reducing the resolution of our genetic findings.

Nonetheless, our study sheds light on how genetic risk for higher BMI, along with increasing internalising and externalising problems experienced during adolescence, distinctly contributes to unhealthy eating through their effects on brain maturation. The implications of these findings underscore the potential benefits of education targeting early maladaptive coping mechanisms and dietary habits to prevent eating disorders while promoting brain health.

Methods

Participants

Data analysed in this study was collected as part of IMAGEN, a longitudinal genetic × neuroimaging cohort study of adolescents recruited from eight study centres in England, Ireland, France and Germany[50]. Information on specific ethnic categories was not collected, but the study, aimed at identifying the genetic and neurobiological basis of individual variability in behaviour, was designed to include predominantly participants of European ancestry (White), based on their self-reports. To further account for population stratification, statistical approaches were applied to identify and exclude genetic ancestries other than European, when analysing the genetic data. The IMAGEN study was approved by local research ethics committees at each study site, and informed consent was obtained from participants and their parents/guardians. A detailed description of the study protocol and data acquisition can be found in[50]. Specifically, the Strengths and Difficulties Questionnaire (SDQ) questionnaire data used in this study were acquired at ages 14, 16, 19 and 23 years; neuroimaging data (N = 949) were acquired at ages 14 and 23 years, and the Three-Factor Eating Questionnaire (TFEQ) data were obtained at age 23 (N = 996).

Neuropsychological assessments

Eating behaviours

The short version (18 items) of the Three-Factor Eating Questionnaire (TFEQ) was used to assess eating behaviours. It contains three subscales: cognitive restraint, which measures the tendency to restrict one's food intake constantly and consciously instead of using physiological cues, hunger and satiety, as regulators of food intake (6 items); emotional

eating, which reflects the tendency to eat in response to negative emotions (3 items); and uncontrolled eating, which characterise the tendency to overeat, with the feeling of being out of control (9 items). It has good structural validity and has been used and validated in different European populations[7,51], and was found to distinguish different eating patterns in the general population[52].

Eating disorder symptoms

Dieting, binge eating and purging symptoms were assessed using the self-reports from the eating disorder section (section P) of the Development and Well-being Assessment[21,53]. Dieting symptoms were evaluated based on responses to questions P18a, P18b, and P18c, which asked about eating less at meals, skipping meals, and fasting, respectively. Binge eating symptoms were assessed using the question P15, which inquired about eating a large amount of food and losing control overeating. Purging symptoms were measured using the questions P1c, P18f, and P18g, which asked about self-induced vomiting or taking pills or medicines to lose weight.

Emotional and behavioural problems

The Strengths and Difficulties Questionnaire (SDQ) was used to assess emotional and behavioural problems in adolescents. It has five hypothesised subscales, including emotional symptoms, conduct problems, hyperactivity/inattention, peer relationship problems and prosocial behaviours[54]. In low-risk and general population samples, the emotional and peer subscales can be combined into an "internalising" subscale (10 items) and the behavioural and hyperactivity subscales into an "externalising subscale (10 items), respectively[55]. We

used self-reported scores at ages 14, 16, 19 and 23 years for internalising problems (IP) and externalising problems (EP) in further analyses.

Structural magnetic resonance imaging acquisition and processing

MRI images were acquired with 3T MRI scanners from different manufacturers (Siemens, Munich, Germany; Philips, Best, The Netherlands; General Electrics, Chalfont St Giles, UK; Bruker, Ettlingen, Germany) from eight IMAGEN recruitment sites. The high-resolution anatomical MRI images acquired included a three-dimensional T1-weighted magnetisation prepared gradient echo sequence (MPRAGE) based on the ADNI protocol (http://adni.loni.usc.edu/methods/documents/mri-protocols/), T2 weighted fast-spin echo, and FLAIR scans for visual assessment.

All raw images were visually inspected to exclude images with movement artefacts, brace artefacts, or field inhomogeneities prior to pre-processing. The pre-processing procedures were then conducted using the Computational Anatomy Toolbox (CAT 12.8 (r1907); https://neuro-jena.github.io/cat/) in SPM 12 (Wellcome Department of Cognitive Neurology). We used the "segment longitudinal data" procedure with default settings. Intra-subject co-registration was performed on the baseline (at age 14) and follow-up (at age 23) images. The co-registered images were then realigned across participants and bias-corrected with reference to the mean images computed from each subject's baseline and follow-up images. Next, the baseline and follow-up images as well as their means images were segmented into grey matter, white matter and cerebrospinal fluid based on the default tissue classification map. Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) normalisation was subsequently performed on the segmented mean images using

the default DARTEL template. The derived spatial normalisation parameters were then applied to transform the segmented subject baseline and follow-up grey matter images into the standard Montreal Neurological Institute (MNI) space. All normalised grey matter images were finally smoothed with an isotropic Gaussian kernel of 6 mm full width at half maximum (FWHM). The quality measures created during pre-processing for each participant at each time point were examined, and images with sufficient quality (corresponding to grade D or above) were included in further analyses. Changes in grey matter volumes (GMV) were analysed using whole-brain voxel-based morphometry (VBM). Measures of cortical thickness (CT) and sqrt-transformed sulcal depth (SD), which were then resampled to 12 mm in line with the recommendation for surface measures, were also derived. Longitudinal changes in mean CT and SD were extracted for different regions of interest (ROIs) using the Desikan-Killiany atlas (*N* of ROIs = 68).

BMI Polygenic scores (PGS)

A total of 2,087 participants were genotyped with the Illumina Human610-Quad BeadChip and Illumina Human660-Quad BeadChip during the baseline assessments. Stringent quality control procedures were performed prior to imputation (**Supplementary Information**). In brief, multi-dimensional scaling analysis and principal component analysis were conducted to identify genetic ancestry. Participants who were outliers from the European superpopulation were excluded (**Supplementary Fig. S4** and **S5**) due to the limited portability across ancestries for polygenic scores. Consequently, 1,899 Participants (49.66% males) who passed genotyping QC and were identified as of European ancestry were selected for generating the BMI PGS. IMAGEN genotype data was integrated into the European ethnicity 1KGP (phase 3 release v5) reference panel[56] for imputation. Summary statistics of genome-wide

association study (GWAS) of BMI from ~681,275 individuals of European ancestry[57] was used to calculate BMI PGS. This was achieved using PRS-CS[58], which utilises high-dimensional Bayesian regression and a continuous shrinkage prior to SNP effect sizes. The global shrinkage parameter was set to 0.01 as recommended for highly polygenic traits. A total of 905,362 SNPs were used to predict BMI PGS. Participants with available TFEQ scores were included in the subsequent analyses (RE: N = 255; E/UE: N = 194; HE: N = 347). The BMI PGS was residualised for the first 10 PCs and batch effects before being Z-scored for the subsequent analyses.

Statistical analyses

Identification of groups with distinct eating behaviours by K-means clustering

K-means clustering using the TFEQ subscale scores (i.e., cognitive restraint, emotional eating and uncontrolled eating) at age 23 was performed to identify clusters exhibiting different eating behaviours. All continuous variables were transformed into z-scores. We used the "NbClust" package to identify the optimal cluster number and validity of the cluster solution, and the "fpc" package to examine the clustering stability with the Jaccard coefficient and a bootstrap technique (N = 1000) in R.

Group differences in trajectories of eating disorder symptoms across adolescence

Linear mixed models were used to examine group differences in the trajectories of dieting, binge eating and purging from ages 14 to 23. Age (i.e., 14, 16, 19 and 23) was treated as a categorical variable. The models included age, group, and age-by-group interactions as fixed effects and adjusted for sex. Random intercepts for participants nested within recruitment

sites accounted for the dependence of repeated measures. Group-by-age interactions were investigated using healthy eaters (HEs) and age 14 as reference. A Bonferroni correction accounting for 18 tests (3 ED symptoms × 2 groups comparisons × 3 age comparisons) was applied (i.e., $p_{\text{Bonferroni}} = 2.78 \times 10^{-3}$).

Group differences in trajectories of internalising and externalising problems

The latent growth curve models (LGCM) using the "lavaan" package in R were conducted in these analyses.

Univariate LGCM analyses: Latent factors of intercept and slope were estimated for repeated measures (at ages 14, 16, 19, and 23 years) of IP and EP scores separately. Sex, groups and recruitment sites were considered time-invariant covariates. For these analyses, we included only those participants who had TFEQ scores at age 23 and had at least one measure of IP or EP at ages 14, 16, 19 and 23. For both IP and EP, we attempted to fit a quadratic term; however, this specification resulted in a non-positive definite covariance matrix, driven by a correlation greater or equal to one between the linear and quadratic terms. Hence, we decided not to include a quadratic term as the information contained within it was not adding any extra information over the linear term. The full information maximum likelihood estimator was utilised to account for data missing at random. We investigated group differences in intercepts and slopes of IP and EP trajectories, taking HEs as a reference. Bonferroni-corrected *p*-value threshold of 0.05/(2 behaviours × 2 measures × 2 groups) = 6.25×10^{-3} was considered statistically significant.

Multivariate LGCM analyses within each group were also run to estimate models for IP and EP trajectories simultaneously and investigate covariances between latent factors (i.e., IP

intercept, IP slope, EP intercept, and EP slope). Sex and recruitment sites were included as covariates.

Group differences in brain maturation: Longitudinal MRI analyses

Participants were excluded from the analysis if they had missing MRI data or failed to meet quality control criteria (N = 47; see **Methods** for image pre-processing and QC). Consequently, a total of 949 participants (306 REs, 236 E/UEs, and 407 HEs) were included in the whole-brain VBM analysis and linear mixed models for cortical thickness (CT) and sulcal depth (SD).

VBM analysis: longitudinal whole-brain voxel-based morphometry (VBM) analyses were performed using the CAT 12.8 (r1932) toolbox. To identify brain regions reflecting significant changes in grey matter volumes (GMVs) between ages 14 and 23 among the groups identified above, we performed a 2 × 2 mixed ANOVA on the smoothed images using the "Flexible Factorial" model. The two factors were age (age 14 or age 23; within-subject) and group (i.e., comparison of each of 2 groups, namely REs versus HEs, E/UEs versus HEs, or REs versus E/UEs; between-subject). Intracranial volumes (TIVs) were estimated by CAT 12.8 as the sum of the grey matter, white matter and cerebrospinal fluid volume. Analyses were controlled for the effects of participants' sex, the scanning site and TIV at each time point (at ages 14 or 23). An absolute threshold masking of 0.1 was applied. The grey matter morphological differences showing significant age-by-group interactions were reported after a cluster-level family-wise error correction with a p-value < 0.05, and a cluster-forming threshold of p-value < 0.001 without correction.

Linear mixed models: For group differences in changes in CT and SD, we performed regions of interest (ROIs)-based linear mixed models, investigating interactions between age and

groups. Models included age, groups, and their interactions as fixed effects, with the participant nested within recruitment sites as a random effect and adjusted for sex. For both measures, the Bonferroni correction was applied to adjust for multiple testing ($p = 0.05/68$ ROIs × 3 group comparisons = 2.45×10^{-4}).

Mediation analyses

Simple mediation models were performed using the PROCESS v4.0 macro for R to test whether the between-group differences in brain changes mediated the relationships between differences in IP or EP trajectories and eating behaviours. We refer to this model as the "psychopathology-brain maturation-eating behaviours" model). Brain clusters that significantly differentiated REs from HEs, E/UEs from HEs, or REs from E/UEs were considered regions of interest (ROIs). For group comparisons involving several brain clusters, these clusters were combined into a single ROI for each structural measure (GMV, CT or SD). For comparisons between REs and HEs, one mediation model was tested – relating GMV differences in the left cerebellum to differences in IP slope–, therefore, a p-value threshold of 0.05 was considered significant. Comparisons between E/UEs and HEs: these two groups differed behaviourally in IP intercept, IP slope, and EP intercept, and in their changes of GMVs, CTs, and SDs, therefore 9 mediation models were tested. The Bonferroni-corrected significance threshold of 0.05/(3 trajectory measures × 3 structural brain measures) = 5.56×10^{-3} was applied.

Subsequent analyses investigated the potential contributions of the BMI PGS on brain mediation models identified above, referred to as the "genetics-brain maturation-eating behaviours" models. The same brain ROIs were considered as mediators in these models. For models comparing REs to HEs, the significance was set at $p = 0.05/(1$ structural measure) =

0.05. For models comparing E/UEs to HEs, the significance was set at $p = 0.05/3$ structural measures = 1.67×10^{-2}.

Multivariate mediation models were conducted using AMOS 29, to explore the unique contributions of brain ROIs, psychopathology (IP and EP trajectories) and BMI PGS to mediation models identified in simple mediation analyses, referred to as the "genetics-psychopathology-brain maturation-eating behaviours" model. Continuous variables were transformed into z-scores for these analyses. Confidence intervals (CIs) for the mediation effect were estimated from 5000 bootstrap samples.

Covariates

Covariates for all analyses included sex and recruitment sites. For analyses involving GMV, total intracranial volume (TIV) at the corresponding age was additionally included as a covariate. Since there were no significant group differences in age at each data collection, age was considered as a categorial variable in the linear mixed models, and as time points in repeated measures in the LGCM analysis. For the longitudinal MRI analysis (VBM analysis and linear mixed models), participants nested within recruitment were modelled as a random effect, and sex was considered a fixed effect in the model.

Other covariates: To examine the robustness of findings from our primary analyses, sensitivity analyses were conducted by including pubertal status, IQ, educational attainment (EA), and age- and sex-adjusted BMI as additional covariates. Pubertal status was assessed using the Puberty Development Scale[59], an 8-item self-report measure of physical development based on Tanner stages, separate for males and females. IQ was calculated as the average of Perceptual Reasoning Index (PRI) and Verbal Comprehension Index (VCI)

scores based on age norms using the Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV; Pearson Clinical Assessment UK). We administered the block design, matrix reasoning, similarities and vocabulary subtests. Raw scores from each subtest were converted into scaled scores based on age norms. For both the PRI and VCI, we calculated prorated sums of scaled scores and then converted these sums into index scores according to the WISC-IV manual. EA was assessed by self-report of the "average grade at the end of the last term completed". The age- and sex-adjusted BMI Z-score at age 14 was calculated using the jBmi R package based on the CDC recommendations.

Data availability

Access to individual-level data from the IMAGEN project is accessible to bona fide researchers upon reasonable request and approval of a project proposal by IMAGEN consortium PIs. Contact the corresponding author for requests related to this study.

Summary statistics from the BMI GWAS, used in this study for computing BMI PGS, are accessible via[57], and can be downloaded from their website at https://portals.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium_data_files. Data from the 1000 Genomes Project Phase 3 may be accessed from https://www.internationalgenome.org/category/phase-3/.

Code availability

R (version 4.3.2) was employed to perform ANOVA and mixed linear model analysis. Mediation analysis was performed with the PROCESS R macro (version 4.3) and AMOS (version 20.0). MATLAB (version: 2022b) was employed to process the structural MRI

images and perform VBM analysis. The polygenic score was calculated using the publicly available PRS-cs toolbox (https://github.com/getian107/PRScs) and LD references constructed using the 1000 Genome Project phase 3 samples with European ancestry. MRIcro (version 1.9.1; https://www.nitrc.org/projects/mricro), BrainNet Viewer (version: 20191031; https://www.nitrc.org/projects/bnv) and ENIGMA visualisation tool (https://github.com/MICA-MNI/ENIGMA/tree/master/enigmatoolbox) were used to visualise images. Other scripts used to analyse the data of this study are publicly available https://github.com/XinyangYu918/EatingBehaviours-BrainMaturation-Psychopathology-Genetics.

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Disclosures

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Figures and figure legends

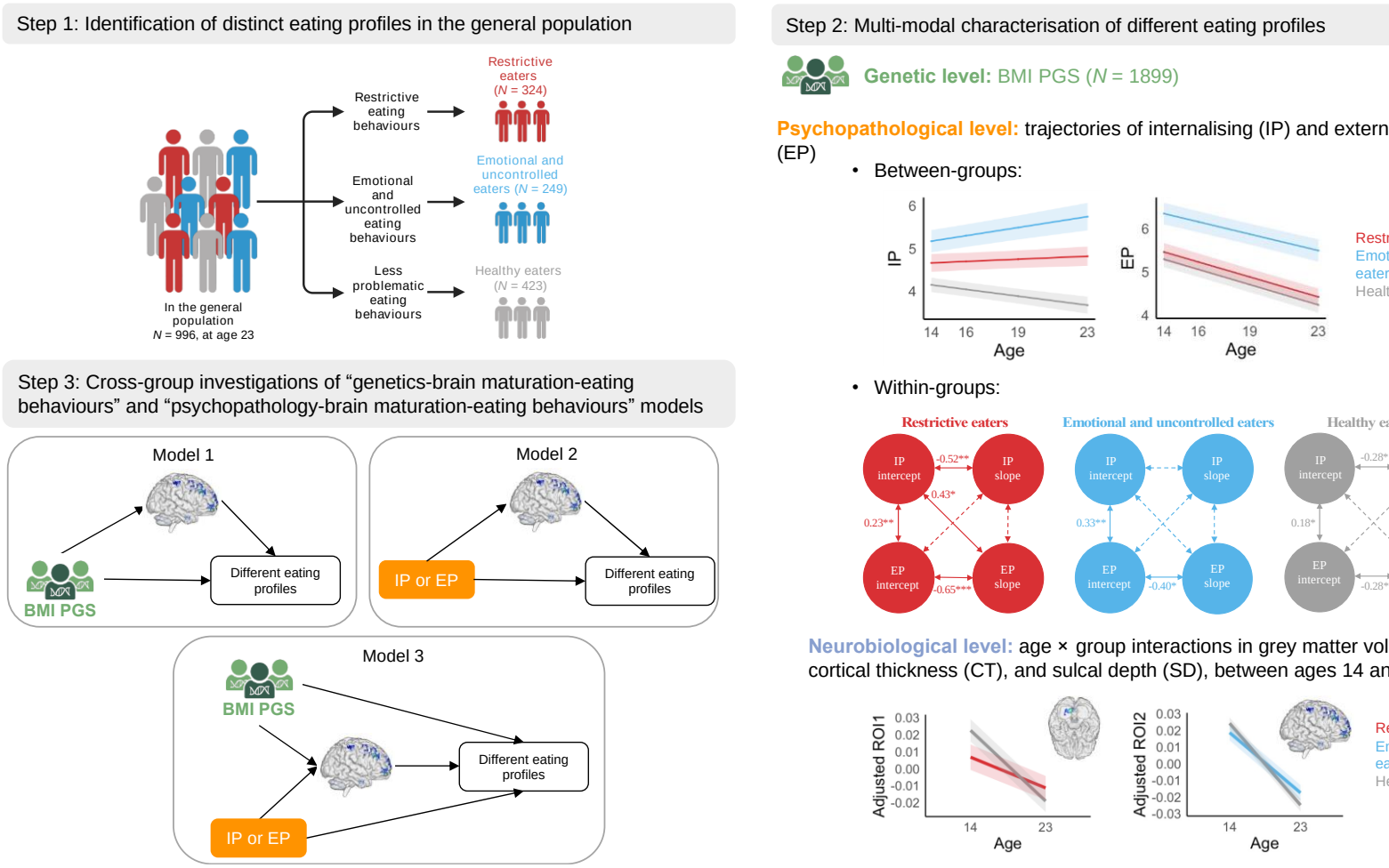


Fig. 1. Workflow of research questions and analyses.

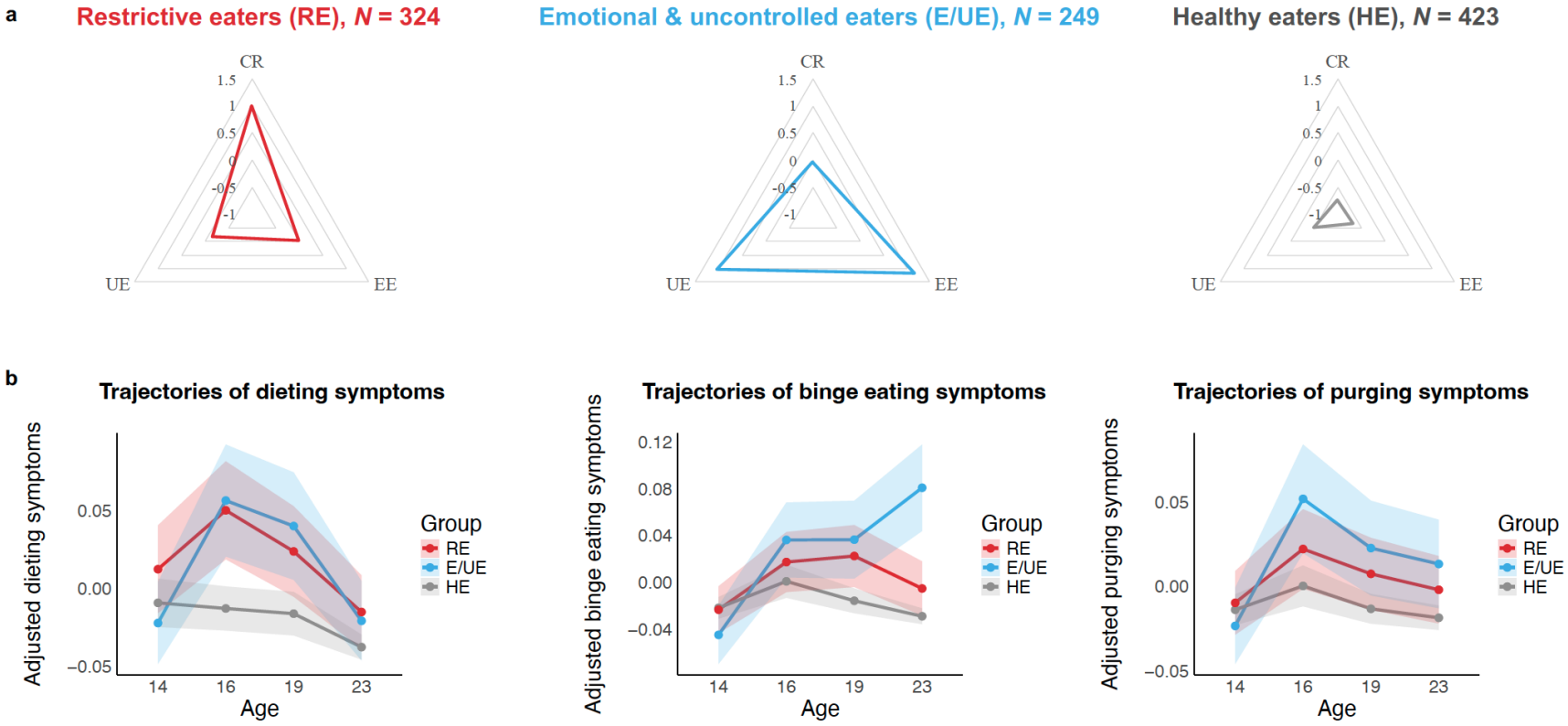
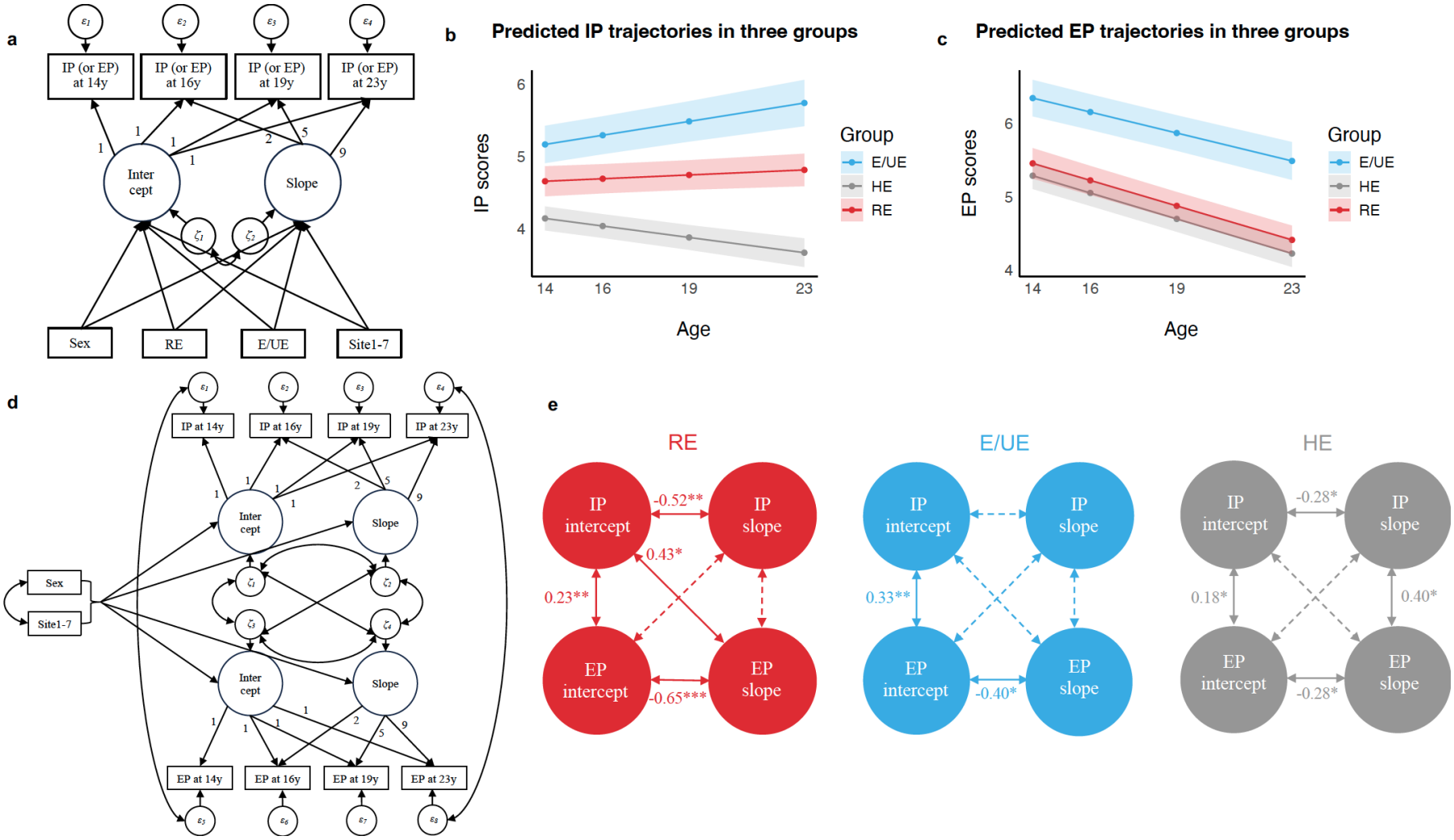


Fig. 2. a, Three groups of distinct eating behaviour profiles were identified by K-means clustering at age 23. CR, cognitive restraint; EE, emotional eating; UE, uncontrolled eating. The radar charts display the average standardised scores for CR, EE, and UE across these groups. **b**, Trajectories of eating disorder symptoms (dieting, binge eating and purging symptoms) from ages 14 to 23 across the three identified groups. The lines represent the mean symptom scores, and the shaded areas show the 95% confidence intervals. Analyses were adjusted for sex and recruitment sites. The y-axis indicates the adjusted symptoms scores after regressing out the effects of sex and recruitment sites.



841

842 **Fig. 3.** Psychopathological characterisation across groups using internalising and externalising problems. **a**, Path diagram for the conditional

843 linear latent growth curve model for individual IP and EP trajectories among three groups. Two dummy variables, RE and E/UE, were included

to represent three groups (HE was considered the reference group in the model). Gender and seven dummy variables for different recruitment sites were included as covariates in the analysis. Post-hoc analyses were conducted to examine the differences between the RE and E/UE groups. **b**, Predicted trajectories of IP across three groups. **c**, Predicted trajectories of EP across three groups. **d**, Path diagram for the multivariate latent growth curve model for each group separately. **e**, Significant within-construct and cross-construct correlations between IP and EP trajectories were found within each group. The numbers indicate standardised covariances (i.e., correlations) values. *, $p < 0.05$, **, $p < 0.01$, ***, $p < 0.001$.

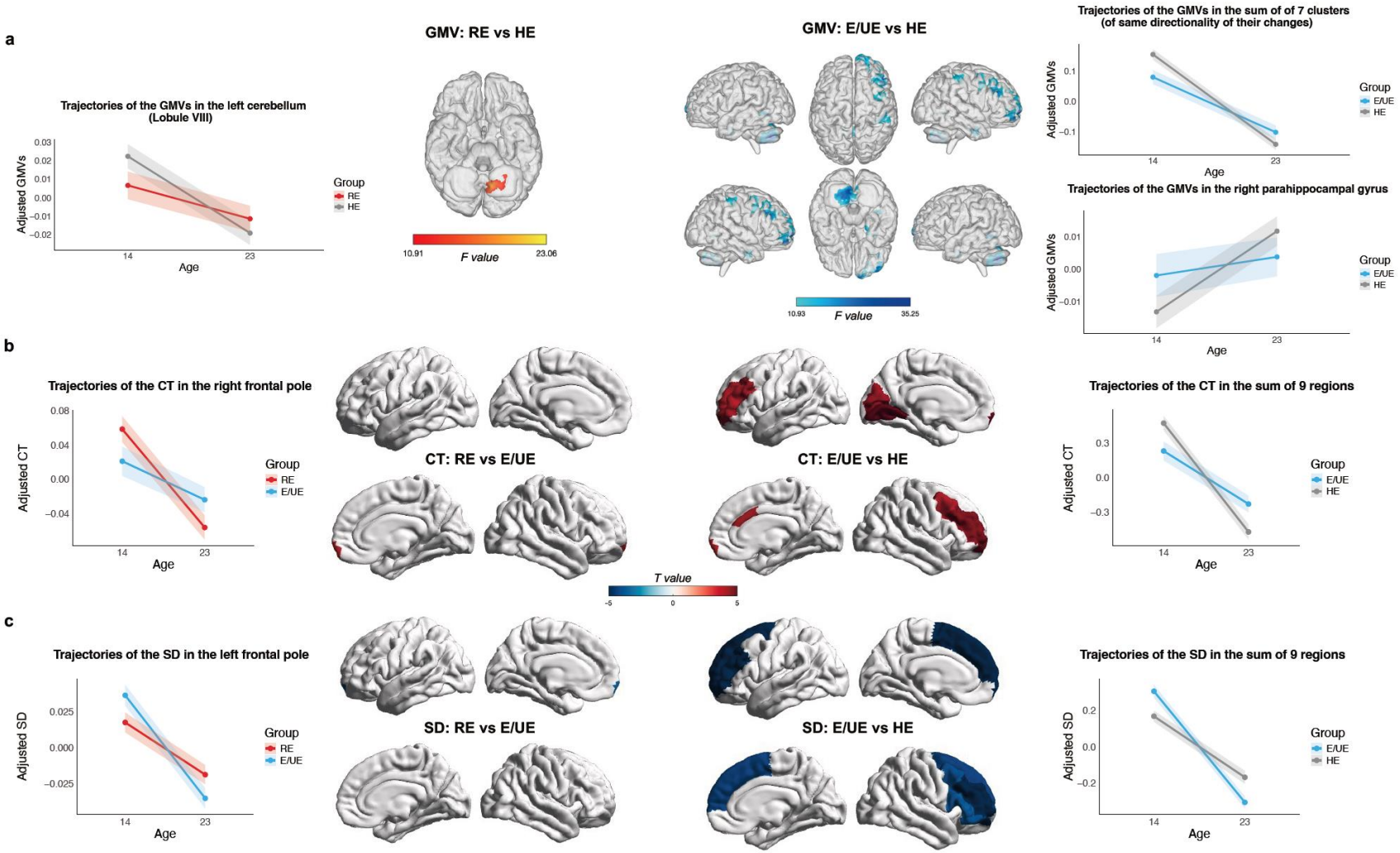


Fig. 4. Significant age-by-group interactions were identified in various brain morphological features, including grey matter volume (GMV; **a**), cortical thickness (CT; **b**) and sulcal depth (SD; **c**). **a**, A significant age-by-group interaction was observed between REs and HEs, ages 14 to 23,

indicating that REs experienced a smaller volumetric reduction in the left cerebellum compared to HEs over time. E/UEs exhibited less volumetric reductions in multiple brain regions, including the left cerebellum, right middle frontal gyrus, right medial superior frontal gyrus, right postcentral gyrus, and right putamen compared to HEs. However, E/UEs had volumetric increases in the right parahippocampal gyrus compared to HEs. **b**, Comparisons of CT trajectories between REs and E/UEs showed that REs experienced more pronounced CT reductions in the right frontal pole. CT trajectory comparisons between HEs and E/UEs revealed that HEs experienced more pronounced CT reductions across a wide range of brain regions, including the frontal and occipital gyri, and the anterior cingulate gyrus, compared to E/UEs. **c**, SD trajectory comparisons between REs and E/UEs indicated that REs had less pronounced SD reductions in the left frontal pole. Comparisons of SD trajectories between HEs and E/UEs revealed that HEs had less pronounced SD reductions in the frontal and temporal regions. All analyses were adjusted for sex, recruitment sites, and total intracranial volume. The lines in the figures represent mean values for brain morphological features and the shaded areas represent the corresponding 95% confidence intervals. The y-axis indicates the adjusted symptom scores after regressing out the sex, recruitment sites, and total intracranial volume.

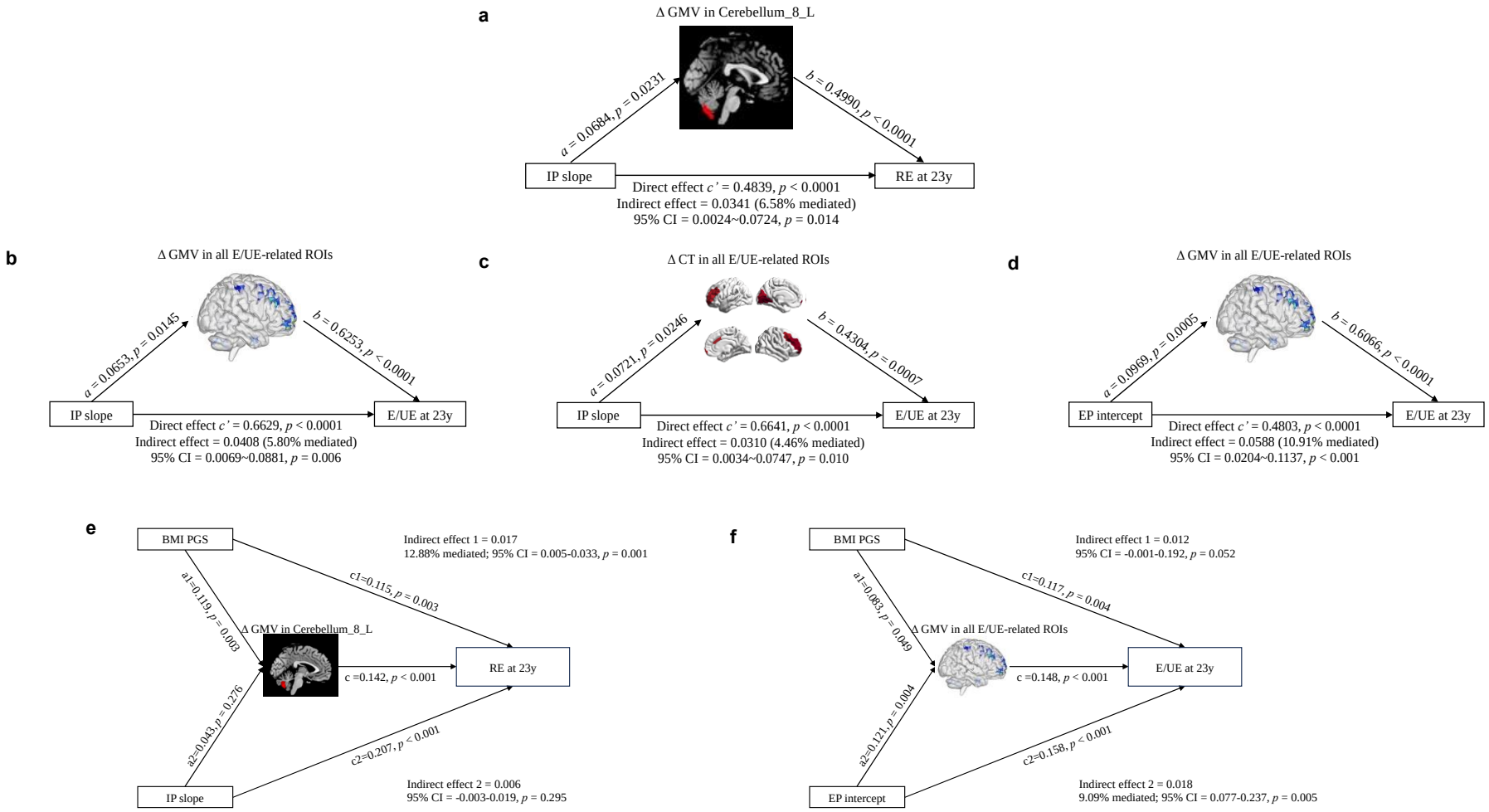


Fig. 5. The "psychopathology-brain maturation-eating behaviours" and "BMI PGS-brain maturation-eating behaviours" models. **a**, Mediation effect of GMV reductions in the left cerebellum (ages 23-14) on the relationship between age-related IP (IP slope) and RE at age 23. **b**,

Mediation effects of GMV reductions on the relationship between age-related IP changes (IP slope) and E/EU at age 23, considering all E/UE-related ROIs (except right parahippocampal gyrus, due to the different directionality of its changes compared to other ROIs). **c**, Mediation effects of CT reductions on the relationship between age-related IP changes (IP slope) and E/EU at age 23, considering all E/UE-related ROIs. **d**, Mediation effects of GMV reductions on the relationship between EP intercept and E/EU at age 23, considering in all ROIs (except right parahippocampal gyrus, due to the different directionality of its changes compared to other ROIs). **e**, The unique contribution of smaller cerebellar GMV reductions in mediating the effects of BMI PGS on restrictive eating, when IP trajectory was also included in the model. **f**, The unique contribution of GMV changes in all E/UE-related ROIs (except right parahippocampal gyrus) in the relationship between EP intercept and E/UE at age 23, beyond the effects of BMI PGS. All mediation models were adjusted for gender, recruitment sites, and TIV differences (between ages 14 and 23).

Table 1. Sample sizes and demographic characteristics of the three groups of participants with distinct eating profiles at age 23.

	Restrictive eaters, REs (N = 324)	Emotional and uncontrolled eaters, E/UEs (N = 249)	Healthy eaters, HEs (N = 423)	$F/\chi 2$	p	Post hoc tests (Bonferroni corrected)
Age at data collection: Mean (SD)						
Baseline	14.56 (0.43)	14.49 (0.41)	14.49 (0.42)	4.93	0.027	*NS*
Follow-up 1	16.46 (1.15)	16.26 (1.66)	16.44 (1.39)	0.00	0.997	-
Follow-up 2	19.37 (0.95)	19.29 (1.01)	19.30 (0.98)	0.70	0.403	-
Follow-up 3	22.75 (0.74)	22.68 (0.72)	22.66 (0.73)	2.81	0.094	-
Male/female (% females)	133/191 (58.95%)	92/157 (63.05%)	253/170 (40.19%)	42.10	< 0.001	REs vs HEs: p < 0.001; E/UEs vs HEs: p < 0.001
Eating behaviours: Mean (SD)						
Cognitive restraint	17.55 (3.03)	12.90 (3.70)	9.78 (2.42)	623.94	< 0.001	REs > E/UEs: p < 0.001; REs > HEs: p < 0.001; E/UEs > HEs: p < 0.001
Emotional eating	5.47 (1.76)	8.34 (2.13)	3.87 (1.22)	567.89	< 0.001	E/UEs > REs: p < 0.001; E/UEs > HEs: p < 0.001, REs > HEs: p < 0.001
Uncontrolled eating	18.84 (3.53)	25.15 (4.25)	17.06 (4.52)	307.45	< 0.001	E/UEs > REs: p < 0.001; E/UEs > HEs: p < 0.001, REs > HEs: p < 0.001
Developmental stage: Mean (SD)						
Pubertal status, at age 14	3.03 (0.53)	2.99 (0.53)	2.79 (0.58)	34.47	< 0.001	REs > HEs: p < 0.001; E/UEs > HEs: p < 0.001
Cognition: Mean (SD)						
IQ[a]	109.91 (12.51)	108.51 (12.93)	112.12 (12.85)	6.04	0.014	E/UEs < HEs: p = 0.0018
Educational attainment	2.78 (1.32)	3.02 (1.62)	2.66 (1.18)	1.88	0.170	-
Anthropometric variable: Mean (SD)						
BMI-Zscore, at age 14[b]	0.43 (0.77)	0.27 (0.90)	-0.17 (0.93)	83.34	< 0.001	REs > HEs: p < 0.001; E/UEs > HEs: p < 0.001
N (%) of available MRI data for longitudinal MRI analysis[c]	306 (94.44%)	236 (94.78%)	407 (96.22%)			
Polygenic scores: Mean (SD)						
N (%) of available genotyping data of European ancestry	285 (87.96%)	220 (88.35%)	376 (88.89%)			
BMI PGS-Zscore[d]	0.03 (1.02)	0.08 (0.88)	-0.24 (0.96)	13.56	< 0.001	REs > HEs: p = 0.001; E/UEs > HEs: p < 0.001

[a]IQ was calculated as the average of the Perceptual Reasoning Index and Verbal Comprehension Index scores based on age norms using the Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV; Pearson Clinical Assessment UK). [b]Age- and sex-adjusted BMI-Zscore was calculated using the jBMI R package (https://github.com/jbirstler/jBmi) based on the CDC recommendations. [c]Participants were excluded from the analysis if they had missing MRI data or failed to meet quality control criteria ($N = 47$; see Methods for image pre-processing and QC). [d]Participants who passed genotyping QC (see Supplementary Information) and were identified as of European ancestry were selected for generating the BMI PGS. BMI polygenic score (BMI PGS) was calculated using the publicly available PRScs and 1000 Genome Project 3 European LD panels (https://github.com/getian107/PRScs) and adjusted for the first 10 principal components of genetic ancestry and batch effects. The scores were Z-scored prior to analysis.