Evidence for Genetic Overlap Between Schizophrenia and Age at First Birth in Women

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IMPORTANCE A recently published study of national data by McGrath et al in 2014 showed increased risk of schizophrenia (SCZ) in offspring associated with both early and delayed parental age, consistent with a U-shaped relationship. However, it remains unclear if the risk to the child is due to psychosocial factors associated with parental age or if those at higher risk for SCZ tend to have children at an earlier or later age.

OBJECTIVE To determine if there is a genetic association between SCZ and age at first birth (AFB) using genetically informative but independently ascertained data sets.

DESIGN, SETTING, AND PARTICIPANTS This investigation used multiple independent genome-wide association study data sets. The SCZ sample comprised 18 957 SCZ cases and 22 673 controls in a genome-wide association study from the second phase of the Psychiatric Genomics Consortium, and the AFB sample comprised 12 247 genotyped women measured for AFB from the following 4 community cohorts: Estonia (Estonian Genome Center Biobank, University of Tartu), the Netherlands (LifeLines Cohort Study), Sweden (Swedish Twin Registry), and the United Kingdom (TwinsUK). Schizophrenia genetic risk for each woman in the AFB community sample was estimated using genetic effects inferred from the SCZ genome-wide association study.

MAIN OUTCOMES AND MEASURES We tested if SCZ genetic risk was a significant predictor of response variables based on published polynomial functions that described the relationship between maternal age and SCZ risk in offspring in Denmark. We substituted AFB for maternal age in these functions, one of which was corrected for the age of the father, and found that the fit was superior for the model without adjustment for the father's age.

RESULTS We observed a U-shaped relationship between SCZ risk and AFB in the community cohorts, consistent with the previously reported relationship between SCZ risk in offspring and maternal age when not adjusted for the age of the father. We confirmed that SCZ risk profile scores significantly predicted the response variables (coefficient of determination R^2 = 1.1E-03, P = 4.1E-04), reflecting the published relationship between maternal age and SCZ risk in offspring by McGrath et al in 2014.

CONCLUSIONS AND RELEVANCE This study provides evidence for a significant overlap between genetic factors associated with risk of SCZ and genetic factors associated with AFB. It has been reported that SCZ risk associated with increased maternal age is explained by the age of the father and that de novo mutations that occur more frequently in the germline of older men are the underlying causal mechanism. This explanation may need to be revised if, as suggested herein and if replicated in future studies, there is also increased genetic risk of SCZ in older mothers.

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Parental age is a risk factor for a range of adverse mental health outcomes in children, including common psychiatric disorders, such as schizophrenia (SCZ).[1-3] Advanced paternal age has received the most attention, with risk to children widely assumed to be explained by de novo mutations that occur more frequently in the germline of older men,[4-6] although other studies[7,8] question the de novo mutation hypothesis. There is also emerging evidence to suggest that children of both younger[9] and older[10] mothers are at increased risk of psychosis.

One recent major study is by McGrath et al,[11] who performed a comprehensive analysis using family data extracted from the Danish Psychiatric Central Register and reported a U-shaped relationship between maternal age and risk of SCZ in offspring. They showed that there was higher risk in children of younger and older mothers compared with those of intermediate age (25-29 years). In their secondary analyses that were adjusted for the age of the father, which tends to be highly correlated with mother's age, increased risk of SCZ was associated with younger mothers (<25 years) but not older mothers. Conversely, children of older fathers (>29 years) were at increased risk, even after correcting for the age of the mother, but children of younger fathers were not. These epidemiological findings for the association of maternal age and risk of SCZ cannot dissect cause from consequence. That is, it is unclear if risk to offspring is due to psychosocial, lifestyle, or biological aging factors associated with maternal age or if women at higher risk for SCZ tend, on average, to have their first child at an earlier or later age. Herein, our analyses use a novel design to explore the relationship between age at motherhood and SCZ.

Recently developed whole-genome analysis methods provide an opportunity to investigate this question in a novel way that is independent of potential confounding factors. Genomic relationships and risk profile scores on unrelated individuals derived from genome-wide single-nucleotide polymorphism (SNP) data can be used to dissect the shared genetic architecture of complex traits.[12] For instance, independently collected unrelated individuals can be linked through genomic information, correlating their genotype sharing with similarities in their phenotypes. Because the individuals who are compared are not related in the conventional sense, any covariance between their shared genome and their phenotype is most likely genetic and likely free of confounding environmental effects. This novel design enables the use of independent genome-wide association study (GWAS) data sets to quantify the extent of genetic overlap across complex traits.

Herein, we investigated the genetic relationship between SCZ and age at first birth (AFB) in women using multiple independent GWAS data sets. Specifically, we used genetic risk alleles and their effect sizes estimated from SCZ GWAS data to create a genetic SCZ risk profile score for each woman in the AFB data set. The AFB data set comprises community samples of women (ie, not ascertained for psychiatric disorders) who had their age at birth of their first child recorded. While both SCZ and AFB are heritable traits,[13-15] here the genetic contribution underpinning the trait age at first motherhood is not dependent on the age of her partner. We tested if the relationship between a woman's AFB and her SCZ risk profile score matched that reported

by McGrath et al[11] between the age of mothers and the incidence rate ratio (IRR) for SCZ in their children.

Key Points

Question Is there a genetic association between schizophrenia (SCZ) and age at first birth (AFB) in women?

Findings In the analyses, the SCZ genome-wide association study (GWAS) comprised 18 957 cases and 22 673 controls, and the AFB GWAS comprised 12 247 women. Using these multiple independent GWAS data sets, we found a significant genetic association between SCZ risk and AFB.

Meaning SCZ risk in offspring associated with early and delayed maternal age is partly explained by the genetic association between SCZ and AFB

Methods

Each study obtained ethical board approval and written informed consent from all participants (eAppendix 1 in the Supplement). The SCZ sample comprised 18 957 SCZ cases and 22 673 controls in a GWAS from the second phase of the Psychiatric Genomics Consortium (PGC2-SCZ),[15] and the AFB sample comprised 12 247 genotyped women measured for AFB from the following 4 community cohorts: Estonia (Estonian Genome Center Biobank, University of Tartu), the Netherlands (LifeLines Cohort Study), Sweden (Swedish Twin Registry), and the United Kingdom (TwinsUK) (eAppendix 1 in the Supplement contains full details). These community cohorts measured for AFB were not enriched for psychiatric disorders. We used genomic best linear unbiased prediction (GBLUP), implemented in the MTG software,[16] to estimate SNP effects in our quality-controlled PGC2-SCZ data set (n = 41 630) (eTable 1 in the Supplement lists sample details). Briefly, SNP effects were estimated jointly within a linear mixed model that intrinsically accounts for linkage disequilibrium between SNPs. In estimating SNP effects, we fitted sex, cohort, and 20 ancestry principal components obtained from the sample to control for potential confounding effects, such as population stratification and potential batch effects. The SNP risk predictors were projected into the AFB samples, resulting in a GBLUP risk profile score for each individual. We repeated our analyses using standard genetic risk profile scores[17,18] (eAppendix 2 in the Supplement), in which the SCZ risk scores in the women measured for AFB were estimated by summing the count of the SCZ risk alleles weighted by their effect sizes (log[odds ratio]) estimated from our quality-controlled SCZ GWAS data. A regression of phenotype on genetic risk profile score tests for association between the measures. The GBLUP risk profile score is expected to be more accurate than a standard risk profile score because the available data in the SCZ sample are used more optimally in the GBLUP linear mixed-model methodology. In particular, arbitrary decisions about P value and linkage disequilibrium clumping that are inherent in standard profile scoring are avoided.

Table 1. Sample Size and Age at First Birth Across 4 Cohorts

| Cohort	Sample Size	Age at Interview, Mean (Range), y	Age at First Birth, Mean (Range), y
Estonian Genome Center Biobank, University of Tartu	1660	67.3 (45-101)	24.8 (15-46)
LifeLines Cohort Study	5344	53.1 (27-93)	26.7 (16-43)
Swedish Twin Registry	3262	58.2 (45-86)	25.1 (14-52)
TwinsUK	1981	55.4 (25-86)	25.7 (14-44)

The distribution of AFB and year of birth for each cohort are summarized in **Table 1** and eFigure 1 and eFigure 2 in the Supplement. In analyses for AFB, we generated 2 response variables using polynomial functions derived from McGrath et al[11] to describe the relationship between IRR for SCZ in offspring and maternal age (model 1 [$2.7214 + 0.0018x^2 - 0.1105x$]) or maternal age adjusted for the age of the other parent and urbanization of the place of birth (model 2 [$2.5438 + 0.0012x^2 - 0.0889x$]). eFigure 3 and eFigure 4 in the Supplement show how we derived the polynomial functions. In generating the model 1 and model 2 values for each individual, AFB was used as the x variable in the equations. In analyses, we used the residuals of the model 1 or model 2 values after regression on covariates, such as age at interview, 20 ancestry principal components, and cohort. We did not include year of birth as a covariate because its negative value was highly correlated with age at interview (>0.9). The fitted residuals were regressed against risk profile scores, and we report the proportion of variance (R^2) attributable to the polygenic score. The P value results from the test of the hypothesis $R^2 = 0$. The purpose of these analyses was to test if the SCZ polygenic risk values are a better fit to the phenotypic risk values predicted by model 1 or model 2. A smaller P value for model 1 would imply a better fit to the AFB data compared with model 2, for which the linear and quadratic coefficients were derived from models that adjusted for the age of the partner. Analyses were performed for the entire AFB sample and for subsets of women stratified by the mean AFB (26 years) into younger AFB (<26 years) and older AFB (≥26 years).

Results

We sought to provide insight to the relationship between maternal age and SCZ by exploring genetic overlap between SCZ risk in women measured for AFB. We observed a U-shaped relationship between AFB and SCZ risk profile scores derived using GBLUP (**Figure**), consistent with the relationship reported by McGrath et al[11] between SCZ risk in offspring and maternal age not adjusted for the father's age. The mean risk profile score from GBLUP analysis was significantly higher in women with early AFB (ie, <20 years) than in women with intermediate AFB ($P = 8.8E-03$ for AFB of 25 to <30 years and $P = 1.3E-02$ for AFB of 30 to <35 years) (eTable 2 in the Supplement). The results from standard profile score were very similar to those from GBLUP but showed weaker signals (eFigure 5 and eFigure 6 in the Supplement).

We further investigated if SCZ genetic risk profiles significantly predicted the model 1 or model 2 response variables,

Figure. Mean Schizophrenia Profile Scores From Genomic Best Linear Unbiased Prediction (GBLUP) in Community Samples of Women (No Ascertainment Based on Psychiatric Disorders) Grouped by Age at Birth of Their First Child
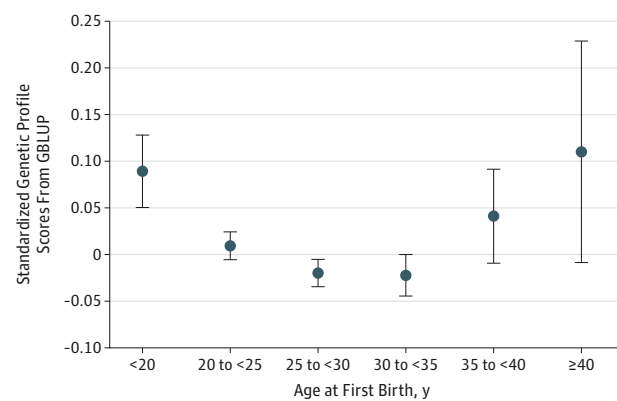
The error bars are SEs.

Table 2. Coefficients of Determination and P Values[a]

Data Set	Response Variable	R^2	P Value[b]
Full range of age at first birth (n = 10 836)	Model 1	1.1E-03	4.1E-04
	Model 2	6.4E-04	5.0E-03
Age at first birth <26 y (n = 5827)	Model 1	1.8E-03	6.2E-04
	Model 2	1.9E-03	5.1E-04
Age at first birth ≥26 y (n = 5009)	Model 1	1.0E-03	1.4E-02
	Model 2	6.5E-05	2.5E-01

[a] In the analyses, either the model 1 or model 2 variables were used as the dependent variables in regression on the genomic best linear unbiased prediction risk profile score using only women 45 years or older at recruitment. Age at first birth was used as the x variable in this study. The analyzed model 1 and model 2 variables were the residuals from a regression fitting potential confounders as covariates. Including the genetic profile score for educational attainment as a covariate had little impact on these results (eTable 8 in the Supplement). Model 1 polynomial function is derived from the incidence rate ratio for schizophrenia by maternal age (x) by McGrath et al[11] ($2.7214 + 0.0018x^2 - 0.1105x$). Model 2 polynomial function is derived from the incidence rate ratio for schizophrenia by maternal age adjusted for the age of the other parent and urbanization of the place of birth (x) by McGrath et al[11] ($2.5438 + 0.0012x^2 - 0.0889x$).

[b] P value for the null hypothesis $R^2 = 0$.

which are the phenotypic predictors of SCZ risk derived from the results reported by McGrath et al[11] (**Table 2**). We initially focused on a subsample of women 45 years or older at recruitment (n = 10 836) to avoid any potential bias owing to the inclusion of women who were childless at recruitment but still of childbearing age. In analyses of the full range of AFB in this sample, the model 1 and model 2 response variables were strongly predicted by GBLUP-derived SCZ risk profile scores ($P = 4.1E-04$ and $P = 5.0E-03$ for model 1 and model 2, respectively). The smaller P value for model 1 implies a better fit to the AFB data compared with model 2, which is consistent with the suggestion that adjusting for paternal age removes a true association between maternal age and IRR for SCZ. When restricting the analysis to younger mothers whose AFB was less

than the mean (AFB <26 years), the P values were P = 6.2E-04 and P = 5.1E-04 for model 1 and model 2, respectively. On the other hand, assessing only older mothers (AFB ≥26 years), GBLUP profile score weakly predicted model 1 (P = 1.4E-02) but not model 2 (P = 2.5E-01). We repeated the analyses using the total sample of 12 247 women and found almost identical results (eTable 3 in the Supplement), suggesting very little if any bias arising from the inclusion of an additional 1411 women younger than 45 years at recruitment. Again, analyses based on the profile score approach gave similar but weaker significance than GBLUP (eTable 4 in the Supplement).

In our primary analyses, we excluded women without children because the appropriate way to include such women in our analyses is difficult to determine. Delayed AFB and childlessness might have a common genetic predisposition or might be on distinct dimensions of liability. To explore this, we repeated the analyses with the inclusion of women having no children, whose age at recruitment was 45 years or older. In this analysis, we assigned women having no children an AFB of 45 years, which has been reported as the end of reproductive age.[19] Both response variables were predicted in analyses across the full range of AFB; however, the significance of the prediction was considerably decreased, and neither response variable was predicted in analyses of women with AFB of 26 years or older (eTable 5 in the Supplement). These results must be interpreted with caution because there could be many reasons why women have no children, with the most common being infertility, which is likely to be genetically independent of AFB among those able to conceive.

In addition to analyses of the total AFB sample, we examined the relationship between SCZ risk profile scores from GBLUP and the model 1 and model 2 response variables in each cohort (eTable 6 in the Supplement), acknowledging that owing to smaller sample size the power to detect a relationship was substantially reduced. For Estonian Genome Center Biobank, University of Tartu, risk profile scores were not significantly associated with AFB (see the Discussion section). However, a significant association remained in the other cohorts for at least 1 response variable. The prediction for the LifeLines Cohort Study was significant for model 1 when using the whole range of AFB or AFB younger than 26 years. For the Swedish Twin Registry, it was significant only for model 1 in analyses of women with AFB of 26 years or older. For TwinsUK, both response variables were predicted in analyses of the full range of AFB and AFB younger than 26 years but not in analyses of women with AFB of 26 years or older (eTable 6 in the Supplement). Due to smaller sample size, the U-shaped relationship observed between SCZ risk and AFB was less apparent in each cohort.

We stratified the AFB sample into birth cohorts born before or after 1945, a demarcation based on the second demographic transition that is linked in the literature to postponement of AFB.[20] For individuals born after 1945, SCZ risk profile scores from GBLUP significantly predicted AFB for the entire sample and the younger AFB group but not for the older AFB group (eTable 7 in the Supplement). For individuals born before 1945, SCZ risk profile scores from GBLUP did not significantly predict AFB.

Discussion

Maternal age is a risk factor for a number of adverse mental health outcomes, including common psychiatric disorders, such as SCZ.[21,22] In a recent study, McGrath et al[11] reported a U-shaped relationship between maternal age and risk of SCZ in children, although in analyses corrected for the age of the other parent only children of younger mothers were at increased risk. Their study implied that risk of SCZ in children of older mothers was attributable to the father's age, consistent with the hypothesis of risk arising from paternal age–related de novo mutations and the presence of a strong correlation between maternal and paternal age. However, because a larger proportion of older men have younger partners than is the case for older women, there is a possibility that correcting for the age of the spouse may remove a true effect due to advanced maternal age. In other words, the well-known problem of collinearity,[23-25] which can lead to biased estimates for explanatory variables that are adjusted for a correlated variable (eg, maternal age adjusted for paternal age), may result in an underestimate of the risk due to older maternal age in analyses, such as that reported by McGrath et al.[11] Our study uses a novel experimental design that is free of effects of the partner's age; therefore, there is no concern about such a collinearity problem in our analyses.

Maternal age is a proxy for factors other than parental age, including de novo chromosomal abnormalities, and psychosocial factors related to socioeconomic status and educational attainment, both of which are associated with risk of SCZ. Conversely, relatives of individuals affected with SCZ tend to have poor social interactions,[26] which may increase the time taken to find a mate and thereby delay AFB. Schizophrenia risk may also predispose to risk taking and impulsive behavior, which is associated with early pregnancy and childbirth in women.[27-29] Consequently, risk of SCZ in offspring due to maternal AFB may be influenced by shared genetic factors between mothers and offspring, as has been suggested for paternal AFB.[7,8]

In this study, we investigated genetic overlap between SCZ and AFB using a novel experimental design based on genomic data that enables genetic effects to be disentangled from other confounding factors. This is achieved through independently collected SCZ and AFB data sets that are genetically informative. The AFB data are collected from community samples with no known enrichment for psychiatric disorders. In particular, we sought to determine if response variables based on the relationships reported by McGrath et al[11] between maternal age and SCZ risk in children (model 1 and model 2) could be predicted by SCZ risk profile scores in our independent data. We found that SCZ risk profile scores predicted both model 1 and model 2, implying that polygenic variation for SCZ contributes to the relationships reported by McGrath et al[11] between maternal age and risk of SCZ.

Our results were stronger for the U-shaped model 1 response variable (based on unadjusted IRR) than model 2 (in which IRR was adjusted for paternal age and urbanization of the place of birth), suggesting that polygenic variation

contributes to risk of SCZ associated with both early and delayed maternal AFB. In analyses stratified by the mean AFB, evidence for genetic overlap between SCZ and AFB was strongest in women with early AFB (<26 years). In analyses of women with delayed AFB (≥26 years), we observed an association with the SCZ risk profile score but only for the model 1 response based on unadjusted IRR. Given that our methodology explores the relationship between AFB genetic risk and SCZ in a way that is independent of correlation between the ages of the parents, our analyses suggest that risk of SCZ in children of older mothers is not solely attributable to factors associated with advanced paternal age.

A caveat of our findings is that the genetic association between risk of SCZ and delayed AFB was only marginally significant given the number of analyses performed, perhaps reflecting smaller sample size and correspondingly larger standard errors for women with delayed AFB, and so require replication in a larger sample. Provided that this finding is confirmed in a future study, it has important implications because it implies that risk of SCZ associated with increased age in mothers is not entirely due to the father's age.

Although we demonstrate that SCZ genetic risk can be disentangled from psychosocial, lifestyle, and biological aging factors in assessing the relationship between SCZ risk and AFB, we cannot explicitly determine mechanism, and it is possible that subtle correlations between genetic and nongenetic factors might influence this relationship. Several mechanisms, such as correlation of SCZ risk with socioeconomic status and other environmental and biological factors, might also influence the genetic relationship between SCZ and AFB. For instance, SCZ risk could predispose to impulsive behavior[29] and substance use,[27] which are associated with early pregnancy and childbirth.[28] On the other hand, poor social competence in SCZ might delay the time to meet a partner or have offspring, causing delayed AFB. Other plausible mechanisms, such as low IQ and poor educational attainment, which are strong risk factors for both SCZ[30] and early pregnancy,[21] need to be explored, although the inclusion of the genetic profile score for educational attainment as a covariate had little impact on our results (eTable 8 in the Supplement). Assessing these factors is beyond the scope of this study. Future research that includes social science measures and information on nongenetic factors will facilitate a deeper understanding of causal pathways underlying the association between SCZ and AFB.

The analyses by McGrath et al[11] explored the relationship between parental age and a broad range of psychiatric disorders. Herein, we have only considered genetic risk for SCZ because sample size, and hence the power to estimate risk allele effect sizes, is greatest. For example, 108 independent risk loci for SCZ have been identified as being genome-wide significant[15] compared with only 3 for bipolar disorder.[31] As GWAS sample sizes for other psychiatric disorders increase, then replication of our analyses based on these disorders will be possible.

Conclusions

In summary, this study provides evidence for a significant overlap between genetic factors associated with risk of SCZ and genetic factors associated with AFB. To our knowledge, this is the first study to explore a genetic relationship between SCZ and AFB using independent unrelated samples based on genomic data. We conclude that women with high genetic predisposition to SCZ tend to have their first child at an early age or a later age compared with women in the general population.

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