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

Divya Mehta, PhD; Felix C. Tropf, MSc; Jacob Gratten, PhD; Andrew Bakshi, MSc; Zhihong Zhu, PhD; Silviu-Alin Bacanu, PhD; Gibran Hemani, PhD; Patrik K. E. Magnusson, PhD; Nicola Barban, PhD; Tõnu Esko, PhD; Andres Metspalu, MD; Harold Snieder, PhD; Bryan J. Mowry, MD; Kenneth S. Kendler, MD; Jian Yang, PhD; Peter M. Visscher, PhD; John J. McGrath, MD; Melinda C. Mills, PhD; Naomi R. Wray, PhD; S. Hong Lee, PhD; for the Schizophrenia Working Group of the Psychiatric Genomics Consortium, LifeLines Cohort Study, and TwinsUK

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 $R^2 = 1.1E\cdot03, P = 4.1E\cdot04$), 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.

Published online March 23, 2016.

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The Schizophrenia Working Group of the Psychiatric Genomics Consortium, LifeLines Cohort Study, and TwinsUK consortium authors and consortium collaborators are listed at the end of this article.

Corresponding Author: S. Hong Lee, PhD, School of Environmental and Rural Science, University of New England, Armidale, New South Wales, Australia 2351 (hong.lee@une.edu.au).
Parenteral age is a risk factor for a range of adverse mental health outcomes in children, including common psychiatric disorders, such as schizophrenia (SCZ).\(^4\) 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.\(^4\) 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,\(^13\) 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.

### 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

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

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 al11 to describe the relationship between IRR for SCZ in offspring and maternal age (model 1 (2.7214 + 0.0018x2 − 0.1105x)) or maternal age adjusted for the age of the other parent and urbanization of the place of birth (model 2 (2.5438 + 0.0012x2 − 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 (R²) attributable to the polygenic score. The P value results from the test of the hypothesis R² = 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 al11 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, which are the phenotypic predictors of SCZ risk derived from the results reported by McGrath et al11 (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. 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. 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.

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 al11 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 al11 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 con-
Genetic Overlap Between Schizophrenia and Age at First Birth in Women

Henry J. McCarley, MD, PhD; Patricia T. Michie, PhD; Derek W. MD, FRCPsych; Andrew McQuillin, PhD; Bela Melegh, PhD; Robert W. McCarley, MD; Andrew M. McIntosh, Joa, PhD; Antonio Julià, PhD; Andrey Khrunin, PhD; Henskens, BMath, DipEd, DipCompSc, PhD; Inge Georgieva, PhD; Lieuwe de Haan, MD, PhD; Frans A. Escott-Price, PhD; Nelson B. Freimer, MD; Lyudmila PhD; Ariel Darvasi, PhD; Lynn E. DeLisi, MD; Timothy Cohen, MD, PhD; Benedicto Crespo-Facorro, MD, PhD; Ole A. Andreassen, MD, PhD; Elvira Bramon, MD; Department of Neuroscience, Icahn School of Medicine at Mount Sinai, New York, New York Department of Human Genetics, Icahn School of Medicine at Mount Sinai, New York, New York Department of Psychiatry, Santander, Spain Department of Genetics, The Icahn School of Medicine at Mount Sinai, New York, New York (Buxbaum, Drapeau), Schizophrenia Research Institute, Sydney, Australia (Cairns, DeLisi, Henskens, Loughland, Miche, Pantelis, Schall, Scott, Tooney, Wu); Priority Centre for Translational Neuroscience and Mental Health, University of Newcastle, Newcastle, Australia (Cairns, Loughland, Schall); School of Biomedical Sciences and Pharmacy, University of Newcastle, Callaghan, Australia (Cairns, Scott, Tooney, Wu); Department of Human Genetics, David Geffen School of Medicine, University of California, Los Angeles (Cantor); Department of Psychiatry, Washington University in St Louis, St Louis, Missouri (Cloninger); Department of Child and Adolescent Psychiatry, Assistance Publique Hôpitaux de Paris, Pierre and Marie Curie University, and Institute for Intelligent Systems and Robotics, Paris, France (Cohen); CIBERSAM, University Marqués de Valdecilla, University of Cantabria–IDIVAL, Department of Psychiatry, Santander, Spain (Crespo-Facorro); Centro Investigación Biomédica en Red Salud Mental, Madrid, Spain (Crespo-Facorro); Department of Genetics, The Hebrew University of Jerusalem, Jerusalem, Israel (Davasi); VA Boston Health Care System, Brockton, Massachusetts (DeLisi, McCarley); Department of Psychiatry, Psychiatry University Cork, Cork, Ireland (Dinan); NORMENT, KG Jebsen Centre for Psychosis Research, Department of Clinical Science, University of Oslo, Oslo, Norway (Andreassen); Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway (Andreassen); University College London, London, England (Bramon); University Medical Center Groningen, Department of Psychiatry, University of Groningen, Groningen, the Netherlands (Bruggeman); Department of Human Genetics, Icahn School of Medicine at Mount Sinai, New York, New York (Buxbaum); Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, New York, New York (Buxbaum); Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, New York (Buxbaum, Drapeau), Schizophrenia Research Institute, Sydney, Australia (Cairns, DeLisi, Henskens, Loughland, Miche, Pantelis, Schall, Scott, Tooney, Wu); Priority Centre for Translational Neuroscience and Mental Health, University of Newcastle, Newcastle, Australia (Cairns, Loughland, Schall); School of Biomedical Sciences and Pharmacy, University of Newcastle, Callaghan, Australia (Cairns, Scott, Tooney, Wu); Department of Human Genetics, David Geffen School of Medicine, University of California, Los Angeles (Cantor); Department of Psychiatry, Washington University in St Louis, St Louis, Missouri (Cloninger); Department of Child and Adolescent Psychiatry, Assistance Publique Hôpitaux de Paris, Pierre and Marie Curie University, and Institute for Intelligent Systems and Robotics, Paris, France (Cohen); CIBERSAM, University Marqués de Valdecilla, University of Cantabria–IDIVAL, Department of Psychiatry, Santander, Spain (Crespo-Facorro); Centro Investigación Biomédica en Red Salud Mental, Madrid, Spain (Crespo-Facorro); Department of Genetics, The Hebrew University of Jerusalem, Jerusalem, Israel (Davasi); VA Boston Health Care System, Brockton, Massachusetts (DeLisi, McCarley); Department of Psychiatry, Psychiatry University Cork, Cork, Ireland (Dinan); NORMENT, KG Jebsen Centre for Psychosis Research, Department of Clinical Science, University of Oslo, Oslo, Norway (Andreassen); Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway (Andreassen); University College London, London, England (Bramon); University Medical Center Groningen, Department of Psychiatry, University of Groningen, Groningen, the Netherlands (Bruggeman); Department of Human Genetics, Icahn School of Medicine at Mount Sinai, New York, New York (Buxbaum); Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, New York, New York (Buxbaum); Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, New York (Buxbaum, Drapeau), Schizophrenia Research Institute, Sydney, Australia (Cairns, DeLisi, Henskens, Loughland, Miche, Pantelis, Schall, Scott, Tooney, Wu); Priority Centre for Translational Neuroscience and Mental Health, University of Newcastle, Newcastle, Australia (Cairns, Loughland, Schall); School of Biomedical Sciences and Pharmacy, University of Newcastle, Callaghan, Australia (Cairns, Scott, Tooney, Wu); Department of Human Genetics, David Geffen School of Medicine, University of California, Los Angeles (Cantor); Department of Psychiatry, Washington University in St Louis, St Louis, Missouri (Cloninger); Department of Child and Adolescent Psychiatry, Assistance Publique Hôpitaux de Paris, Pierre and Marie Curie University, and Institute for Intelligent Systems and Robotics, Paris, France (Cohen); CIBERSAM, University Marqués de Valdecilla, University of Cantabria–IDIVAL, Department of Psychiatry, Santander, Spain (Crespo-Facorro); Centro Investigación Biomédica en Red Salud Mental, Madrid, Spain (Crespo-Facorro); Department of Genetics, The Hebrew University of Jerusalem, Jerusalem, Israel (Davasi); VA Boston Health Care System, Brockton, Massachusetts (DeLisi, McCarley); Department of Psychiatry, Psychiatry University Cork, Cork, Ireland (Dinan); NORMENT, KG Jebsen Centre for Psychosis Research, Department of Clinical Science, University of Oslo, Oslo, Norway (Andreassen); Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway (Andreassen); University College London, London, England (Bramon); University Medical Center Groningen, Department of Psychiatry, University of Groningen, Groningen, the Netherlands (Bruggeman); Department of Human Genetics, Icahn School of Medicine at Mount Sinai, New York, New York (Buxbaum); Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, New York, New York (Buxbaum); Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, New York (Buxbaum, Drapeau), Schizophrenia Research Institute, Sydney, Australia (Cairns, DeLisi, Henskens, Loughland, Miche, Pantelis, Schall, Scott, Tooney, Wu); Priority Centre for Translational Neuroscience and Mental Health, University of Newcastle, Newcastle, Australia (Cairns, Loughland, Schall); School of Biomedical Sciences and Pharmacy, University of Newcastle, Callaghan, Australia (Cairns, Scott, Tooney, Wu); Department of Human Genetics, David Geffen School of Medicine, University of California, Los Angeles (Cantor); Department of Psychiatry, Washington University in St Louis, St Louis, Missouri (Cloninger); Department of Child and Adolescent Psychiatry, Assistance Publique Hôpitaux de Paris, Pierre and Marie Curie University, and Institute for Intelligent Systems and Robotics, Paris, France (Cohen); CIBERSAM, University Marqués de Valdecilla, University of Cantabria–IDIVAL, Department of Psychiatry, Santander, Spain (Crespo-Facorro); Centro Investigación Biomédica en Red Salud Mental, Madrid, Spain (Crespo-Facorro); Department of Genetics, The Hebrew University of Jerusalem, Jerusalem, Israel (Davasi); VA Boston Health Care System, Brockton, Massachusetts (DeLisi, McCarley); Department of Psychiatry, Psychiatry University Cork, Cork, Ireland (Dinan); NORMENT, KG Jebsen Centre for Psychosis Research, Department of Clinical Science, University of Oslo, Oslo, Norway (Andreassen); Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway (Andreassen); University College London, London, England (Bramon); University Medical Center Groningen, Department of Psychiatry, University of Groningen, Groningen, the Netherlands (Bruggeman); Department of Human Genetics, Icahn School of Medicine at Mount Sinai, New York, New York (Buxbaum); Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, New York, New York (Buxbaum); Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, New York (Buxbaum, Drapeau), Schizophrenia Research Institute, Sydney, Australia (Cairns, DeLisi, Henskens, Loughland, Miche, Pantelis, Schall, Scott, Tooney, Wu); Priority Centre for Translational Neuroscience and Mental Health, University of Newcastle, Newcastle, Australia (Cairns, Loughland, Schall); School of Biomedical Sciences and Pharmacy, University of Newcastle, Callaghan, Australia (Cairns, Scott, Tooney, Wu); Department of Human Genetics, David Geffen School of Medicine, University of California, Los Angeles (Cantor); Department of Psychiatry, Washington University in St Louis, St Louis, Missouri (Cloninger); Department of Child and Adolescent Psychiatry, Assistance Publique Hôpitaux de Paris, Pierre and Marie Curie University, and Institute for Intelligent Systems and Robotics, Paris, France (Cohen); CIBERSAM, University Marqués de Valdecilla, University of Cantabria–IDIVAL, Department of Psychiatry, Santander, Spain (Crespo-Facorro); Centro Investigación Biomédica en Red Salud Mental, Madrid, Spain (Crespo-Facorro); Department of Genetics, The Hebrew University of Jerusalem, Jerusalem, Israel (Davasi); VA Boston Health Care System, Brockton, Massachusetts (DeLisi, McCarley); Department of Psychiatry, Psychiatry University Cork, Cork, Ireland (Dinan); NORMENT, KG Jebsen Centre for Psychosis Research, Department of Clinical Science,
University of Bergen, Bergen, Norway (Djuric); Department of Medical Genetics, Oslo University Hospital, Oslo, Norway (Djuric); Cognitive Genetics and Therapy Group, School of Psychology and Discipline of Biochemistry, National University of Ireland Galway, Galway, Ireland (Donohoe, Morris); Neuropsychiatric Genetics Research Group, Department of Psychiatry, Trinity College Dublin, Dublin, Ireland (Donohoe, Morris); MRC Centre for Neurobiological Genetics and Genomics, Institute of Psychological Medicine and Clinical Neurosciences, School of Medicine, Cardiff University, Cardiff, Wales (Escott-Price, Georgieva); Center for Neurobehavioral Genetics, Semel Institute for Neuroscience and Human Behavior, University of California, Los Angeles (Freimer); Department of Psychiatry, Academic Medical Centre, University of Amsterdam, Amsterdam, the Netherlands (de Haan); School of Electrical Engineering and Computer Science, University of Newcastle, Newcastle, Australia (Henskens); Priority Research Centre for Health Behaviour, University of Newcastle, Newcastle, Australia (Henskens); Regional Centre for Clinical Research in Psychosis, Department of Psychiatry, Stavanger University Hospital, Stavanger, Norway (Joan); Rheumatology Research Group, Vall d’Hebron Research Institute, Barcelona, Spain (Julià, Macek); Institute of Molecular Genetics, Russian Academy of Sciences, Moscow, Russia (Khrunin, Limborska); Department of Psychiatry, Hadassah-Hebrew University Medical Center, Jerusalem, Israel (Lerer); Department of Biology and Medical Genetics, Second Faculty of Medicine and University Hospital Motol, Prague, Czech Republic (Macek); Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden (Magnusson); Department of Psychiatry, Harvard Medical School, Boston, Massachusetts (McCarley, Seidman); Division of Psychiatry, University of Edinburgh, Edinburgh, Scotland (McIntosh); Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, Scotland (McIntosh); Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden (Magnusson); Institute of Medical Genetics, National University of Ireland, Dublin, Ireland (Murphy); Center for Contextual Psychiatry, Department of Neuroscience, KU Leuven, Leuven, Belgium (Myin-Germeys); Department of Psychiatry, University of Colorado Denver, Aurora, Colorado (Olinty); Institute of Psychiatry, King’s College London, London, England (Van Os); Maastricht University Medical Centre, South Limburg Mental Health Research and Teaching Network, EURON, Maastricht, the Netherlands (Van Os); Melbourne Neuropsychiatry Centre, Department of Psychiatry, University of Melbourne and Melbourne Health, Melbourne, Australia (Pantelis); Department of Functional Genomics, Center for Neurogenomics and Cognitive Research, Neuroscience Campus Amsterdam, VU University, Amsterdam, the Netherlands (Posthuma); Department of Complex Trait Genetics, Neuroscience Campus Amsterdam, VU University Medical Center Amsterdam, Amsterdam, the Netherlands (Posthuma); Department of Child and Adolescent Psychiatry, Erasmus University Medical Centre, Rotterdam, the Netherlands (Posthuma); Department of Psychiatry, University of Oxford, Oxford, England (Queased); Hunter New England Health Service, Newcastle, Australia (Scott); Massachusetts Mental Health Center Public Psychiatry Division, Beth Israel Deaconess Medical Center, Boston (Seidman); Department of Medical Genetics, Medical University, Sofia, Bulgaria (Tonecheva); Priority Research Centre for Translational Neuroscience and Mental Health, University of Newcastle, Newcastle, Australia (Tooney); Molecular and Cellular Therapeutics, Royal College of Surgeons in Ireland, Dublin, Ireland (Waddington); Lieber Institute for Brain Development, Baltimore, Maryland (Weinberger); Department of Psychiatry and Behavioral Sciences, The Johns Hopkins School of Medicine, Baltimore, Maryland (Weinberger); Department of Neurology, The Johns Hopkins School of Medicine, Baltimore, Maryland (Weinberger); Department of Neuroscience, The Johns Hopkins School of Medicine, Baltimore, Maryland (Weinberger); Institute of Genetic Medicine, The Johns Hopkins School of Medicine, Baltimore, Maryland (Weinberger); Sheba Medical Center, Tel Hashomer, Israel (Weiser).

Author Affiliations: Queensland Brain Institute, The University of Queensland, Brisbane, Australia (Mehta, Gratten, Baksh, Zhu, Moray, Yang, Vischer, McGrath, Whay, Lee); Department of Sociology, Interuniversity Center for Social Science Theory and Methodology, University of Groningen, Groningen, the Netherlands (Tropf); Department of Sociology, Nuffield College, University of Oxford, Oxford, England (Tropf, Barban, Mills, Whay, Lee, Bramon, Brugge, Buxbaum, Cairns, Toncheva, Cohen, Crespo-Facorro, Darvsi, Dinan, Drijovic, McIntosh, Escott-Price, Freimer, Georgieva, de Haan, Henskens, Joa, Khrunin, Lerer, Limborska, Lowland, Macel, Magnusson, Marsal, McCarley, McIntosh, McQuillin, Melegh, Michie, Morris, Murphy, Myin-Germeys, Olincy, Van Os, Pantelis, Posthuma, Queased, Scott, Seidman, Tonecheva, Tooney, Waddington, Weinberger, Weiser, Wu).


CRITICAL REVISION OF THE MANUSCRIPT FOR IMPORTANT INTELLIGIBLE CONTENT: Mehta, Tropf, Gratten, Baksh, Zhu, Baranu, Hennemi, Magnusson, Barban, Esko, Metspalu, Snieder, Mowry, Kendler, Yang, Vischer, McGrath, Mills, Whay, Lee, Andreassen, Bramon, Brugge, Buxbaum, Cairns, Canter, Cloninger, Cohen, Crespo-Facorro, Darvasi, Drijovic, Donohoe, Drapeau, Escott-Price, Freimer, Georgieva, de Haan, Henskens, Joa, Khrunin, Lerer, Limborska, Lowland, Macel, Magnusson, Marsal, McCarley, McIntosh, McQuillin, Melegh, Michie, Morris, Murphy, Myin-Germeys, Olincy, Van Os, Pantelis, Posthuma, Queased, Scott, Seidman, Tonecheva, Tooney, Waddington, Weinberger, Weiser, Wu.

Statistical analysis: Mehta, Lee, Escott-Price.

Funding/support: Obtained funding: Whay, Lee, Bramon, Drijovic, Henskens, McIntosh, Michie, Morris, Murphy, Pantelis, Posthuma, Scott. Administrative, technical, or material support: Mehta, Tropf, Gratten, Baksh, Zhu, Baranu, Hennemi, Magnusson, Barban, Esko, Metspalu, Snieder, Mowry, Kendler, Yang, Vischer, McGrath, Mills, Whay, Lee, Bramon, Brugge, Buxbaum, Cairns, Cloninger, Darvsi, Donohoe, Henskens, Joa, Khrunin, Lerer, Limborska, Lowland, Magnusson, Marsal, McIntosh, McQuillin, Melegh, Morris, Olincy, Van Os, Schall, Seidman, Tonecheva, Waddington, Weinberger, Wu. Study supervision: Lee, Dinan, Murphy, Queased, Scott, Weinberger.

Conflict of Interest Disclosures: None reported.

Funding/support: This research is supported by grants 63667, 1047956, 1078901, 1080157, 1087889, and 1067795 from the Australian National Health and Medical Research Council and by grants DE1010D064 and DP16102216 from the Australian Research Council. Key analyses of the Schizophrenia Working Group of the Psychiatric Genomics Consortium data were conducted on the Genetic Cluster Computer (http://www.geneticcluster.org) hosted by SURFsara and supported by grant NOW 480-05-O03 from the Netherlands Scientific Organizational, along with a supplement from the Dutch Brain Foundation and the Vrije Universiteit Amsterdam. TwinsUK was funded by the Wellcome Trust, by grant FP7/2007-2013 from the European Community’s Seventh Framework Programme, and by support from the National Institute for Health Research-funded BioResource, Clinical Research Facility, and Biomedical Research Centre based at Guy’s and St Thomas’ National Health Service Foundation Trust in partnership with King’s College London, and single-nucleotide polymorphism genotyping was performed by the Wellcome Trust Sanger Institute and National Eye Institute via the National Institute for Health/Center for Inherited Disease Research. Estonian Genome Center Biobank, University of Tartu, received targeted financing by grant IUT20-60 from the Estonian Research Council, Center of Excellence in Genomics, and University of Tartu, and data analyses were carried out in part in the High Performance Computing Center of the University of Tartu. The Swedish Twin Registry is supported by Karolinska Institutet. Mr Tropf received funding
Genetic Overlap Between Schizophrenia and Age at First Birth in Women

Original Research

from sciencemag.org for a research visit to the University of Queensland. The research leading to these results received funding from the European Research Council via an ERC Consolidator Grant SOCIOGENOME (grant 615639 awarded to Dr Mills [http://www.sociogenome.com]).

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Data Availability Statement: This study was conducted through approved data analysis applications made to the consortia involved. For ethical and legal reasons, we are not allowed to distribute them. The data of the Schizophrenia Working Group of the Psychiatric Genomics Consortium can be accessed through secondary analysis proposals (http://www.med.unc.edu/pgc). The data cannot be released without assessment by the LifeLines Scientific Committee with transfer agreements because the phenotypic data can be sensitive and may in some cases lead to the identification of individuals involved in the study. These procedures have been put in place by the LifeLines Scientific Board and local ethics committees. For more information, see the following article: Scholtens S, Smidt N, Swertz MA, et al. Cohort profile: LifeLines, a three-generation cohort study and biobank. Int J Epidemiol. 2015;44(4):1172-1180.

Medline:25502107. TwinsUK data are available on request by contacting the Twin Research Unit (http://www.twinuk.ac.uk/data-access) submission procedure. The data cannot be released without assessment by a steering committee with transfer agreements because the phenotypic data can be sensitive and may in some cases lead to the identification of individuals involved in the study. These procedures have been put in place by the local ethics committee and the Wellcome Trust.

Group Information: The Schizophrenia Working Group of the Psychiatric Genomics Consortium, LifeLines Cohort Study, and TwinsUK consortium collaborators are as follows: Department of Clinical Sciences, Psychiatry, Umeå University, Umeå, Sweden (Rolf Adolfsson, MD, PhD, and Annelie Nordin, PhD); NORMENT, KG Jebsen Centre for Psychiatry Research, Institute of Clinical Medicine, University of Oslo, Oslo, Norway (Ingrid Agartz, MD, PhD, Erik G. Jönsson, MD, PhD, Morten Mattingsdal, MS, and Ingrid Melle, MD, PhD); Department of Psychiatry, Diakonhjemmet Hospital, Oslo, Norway (Ingrid Agartz, MD, PhD); Department of Clinical Neuroscience, Psychiatry Section, Karolinska Institutet, Stockholm, Sweden (Ingrid Agartz, MD, PhD); State Mental Hospital, Haar, Germany (Margot Albus, MD, MD); Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, California (Madeleine Alexander, PhD, Claudine Laurent, MD, PhD, and Douglas F. Levinson, MD); Department of Psychiatry and Behavioral Sciences, Emory University, Atlanta, Georgia (Faroq Amin, MD); Department of Psychiatry and Behavioral Sciences, Atlanta Veterans Affairs Medical Center, Atlanta, Georgia (Faroq Amin, MD); Virginia Institute for Psychiatric and Behavioral Genetics, Department of Psychiatry, Virginia Commonwealth University, Richmond (Silvia A. Baccalieri, PhD, Tim B. Bigdell, PhD, and Brandon K. Wormley, BA); Clinical Neuroscience, Max Planck Institute of Experimental Medicine, Göttingen, Germany (Martin Beggeman, MD, Hannelore Ehrenreich, MD, DVM, Christian Hammer, PhD, and Sergi Papiol, PhD); Stanley Center for Psychiatric Research, Broad Institute of MIT and Harvard, Massachusetts (Richard A. Belliveau Jr, BA, Elizabeth Bevilacqua, BS, Kimberley D. Chambert, MSc, Giulio Genovese, PhD, Steven A. McCarroll, PhD, Jennifer L. Moran, PhD, and Edward M. Scolnick, MD); Department of Medical Genetics, University of Pécs, Pécs, Hungary (Judit Béne, PhD); Szentlaghai Research Center, University of Pécs, Pécs, Hungary (Judit Béne, PhD); Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden (Sarah E. Bergen, PhD, Christina M. Hultman, PhD, Anna K. Kähler, PhD, and Patrick F. Sullivan, MD, FRCP); Centre for Integrative Psychiatric Research, Broad Institute of MIT and Harvard, Cambridge, Massachusetts (Sarah E. Bergen, PhD, Menachem Fromer, PhD, Arno Palotie, MSc, PhD, Tracey L. Petryshen, PhD, and Jordan W. Smoller, MD, ScD); Department of Psychiatry, University of California, San Francisco, California (William Byerley, MD); University of California at San Francisco, San Francisco, California (Madeline Haar, Germany (Margot Albus, MD); Department of Psychiatry, University Medical Center, Utrecht, the Netherlands (Wiepke Cahn, MD, PhD, René S. Kahn, MD, PhD); Aarhus University Hospital, Risskov, Denmark (Anders D. Bergum, MD, PhD, Ditte Demontis, MSc, PhD, and Jakob Grove, MSc, PhD); Centre for Integrative Sequencing, GEQ, Aarhus University, Aarhus, Denmark (Anders D. Bergum, MD, PhD, Ditte Demontis, MSc, PhD, Jakob Grove, MSc, PhD, Ole Mors, MD, PhD, and Preben B. Mortensen, MD, DMSc); Aarhus University Hospital, Risikov, Denmark (Anders D. Bergum, MD, PhD, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, IPSYCH, Aarhus, Denmark (Anders D. Bergum, MD, PhD, Ditte Demontis, MSc, PhD, Jakob Grove, MSc, PhD, Ole Mors, MD, PhD, and Preben B. Mortensen, MD, DMSc); School of Nursing, Louisiana State University Health Sciences Center, New Orleans (Nancy G. Bucella, APRN, BC); Center for Brain Science, Harvard University, Cambridge, Massachusetts (Randy L. Buckner, PhD); Department of Psychiatry, Massachusetts General Hospital, Boston (Randy L. Buckner, PhD); Athinoula A. Martinos Center, Massachusetts General Hospital, Boston (Randy L. Buckner, PhD, and Joshua L. Roffman, MD, MSc); Department of Psychiatry, University of California at San Francisco (William Byerley, MD); University Medical Center Utrecht, Department of Psychiatry, Rudolf Magnus Institute of Neuroscience, Utrecht, the Netherlands (Wiepke Cahn, MD, René S. Kahn, MD, PhD, Roel A. Ophoff, PhD, and Eric Stengram, BSc); Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, New York (Guoming Cai, MD, MD, Kenneth L. Davis, MD, Joseph I. Friedman, MD, Karen Haroutunian, PhD, Elena Parakhomenko, PhD, Abraham Reichenberg, PhD, and Jeremy M. Silverman, PhD); Department of Human Genetics, Icahn School of Medicine at Mount Sinai, New York, New York (Guoming Cai, MD); Centre Hospitalier du Rouvray and INSERM U1079 Faculty of Medicine, Rouen, France (Dominique Campion, MD, PhD); Schizophrenia Research Institute, Sydney, Australia (Vaughan J. Carr, MD, FRANZCP, FRCPA), Genomic Epidemiology, University of Washington, Seattle, Washington, USA (Stanley V. Catts, MD, FRANZCP, and Asen V. Jablensky, MD, DMSc, FRANZCP, FRPsych); School of Psychiatry, University of New South Wales, Sydney, Australia (Vaughan J. Carr, MD, FRANZCP, FRCPA), MRC Centre for Neurosychiatric Genetics and Genomics, Institute of Psychological Medicine and Clinical Neurosciences, School of Medicine, Cardiff University, Cardiff, England (Nina Carrera, PhD, Nick Craddock, MD, PhD, Marian L. Hannire, PhD, Peter A. Holmans, PhD, David Kavanagh, PhD, George Kirov, MD, PhD, Sophie E. Legge, BSc, Michael C. O’Donovan, MD, PhD, Michael J. Owen, MD, PhD, Andrew J. Pocklington, PhD, Alexander L. Richards, PhD, James T. R. Walters, MD, PhD, and Nigel M. Williams, PhD); Royal Brisbane and Women’s Hospital, The University of Queensland, Brisbane, Australia (Stanley V. Catts, MD, FRANZCP), University of Amsterdam, Institute of Medical Sciences, Amsterdam, the Netherlands (David St Clair, MD, PhD); Neuropsychiatric Genetics Research Group, Department of Psychiatry, Trinity College, Dublin, Ireland (Paul Cormican, PhD, and Jonathan Pimm, MB, BS, MRCPsych); Sheba Medical Center, Tel Hashomer, Israel (Michael Davidson, MD); First Department of Psychiatry, University of Athens Medical School, Athens, Greece (Dimitris Dikeos, MD, and George N. Papadimitriou, MD); Department of Psychiatry and Behavioral Sciences, NorthShore University HealthSystem, Evanston, Illinois (Jubao Duan, PhD, Pablo V. Gejman, MD, and Alan R. Sanders, MD); Department of Psychiatry and Behavioral Neuroscience, University of Chicago, Chicago, Illinois (Jubao Duan, PhD, Pablo V. Gejman, MD, and Alan R. Sanders, MD); Department of Non-Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, England (Frank Dudbridge, PhD); Department of Psychiatry, University of Regensburg, Regensburg, Germany (Peter Eichhammer, MD, PhD); Estonian Genome Center, University of Tartu, Tartu, Estonia (Tõnu Esko, PhD, Andres Metspalu, MD, PhD, Liil Miligat, PhD, Dorian Rich, PhD, and Lucius Kõiv, PhD); Division of Endocrinology and Center for Basic and Translational Obesity Research, Boston Children’s Hospital, Boston, Massachusetts (Tõnu Esko, PhD); Department of Genetics, Harvard Medical School, Boston, Massachusetts (Tõnu Esko, PhD, and Steven A. McCarroll, PhD); Medical and Population Genetics Program, Broad Institute of MIT and Harvard, Cambridge, Massachusetts (Tõnu Esko, PhD, and Elia A. Stahl, PhD); Mental Health Service Line, Washington VA Medical Center, Washington, DC (Ayman H. Fanous, MD); Department of Psychiatry, Georgetown University School of Medicine, Washington, DC (Ayman H. Fanous, MD); Department of Psychiatry, Virginia Commonwealth
Genetic Overlap Between Schizophrenia and Age at First Birth in Women

Original Investigation Research


Additional Contributions: The acknowledgments for the Schizophrenia Working Group of the Psychiatric Genomics Consortium data are listed in reference 15 and in Appendix 3 in the Supplement. The SNP&SEQ Technology Platform at Uppsala University Sweden is acknowledged for performing genotyping and for excellent technical assistance. We acknowledge Estonian Genome Center Biobank, University of Tartu, technical personnel, especially Viljo Soo and Steve Smith.

REFERENCES