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Age of onset and family history as indicators of polygenic risk for major depression

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Abstract

Background—The extent to which earlier age of onset (AO) is a reflection of increased genetic risk for major depression (MD) is still unknown. Previous biometrical research has provided mixed empirical evidence for the genetic overlap of AO with MD. If AO is demonstrated to be relevant to molecular polygenic risk for MD, incorporation of AO as a phenotype could enhance future genetic studies.

Methods—This research estimated the SNP-based heritability of AO in the China, Oxford and VCU Experimental Research on Genetic Epidemiology (CONVERGE) case-control sample (N = 9854, MD case n = 4,927). Common SNP heritability of MD was also examined across both high and low median-split AO groups, and best linear unbiased predictor (BLUP) scores of polygenic risk, in split-halves, were used to predict AO. Distributions of genetic risk across early and late AO were compared, and presence of self-reported family history of MD was also examined as a predictor of AO.

Results—AO was not significantly heritable and polygenic risk derived from the aggregated effects of common genetic variants did not significantly predict AO in any analysis. AO was modestly but significantly lower in cases with a first-degree genetic family history of MD.

Conclusions—Findings indicate that AO is associated with greater self-reported genetic risk for MD in cases, yet not associated with common variant polygenic risk for MD. Future studies of early MD may benefit more from the examination of important moderating variables such as early life events.

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Keywords

age of onset; CONVERGE; depression; family history; GCTA; genome; genome-wide complex trait analysis

Introduction

Age at onset (AO) has been considered a potential quantitative indicator of underlying genetic risk for major depression (MD). However, the nature of any association of AO with genetic risk for MD is still unclear, and to date, twin and family research has provided mixed evidence to support this theory. Over the last several decades, multiple studies have observed that early AO is associated with increased familial risk,[1-7] with many others finding no association.[8-10] Contributing to the mixed evidence is the fact that AO has been studied at a variety of age thresholds, with some studies defining early-onset at under 18, while others examine the presence of MD at 30 years and younger. Differences in age thresholds have an impact on the study's generalizability and interpretability.

Family studies traditionally seek to compare the risk of disease in first-degree relatives to the risk found in the general population, and this is termed relative risk (RR). An increase in RR for family members has been predicted by an earlier AO in MD probands.[1,11-18] Family studies focusing on childhood-onset MD have also found an increase in severity and rate of affective disorders in relatives of children with MD,[19] as well as compared to adult MD probands and their families.[20] This relationship was also found in the reverse, wherein one study of children of MD parents showed an increased risk of psychopathology and earlier onset of MD.[3] However, other family studies have not found significant support for differences in genetic influences on MD predicted by AO.[21-22]

Studies on the heritability of AO itself have also yielded conflicting results. One twin study reported an AO heritability estimate of 0.47,[23] while another observed AO to be primarily due to environmental factors.[24] It is of note that a pair of Swedish twin studies found a modest association of AO with familial liability to MD,[5,7] but other twin studies of Swedish and English samples have failed to confirm this finding.[8,25,26]

Using molecular data on common variants, preliminary research thus far has found a marginally significant SNP-based heritability estimate of 0.17 (p=0.04)[27] for presence/absence of early AO. A genome-wide association study has examined AO of MD as a quantitative trait (in European samples with mean AO of ~20 years of age, N < 2,000 cases and controls).[28] While specific genome-wide hits did not replicate, results did suggest that common genetic variants may explain a large portion of the variance in AO in European samples (55%, p=.02). Finally, in a report by the Psychiatric Genomics Consortium working group, polygenic score analyses across mixed-ancestry samples suggested that earlier-onset MD is genetically more similar to major psychiatric disorders like schizophrenia and bipolar disorder than is adult-onset MDD. A potential implication of this finding is an increased genetic loading for MD in earlier-onset cases.[29]

Further examination of molecular genomic data may help to clarify whether AO is a heritable phenotype and whether it is associated with genetic liability to MD. Additional research is also needed to assess whether common variant heritability of AO may be significant in non-European samples. The China, Oxford and VCU Experimental Research on Genetic Epidemiology (CONVERGE) group recently detected and replicated the first robustly genome-wide statistically significant association between specific molecular variants and MD.[30] In addition, earlier age at worst episode was significantly associated with telomere shortening in this sample[31]. In the context of this success, it is useful to maximize statistical power and to examine AO as a potentially relevant quantitative phenotype. This includes 1) the examination of dimensional, aggregated effects from all measured common genetic variants in over 10,000 cases and controls, and 2) the examination of AO as both a continuous and a binary (early/late) phenotype.

Dimensional examination of aggregated effects across the genome has been useful in the examination of several complex phenotypes such as affective disorders, Parkinson's disease, and autism.[32-34] Analyses of other phenotypes have illustrated how a significant proportion of the genetic variance impacting complex traits, though not at genome-wide significance thresholds, can be detected with genetic profile scoring approaches and with genome-wide complex trait analysis (GCTA). [35]

This study sought to test the hypotheses that 1) continuous AO is a demonstrably heritable quantitative phenotype, and 2) that earlier AO reflects increased polygenic risk for MD. GCTA was first conducted with the entire MD case sample examining AO as a continuous variable. This research also examined whether polygenic risk for MD, derived using best linear unbiased predictor (BLUP) scores in split-half samples, predicted AO. In addition, the case sample was divided at the AO median, and estimates of SNP-based heritability were compared across groups. Each AO group (early vs. late) was also compared to the entire set of controls to determine whether AO groups would differ in subsequent SNP-based heritability estimates of MD. MD BLUP score distributions across very low AO (<16) and median split AO groups (<34 and =>34) were directly compared with nonparametric tests of equal densities. Finally, AO was compared across cases with and without a positive history of MD in first-degree relatives.

Materials and Methods

Sample Ascertainment

Data were drawn from the CONVERGE study of MD. Analyses of AO were based on cases (age M[SD] = 44.4[8.9]) and controls (age = 47.7[5.6]) recruited from 51 mental health centers and psychiatric departments of general medical hospitals, in 40 cities across 21 provinces of China. Genetic samples for AO analyses included 4,927 MD cases and 5,701 controls (total N = 10,628). Please refer to previously published research for full details of sample ascertainment.[30] Due to some evidence that heritability of MDD differs by sex,[36-38] we controlled for potential clinical and etiologic heterogeneity by collecting only female participants. To reduce population stratification, only participants only whose grandparents (all four) were of Han Chinese descent were recruited. Cases were excluded for history of

bipolar disorder, any psychosis, and any significant mental disability such as a diagnosis of mental retardation. AO data were missing for 55 of the cases.

All cases were recruited to be between 30 and 60 years of age and had had at least two major depressive episodes, with the first episode occurring prior to age 50. Prior research supports a greater genetic loading for MDD in more strictly ascertained cases, and the resultant assurance of MDD case status based on recurrence is a strength of this sample. Moreover, research on recurrent cases here is consistent with sampling methods from the previous molecular studies on AO. [27-29]

Cases could not have abused drugs or alcohol prior to their first episode of depression. All subjects were interviewed using computerized assessment administered by a trained clinician, Axis I disorders were assessed, and all cases met diagnostic criteria for major depressive disorder. All of the clinical data were collected through face-to-face interviews by trained interviewers with clinical backgrounds. The interviewing process was recorded and monitored by experienced supervisors who provided feedback to ensure continued high quality interviewing.

Diagnoses of depressive disorders were completed using the Composite International Diagnostic Interview,[39] which classifies diagnoses according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria.[40] Previous research on structural invariance of MD measurement has been reported elsewhere, indicating that the DSM criteria perform similarly in this sample relative to European and U.S. samples.[41] Representativeness of the sample with regard to severity, chronicity, and number of depressive episodes has also been reported previously, and the mean illness duration of this sample was 9.75 years. [42]

The diagnostic interview was originally translated into Mandarin by a team of psychiatrists in Shanghai Mental Health Center, with the translation reviewed and modified by members of the CONVERGE team. While cases were excluded for schizophrenia-spectrum/bipolar disorders, anxiety disorders were co-morbid with many of the depression diagnoses, and these co-morbidities have been examined and reported previously.[41] The mean number of co-morbid anxiety disorders among the MDD patients was 1.35 (S.D.=1.56).

The history of lifetime major depression in parents and siblings was assessed using the Family History Research Diagnostic criteria[43] and was adapted from the interview used in the Virginia Adult Twin Study of Psychiatric and Substance Use Disorders.[44] It should be noted that underreporting of family history can be present in non-family studies where multiple informants are unavailable for assessment. However, using diagnostic criteria in case-control designs, as was done here, significantly increases the sensitivity of family history reporting.[46]

AO was assessed retrospectively by the participants' self-report, and was defined as the age at which the first manifestation of a depressive episode occurred based on the MD diagnostic criteria assessed during the interview. Clinical characteristics as they relate to AO have been examined previously in this sample, with earlier AO being associated with increased neuroticism and greater psychiatric co-morbidity.[42]

This study protocol was approved centrally by the Ethical Review Board of Oxford University, and by the ethics committees of all of the participating hospitals in China. Informed consent was obtained for subjects after the nature of the procedure(s) and research were explained. All research was performed in compliance with the Code of Ethics of the World Medical Association (Declaration of Helsinki), as well as the standards established by the Ethical Review Board and granting agency.

DNA Sequencing

DNA extraction and sequencing details have previously been reported.[11] Briefly, DNA was extracted from saliva using Oragene and sequenced reads were obtained from Illumina HiSeq machines aligned to Genome Reference Consortium Human Build 37 patch release 5 (GRCh37.p5) with Stampy (v1.0.17) with default parameters. Reads consisting of base quality <= 5 or containing adaptor sequencing were filtered out.

Calling and Imputation of Genotypes

Details of genotype calling and imputation from low pass sequencing data are detailed elsewhere.[11] In brief, 6,242,619 SNPs were available after quality control, which included (a) *P*-value for violation of the Hardy–Weinberg equilibrium $>10^{-6}$; (b) information score >0.9; (c) minor allele frequency (MAF) in CONVERGE >0.5%.

Statistical Analyses

GCTA was used to construct a genetic relationship matrix (GRM) containing identical by state (IBS) relationship calculations for all pair-wise sets of individuals. The first two principal components of ancestry were included as covariates. Restricted maximum likelihood (REML) analyses were then performed using the GRM and quantitative principal component covariates. GCTA typically requires a sample size of N=5,000 for a well-powered heritability analysis, thus CONVERGE is the only non-European depression sample to our knowledge that is large enough for such an examination.

Genetic profile scores (or polygenic scores) were constructed using estimated common SNP effects by the BLUP method, using a random half of the sample (in the analysis of AO, the case sample, and in the analysis of MD, the entire sample) and testing the prediction of the phenotype from the training half on the remaining half. We then reversed the analysis, to predict AO or MD status in the first half of the sample from polygenic data in the second half.

Linear regressions were conducted in R including a full model (e.g., BLUP score and the two primary principal components as predictors) and a restricted model, removing the BLUP score. The difference in Nagelkerke R^2 between the models (rsq) was computed and the *p*-value associated with the SNP-based score variable from the full model was examined. The Nagelkerke rsq generated from these models is a difference in pseudo-R^2, thus *p*-values are not derived from full and restricted model comparisons. Instead, the *p*-value associated with the dropped component (score) is reported here. We then performed non-parametric density tests to examine score distribution overlap across three AO groups: <16 years of age, <34, and ≥ 34. Finally, we examined self-reported first-degree family history (FH) with respect to

whether SNP-based BLUP scores differ across FH groups, and whether FH groups differ with respect to AO as a quantitative variable.

Results

Age of Onset as a Continuous Phenotype

The distribution of AO across the entire CONVERGE case sample is presented in Figure 1. SNP-based heritability of AO, as a continuous quantitative trait, was examined in the full case sample and in the split-half case samples, and these SNP-based heritabilities are presented in Table 1. All were nonsignificant, despite adequate power in this sample to detect genetic effects. The results in Table 1 present V_G/V_P, or the proportion of total variance due to genetic factors (standardized genetic variance) in each sample. Despite small standard errors, heritability estimates were negligible.

Split-half case-control samples were used to create MD BLUP scores, and these scores were used to predict AO in the cases as a quantitative phenotype. AO did not significantly vary as a function of BLUP score when regression models with and without BLUP score, accounting for ancestry principle components, were directly compared. Scores in the cases were also uncorrelated with AO as a quantitative phenotype (*rho* = -0.01, $p = .48$). Because this was a large sample, it was also possible to examine age cohort effects by restricting the sample to individuals 50 and older, and there was no significant correlation of BLUP score with AO in these cases (*rho* = 0.02, $p = .52$).

Age of Onset by Median Split

In this sample, mean AO was 35.9 and the median was 34; AO was likely somewhat high relative to other samples due to cases being at least 30 years of age. We elected to test whether groups divided by the median would differ in SNP-based heritability of MD. The MD sample was divided by age at onset into low-half AO (<34 years) yielding 2767 cases, and high-half AO (=>34 years) yielding 2578 case samples. Results of heritability analyses for these samples are presented in Table 2, showing that the SNP-based heritability of MD of earlier AO was estimated at 19% (SE = 0.03) and for MD at later AO, SNP-based heritability was estimated at 22% (SE = 0.04). For illustrative purposes, and to examine the smaller group of very early onset (<16 years of age), distributions of BLUP scores for the samples with AO <16 and AO ≥ 34 are presented in Figure 2. These distributions can be seen to overlap almost entirely, indicating minimal genetic association of MD with AO. All nonparametric tests of equal densities were nonsignificant, indicating that no two AO groups (AO <16, <34, and ≥ 34) differed with respect to distribution of BLUP score.

Age of Onset and Family History of Major Depression

Groups with and without self-reported family history of MD were also compared with respect to AO. Interestingly, cases with first-degree FH had a significantly lower AO than cases without FH (M[SD] = 33.62[9.76] and 35.21[9.75], respectively, t[5338] = 5.21, $p = 2.13 \times 10^{-7}$, Cohen's $d = 0.16$, [95%CI 0.10, 0.22]). While it was originally our intention to test whether AO heritabilities differed in samples with and without self-reported FH, the

tests of AO SNP-based heritabilities in this sample were non-significant. Case samples with and without FH did not differ with respect to BLUP score (p = .23).

Discussion

This well-powered study leveraged molecular data as an alternative to estimating heritability based on biometrical models in an effort to resolve the previous contradictory findings on AO. This study examined whether earlier AO reflects increased genetic liability for MD as measured by 1) common molecular genetic variants and 2) by self-reported family history. AO was examined as a continuous and median-split variable, and was not associated with genetic risk for depression as measured by common genetic variants. However, the self-reported presence of family history in MD cases was significantly predictive of earlier AO with a modest effect (d = .16). Here, the mean AO difference between FH groups was on the order of 2-3 years. Thus, while the significance of the difference between groups is consistent with some previous research reporting association of genetic risk for MD with AO, altogether results indicate that family history and SNP-based risk for MD do not lead to clinically significant differences in AO (for example, to very early onsets of <16 years).

Some limitations are important to consider. First, AO is a censored variable, and can only be equal to or younger than the proband's age at interview. Since later AO can only be found in older probands, cohort effects could be confounded. Second, this case-control sample is comprised of only females, thus results cannot generalize to AO in males. However, as rates of depression are higher in females than in males, these results may generalize well to the MD population. In addition, this sample is comprised of individuals of Han Chinese descent, and the genetic variants predicting MD or AO may not generalize to other ethnic samples. However, CONVERGE was ascertained for only individuals with four Han grandparents, thus there is arguably more genetic homogeneity than can be found in many European samples. In addition, our group recently predicted MDD case status and neuroticism (N) in CONVERGE from N polygenic risk scores derived from European samples, thus there may be reason to believe the Han sample is comparable with respect to prediction of psychopathology based on common variants. Cross-ancestry analyses of whether MD, schizophrenia, bipolar disorder, and anxiety polygenic risk scores derived from European summary statistics predict AO in CONVERGE were also nonsignificant,[47] consistent with a lack of robust relationship between SNP-based polygenicity for MD and quantitative AO.

Conclusions

These analyses took advantage of a dimensional approach to examining genetic risk for MD by aggregating the effects of all measured common variants. Taken together, the results of this research suggest that AO likely cannot be predicted with polygenic metrics based on common variants. Our results are consistent with recent research indicating that earlier AO MD is more genetically similar to schizophrenia and bipolar disorder, but also indicate that the relationship of AO to MD polygenicity is quite nuanced. The research reported here should inform priorities for future studies of AO and MD: For example, any role of genetic risk for MD in early AO is likely subtle, and it is possible that other factors relating to family history of MD may be more relevant to AO than are genetic factors. Future studies may

benefit from examining potential mediating factors in early childhood, such as stressful life events or childhood trauma. It is also possible that family-specific or rare genetic variants, comprising an MD subtype, are uniquely associated with early AO. In addition, cross-disorder, cross-ancestry polygenicity (i.e., polygenic scoring based on Han Chinese schizophrenia and bipolar disorder genome-wide association study summary statistics) may be more associated with earlier AO of MD in a Chinese sample, thus future research should focus on procuring more summary statistics of non-European samples. Finally, future studies aimed at understanding the genetic control of neurocircuitry in MD may benefit from testing the association of shared genetic risk for MD (i.e., common polygenic brain eQTLs) with other well-defined quantitative phenotypes.

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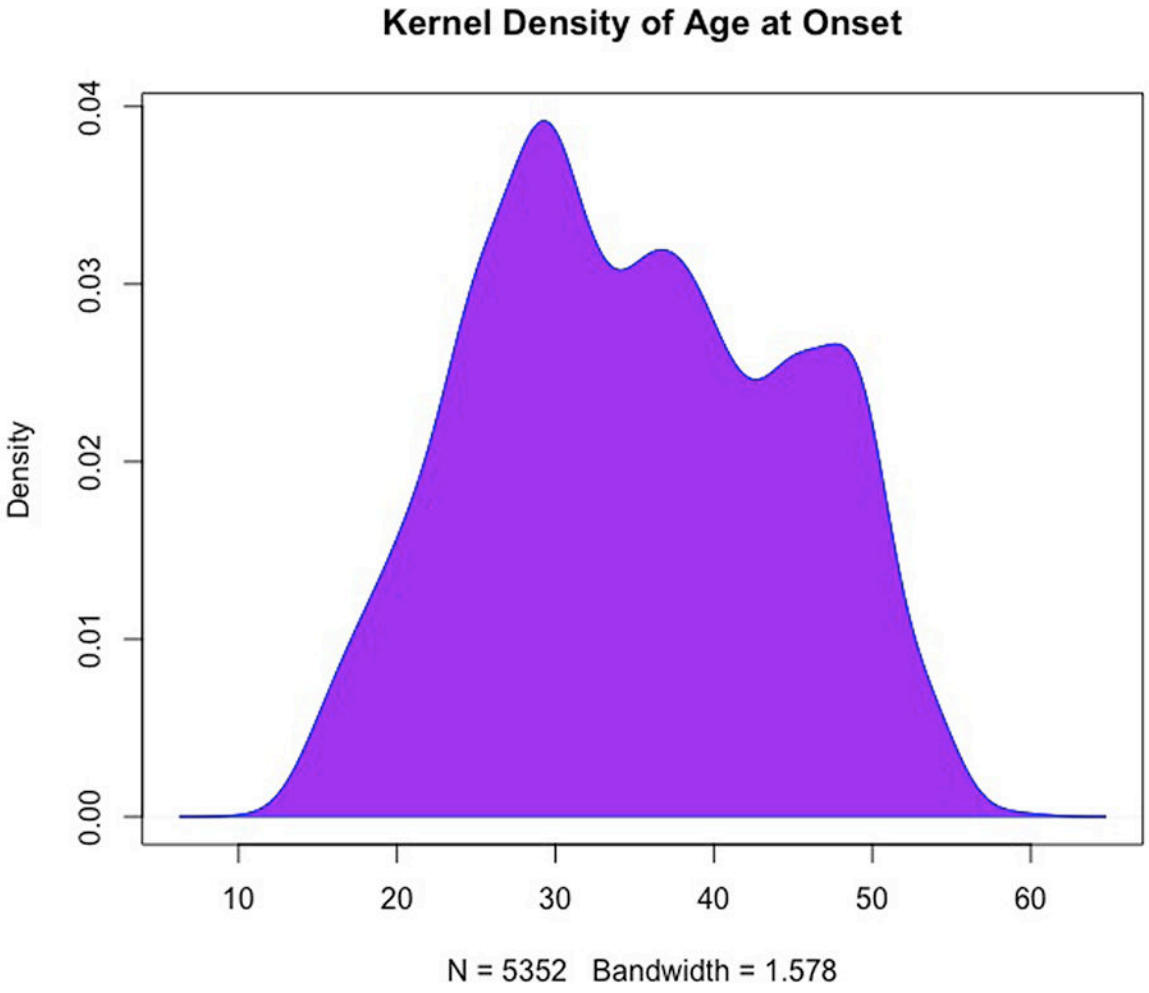

Figure 1. Kernel density plot of age at onset in CONVERGE major depression cases

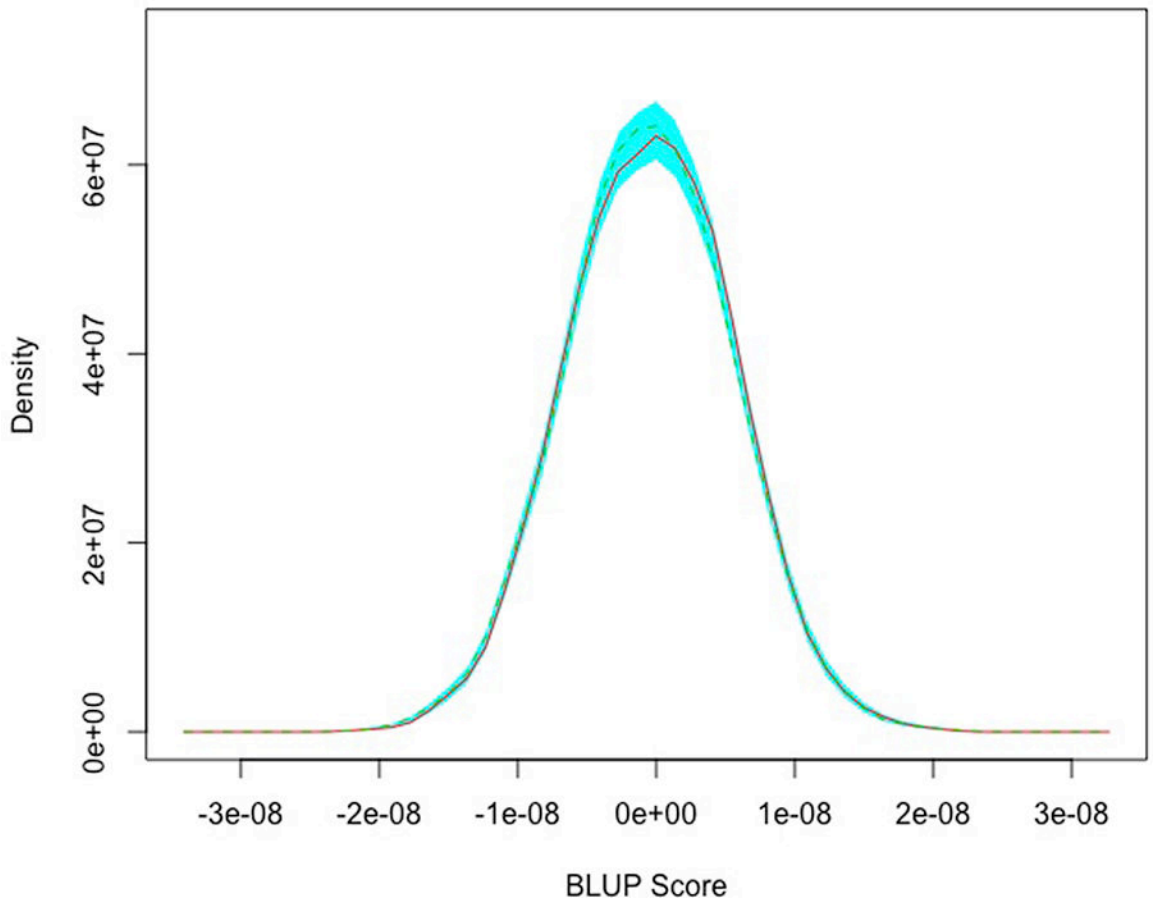

Figure 2. Major depression best linear unbiased predictor score densities across <16 and ≥ 34 AO groups

The solid line reflects cases with age at onset <16, the dotted line reflects age at onset of the median (34) and above. The band reflects upper and lower end-points of the reference band for equality. This test of equal densities is a permutation test, where the standard error of the sum of the squared differences of the density distributions is used to paint the band shown here. This plot conveys that the distributions of polygenic scores across groups of early and high AO groups are roughly equivalent.