The impact of anorexia nervosa and obesity polygenic risk on childhood growth: a 20-year longitudinal population-based study

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Keywords: Eating disorder; Avon Longitudinal Study of Parents and Children (ALSPAC); growth trajectories; body mass index; fat mass index; fat-free mass index; bone mineral density; lean mass index.

Abstract

Background: Deviating growth from the norm during childhood has been associated with anorexia nervosa (AN) and obesity later in life. In this study, we examined whether polygenic scores (PGS) for AN and obesity are associated, individually or combined, with a range of anthropometric trajectories spanning the first two decades of life. **Methods:** AN-PGS and obesity-PGS were calculated for participants of the Avon Longitudinal Study of Parents and Children (ALSPAC; N= 8,654 participants with genotype data and at least one outcome measure). Using generalized (mixed) linear models, we associated PGS with trajectories of weight, height, body mass index (BMI), fat mass index (FMI), lean mass index (LMI), and bone mineral density (BMD). Growth trajectories were derived using spline modeling or mixed effects modeling. **Results:** Between age 5-24 years, Females with one SD higher AN-PGS had on average a 0.01% lower BMI trajectory, and between age 10-24 years a 0.01% lower FMI trajectory and 0.05% lower weight trajectory. Higher obesity-PGS was associated with higher BMI, FMI, LMI, BMD, weight, and lower height trajectories in both sexes. The average growth trajectories of females with high AN-PGS/low obesity-PGS remained consistently lower than those with low AN-PGS/low obesity-PGS; this difference did not reach statistical significance. However, post-hoc comparisons suggest that females with high AN-PGS/low obesity-PGS did follow lower growth trajectories compared to those with high PGS for both traits. **Conclusion:** AN-PGS and obesity-PGS have detectable sex-dependent effects on a range of anthropometry trajectories. These findings encourage further research in understanding how the AN-PGS and the obesity-PGS co-influence growth during childhood in which the obesity-PGS can mitigate the effects of the AN-PGS.

Introduction

Anorexia nervosa (AN) is a serious psychiatric disorder that is characterized by low fat and lean mass [1–3]. Observations from genome-wide association studies (GWAS) point toward the contribution of genomic variants that influence body composition as well as psychiatric traits [4]. Genetically, AN is negatively correlated with body mass index (BMI), fat mass, fat-free mass, and obesity [4], suggesting that biological mechanisms contributing to AN may also drive changes in body composition. This is supported by several studies showing that low premorbid BMI is associated with AN in adolescence [5,6] including an Avon Longitudinal Study of Parents and Children (ALSPAC) study that reported individuals who go on to develop AN followed lower BMI trajectories (as early as age 2 years) compared to their peers that did not develop an ED [7].

In contrast to low weight, obesity (i.e., BMI $\geq$ 30 kg/m^2) has been associated with increased risk for cardiovascular disease but also for psychiatric disorders [8,9]. In addition, individuals with higher body weight face stigmatization and prejudice from the public and health professionals, which can exacerbate the negative health effects of obesity [10–12]. Similar to AN, BMI has been extensively studied on a genetic level and has been shown to be a heritable polygenic trait [13,14]. Khera et al. [15] reported that an obesity polygenic score (obesity-PGS), constructed from genomic variants associated with BMI weighted by their reported effect sizes from a BMI GWAS [13], is associated with body weight at different timepoints during childhood and adolescence. For example, individuals with an obesity-PGS in the top decile show significantly, but modestly higher birth weight (+60 grams) than individuals with an obesity-PGS in the bottom decile [15]. However, this difference in weight becomes more pronounced over time with 3.5 kg at age 8 years and 12.3 kg at age 18 years [15]. These findings highlight differences in growth associated with the polygenic liability to higher BMI.

In summary, both AN and obesity have a genetic component that can be indexed by polygenic scores, and these genetic components are inversely correlated. However, it is unclear how genetic risk for both traits, individually and combined, affect growth developmentally during the first two decades of life. We identified individuals considered to be at high risk (defined as polygenic scores in the top deciles) for either AN or obesity and compared them with their peers with low polygenic risk on the same trait [16]. We then studied the longitudinal effects of the AN and obesity-PGS (separate and combined) on growth across development using data from ALSPAC.

Specifically, the aims of this study were to determine the effect (separate and combined) of an AN-PGS [4] and obesity-PGS [17] on weight, height, and BMI, as well as fat mass index (FMI), lean mass index (LMI), and bone mineral density (BMD) growth trajectories during the first two decades of life in the longitudinal population-based ALSPAC study [18–22]. We hypothesized that a higher AN-PGS would be associated with below average growth trajectories for weight, BMI, FMI, LMI, and BMD. Previous studies reported no genetic correlation between height and AN and therefore a height trajectory was included as a negative control as we predicted no association with the AN-PGS (3). We also hypothesized that a higher obesity-PGS would be associated with above average growth trajectories. Lastly, we hypothesized that individuals with a high AN-PGS and low obesity-PGS would represent a subgroup at higher risk for poor growth (below average growth trajectories) compared to those with both a low AN-PGS and a low obesity-PGS.

Methods

Participants

The ALSPAC study is an ongoing population-based birth cohort (14,541 pregnancies) study of mothers and their children (that were born between 1 April 1991 and 31 December 1992) residing in the southwest of England (UK) [18–22]. From the 14,541 pregnancies, 13,988 were alive at 1 year. At age 7 years this sample was bolstered with an additional 913 children. The total sample size for analyses using any data collected after the age of seven is therefore 15,454 pregnancies; of these 14,901 were alive at 1 year of age. Participants are assessed at regular intervals using clinical interviews, self-report questionnaires, medical records, and physical examinations. Study data were collected and managed using REDCap electronic data capture tools hosted at University of Bristol [23,24]. REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources. Please note that the study website contains details of all the data that is available through a fully searchable data dictionary at the following webpage: http://www.bristol.ac.uk/alspac/researchers/our-data/. To avoid potential confounding due to relatedness, one sibling per set of multiple births was randomly selected to guarantee independence of participants (N = 75). Furthermore, individuals who were closely related to each other, defined as a phi hat > 0.2 (calculated using PLINK v1.90b), were removed. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. Ethical approval for the study was obtained from the ALSPAC Ethics and Law

Committee and the Local Research Ethics Committees (Bristol and Weston Health Authority: E1808 Children of the Nineties: ALSPAC, 28th November 1989 (for details see: www.bristol.ac.uk/alspac/researchers/research-ethics/).

Consent for biological samples has been collected in accordance with the Human Tissue Act (2004). Informed consent for the use of data collected via questionnaires and clinics was obtained from participants following the recommendations of the ALSPAC Ethics and Law Committee at the time. The main caregiver initially provided consent for child participation and from the age 16 years the offspring themselves have provided informed written consent.

Measures

Weight, height, and body mass index (BMI). Numerous measurements on weight and height were collected from different sources (i.e., routine clinic visits, information collected from midwives, linkage to child health records) between birth and age 24 years. Information on weight was collected at research clinic visits annually up to the age 14 years and further clinic measurements at the ages 16, 18, and 24 years using the Tanita Body Fat Analyzer (Tanita TBFUK Ltd.) to the nearest 50 grams. During the same clinic visits, height (standing) was measured to the nearest millimeter with shoes and socks removed using a Holtain stadiometer (Holtain Ltd, Crymych, Pembs, UK). The different measurements of weight and height were highly correlated across various methods [18]. Information on child and adolescent BMI (weight in kilograms / height squared in meters) was derived using weight and height measurement obtained during clinic visits.

Fat mass index, lean mass index, and bone mineral density (BMD). All ALSPAC participants were invited to undergo a whole-body dual-energy x-ray absorptiometry (DXA) scans using the Lunar Prodigy dual-energy X-ray absorptiometry scanner as part of face-to-face visits at the ages of 10, 12, 14, 16, 18, and 24 years. Fat mass index was calculated by

dividing total body fat mass (in kilograms) by height (in meters) squared. Similarly, lean mass index was calculated by dividing total lean mass divided by height (in meters) squared. Additionally, whole-body (minus head) BMD was also estimated using the Lunar Prodigy dual-energy X-ray absorptiometry scanner.

Trajectory modeling

Censoring for the presence of an eating disorder

To derive the trajectories for each outcome, we censored for the presence of any eating disorder (ED); i.e., AN, bulimia nervosa, and binge-eating disorder. Information on a probable ED was available at age 14, 16, and 18 years [see [25,26] for more information on how ED diagnoses were derived]. The presence of an ED diagnosis at age 14 years meant that all values for that individual regarding their measurement (BMI, FMI, LMI, etc.) at age 14 years up to age 24 years were set to missing. This was also done for the presence of an ED diagnosis at age 16 years (set values at age 16 and beyond to missing), and 18 years (set values at age 18 and beyond to missing). Therefore, censoring did not lead to loss of participants in the analyses, but rather loss of observations (N = 1,055). This censoring allowed us to derive unbiased results in the following spline and trajectory modelling, while retaining the largest amount of data possible. This is important, as these models are sensitive to outliers and including individuals with EDs would be likely to introduce extreme values in the distribution.

Spline modeling (Table S1 and Figure S1)

Prior to analyses, BMI values (Table S1 and Figure S1) were transformed using the natural log due to the right-skewed distribution of the data. Spline models involve placing spline points (knots) at time points during longitudinal data collection where the direction of

growth changes. This is necessary as children's growth in the first two decades of life is not linear, following a more complex pattern, rendering standard growth models unsuitable to accurately reflect the data [27]. The advantage of linear spline models is that they allow knot points to be fitted at different ages to derive periods of change (between the knots) that are approximately linear. After visual inspection of the BMI means at each time point, three spline points (knots) were placed creating the following periods of linear growth between: age 4 months and 1 year, age 1 year and 5 years, and age 5 and 24 years. The linear spline modeling resulted in four parameters (coefficients) which we will refer to as: intercept (BMI at age 4 months), slope 1 (age 4 months - 1 year), slope 2 (age 1 year - 5 year), and slope 3 (age 5 year - 24 year; see figure S1). Spline models were obtained using STATA (v 15).

Mixed effects modeling (Table S1 and Figure S1)

We used mixed effects models to estimate growth over time for weight, height, FMI, LMI, BMD [28]. For each outcome, we estimated two parameters per participant; an intercept (measurement of the body composition measure at age 10 years) and a slope (a measure of linear growth). Prior to estimation of the parameters we log-transformed weight, height, FMI, LMI, and BMD due the right-skewed distribution of the data. We also calculated the squared slope, to examine if a non-linear, quadratic shape was necessary to capture the change in measures across time. Data for FMI, LMI, and BMD were measured objectively at 10, 12, 14, 16, 18, and 24 years during face-to-face visits as described above. For uniformity among analyses, we restricted analyses of weight and height to measurements at these ages. Height was included to test the quality of methodological approach as a negative control for the association with the AN-PGS. Previous studies reported no genetic correlation between height and AN and therefore we do not expect an association between

the AN-PGS and the height trajectory (3). Mixed effects modeling was carried out using STATA (v 15).

Genotyping

Genotype data were available for 9,915 children out of the total of 15,247 ALSPAC participants. Participants were genome-wide genotyped on the Illumina HumanHap550 quad chip. Following quality control of the genetic data, a total of 8,654 participants with genotyping data and at least one outcome measure were included in the analyses (Table 1). Details of the quality control checks are described in the Supplementary information.

PGS calculations

The AN-PGS was derived from the GWAS on AN by the Eating Disorders Working Group of the Psychiatric Genomics Consortium (PGC-ED; n_{cases} = 16,992, $n_{controls}$ = 55,525) [4] and the obesity-PGS was derived from the obesity GWAS conducted by the Genetic Investigation of ANthropometric Traits (GIANT; n_{cases} = 32,858, $n_{controls}$ = 65,839) [17]. The datasets will be referred to as the AN and obesity discovery cohorts, respectively. The calculation, application, and evaluation of the PGS was carried out with PRSice (2.1.3 beta; github.com/choishingwan/PRSice/) [29,30]. PRSice relies on PLINK to conduct necessary cleaning steps prior to PGS calculation [29,31]. Strand-ambiguous SNPs were removed prior to the scoring. Clumping was applied to extract independent SNPs according to linkage disequilibrium and *P*-value: the SNP with the smallest *P*-value in each 250 kilobase window was retained and all those in linkage disequilibrium ($r^2 > 0.1$) with this SNP were removed. To calculate the PGS, for each participant, the sum of the risk alleles was calculated then weighted by the effect size estimated from the discovery cohort. This was

done separately of the AN and the obesity discovery cohort. PGS were calculated at nine different P-value thresholds; 0.001, 0.01, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, and 1.

Furthermore, we derived a categorical variable using the AN-PGS and obesity-PGS as following; for each trajectory parameter, we first dichotomized the AN and the obesity PGS based on a cut-off value of the 8th decile of the scores. This value was selected based on previous studies that reported that individuals in top deciles of obesity-PGS and schizophrenia-PGS are at greater risk than those in lower deciles [15,32].We did not choose the highest decile as cut-off as this would have resulted in a small sample size for this particular bin and therefore a reduction in statistical power. Individuals with a PGS lower than the 8th decile were grouped into a "low PGS" group while those with a PGS score at or higher than 8th decile were grouped into a "high PGS" group. Considering that the PGS were calculated at nine different P-value thresholds (0.001, 0.01, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, and 1) we evaluated whether each individual would fall into the high or low group for each P-value threshold. Individuals the fell into the high PGS group consistently (five or more times) for the nine thresholds were grouped into the high PGS group with the remaining individuals grouped into the low PGS group; note that this was done separately for the AN-PGS and the obesity-PGS. Based on this grouping we were able to determine four categories; individuals with a (1) low PGS for both AN and obesity, (2) high PGS for AN and low PGS for obesity, (3) low PGS for AN and high PGS for obesity, and (4) high PGS for both obesity and AN. The "low AN-PGS/low obesity-PGS" group was used as the reference category in the analyses.

Statistical analyses

Univariate polygenic score analyses

In the first set of analyses, we determined the association between the AN-PGS or obesity-PGS and each body composition trajectory parameter (i.e., intercept and slopes for the BMI trajectory splines and intercept, slope, and squared slope for the remaining trajectories). We stratified our analyses on biological sex and regressed each estimated parameter on the AN-PGS or the obesity-PGS adjusting for the first four ancestry informative principal components using linear regression models; phenotypic sex differences in body composition have been reported in the general population that are detectable as early as adolescence [33,34]. Considering that the BMI growth parameters are highly correlated, we included the intercept in the regression model of slope 1; intercept and slope 1 in the regression model of slope 2; intercept, slope 1, and slope 2 in the regression model of slope 3. Similarly, for the FMI, LMI, BMD, weight, and height trajectories, we included the intercept in the model of the slope; intercept and slope in the model of the squared slope. We report for each model the R^2 (Nagelkerke's Pseudo squared multiple correlation, a measure the proportion of variance explained) and the beta (as a measure of effect size, with 95% confidence intervals), and the percent change in outcome for the log-transformed outcome measures to ease the interpretation of the beta point estimates.

Correction for multiple testing was done by calculating False Discovery Rate-corrected *Q*-values [35]. The significance threshold was met if the False Discovery Rate-adjusted Q was < 0.05.

Extreme group comparison of the polygenic score analyses

In the second set of analyses, we used linear mixed effects regression (LMER) to determine the association between the body composition measures (BMI, FMI, LMI, BMD, weight, and height) and the derived categorical AN and obesity PGS, using the lmer function from the lme4 package in R [36]. For each regression model, the derived categorical variable

of the AN-PGS/obesity-PGS, age, and the first four ancestry informative principal components were included as fixed effects. We included random intercepts for each individual in the model, to take into account variance in body composition measures that is due to inter-individual differences. The analyses were stratified by sex given differences in body composition [34]. The "low AN-PGS/low obesity-PGS" group was used as the reference category in the analyses. Correction for multiple testing was done by calculating False Discovery Rate-corrected *Q*-values [35]. The significance threshold was met if the False Discovery Rate-adjusted Q was < 0.05.

Post-hoc analyses of the extreme group comparisons

Based on the reported negative genetic correlations between AN and obesity [4] we also sought to understand whether the obesity-PGS could mitigate the effect of the AN-PGS. Therefore, we also carried out post-hoc of the above extreme group comparisons by specifically focusing on the difference between the "high AN-PGS / low-obesity-PGS" and the "high AN-PGS / high obesity-PGS".

Results

Sample Description

Following quality control of the genetic data, a total of 8,654 children with genotyping data and at least one outcome measure were included in the analyses (Table 1; Table S1; Figure S1).

Table 1: Descriptive data from the Avon Longitudinal Study of Parents and Children (ALSPAC). Data presented on age, body mass index (BMI), fat mass index (FMI), lean mass index (LMI), weight, and height are from the data collection at age 24 years.

		Female		Male	
Body composition measure	**Age (years)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**
BMI (kg/m^2)[a]	10	3,105	17.89 (2.94)	3,062	17.46 (2.71)
	12	3,006	19.28 (3.45)	2,959	18.79 (3.28)
	14	2,767	19.99 (3.49)	2,662	19.51 (3.46)
	16	2,325	21.74 (3.59)	2,108	21.01 (3.38)
	18	2,216	22.93 (4.21)	1,754	22.57 (3.84)
	24	1,785	24.79 (5.25)	1,120	24.80 (4.31)
FMI (kg/m^2)[b]	10	2,930	6.88 (3.42)	2,876	5.19 (3.28)
	12	2,861	8.45 (4.19)	2,746	6.84 (4.19)
	14	2,405	10.20 (4.50)	2,350	6.72 (4.56)
	16	2,048	11.65 (4.87)	1,950	6.54 (4.74)
	18	1,895	13.17 (5.62)	1,623	7.85 (5.50)
	24	1,562	14.96 (6.20)	1,079	11.50 (5.24)
LMI (kg/m^2)[b]	10	2,930	16.91 (1.62)	2,876	18.21 (1.52)
	12	2,861	19.27 (2.18)	2,746	20.05 (2.05)
	14	2,405	21.78 (1.95)	2,350	24.72 (3.27)
	16	2,048	22.53 (1.93)	1,950	28.52 (3.05)
	18	1,895	23.05 (2.09)	1,623	30.85 (2.89)
	24	1,562	24.87 (2.68)	1,079	31.69 (3.64)
BMD (gram/cm^2)	10	2,965	0.77 (0.05)	2,900	0.78 (0.05)
	12	2,865	0.85 (0.07)	2,756	0.85 (0.06)
	14	2,511	0.96 (0.07)	2,394	0.95 (0.09)
	16	2,208	1.00 (0.07)	2,000	1.06 (0.10)
	18	2,110	1.04 (0.07)	1,687	1.14 (0.10)
	24	1,798	1.19 (0.10)	1,138	1.31 (0.12)
Weight (kg)[a]	10	3,105	34.96	3,045	34.36 (7.05)

	12	2,904	44.50	2,801	42.66 (9.67)
	14	2,539	54.53	2,434	54.64 (11.89)
	16	2,303	59.09	2,080	64.23 (12.30)
	18	2,197	62.73	1,736	72.44 (13.47)
	24	1,858	68.43	1,169	80.82 (15.22)
Height (cm)[a]	10	3,074	139.31 (6.40)	3,027	139.80 (6.18)
	12	2,904	151.41 (7.26)	2,797	150.12 (7.16)
	14	2,544	162.03 (6.28)	2,434	164.95 (8.82)
	16	2,309	164.75 (6.09)	2,083	174.44 (7.62)
	18	2,199	165.33 (6.23)	1,736	178.99 (6.75)
	24	1,858	166.10 (6.14)	1,170	180.16 (6.72)

SD = standard deviation.

[a]Body mass index (BMI; weight in kilograms/height^2 in meters) was calculated using objectively measured weight and height during a routine clinic visit at age 24 years. Height was measured to the nearest millimeter using a Harpenden Stadiometer (Holtain Ltd.) and weight was measured using the Tanita Body Fat analyzer (Tanita TBF UK Ltd.) to the nearest 50 grams.

[b]Fat mass, lean mass, and bone mineral density (BMD) were derived using a Lunar Prodigy dual emission x ray absorptiometry (DEXA) scanner (GE Medical Systems Lunar, Madison, WI, USA). Fat mass index (FMI) and lean mass index (LMI) were calculated by dividing each measure (in kilograms) by height^2 (in meters). Bone mineral density (BMD) was calculated for the whole body excluding the head values.

Association of the AN-PGS with growth trajectories (Figure 1, Table 2)

We found several significant associations between the AN-PGS and growth trajectories (on the additive scale) exclusively in the periods of linear growth in female participants. Females with one SD higher AN-PGS had an on average 0.01% lower BMI trajectory between the ages 5 and 24 years. Furthermore, in females, on average a one SD higher AN-PGS was associated with a 0.001% lower FMI trajectory and a 0.05% lower weight trajectory between the ages 10 and 24 years. There was no significant association between the AN-PGS and the growth trajectories in male participants.

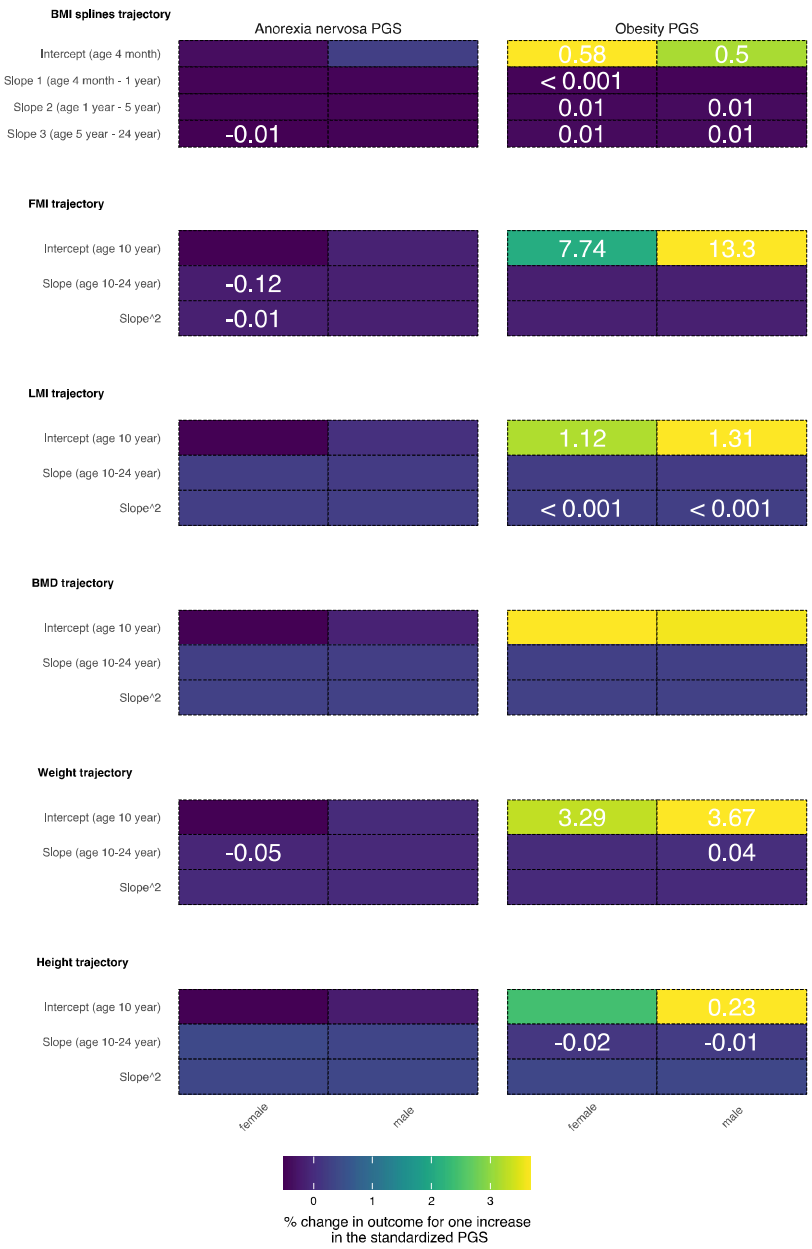

Figure 1: Associations of the anorexia nervosa (AN) and the obesity polygenic score with the body composition trajectory parameters stratified for biological sex in the Avon Longitudinal Study of Parents and Children [18–22]. The depicted tiles reflect the % change in outcome for one SD increase in the standardized PGS for the associations that remained significant after correcting for multiple testing using the Benjamini & Hochberg False Discovery Rate [35]. The PGS were calculated at P-value thresholds 0.001, 0.01, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, and 1. Presented here are the AN-PGS calculated at P-value threshold of 0.05 and the obesity-PGS calculated at a P-value threshold of 0.01; the results for the PGS calculated for the remaining P-value thresholds can be found in supplemental Table S3. **The body mass index (BMI) trajectory:** was derived using spline modeling. Prior to deriving the trajectory, BMI was transformed using the natural logarithm. For the spline modeling three spline points (Slopes) were placed: Slope 1, between age 4 months and 1 year; Slope 2, between age 1 year and 5 years; and Slope 3, between age 5 year and 24 years. Intercept reflect BMI value at age 4 months. **Fat mass index (FMI), lean mass index (LMI), bone mineral density (BMD), weight, and height trajectories**: were derived using mixed effects models [28]. Prior to trajectory modeling we log-transformed weight, height, FMI, and LMI (but not BMD) due the right-skewed distribution of the data. For each trajectory, we derived for each participant two trajectory parameters, an intercept (measurement of the body composition measure at age 10 years), and a slope (a measure of linear growth). We also calculated the squared slope, to examine if a non-linear, quadratic shape was suitable for the change in measures across time.

Table 2: Associations of the anorexia nervosa polygenic score with the body composition parameters stratified for biological sex in the Avon Longitudinal Study of Parents and Children[a]

		Female				**Male**			
Outcome	**Parameter**	**PGS R^2 [b]**	**% Change [c]**	**β [d]**	**Q [e]**	**PGS R^2 [b]**	**% Change [c]**	**β [d]**	**Q [e]**
BMI [f]	Intercept (age 4 months)	<0.0001	0.01	1 (1-1)	0.95	0.001	0.10	1 (1-1)	0.21
	Slope 1 (age 4 months - 1 year)	<0.0001	<0.001	1 (1-1)	0.79	<0.0001	<0.001	1 (1-1)	0.54
	Slope 2 (age 1 year – 5 year)	<0.0001	<0.001	1 (1-1)	0.58	<0.0001	<0.001	1 (1-1)	0.82
	Slope 3 (age 5 year – 24 year)	0.005	-0.01	1 (1-1)	**<0.0001***	0.001	<0.001	1 (1-1)	0.19
FMI [g]	Intercept (age 10 year)	0.001	-1.25	0.99 (0.97-1)	0.20	<0.0001	0.08	1 (0.98-1.02)	0.98
	Slope (age 10 – 24 year)	0.002	-0.12	1 (1-1)	**0.02***	<0.0001	-0.01	1 (1-1)	0.94
	$Slope^2$ (age 10 – 24 year)	0.001	-0.01	1 (1-1)	**<0.0001***	<0.0001	<0.001	1 (1-1)	0.17

LMI [g]	Intercept (age 10 year)	0.001	-0.29	1 (0.99-1)	0.14	<0.0001	-0.07	1 (1 -1)	0.88
	Slope (age 10 – 24 year)	<0.0001	<0.001	1 (1-1)	0.82	<0.0001	-0.01	1 (1-1)	0.24
	Slope^2 (age 10 – 24 year)	<0.0001	<0.001	1 (1-1)	0.97	<0.0001	<0.001	1 (1-1)	0.52
BMD [g]	Intercept (age 10 year)	0.001	-0.22	0 (0-0)	0.16	<0.0001	-0.12	0 (0-0)	0.61
	Slope (age 10 – 24 year)	<0.0001	-0.21	0 (0-0)	0.29	<0.0001	-0.27	0 (0-0)	0.15
	Slope^2 (age 10 – 24 year)	<0.0001	<0.001	0 (0-0)	0.97	<0.0001	<0.001	0 (0-0)	0.93
Weight [g]	Intercept (age 10 year)	0.001	-0.49	1 (0.99-1)	0.25	<0.0001	0.01	1 (1-1)	0.99
	Slope (age 10 – 24 year)	0.003	-0.05	1 (1-1)	**0.01***	<0.0001	-0.02	1 (1-1)	0.50
	Slope^2 (age 10 – 24 year)	0.003	<0.001	1 (1-1)	0.13	<0.0001	<0.001	1 (1-1)	0.17
Height [g]	Intercept (age 10 year)	<0.0001	-0.06	1 (1-1)	0.57	<0.0001	-0.04	1 (1-1)	0.79
	Slope (age 10 – 24 year)	<0.0001	<0.001	1 (1-1)	0.69	<0.0001	<0.001	1 (1-1)	0.89
	Slope^2 (age 10 – 24 year)	<0.0001	<0.001	1 (1-1)	0.96	<0.0001	<0.001	1 (1-1)	0.93

AN = anorexia nervosa; PGS = polygenic score; BMI = body mass index (weight in kilograms/height^2 in meters); FMI = fat mass index (fat mass in kilogram /height^2 in meters); LMI = lean mass index (lean mass in kilograms/height^2 in meters); BMD = bone mineral density (gram/cm2); R^2, Nagelkerke's Pseudo squared multiple correlation.

[a]Full description of the Avon Longitudinal Study of Parents and Children is described elsewhere; [18–22].

[b]Presented here are at the results for the anorexia PGS calculated at a P-value threshold of 0.05. The results tables for PGS calculated at P-value thresholds 0.001, 0.01, 0.1, 0.2,0.3,0.4,0.5, and 1 can be found in supplemental table S3.

[c]Considering that the outcomes were log-transformed we report the percent change in the outcome for one SD increase in the PGS to ease the interpretation of the betas.

[d]Betas reflect one standard deviation change in the standardized (to mean zero and standard deviation of one) AN-PGS.

[e]Benjamini & Hochberg False Discovery Rate adjustment for the number tests performed [35].

[f]BMI trajectory was derived using spline modeling. Prior to deriving the trajectory, BMI was transformed using the natural logarithm. For the spline modeling three spline points (Slopes) were placed: Slope 1, between age 4 months and 1 year; Slope 2, between age 1 year and 5 years; and Slope 3, between age 5 year and 24 years. Intercept reflect BMI value at age 4 months.

[g]FMI, LMI, BMD, weight, and height trajectories were derived using mixed effects models [28]. For each trajectory, we derived for each participant two trajectory parameters; intercept (measurement of the body composition measure at age 10 years) and a slope (a measure of linear growth). We also calculated the squared slope, to examine if a non-linear, quadratic shape was suitable for the change in measures across time. The intercept and the slope were all allowed to vary randomly across individuals.

* Significant after accounting for multiple testing using the false discovery rate-corrected Q-values. Significance was set at $Q < 0.05$.

Association of the obesity-PGS with growth trajectories (Figure 1, Table 3)

As early as age 4 months, a one SD higher obesity-PGS was associated with 0.58% and a 0.50% higher BMI trajectory in female and male participants, respectively. The obesity-PGS was also associated with periods of linear growth of the BMI trajectory between the ages 1-24 years, a one SD higher obesity-PGS was associated with a 0.01% higher BMI trajectory in females and males. At age 10 years, a one SD higher obesity-PGS was associated with a 7.74% higher FMI, 1.12% higher LMI, 0.94% higher BMD, 3.29% higher weight trajectory in females. Furthermore, in females, a one SD higher obesity-PGS was associated with a 0.02% lower slope in the height trajectory. We observed a similar pattern of results in males with a notable exception for the FMI trajectory in which a one SD higher obesity-PGS was associated with a 13.30% higher FMI trajectory; this is nearly double that observed in females. In addition, in males, a one SD higher obesity-PGS was associated with a 0.23% higher height trajectory at age 10 years; however, a one SD increase in the obesity-PGS also corresponded with a 0.01% lower slope for height trajectory between the ages and 10 and 24 years.

Table 3: Associations of the obesity polygenic score with body composition parameters stratified for biological sex in the Avon Longitudinal Study of Parents and Children[a]

		Female				Male			
Outcome	**Parameter**	**PGS R^2 [b]**	**% change [c]**	**β [d]**	**Q [e]**	**PGS R^2**	**% change [c]**	**β [d]**	**Q [e]**
BMI [f]	Intercept (age 4 month)	0.023	0.58	1.01 (1-1.01)	**<0.001***	0.019	0.50	1.01 (1-1.01)	**<0.001***
	Slope 1 (age 4 month - 1 year)	<0.001	<0.001	1 (1-1)	**0.02***	<0.001	<0.001	1 (1-1)	0.10
	Slope 2 (age 1 year – 5 year)	0.001	0.01	1 (1-1)	**<0.001***	0.004	0.01	1 (1-1)	**<0.001***
	Slope 3 (age 5 year – 24 year)	0.012	0.01	1 (1-1)	**<0.001***	0.019	0.01	1 (1-1)	**<0.001***
FMI [g]	Intercept (age 10 year)	0.031	7.74	1.08 (1.06-1.09)	**<0.001***	0.049	13.30	1.13 (1.11-1.15)	**<0.001***
	Slope (age 10 – 24 year)	<0.001	-0.03	1 (1-1)	0.66	<0.001	-0.01	1 (1-1)	0.94
	$Slope^2$ (age 10 – 24 year)	<0.001	<0.001	1 (1-1)	0.62	<0.001	<0.001	1 (1-1)	0.23
LMI [g]	Intercept (age 10 year)	0.016	1.12	1.01 (1.01-1.01)	**<0.001***	0.018	1.31	1.01 (1.01-1.02)	**<0.001***
	Slope (age 10 – 24 year)	<0.001	-0.01	1 (1-1)	0.61	<0.001	-0.02	1 (1-1)	0.20
	$Slope^2$ (age 10 – 24 year)	<0.001	<0.001	1 (1-1)	**0.01***	<0.001	<0.001	1 (1-1)	**0.01***
BMD [g]	Intercept (age 10 year)	0.018	0.94	1 (1-1)	**<0.001***	0.015	0.91	0.01 (0.01-0.01)	**<0.001***
	Slope (age 10 – 24 year)	<0.001	-0.06	1 (1-1)	0.83	<0.001	-0.08	0 (0-0)	0.80
	$Slope^2$ (age 10 – 24 year)	<0.001	<0.001	1 (1-1)	0.62	<0.001	<0.001	0 (0-0)	0.69
Weight [g]	Intercept (age 10 year)	0.030	3.29	1.03 (1.03-1.04)	**<0.001***	0.038	3.67	1.04 (1.03-1.04)	**<0.001***
	Slope (age 10 – 24 year)	0.001	0.02	1 (1-1)	0.32	0.003	0.04	1 (1-1)	**0.01***
	$Slope^2$ (age 10 – 24 year)	<0.001	<0.001	1 (1-1)	0.94	<0.001	<0.001	1 (1-1)	0.33
Height [g]	Intercept (age 10 year)	0.001	0.14	1 (1-1)	0.08	0.003	0.23	1 (1-1)	**<0.001***
	Slope (age 10 – 24 year)	0.004	-0.02	1 (1-1)	**<0.001***	0.002	-0.01	1 (1-1)	**0.02***
	$Slope^2$ (age 10 – 24 year)	<0.001	<0.001	1 (1-1)	0.91	<0.001	<0.001	1 (1-1)	0.45

PGS = polygenic score; BMI = body mass index (weight in kilograms/height^2 in meters); FMI = fat mass index (fat mass in kilogram /height^2 in meters); LMI = lean mass index (lean mass in kilograms/height^2 in meters); BMD = bone mineral density (gram/cm^2).

[a]Full description of the Avon Longitudinal Study of Parents and Children is described elsewhere; [18–22].

[b]Presented here are at the results for the obesity PGS calculated at a P-value threshold of 0.01. The results tables for PGS calculated at P-value thresholds 0.001, 0.05, 0.1, 0.2,0.3,0.4,0.5, and 1 can be found in supplemental table S3.

[c]Considering that the outcomes were log-transformed we report the percent change in the outcome for one SD increase in the PGS to ease the interpretation of the betas.

[d]Betas reflect one standard deviation change in the standardized (to mean zero and standard deviation of one) obesity-PGS.

[e]Benjamini & Hochberg False Discovery Rate adjustment for the number tests performed [35].

[f]BMI trajectory was derived using spline modeling. Prior to deriving the trajectory, BMI was transformed using the natural logarithm. For the spline modeling three spline points (Slopes) were placed: Slope 1, between age 4 months and 1 year; Slope 2, between age 1 year and 5 years; and Slope 3, between age 5 year and 24 years. Intercept reflect BMI value at age 4 months.

[g]FMI, LMI, BMD, weight, and height trajectories were derived using mixed effects models [28]. For each trajectory, we derived for each participant two trajectory parameters; intercept (measurement of the body composition measure at age 10 years) and a slope (a measure of linear growth). We also calculated the squared slope, to examine if a non-linear, quadratic shape was suitable for the change in measures across time. The intercept and the slope were all allowed to vary randomly across individuals.

* Significant after accounting for multiple testing using the false discovery rate-corrected Q-values. Significance was set at $Q < 0.05$.

Extreme group comparisons (Table 4)

Across both sexes, individuals grouped in the low AN-PGS/high obesity-PGS followed on average a higher growth trajectory between the ages 10-24 year compared to individuals with a low AN-PGS and a low obesity-PGS; the difference was most pronounced for the FMI trajectory in which female participants with a low AN-PGS and a high obesity-PGS had 12.95% higher FMI while male participants showed 25.6% higher FMI compared to the reference group with a low AN-PGS and a low obesity-PGS (Table 4). Furthermore, although these associations did not reach statistical significance, we found a trend in which female individuals with a high AN-PGS and a low obesity-PGS consistently had lower BMI, FMI, LMI, BMD, weight, and height trajectories compared to the reference category of individuals with a low AN-PGS and a low-obesity-PGS.

Post-hoc analyses extreme group comparisons (Table 5)

In the post-hoc analyses of the extreme group comparisons we found that both females with a high AN-PGS and low obesity-PGS had on average 4.8% lower BMI, 16.99% lower FMI, 1.4% lower BMD, and 6.78% lower height trajectories compared to females with high PGS on both traits (Table 5). In males we found that individuals with high AN-PGS and low obesity-PGS had on average 4.61% lower BMI, 22.28% lower FMI, and 7.16% lower height trajectories compared to individuals with high AN-PGS and high obesity-PGS.

Table 4: Associations of the combined anorexia nervosa and obesity polygenic score with the body composition measures stratified for biological sex using linear mixed models in the Avon Longitudinal Study of Parents and Children[a]

		Female			Male		
Outcome	**PGS category [b]**	**% change [c,d]**	**Beta (95% CI) [c,d]**	**Q [e]**	**% change [c,d]**	**Beta (95% CI) [c,d]**	**Q [e]**
BMI	Low AN / high obesity	4.77	1.05 (1.03,4.77)	**<0.001***	4.33	1.04 (1.03,4.33)	**<0.001***
BMI	High AN / high obesity	4.47	1.04 (1.02,4.47)	**0.002***	5.62	1.06 (1.03,5.62)	**<0.001***
BMI	High AN / low obesity	-0.53	0.99 (0.98,-0.53)	0.50	0.75	1.01 (1,0.75)	0.31
FMI	Low AN / high obesity	12.94	1.13 (1.09,12.94)	**<0.001***	25.56	1.22 (1.16,22.35)	**<0.001***
FMI	High AN / high obesity	16.63	1.17 (1.08,16.63)	**<0.001***	21.27	1.29 (1.17,29.09)	**<0.001***
FMI	High AN / low obesity	-3.13	0.97 (0.93,-3.13)	0.21	-1.68	1 (0.95,0.37)	0.94
LMI	Low AN / high obesity	1.51	1.02 (1.01,1.51)	**0.002***	2.66	1.02 (1.01,2.09)	**<0.001***
LMI	High AN / high obesity	0.3	1 (0.99,0.3)	0.80	1.77	1.01 (0.99,1.34)	0.28
LMI	High AN / low obesity	-0.86	0.99 (0.98,-0.86)	0.10	-0.43	1 (0.99,0.36)	0.55
BMD	Low AN / high obesity	1.22	1.01 (1.01,1.22)	**<0.001***	NA	1.01 (1.01,1.25)	**0.002***
BMD	High AN / high obesity	0.78	1.01 (1,0.78)	0.32	NA	1.01 (0.99,0.64)	0.47
BMD	High AN / low obesity	-0.66	0.99 (0.99,-0.66)	0.08	NA	1 (1,0.31)	0.49
Weight	Low AN / high obesity	4.64	1.05 (1.03,4.64)	**<0.001***	8.01	1.06 (1.04,6.39)	**<0.001***
Weight	High AN / high obesity	5.14	1.05 (1.02,5.14)	**0.01***	6.9	1.08 (1.04,8.13)	**<0.001***
Weight	High AN / low obesity	-1.92	0.98 (0.96,-1.92)	0.06	-0.91	1 (0.99,0.31)	0.80
Height	Low AN / high obesity	-0.21	1 (0.99,-0.21)	0.39	0.64	1 (1,0.32)	0.28
Height	High AN / high obesity	0	1 (0.99,0)	0.99	0.58	1.01 (1,0.55)	0.31
Height	High AN / low obesity	-0.26	1 (0.99,-0.26)	0.29	-0.20	1 (1, -0.02)	0.95

AN = anorexia nervosa; PGS = polygenic score; BMI = body mass index (weight in kilograms/height^2 in meters); FMI = fat mass index (fat mass in kilogram /height^2 in meters); LMI = lean mass index (lean mass in kilograms/height^2 in meters); BMD = bone mineral density (gram/cm^2).

[a]Full description of the Avon Longitudinal Study of Parents and Children is described elsewhere; [18–22].

[b]Categorical variable derived from dichotomizing the AN-PGS and the obesity-PGS. For both the AN and the obesity PGS, individuals with scores at or greater than the 8th decile point were regarded as the "high PGS group" while those with scores lower were considered the "low PGS group". Considering that the PGS were calculated at nine different P-value thresholds (0.001, 0.01, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, and 1) we evaluated whether each individual would fall into the high or low group for each P-value threshold. Individuals that fell into the "high PGS group" consistently (five or more times) for the nine thresholds were grouped into the "high PGS group" with the remaining individuals were grouped into the "low PGS group. From the dichotomized AN-PGS and obesity-PGS we were able to create a categorical variable with four levels (1) low AN-PGS / low obesity-PGS (2) high AN-PGS / low obesity-PGS (3) high AN-PGS / high obesity-PGS (4) low AN-PGS / high obesity-PGS. The "low AN-PGS/low obesity-PGS" group was used as the reference category in the analyses.

[c]Considering that the outcomes were log-transformed we report the percent change in the outcome in the comparison to the reference group ("low obesity-PGS / low AN-PGS") to ease the interpretation of the betas.

[d]Beta reflect change in outcome compared to the reference category "low obesity-PGS / low AN-PGS".

[e]Benjamini & Hochberg false discovery rate adjusting for the number of phenotypes tested [35].

* Significant after accounting for multiple testing using the false discovery rate-corrected Q-values. Significance was set at Q < 0.05.

Table 5: Associations of the combined anorexia nervosa and obesity polygenic score with the body composition measures stratified for biological sex using linear mixed models in the Avon Longitudinal Study of Parents and Children: Post-hoc analyses comparing the "High AN-PGS/ low obesity-PGS" group to the "High AN-PGS/ high obesity-PGS" group [a]

		Female			**Male**		
Outcome	**PGS category** [b]	**% change** [c,d]	**Beta (95% CI)** [c,d]	**P** [e]	**% change** [c,d]	**Beta (95% CI)** [c,d]	**P** [e]
BMI	High AN / low obesity	-4.85	0.95 (0.93,0.98)	**<0.001**	-4.61	0.95 (0.93,0.98)	**<0.001**
FMI	High AN / low obesity	-16.99	0.83 (0.77,0.9)	**<0.001**	-22.28	0.78 (0.7,0.87)	**<0.001**
LMI	High AN / low obesity	-1.14	0.99 (0.97,1.01)	0.24	-0.85	0.99 (0.97,1.01)	0.41
BMD	High AN / low obesity	-1.4	0.99 (0.97,1)	**0.04**	-0.23	1 (0.98,1.01)	0.76

Weight	High AN / low obesity	-6.78	0.93 (0.9,0.97)	**<0.001**	-7.16	0.93 (0.89,0.97)	**<0.001**
Height	High AN / low obesity	-0.27	1 (0.99,1.01)	0.52	-0.54	0.99 (0.99,1)	0.23

AN = anorexia nervosa; PGS = polygenic score; BMI = body mass index (weight in kilograms/height^2 in meters); FMI = fat mass index (fat mass in kilogram /height^2 in meters); LMI = lean mass index (lean mass in kilograms/height^2 in meters); BMD = bone mineral density (gram/cm^2).

[a]Full description of the Avon Longitudinal Study of Parents and Children is described elsewhere; [18–22].

[b]Categorical variable derived from dichotomizing the AN-PGS and the obesity-PGS. For both the AN and the obesity PGS, individuals with PGS scores at or greater than the 8th decile point were regarded as the "high PGS group" while those with scores lower were considered the "low PGS group". Considering that the PGS were calculated at nine different P-value thresholds (0.001, 0.01, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, and 1) we evaluated whether each individual would fall into the high or low group for each P-value threshold. Individuals that fell into the "high PGS group" consistently (five or more times) for the nine thresholds were grouped into the "high PGS group" with the remaining individuals were grouped into the "low PGS group. From the dichotomized AN-PGS and obesity-PGS we were able to create a categorical variable with two levels (1) high AN-PGS / high obesity-PGS (2) high AN-PGS / low obesity-PGS. The "high AN-PGS / high obesity-PGS" group was used as the reference category in the analyses.

[c]Considering that the outcomes were log-transformed we report the percent change in the outcome in the comparison to the reference group ("high obesity-PGS / high AN-PGS") to ease the interpretation of the betas.

[d]Beta reflect change in outcome compared to the reference category "high obesity-PGS / high AN-PGS".

[e]The P-value are unadjusted as these analyses are post-hoc comparisons of the results reported in table 4.

Discussion

We report that common genomic variants associated with AN and obesity are significantly associated with growth trajectories during the first two decades of life. We found that the AN-PGS is associated with lower BMI, FMI, and weight trajectories in females but not males. We did not observe a significant association of the AN-PGS with the LMI nor with the BMD trajectory. In line with our expectations, the AN-PGS was not significantly associated with height trajectory (i.e., negative control [3,4]). In contrast, individuals with higher obesity-PGS had higher BMI, FMI, LMI, BMD, height, and weight trajectories during the first two decades of life. Further, by combining the AN-PGS and obesity-PGS we were able to distinguish subgroups within each growth trajectory. Females with high AN-PGS and low obesity-PGS deviated consistently below growth trajectories of female participants with low AN-PGS and obesity-PGS for all investigated trajectories; however, these associations were not statistically significant. However, females with high AN-PGS and low obesity-PGS had significantly lower BMI, FMI, BMD, and weight trajectories compared to individuals with high PGS on both traits.

We demonstrate, with multiple measures of growth, that individuals with high AN genetic liability differ significantly in growth as marked by slower growth as early as age 5 years for BMI and, as well as for FMI and weight trajectories between the ages of 10-24 years. However, females with high AN-PGS and a low obesity-PGS did not significantly differ from the reference group with a low AN-PGS and low obesity-PGS, though the direction of difference was in line with what we expected; individuals with high AN-PGS and a low obesity-PGS have lower growth trajectories compared to the reference group. Interestingly, female participants with high genetic liability for AN and low genetic liability for obesity followed lower growth trajectories compared to individuals with high PGS on both traits, suggesting that the obesity-PGS might have mitigated the effects of the AN-PGS.

This view is consistent with reports of a negative genetic correlation between AN and obesity [4,37]. Taken together, the findings from the univariate AN-PGS analyses and the findings from the extreme-group comparisons suggest that genetic liability for obesity exerts a modulating role in the association between the AN-PGS and growth trajectories. However, we cannot exclude that other PGS could also exert influence on these associations. Overall, our findings lend further support to an earlier report that found differences in growth trajectories that are associated with later onset of AN were detectable as early as age 2 years [7,38,39] . Importantly, this impact of genetic liability for AN arises prior to any diagnosis of the illness, highlighting that individuals at higher genetic risk for AN have slightly different growth development during childhood before the average of onset that typically occurs during early adolescence [1,7,38,39]. Sex differences in body composition have been well-documented in the medical literature in which males on average having higher lean body mass, BMD, and body height but lower fat mass than females [40]. These biological differences are driven by both environmental and genetic factors [34,41]. In a recent study, our group [41] reported a negative genetic correlation between body fat percentage and AN and that this genetic correlation was more pronounced in females than in males (female SNP-r_g = −0.44, SE = 0.04; male SNP-r_g = −0.26; SE = 0.04). Findings in this study are in agreement with our earlier work on this sample by showing that polygenic risk for AN is negatively correlated with growth trajectories in females but not in males. The observations from this study and our previous work [41] support a hypothesis that a specific set of common genetic variants may be differentially active in females and may increase the liability for AN. These results also underscore the importance of collecting adequate samples from males with AN and all EDs to ensure our ability to identify differential genetic effects.

In this study we demonstrate that developmental changes in body composition may in part be driven by the AN-PGS as early as age 5 years and by the obesity-PGS by age 4

months. Further, by decomposing BMI into its respective components (i.e., FMI and LMI) we report that the AN-PGS is significantly associated with FMI changes across development but not with LMI, suggesting that the AN-PGS might drive these changes in growth trajectories specifically via fat mass.

That AN and obesity polygenic risk co-influence growth trajectories is a novel finding that encourages exploration of the underlying biology. Common genomic variants that are associated with AN or obesity are primarily expressed in central nervous system [4,13,42], suggesting that body mass is behaviorally influenced. This view is also supported by our previous work, showing that PGS for a higher BMI are associated with several adolescent eating behaviors including higher propensity to engage in binge eating [43]. Therefore, potentially, polygenic risk for AN or obesity may impact growth at least in part via eating behaviors.

This study has several strengths including the large sample size (N =8,654 with genotype data and at least one outcome measure) and the prospective and repeat collection of objective body composition measures spanning more than 20 years. We included a negative control (i.e., the height trajectory was not associated with AN), adequately controlled for multiple testing, and controlled for potential genetic confounders using ancestry informative principal components. The use of spline modeling enabled modeling of BMI trajectories more accurately as growth throughout childhood is not linear. Further, by stratifying on gender, we were able to identify sex-related effects that otherwise would have been masked, and censoring on ED ruled out that growth changes during puberty were a consequence of an eating disorder.

Findings from this study should be interpreted in the context of some limitations. Participants were recruited from the same geographical region in the south-west of England and therefore the results may not be generalizable to other populations. However, the

homogeneity of this sample lends itself to genetic analyses as bias from population stratification is low [44]. Considering the longitudinal nature of the study, participants tend to drop out over time leading to missing data. We maximized available data by using mixed effects models, which allowed us to use all available data points in deriving the growth trajectories rather than only including complete cases. We acknowledge that any bias as a consequence of missing data in our analyses could have biased our results towards the null. The effect sizes observed in this study were relative small but are consistent with those previously reported in other PGS studies and aid our understanding of the disorder [15,45].

In conclusion, our results suggest that polygenic risk for AN and obesity have detectable sex-related effects on growth during the first two decades of life. Especially, female participants with high polygenic risk for AN and a low polygenic risk for obesity likely constitute a high-risk group as they followed lower growth trajectories, which have previously been associated with AN in the ALSPAC sample [7]. This study adds to a growing body of evidence suggesting that risk for AN could emerge during early childhood and that a combination of AN and obesity polygenic risk could aid the early identification of individuals at high risk for AN. These findings encourage further research in understanding how the AN-PGS and the obesity-PGS co-influence growth during childhood in which the obesity-PGS can amplify or mitigate the effects of the AN-PGS.

List of abbreviations

ALSPAC	Avon Longitudinal Study of Parents and Children
AN	Anorexia nervosa
BMD	Bone mineral density
BMI	Body mass index
cm^2	Centimeters squared
DEXA	Dual emission X-ray absorptiometry
ED	Eating disorder
FMI	Fat mass index
GIANT	Genetic investigation of anthropometric traits
GWAS	Genome-wide association study
kg	Kilogram
LMER	Linear mixed effects regression
LMI	Lean mass index
m^2	Meters squared
PGC	Psychiatric genomics consortium
PGS	Polygenic score
REDCap	Research Electronic Data Capture
r_g	Genetic correlation
SD	Standard deviation
SE	Standard error
SNP	Single nucleotide polymorphism
STATA	Statistics and data

Declarations

Ethics approval and consent to participate

Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees (Bristol and Weston Health Authority: E1808 Children of the Nineties: ALSPAC, 28th November 1989 (for details see: www.bristol.ac.uk/alspac/researchers/research-ethics/). Consent for biological samples has been collected in accordance with the Human Tissue Act (2004). Informed consent for the use of data collected via questionnaires and clinics was obtained from participants following the recommendations of the ALSPAC Ethics and Law Committee at the time. The main caregiver initially provided consent for child participation and from the age 16 years the offspring themselves have provided informed written consent.

Consent for publication

Not applicable.

Availability of data and materials

Details of all the data used in this study are available through a fully searchable data dictionary at the following webpage: http://www.bristol.ac.uk/alspac/researchers/our-data/. Given the nature of the ALSPAC cohort, access to the research data must be requested using the formal procedures described in the ALSPAC access policy (http://www.bristol.ac.uk/alspac/researchers/access/) and is subject to eligibility, the ALSPAC funder's terms and conditions and University of Bristol policies and procedures.

Competing interests

Dr. Breen has received grant funding from and served as a consultant to Eli Lilly, has received honoraria from Illumina and has served on advisory boards for Otsuka. Dr. Bulik is a grant recipient from and has served on advisory boards for Shire and is a consultant for Idorsia. She receives royalties from Pearson. All other authors have indicated they have no conflicts of interest to disclose.

Funding

This study represents independent research part funded by the UK National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. The views expressed are those of the author(s) and not necessarily those of the UK NHS, the NIHR or the Department of Health. High performance computing facilities were funded with capital equipment grants from the GSTT Charity (TR130505) and Maudsley Charity (980). This work was supported by the UK Medical Research Council and the Medical Research Foundation (ref: MR/R004803/1). The UK Medical Research Council and Wellcome (Grant ref: 102215/2/13/2 and 217065/Z/19/Z) and the University of Bristol provide core support for ALSPAC. A comprehensive list of grants funding is available on the ALSPAC website (http://www.bristol.ac.uk/alspac/external/documents/grant-acknowledgements.pdf); This research was specifically funded by the NIHR (CS/01/2008/014), the NIH (MH087786-01). GWAS data was generated by Sample Logistics and Genotyping Facilities at Wellcome Sanger Institute and LabCorp (Laboratory Corporation of America) using support from 23andMe. NM and CB acknowledge funding from the National Institute of Mental Health (R21 MH115397). CB acknowledges funding from the Swedish Research Council (VR Dnr: 538-2013-8864), the National Institute of Mental Health (R21MH115397; R01 MH109528; R01MH120170; R01MH119084). The content is solely the responsibility of the authors and

does not necessarily represent the official views of the National Institutes of Health. The funders were not involved in the design or conduct of the study; collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript.

Authors' contributions

MA, CH, and MH analyzed the data. MA, CH, and MH drafted the manuscript. NM, CMB, RFL, and GB supervised the work. All authors substantially contributed to the conception and interpretation of the work, revised the manuscript for important intellectual content and approved the final version. All authors agree to be accountable for all aspects of this work.

Acknowledgements

We are extremely grateful to all the families who took part in this study, the midwives for their help in recruiting them, and the whole ALSPAC team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists and nurses.

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