Archival Report

Common Genetic Variation and Age of Onset of Anorexia Nervosa

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ABSTRACT

BACKGROUND: Genetics and biology may influence the age of onset of anorexia nervosa (AN). The aims of this study were to determine whether common genetic variation contributes to age of onset of AN and to investigate the genetic associations between age of onset of AN and age at menarche.

METHODS: A secondary analysis of the Psychiatric Genomics Consortium genome-wide association study (GWAS) of AN was performed, which included 9335 cases and 31,981 screened controls, all from European ancestries. We conducted GWASs of age of onset, early-onset AN (<13 years), and typical-onset AN, and genetic correlation, genetic risk score, and Mendelian randomization analyses.

RESULTS: Two loci were genome-wide significant in the typical-onset AN GWAS. Heritability estimates (single nucleotide polymorphism–h^2) were 0.01–0.04 for age of onset, 0.16–0.25 for early-onset AN, and 0.17–0.25 for typical-onset AN. Early- and typical-onset AN showed distinct genetic correlation patterns with putative risk factors for AN. Specifically, early-onset AN was significantly genetically correlated with younger age at menarche, and typical-onset AN was significantly negatively genetically correlated with anthropometric traits. Genetic risk scores for age of onset and early-onset AN estimated from independent GWASs significantly predicted age of onset. Mendelian randomization analysis suggested a causal link between younger age at menarche and early-onset AN.

CONCLUSIONS: Our results provide evidence consistent with a common variant genetic basis for age of onset and implicate biological pathways regulating menarche and reproduction.

Anorexia nervosa (AN) is an eating disorder characterized by starvation, low body mass index (BMI), and a morbid fear of weight gain, affecting 0.9% to 1.4% of females and 0.1% to 0.3% of males (1,2). The etiology involves a complex interplay between genetics and the environment (3). Twin-based studies report a heritability of 50% to 60% (4). Common genetic polymorphisms account for a substantial portion of this heritability (single nucleotide polymorphism [SNP]-h^2 = 11%–17%) (5). Peak age of onset is between 16 and 22 years in community-based epidemiological research (1) and 14 to 19 years in clinical populations (6), and onset after age 25 is atypical (7). To our knowledge, there are no genome-wide association study (GWAS) or heritability studies of age of onset of AN, and the factors that contribute to earlier rather than later onset are unknown (7).

The Psychiatric Genomics Consortium (PGC) GWAS of AN identified eight genomic regions associated with the risk of lifetime AN and implicated a psychiatric and metabolic etiology (5). Candidate gene studies have suggested that polymorphisms in serotonergic and appetite-regulating genes might be associated with age of onset (8–11). However, candidate gene studies generally have been subject to important criticisms, including nonreplication. In illnesses such as schizophrenia and bipolar disorder, a higher genetic burden predicts earlier onset and age of onset for some psychiatric traits aggregates in families (12–15). The Brainstorm Consortium combined molecular genetic data from 10 psychiatric disorders including AN and found a modest, significant correlation linking earlier age of onset to higher heritability (16). Meanwhile, twin studies of eating disorder symptoms suggest that genetic contributions change across development such that genetic effects explain negligible variance prepuberty and increase substantially in peripuberty (17). Because genetic factors influence AN risk, the first aim of this study is to investigate whether common genetic polymorphisms account for variation in age of onset (aim 1).

Although GWAS efforts have made tremendous contributions to our understanding of the genetic etiology of AN, phenotypic and genetic heterogeneity can hinder discovery of the genetic architecture of psychiatric traits (18). Insight can be improved by leveraging investigations of etiologically homogeneous illness subphenotypes, such as early-onset presentations. Differences in clinical presentation of AN by age are evident, although not well established because of limited research, with early-onset cases displaying predominantly non–binge/purge profiles, a faster rate of weight loss, less endorsement of psychological symptoms, more favorable long-term outcomes, and a higher male prevalence than typical-onset presentations (19–22). The second aim of this study is to examine a subphenotype of AN, specifically early-onset, to aid in discovering the genetics and biology of AN and age of onset (aim 2).

Early pubertal timing has long been cited as a risk factor for AN, particularly early-onset AN, but the evidence base is weak and observational, and methodological issues complicate investigation (17). The relatively low prevalence of AN impedes prospective designs, and nutritional deficiencies in AN arrest pubertal development and complicate estimates of the causal influence of pubertal traits. Genetic designs, such as Mendelian randomization, can interrogate causality under specific assumptions while avoiding these measurement confounds. Population-based twin research has shown that shared genetic factors influence liability to earlier menarche and disordered eating (23). However, a significant genetic correlation between age at menarche (i.e., a commonly used measure of puberty timing) and AN was not evident in the largest AN GWAS to date (5). Large-scale genomic and phenotypic data collections and new analytic methods (i.e., genetic risk score [GRS] analysis, Mendelian randomization) have become available and present an excellent opportunity to examine whether puberty timing may be a causal risk factor for AN risk and age of onset (aim 3).

METHODS AND MATERIALS

Design and Participants

This is a secondary analysis of individual-level data from a GWAS of AN (5), which we refer to as the parent study. Cohorts

from the parent study were included here if they had cases with age of onset data. This resulted in 13 cohorts and 55% of cases (N = 9335) and 58% of controls (N = 31,981) included in this study from the parent study of 33 cohorts, 16,992 cases, and 55,525 controls (Table S1 in Supplement 2). For some secondary analyses using AN risk as a phenotype, all cases from the 13 cohorts above were included, resulting in 11,632 cases and 31,981 controls for those analyses. More details on recruitment, phenotyping, DNA collection, and genotyping are provided in Supplement 1 and other publications (5,24,25). Supplemental Methods in Supplement 1 and Table S2 in Supplement 2 provide phenotyping information for age of onset and early-onset AN, which was characterized as onset before age 13 years.

GWAS of Age of Onset of AN, Early-Onset AN, and Typical-Onset AN

Three GWASs were conducted: 1) a within-case GWAS on age of onset; 2) a case-control GWAS that stratified a subset of cases by the subphenotype of early-onset AN and compared these with ancestrally matched controls; and 3) a case-control GWAS of typical-onset AN for comparative purposes with respect to the genetic correlations and other secondary analyses, as detailed later (Table S3 in Supplement 2).

Quality control of genotype data is described in Supplement 1. GWASs were conducted using RICOPILI (26). Samples were of European ancestry, and genotypes were imputed to the 1000 Genomes reference (27). The first five principal components were included to capture ancestry-based population stratification. Linear regression for age of onset and logistic regression for early-onset AN and typical-onset AN were carried out on imputed variant dosages using additive models to test for associations between the markers and the phenotypes. Cohort-level GWAS analyses were combined with fixed-effects meta-analysis (including variants with imputation INFO scores > 0.7). The standard genome-wide cutoff ($p < 5 \times 10^{-8}$) was anticonservative, given three GWASs; therefore, results were interpreted at a Bonferroni-corrected threshold ($p < 1.67 \times 10^{-8}$). The GWAS of age of onset had >80% statistical power to detect genetic effects with 0.45% of the variance explained (R^2), or βs between 1.06 and 1.59 (at minor allele frequency 0.05–0.5); the GWAS of early-onset AN had >80% power to detect an odds ratio (OR) between 1.32 and 1.70 (at minor allele frequency 0.05–0.5, assuming a lifetime prevalence of 0.1%) (28); and the GWAS of typical-onset AN had >80% power to detect an OR between 1.14 and 1.31 (at minor allele frequency 0.05–0.5, assuming a lifetime prevalence of 0.9%–4%) (29). Common variant heritability was estimated with linkage disequilibrium score regression (LDSC) (30) and the genomic-relatedness-based restricted maximum-likelihood (GREML) approach (31) implemented in GCTA (31). GREML analyses had 80% power to detect SNP-h^2s $\geq$ 0.1 for age of onset, 0.07 for early-onset AN (liability scale), and 0.03 for typical-onset AN (liability scale) (32). Genetic correlation analyses were conducted on LD Hub (33), and genetic correlation analyses with two AN GWASs (5,34) not on LD Hub and between early- and typical-onset AN used LDSC (30,33). Gene mapping and tissue expression analyses were performed with FUMA (35).

GRSs as Predictors of Age of Onset of AN (GRS$_{age\ of\ onset}$, GRS$_{early-onset\ AN}$, and GRS$_{AN}$)

GRS analyses were conducted for aim 1 to investigate the evidence for a common variant–based genetic etiology. A GRS represents the combined effect of risk alleles carried by the individual and more powerfully predicts a complex trait than a single-SNP association analysis. Three sets of GRS at various p thresholds (p_Ts) were calculated for each individual with PRSice-2 (36) using the leave-one-cohort-out approach: 1) GRS$_{age\ of\ onset}$ using the age of onset GWAS from this study, 2) GRS$_{AN}$ using the GWAS results of the parent study (5), and 3) GRS$_{early-onset\ AN}$ using the case-control GWAS for early-onset AN from this study (Supplemental Methods in Supplement 1). Linear regression quantified the association between GRS$_{age\ of\ onset}$, GRS$_{early-onset\ AN}$, and GRS$_{AN}$ with age of onset with β and R^2. Cohort-level analyses were combined with fixed-effects meta-analysis. p values were corrected using the false discovery rate (FDR) procedure (37).

GRS$_{age\ at\ menarche}$ as a Predictor of Age of Onset of AN, Early-Onset AN, Typical-Onset AN, and AN Risk

Large-scale genetic data have shown moderate to strong correlations between age at menarche and pubertal milestones across sexes, supporting the choice to capture puberty timing with age at menarche (38). GRS$_{age\ at\ menarche}$ was calculated using the summary statistics from Day et al. (38). GRS analyses were carried out using the procedure above to address aim 3 (Supplemental Methods in Supplement 1).

Causal Associations Between Puberty Timing and Age of Onset of AN, Early-Onset AN, Typical-Onset AN, and AN Risk

Mendelian randomization estimated the causal association between age at menarche and age of onset, early-onset AN, typical-onset AN, and AN risk, per aim 3. We used known genetic variants in GWAS summary statistics as instruments (5,38). Analyses were conducted with the TwoSampleMR package of MR-Base (39). We used the inverse-variance weighted estimator, which meta-analyzes the SNP-specific Wald estimates, and sensitivity approaches were applied (Supplement 1). Power calculations implied >80% power to detect a β of 1.01 for age at menarche on AN age of onset, OR of 0.90 for age at menarche on early-onset AN, OR of 1.16 for age at menarche on typical-onset AN, OR of 0.90 for age at menarche on AN risk, and $\beta \leq 0.99$ for AN risk on age at menarche (40). Age at menarche was hypothesized to be inversely associated with early-onset AN and AN risk.

RESULTS

Age of Onset Phenotype Summary

Table S1 in Supplement 2 describes the cohorts. The mean age of onset among the 9335 AN cases (99% female) in the 13 cohorts was 15.91 years (SD = 4.29, range 5–58), and approximately 15% had early-onset AN. A density plot of age of onset is shown in Figure S1 in Supplement 1.

GWASs of Age of Onset, Early-Onset AN, and Typical-Onset AN

The GWAS of age of onset (13 cohorts, 9335 cases) yielded no SNPs with p values $< 1.67 \times 10^{-8}$ (Figure S2 in Supplement 1). The SNP with the lowest p value was rs146976977 ($p = 1.85 \times 10^{-7}$). The phenotypic variance explained by $GRS_{age\ of\ onset}$ was $R^2 = 0.13\%$. SNP-h^2 was 0.04 (SE = 0.05) with LDSC and 0.01 (SE = 0.02) with GREML.

No significant loci ($p < 1.67 \times 10^{-8}$) were observed for the GWAS of early-onset AN (5 cohorts, 1269 cases and 25,042 controls), although one false positive was observed at the standard genome-wide significance threshold (Figure S2 and Supplemental Results in Supplement 1). The false-positive designation was given because the SNP had no nearby linkage disequilibrium friends, an unrealistically large OR, was not genotyped (INFO score = 0.74), is low frequency, occurs in predominantly European populations, and based on the small sample size. $GRS_{early-onset\ AN}$ explained 0.85% of the variance (liability scale R^2), and observed scale SNP-h^2 was 0.08 (SE = 0.02) with LDSC and 0.11 (SE = 0.01) with GREML. Liability scale SNP-h^2 was 0.16–0.19 (SE = 0.04) with LDSC and 0.21–0.25 (SE = 0.02) with GREML, assuming a lifetime prevalence of 0.1% to 0.3% (28).

The GWAS of typical-onset AN (5 cohorts, 6998 cases and 25,042 controls) revealed two genome-wide significant loci (chromosome 3, rs3821875, OR = 1.21, 95% CI 1.14 to 1.29, $p = 5.38 \times 10^{-10}$; chromosome 9, rs4641158, OR = 1.23, 95% CI 1.15 to 1.31, $p = 2.63 \times 10^{-9}$) (Figure S2 in Supplement 1). The first was the top locus in the parent study and is complex and multigenic (i.e., >100 genes) with many chromatin and expression quantitative trait loci interactions. The second single-gene locus was not significant in the parent study and encodes *CNTLN* (centlein, centrosomal protein), which organizes microtubules (41) and is expressed in ovarian cells (42). Gene expression was most enriched in brain tissues, although no tissue expression p values (Figure S3 in Supplement 1), nor gene sets (Table S4 in Supplement 2), were Bonferroni significant. $GRS_{typical-onset\ AN}$ explained 0.25% of the variance (liability scale R^2). Observed scale SNP-h^2 was 0.21 (SE = 0.02) with LDSC and 0.19 (SE = 0.01) with GREML, and liability scale SNP-h^2 assuming a lifetime prevalence of 0.9% to 4% (1,43,44) was 0.17–0.25 (SE = 0.02) with LDSC and 0.15–0.22 (SE = 0.02) with GREML.

The allelic effects at the eight genome-wide significant loci in the AN risk GWAS were investigated in the early- and typical-onset GWASs, and allelic effects were similar (Tables S5a–c in Supplement 2).

Genetic Correlations of Age of Onset, Early-Onset AN, and Typical-Onset AN

The genetic correlation between early- and typical-onset AN did not differ significantly from unity, $r_g = 0.81$ (SE = 0.12). Owing to the low heritability of age of onset, the quantitative trait, we had insufficient power to explore genetic correlations with other traits, and none reached even nominal significance ($p < .05$).

We investigated genetic correlations between early-onset AN and 62 traits prioritized from six categories based on previous evidence from AN (5,17): psychiatric (i.e., schizophrenia,
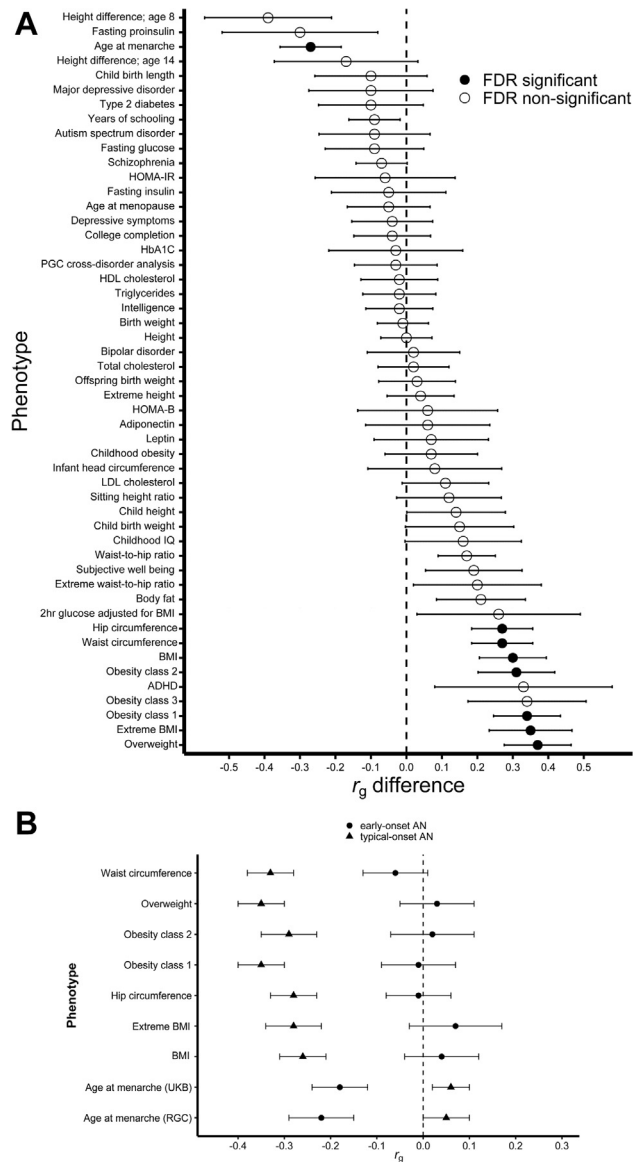

Figure 1. Early-onset and typical-onset AN show significantly different genetic correlation patterns with risk and comorbid traits. FDR-significant differences in genetic correlations were detected in two categories—anthropometric and reproductive—within six previously identified categories of risk or comorbid traits of interest for AN. **(A)** Sixty-two phenotypes were tested; duplicate phenotypes are not plotted (for duplicate phenotypes, we prioritized published summary statistics or the r_g difference with the lowest SE). Full results are shown in Table S9 in Supplement 2. **(B)** Shows the r_gs between the phenotypes and the age of onset subphenotypes. The error bars in both plots represent the SE. ADHD, attention-deficit/hyperactivity disorder; AN, anorexia nervosa; BMI, body mass index; FDR, false discovery rate; HbA1C, hemoglobin A$_{1c}$; HDL, high-density lipoprotein; HOMA-B, homeostatic model assessment for beta cell function; HOMA-IR, HOMA for insulin resistance; LDL, low-density lipoprotein; PGC, Psychiatric Genomics Consortium; RGC, ReproGen Consortium; UKB, UK Biobank.

major depressive disorder), anthropometric (i.e., weight, height), glycemic (i.e., type 2 diabetes, insulin resistance), lipid related (i.e., high-density lipoprotein cholesterol, triglycerides,

leptin), reproductive (i.e., age at menarche, age at menopause), and education and intelligence (i.e., IQ, college completion). Nominally significant ($p < .05$) genetic correlations were observed with eight traits (Table S6 in Supplement 2). Ranked in order of increasing p values, these were reproductive, education, glycemic, and lipid-related traits, but none were significant after FDR correction (37). We also considered the genetic correlations between early-onset AN, all 700+ traits on LD Hub, and previous GWAS of AN (Table S7 in Supplement 2). FDR-significant correlations were observed between early-onset AN and the three previous AN GWASs and a UK Biobank question on whether help was sought from a psychiatrist for nerves, anxiety, tension, or depression. The genetic correlations for typical-onset AN are in Table S8 in Supplement 2.

We compared the early-onset AN and typical-onset AN genetic correlations (Table S9 in Supplement 2). FDR-significant differences emerged for reproductive and anthropometric traits (Figure 1). Early-onset AN evidenced genetic overlap with younger age at menarche, whereas typical-onset AN did not. Early-onset AN did not genetically overlap with anthropometric traits, whereas typical-onset AN showed negative correlations.

GRS$_{age of onset}$, GRS$_{early-onset AN}$, and GRS$_{AN}$ as Predictors of Age of Onset of AN

GRS analyses supported a common genetic basis of age of onset (Figure 2). Higher GRS$_{age of onset}$ significantly predicted higher age of onset at three p_Ts, and GRS$_{early-onset AN}$ significantly predicted a younger age of onset at seven p_Ts. GRS$_{AN}$ did not significantly predict age of onset. The GRSs explained a small amount of phenotypic variance (R^2) in age of onset (Figure 2). The highest R^2s across p_Ts were 0.13% for GRS$_{age of onset}$ (at $p_T < .1$), 0.39% for GRS$_{early-onset AN}$ ($p_T < .4$), and 0.17% for GRS$_{AN}$ ($p_T < 1$). Cochrane Qs for the meta-

analyses in Figure 2 (24 total) were nonsignificant ($p < .05$), indicating that despite methodological differences across cohorts (i.e., age of onset phenotyping, recruitment, and sampling), heterogeneity was not evident. The forest plots in Figure S4 in Supplement 1 depict β estimates across the cohorts; results are shown for the best-performing p_Ts for illustration. We also observed significant associations between GRS quartile groups and age of onset (Supplemental Results in Supplement 1; Figure 2). Descriptive information for the GRS leave-one-cohort-out analyses is provided in Table S10 in Supplement 2.

GRS$_{age at menarche}$ as a Predictor of Age of Onset of AN, Early-Onset AN, Typical-Onset AN, and AN Risk

Per aim 3, we investigated the associations between GRS$_{age at menarche}$ and age of onset (13 cohorts, 9335 cases), early-onset AN (5 cohorts, 1269 cases and 25,042 controls), typical-onset AN (5 cohorts, 6998 cases and 25,042 controls), and AN risk (13 cohorts, 11,632 cases and 31,981 controls). GRS$_{age at menarche}$ significantly predicted age of onset of AN and early-onset AN at all p_Ts (Table 1). For instance, a 1 SD decrease in GRS$_{age at menarche}$ was associated with an age of onset decrease of 0.21 years (95% CI −0.31 to −0.12; at $p_T < .1$) and a 20% higher odds of early-onset AN (95% CI 1.13 to 1.27; at $p_T < 1$).

Age at Menarche as a Causal Risk Factor for Age of Onset of AN, Early-Onset AN, Typical-Onset AN, and AN Risk

Mendelian randomization provided evidence consistent with a causal link between younger age at menarche and early-onset AN (β = −0.21, SE = 0.09, p = .02) (Table 2). For each 1-year decrease in age at menarche below the mean (in the observed range), the odds of early-onset AN increased by 23% (95% CI 3% to 48%). Genetically determined age at menarche
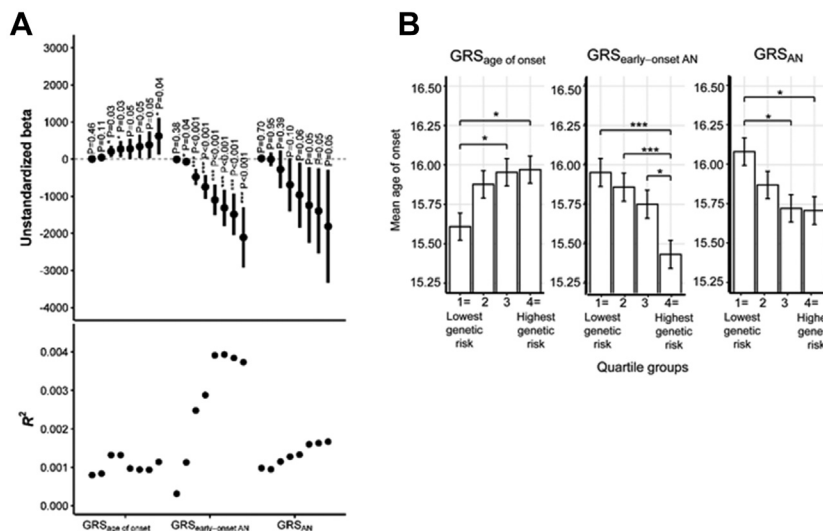

Figure 2. GRS$_{age of onset}$ and GRS$_{early-onset AN}$ significantly predict age of onset of AN. The p values are false discovery rate–corrected for multiple testing. *$p < .05$; ***$p < .001$. **(A)** Unstandardized βs represent the average increase in age of onset (years) per 1-unit increase in GRS. The error bars are 95% confidence intervals. The eight data points in each field, from left to right, represent ascending p value selection thresholds ($p_T < .001$, $p_T < .01$, $p_T < .1$, $p_T < .2$, $p_T < .3$, $p_T < .4$, $p_T < .5$, $p_T < 1$) for inclusion of SNPs from the GWAS into the GRS (i.e., $p_T < 1$ means that all SNPs were included in score calculation). Table S10 in Supplement 2 reports descriptive statistics for GRS. **(B)** Marginal means and standard errors are plotted. The tests of significant difference are from fixed-effects inverse-variance weighted meta-analyses of mean difference in age of onset by GRS quartile. The data include 13 cohorts (n = 9335) for GRS$_{age of onset}$ and GRS$_{AN}$ and 5 cohorts (n = 8267) for GRS$_{early-onset AN}$. AN, anorexia nervosa; GRS, genetic risk score; GRS$_{AAO}$, GRS computed from the within-case age of onset GWAS; GRS$_{AN}$, GRS computed from the case-control AN GWAS (2); GRS$_{early-onset AN}$, GRS computed from the case-control early-onset AN GWAS; GWAS, genome-wide association study; SNP, single nucleotide polymorphism.

Table 1. Association Between GRS$_{\text{age at menarche}}$ and Age at Onset of AN, Early-Onset AN, Typical-Onset AN, and AN Risk

p_T	Age of Onset of AN, 9335 Cases				Early-Onset AN, 1269 Cases, 25,042 Controls				Typical-Onset AN, 6998 Cases, 25,042 Controls				AN Risk, 11,632 Cases, 31,981 Controls			
	Estimates (95% CI)	p Value	Q	R^2	Estimates (95% CI)	p Value	Q	R^2	Estimates (95% CI)	p Value	Q	R^2	Estimates (95% CI)	p Value	Q	R^2
1	−0.19 (−0.28 to −0.10)	2.72×10^{-5}[a]	23.92[a]	0.42%	1.20 (1.13 to 1.27)	4.13×10^{-9}[a]	2.35	0.30%	0.99 (0.96 to 1.01)	.33	9.56	0.02%	1.02 (0.99 to 1.04)	.21	19.96	0.03%
.5	−0.19 (−0.28 to −0.10)	2.48×10^{-5}[a]	22.63[a]	0.42%	1.20 (1.13 to 1.27)	4.81×10^{-9}[a]	2.77	0.31%	0.98 (0.96 to 1.01)	.30	9.58[a]	0.02%	1.01 (0.99 to 1.04)	.23	19.78	0.03%
.4	−0.20 (−0.29 to −0.11)	1.52×10^{-5}[a]	23.45[a]	0.44%	1.19 (1.12 to 1.27)	8.94×10^{-9}[a]	2.96	0.30%	0.98 (0.96 to 1.01)	.29	8.79	0.02%	1.01 (0.99 to 1.04)	.24	19.64	0.03%
.3	−0.21 (−0.30 to −0.12)	8.00×10^{-6}[a]	23.53[a]	0.46%	1.20 (1.13 to 1.27)	5.30×10^{-9}[a]	2.32	0.30%	0.98 (0.95 to 1.01)	.16	8.01	0.02%	1.01 (0.99 to 1.04)	.41	18.72	0.03%
.2	−0.21 (−0.30 to −0.12)	8.59×10^{-6}[a]	22.96[a]	0.46%	1.19 (1.12 to 1.26)	2.24×10^{-8}[a]	2.47	0.27%	0.98 (0.95 to 1.01)	.16	9.37	0.02%	1.01 (0.99 to 1.04)	.39	20.34	0.03%
.1	−0.21 (−0.31 to −0.12)	6.13×10^{-6}[a]	28.06[a]	0.51%	1.19 (1.12 to 1.27)	2.43×10^{-8}[a]	3.74	0.29%	0.98 (0.95 to 1.00)	.10	10.50	0.02%	1.01 (0.99 to 1.04)	.34	20.94	0.03%
.01	−0.21 (−0.29 to −0.12)	7.24×10^{-6}[a]	27.77[a]	0.52%	1.16 (1.09 to 1.23)	1.22×10^{-6}[a]	2.03	0.23%	0.98 (0.95 to 1.00)	.09	5.73	0.02%	1.01 (0.99 to 1.04)	.33	9.95	0.02%
.001	−0.18 (−0.27 to −0.09)	4.96×10^{-5}[a]	16.30	0.35%	1.13 (1.06 to 1.19)	8.00×10^{-5}[a]	2.44	0.15%	0.97 (0.94 to 1.00)	.04	4.68	0.02%	1.01 (0.99 to 1.03)	.43	12.39	0.02%
1×10^{-5}	−0.15 (−0.23 to −0.06)	1.12×10^{-3}[a]	14.32	0.28%	1.10 (1.03 to 1.16)	2.57×10^{-3}[a]	8.93	0.18%	0.96 (0.93 to 0.99)	.01	2.83	0.02%	1.00 (0.98 to 1.03)	.91	15.25	0.02%
5×10^{-8}	−0.12 (−0.20 to −0.03)	.01[a]	10.69	0.19%	1.11 (1.05 to 1.18)	6.17×10^{-4}[a]	4.16	0.14%	0.97 (0.94 to 1.00)	.05	1.40	0.01%	1.00 (0.98 to 1.03)	.73	8.92	0.02%

Estimates are β for age of onset of AN, and odds ratio for AN, early-onset AN, and typical-onset AN, and for interpretation purposes, reflect the effect of a standard deviation decrease in GRS$_{\text{age at menarche}}$ (from the mean). R^2 estimates for early-onset AN, typical-onset AN, and AN risk are liability-scale estimates.

AN, anorexia nervosa; GRS, genetic risk score; p_T, the p value threshold for single nucleotide polymorphism selection for each GRS score.

[a]False discovery rate-adjusted $p < .05$.

did not significantly predict age of onset of AN—although the mostly positive, wide CI precludes definitive interpretation (β = 0.23, 95% CI −0.02 to 0.48, $p = .08$)—and did not predict typical-onset AN (β = 0.06, 95% CI −0.04 to 0.16, $p = .26$) or AN risk (β = −0.04, 95% CI −0.12 to 0.04, $p = .27$). In the opposite direction, AN risk was not a causal risk factor for age at menarche (β = 0.03, 95% CI −0.05 to 0.11, $p = .50$). Given the lack of SNP instruments from the age of onset, early-onset, and typical-onset AN GWASs, their causal effects on age at menarche could not be investigated. Sensitivity analyses complemented the findings of the inverse-variance weighted analyses (Supplement 1).

DISCUSSION

This study provides evidence for a genetic basis for age of onset of AN, which is conferred at least partly through common genetic variants. GRSs capturing the effects of alleles associated with AN age of onset and early-onset AN significantly predicted age of onset. Furthermore, results suggested that the genetic architecture underlying earlier puberty, represented by age at menarche, may bring about an earlier onset of AN.

The SNP-h^2 of the subphenotype of early-onset AN was similar to what has been reported for psychiatric diagnoses including AN (SNP-h^2s 0.10–0.26). The SNP-h^2 of age of onset, a quantitative trait, was low (SNP-h^2s 0.01–0.04). Other psychological and behavioral quantitative traits have been found to have low heritabilities (i.e., depressive symptoms, subjective well-being, cigarette smoking, extraversion: SNP-h^2s 0.05–0.06) (16). Twin-based upper bound estimates of heritability (twin-h^2) of age of onset are lacking but would help to contextualize these results, as would SNP-h^2 estimates from large, homogeneous datasets (>5000) (45). The heritabilities of early-onset and typical-onset AN were similar. This paints a different picture to the Brainstorm Consortium's report combining several psychiatric disorders, which suggested earlier age of onset of psychiatric illness as an indicator for higher heritability (16). The Brainstorm Consortium analysis was a broad brushstroke view that relied on rough single estimates of average age of onset from experts and did not use phenotypic data. Our approach is data based, but the estimates are preliminary, given that the discovery GWASs have small samples for psychiatric GWAS.

No loci reached genome-wide significance in the age of onset and early-onset AN GWASs. Precise epidemiological estimates of early-onset AN are lacking, but prevalence is low and less than the lifetime prevalence of 0.3% in adolescents and 0.9% in adults (1,28). This limits GWAS statistical power at the current sample sizes. The genetic correlation between early-onset AN and AN risk is stronger than the genetic correlation of AN risk with other traits (i.e., psychiatric, anthropometric, metabolic: r_gs −0.36 to 0.45) (5). The genetic correlation between early-onset and typical-onset AN was high, although distinct patterns of genetic correlations with other traits were observed. Early-onset AN correlated with lower age at menarche, and typical-onset AN correlated negatively with anthropometric traits. Studying homogeneous clinical subphenotypes such as early-onset AN may yield novel insight into the etiology of AN but is reliant on large

Table 2. MR Analyses Testing the Causal Associations Between Age at Menarche and Age of Onset of AN, Early-Onset AN, Typical-Onset AN, and AN Risk

Analysis	Age at Menarche → Age of Onset of AN	Age at Menarche → Early-Onset AN	Age at Menarche → Typical-Onset AN	Age at Menarche → AN Risk	AN Risk → Age at Menarche
IVW MR, β (SE)	0.23 (0.13)	−0.21 (0.09)[a]	0.06 (0.05)	−0.04 (0.04)	0.03 (0.04)
Sensitivity Analyses					
Heterogeneity, Q	238.38	212.28	295.16[b]	395.54[b]	3.39
Egger regression, β (SE)	0.29 (0.38)	−0.20 (0.25)	0.17 (0.14)	0.13 (0.11)	0.41 (0.35)
Egger regression, intercept (SE)	−0.002 (0.02)	−0.0003 (0.01)	−0.005 (0.01)	−0.01 (0.004)	−0.03 (0.03)
Weighted median estimate, β (SE)	0.21 (0.20)	−0.09 (0.15)	0.07 (0.07)	0.0002 (0.05)	0.04 (0.04)
MR-PRESSO global	240.42	214.14	297.76[b]	399.03[b]	–
Steiger	Direction: true[a]	Direction: true[b]	Direction: true[b]	Direction: true[b]	Direction: true[b]
GSMR, β (SE)	0.07 (0.10)	−0.11 (0.07)	0.16 (0.03)[b]	0.03 (0.02)	0.03 (0.03)

β values are differences in the outcome per year increase in age at menarche for the analyses with menarche timing as the exposure. Number of single nucleotide polymorphism instruments in IVW, Egger, weighted median, and GSMR analyses: menarche→age of onset of AN = 208, menarche→early-onset AN = 210, age at menarche→typical-onset AN = 210, age at menarche→AN risk = 206, AN risk→age at menarche = 3.

AN, anorexia nervosa; GSMR, generalized summary data-based Mendelian randomization; IVW, inverse-variance weighted; MR-PRESSO, Mendelian randomization pleiotropy residual sum and outlier.

[a]$p < .05$.
[b]$p < .001$.

phenotyping collections. Preliminary findings from this study suggest that a reproductive biology–based etiology for some patients may be worthy of further exploration.

Two loci were associated with typical-onset AN, one highly multigenic locus containing many brain-expressed genes and associated with AN risk (5), and a single-gene locus encoding a centrosomal protein and associated with phenotypes genetically correlated with AN (5), such as body fat distribution (adjusted-for-BMI) (46), high-density lipoprotein cholesterol level (47), and unipolar depression (48). The typical-onset AN GWAS was statistically powered for the initial implication of variants, given that ORs of 1.12 to 1.28 are in the range of the larger effects that we would expect to see in AN.

An important finding in this study was that GRSs for age of onset and early-onset AN significantly predicted age of onset. This provides evidence for a common variant genetic basis for age of onset, although the clinical significance is unclear. The age of onset difference was approximately 6 months between the lowest and highest GRS$_{age of onset}$ quartiles. Future studies characterizing the more extreme ends of the GRS distribution of age of onset (i.e., 5%) may see considerably greater differences in timing of AN onset. Irreversible growth stunting and long-term bone disease (49) are morbidities exacerbated by earlier onset and could be mitigated by risk prediction tools that predict not only illness risk but timing of onset.

The variance in age of onset accounted for by common genetic variants was low. The explanatory power of GRS is influenced by the underlying genetic architecture and heritability and sufficiently powered discovery GWASs. Even so, the ability to account for variance in psychiatric phenotypes has been limited. Schizophrenia, for example, has a large genetic component and a heritability estimate of 80% (50), but GRS has only been able to account for 7% of variation on the liability scale—the most of any psychiatric disorder—with this estimate increasing as GWAS power has increased (51). GRS broadly has proven useful in research applications—by predicting incidence, disease severity, and treatment response—

and can yield benefit to personalized prevention and early intervention of disease even when accounting for low variance (52).

A prevailing difficulty in risk factor research for AN has been how to consider peripuberty as a puzzle piece. Early-onset AN was historically termed premenarchal AN (53), which failed to appreciate that the starvation emblematic of the disease arrests puberty (and omits males). The association between puberty timing and AN can be difficult to study because the low prevalence of AN renders prospective association studies impractical, and in treatment-seeking populations, patients typically have delays in help seeking. Genetic analyses circumvent some of these methodological difficulties. In this study, GRS for earlier age at menarche predicted early-onset AN and lower age of onset. Furthermore, there was evidence consistent with earlier age at menarche being a causal risk factor for early-onset AN. This could suggest a genetically distinct variant of AN, genetically linked to puberty that is predisposed to an earlier age of onset. Indeed, this aligns with previous hypotheses (54,55) that a subset of women with eating disorders may represent an ovarian hormone–sensitive phenotype. Furthermore, twin studies suggest that estrogen plays a role in genetic risk for disordered eating (17). Our results converge with clinical studies implicating early pubertal timing as a risk factor for eating disorders (17) and extend the literature by suggesting a shared or potentially causal genetic molecular basis.

Cases with early-onset AN did not show a genetic relationship with BMI or related anthropometric indices, in contrast to cases with typical-onset AN. Literature comparing premorbid BMI trajectory between these groups is lacking. Because metabolic factors in AN are a burgeoning area of study, this could be an interesting finding to follow up. Continued investigation of the subphenotype of early-onset AN may help to inform etiology and classification.

A limitation of this study is that the phenotyping of age of onset was not standardized across cohorts. The phenotype was age of onset of AN diagnosis in some cohorts and age of first symptoms in others. The reliance on retrospective recall of

age of onset is also a limitation. The generalizability of the findings to non-Europeans and males is not known. Genetic effects may emerge earlier in males according to existing research ([56]). From the statistical power analyses, it seems reasonable to conclude that at this stage, the GWASs of age of onset and early-onset AN are underpowered to identify individual variants.

In conclusion, this study provides evidence that a genetic basis underlies AN age of onset and that reproductive biology may influence the early onset of AN. Larger, well-matched case-control samples with standardized age of onset data will help to further reveal the biological mechanisms that influence age of onset.

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