Why does age of onset predict clinical severity in schizophrenia? A multiplex extended pedigree study

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Abstract
Schizophrenia has substantial variation in symptom severity, course of illness, and overall functioning. Earlier age of onset (AOO) is consistently associated with negative outcomes and yet the causes of this association are still unknown. We used a multiplex, extended pedigree design (total N = 771; 636 relatives from 43 multigenerational families with at least 2 relatives diagnosed with schizophrenia and 135 matched controls) to examine among the schizophrenia relatives (N = 103) the relationship between AOO and negative and positive symptom severity, cognition, and community functioning. As expected, earlier AOO was significantly correlated with increased severity of negative and positive symptoms and poorer cognition and community functioning. Although the genetic correlations between AOO and positive symptoms, cognition, and community functioning were estimated at maximum and in the predicted direction, they were not statistically significant. AOO of schizophrenia itself was modestly heritable, although not significant and negative symptoms, positive symptoms, and cognition were all strongly and significantly heritable. In sum, we replicated prior findings indicating that earlier AOO is associated with increased symptom severity and extended the literature by detecting shared genetic effects between AOO and negative symptoms, suggestive of pleiotropy.

KEYWORDS
age of onset, genetic correlation, heritability, schizophrenia, symptom severity

1 | INTRODUCTION

Schizophrenia is defined by positive symptoms (e.g., hallucinations, delusions) and negative symptoms (e.g., blunted affect, avolition; (American Psychiatric Association, 1994) and it is strongly associated with pervasive cognitive impairments and difficulties in social and occupational functioning. There is considerable variation in symptomatology, cognitive ability, course, and overall functioning, such that 20–40% of individuals are able to lead relatively independent lives and yet 20–45% have “poor” or “severely impaired” overall functional outcome (Lauro et al., 2007; Velthorst et al., 2017). It is generally difficult to predict which individuals may have a more severe course, but one factor has been consistently linked with a host of relevant outcome measures: age of onset. Earlier age of onset in schizophrenia has been consistently correlated with
poorer functional outcomes (Menezes, Arenovich, & Zipursky, 2006), less time spent in remission (Juola, Miettunen, Veijola, Isohanni, & Jaaskelainen, 2013), and increased severity of disorganized symptoms, negative symptoms, and social deficits (though the literature is less clear with respect to severity of positive symptoms; Hafner et al., 1999; Howard, Castle, Wessely, & Murray, 1993; Luoma, Hakko, Ollinen, Jarvelin, & Lindeman, 2008). Earlier age of onset is also associated with increased severity of cognitive deficits across a wide range of domains (Rajji, Ismail, & Mulsant, 2009; van der Werf et al., 2012).

Despite this large and consistent literature, it is unclear why age of onset is correlated with symptom severity and clinical outcome in schizophrenia. Both genetic effects and environmental factors could play a significant role in explaining the correlation between age of onset and clinical variation, but their relative contributions are unknown. Therefore, the current study seeks to increase our understanding of the genetic and environmental causes of the correlations between age of onset and variation in clinical features and functioning in schizophrenia. To the best of our knowledge, this is the first study to directly address this question.

1.1 Age of onset: Background and genetic effects

The developmental timing of schizophrenia onset varies widely among individuals and between males and females. In general, the peak incidence for the diagnosis of schizophrenia is between 20 and 24 years old in males and between 25 and 35 years old in women (with another smaller peak between the ages of 50 and 54, roughly around menopause; e.g., Lauronen et al., 2007; Ochoa, Usall, Cobó, Labad, & Kulkarni, 2012; Welham, Thomis, & McGrath, 2004). Although considerable theoretical (e.g., Pogue-Geile, 1991; Weinberger, 1987) and recent empirical (e.g., Murray, Bhavsar, Tripoli, & Howes, 2017) work has attempted to explain why this peak age of onset occurs in the twenties, the potential cause of the substantial variation in age of onset is a separate question, and one that has received less attention.

Environmental factors such as obstetric complications (McDonald & Murray, 2000) and tobacco and cannabis use (Gurillo, Jauhar, Murray, & MacCabe, 2015; but see Myles et al., 2012) may be associated with earlier age of onset of schizophrenia, although the causal direction in such studies is unclear. Genetic effects also appear to play a role in the variation of age of onset. To the best of our knowledge, there have been 23 family, twin, and extended pedigree studies on age of onset in schizophrenia since 1925 (see Table S1, Supporting Information which updates Kendler, Tsuang, & Hays, 1987). Age of onset heritability ($h^2$) estimates varied considerably, ranging from 0.11 (Larsson & Sjögren, 1954) to 1.00 (e.g., Cannon, Kaprio, Lonnqvist, Huttunen, & Koskenvuo, 1998). The average heritability (weighted by sample size) calculated from the available studies is 0.58 (i.e., 58% of the variance in age of onset can be attributed to genetic effects), and the only extended pedigree study estimated heritability at 0.33 (Hare et al., 2010).

In an effort to better understand this heritability, there have been a number of candidate gene and genome-wide association studies examining age of onset alone, as well as its relationship to symptom dimensions (e.g., Fanous et al., 2012); however, these studies have been largely inconclusive with a lack of replication of positive findings (e.g., Bergen et al., 2014; Wang, Liu, Zhang, Aragam, & Pan, 2011).

1.2 Genetic effects on symptom severity, cognition, and community functioning

Genetic effects are also likely to play a substantial role in variation in cognition, symptom severity, and community functioning in schizophrenia. Cognitive deficits across a wide range of domains (e.g., Cannon, Kaprio, Lonnqvist, Huttunen, & Koskenvuo, 1998). The heritability estimates varied considerably, ranging from 0.11 (Larsson & Sjögren, 1954) to 1.00 (e.g., Cannon, Kaprio, Lonnqvist, Huttunen, & Koskenvuo, 1998). The average heritability (weighted by sample size) calculated from the available studies is 0.58 (i.e., 58% of the variance in age of onset can be attributed to genetic effects), and the only extended pedigree study estimated heritability at 0.33 (Hare et al., 2010).

1.3 The current study

Earlier age of onset of schizophrenia consistently predicts a host of negative outcomes, including greater symptom severity, increased cognitive deficits, and poorer overall functioning. There is considerable evidence that age of onset is moderately heritable and that the relevant clinical correlates also are significantly influenced by genetic effects; but to our knowledge, no study has taken the next step and attempted to examine whether or not there are genetic effects shared between age of onset and clinical outcomes, cognitive, and community functioning. The current project, utilizing a multiplex, extended pedigree design, aimed to answer this question of whether shared genetic effects contribute to this observed correlation between age of onset and symptom and functioning severity.

2 MATERIALS AND METHODS

2.1 Participant ascertainment

The current study is part of a larger multisite project (the Multiplex Genetic Investigation of Schizophrenia [MGI]) based at the
University of Pittsburgh, the University of Pennsylvania, and the Texas Biomedical Research Institute and was approved by each respective Institutional Review Board. Individuals were recruited who had a DSM-IV (American Psychiatric Association, 1994) diagnosis of schizophrenia, had at least one other first-degree relative with schizophrenia or schizoaffective disorder depressed type, and had at least 10 first- to fourth-degree relatives who could be contacted. A control group was also recruited, in which individuals could have psychiatric diagnoses but were excluded if they were diagnosed with a schizophrenia spectrum or psychotic disorder. (For full inclusion and exclusion criteria for the pedigree participants and the control group, please refer to Data S1). All participants provided signed informed consent.

The total MGI sample included 773 participants, with 638 pedigree members from 43 multiplex multigenerational families, and 135 controls. The average family size was 14.79 members, with 2–70 members per family (except for one individual who did not have usable data from their family members, thus adding an additional “family” of one). For the current study, two unrelated individuals diagnosed with schizophrenia were excluded due to missing more than 50% of both community functioning measures and cognitive tests, for a final total sample of 771 participants (636 pedigree members and 135 controls).

2.2 | Diagnostic assessment

All pedigree participants were assessed using the Diagnostic Interview for Genetic Studies (DIGS) 2.0, a structured interview assessing an individual’s symptoms and signs (Nurnberger Jr. et al., 1994) and the Family Interview for Genetic Studies (FIGS), a family history interview administered to an informant in each family (Maxwell, 1992) in-person (typically in the participant’s home) by trained interviewers who were not blind to participant group status. This information was supplemented by inspection of medical records when possible. Lifetime DSM-IV diagnoses for both pedigree and control participants were determined at consensus conferences of at least two investigators who were licensed psychologists or psychiatrists and who were blind to participant status.

Pedigree participants were assigned to one of four hierarchical, mutually exclusive groups based on their DSM-IV diagnoses: Schizophrenia (SC; N = 103, 89 schizophrenia and 14 schizoaffective disorder), Depression (MDD; N = 110, major depressive disorder), Other (Other; N = 167, all other diagnoses), and No Diagnosis (ND; N = 256). The Schizophrenia, Depression, Other, and No Diagnosis groups were used to create factor scores (see Data reduction section in Data S1). The goal of the current investigation is to evaluate the relationship between age of onset of schizophrenia symptoms and severity measures within the Schizophrenia group; therefore, the following analyses only use this diagnostic group (N = 103). Table S2 presents comorbidity information and details regarding assignment to groups.

2.3 | Age of onset assessment

Age of onset was defined as the age of the individual’s first symptoms associated with a schizophrenia diagnosis. This was determined by self-report (or by medical records, when available), from the DIGS (Section K, Item number 64), which reads: “How old were you the first time that you were experiencing (describe delusions, hallucinations, or other criteria for schizophrenia noted by the subject previously)?” Of the 103 individuals in the Schizophrenia group, 85 had available age of onset data. The family size of individuals with available age of onset data ranged from 1 to 4 related individuals, with 58 relative pairs.

2.4 | Symptom assessments

Current negative symptoms were assessed using the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1982) and positive symptoms were assessed using the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984; see Data S1 for details).

2.5 | Cognitive assessments

Participants were administered the Penn Computerized Neurocognitive battery (CNB), which has been used with healthy controls (Gur, Ragland, Moberg, Turner, et al., 2001) and patients with schizophrenia (Gur, Ragland, Moberg, Bilker, et al., 2001). The battery takes approximately 60 minutes to complete and tasks were administered in a fixed order. Each task measures both accuracy and reaction time, which were both standardized based on scores from individuals without any psychiatric diagnosis in the Control group (N = 95). Efficiency scores were then calculated by subtracting standardized reaction time (which was defined as median reaction time for correct responses) from standardized accuracy, divided by two. In this way, higher efficiency scores represent better accuracy and faster performance. The battery assesses eight domains: Abstraction and Mental Flexibility, Attention, Verbal Memory, Facial Memory, Spatial Memory, Spatial Processing, Sensorimotor Dexterity, and Emotion Processing. Each participant also completed three additional noncomputerized tests: The Trail Making Task (Parts A and B; Reitan, 1958), which assesses visual scanning, psychomotor speed, and working memory; the California Verbal Learning Test (CVLT; Delis, Kramer, Kaplan, & Ober, 1987), which assesses verbal learning and memory; and the Word Reading subtest of the Wide Range Achievement Test (WRAT; Wilkinson, 1993), which assesses verbal intelligence (see Data S1 for details).

2.6 | Community functioning

Four different domains of community functioning were assessed: Marital Status, Living Situation, Occupational Status, and Global Functioning. All measures were based on the DIGS and each item was...
scored such that higher scores reflected better functioning (see Data S1 for details).

2.7 | Data reduction

All measures were age and sex adjusted based on the control group and then separate factor analyses were conducted to create more parsimonious outcome measures for cognitive and community functioning. One-factor solutions for cognitive and community functioning were considered appropriate based on exploratory and confirmatory factor analyses (see Data reduction section in Data S1 for details).

2.8 | Study design: Extended pedigree approach

A key advantage of extended pedigree designs (and classical twin designs), as compared to nuclear family first-degree relative designs, is that they tend to be more robust to potential shared environmental effects, which can inflate estimates of genetic effects. This is based on the assumption that environmental effects are uncorrelated (i.e., not confounded) with degree of kinship, which is made plausible for extended pedigree studies because many of the included family members (beyond first degree) are unlikely to have shared a household. If this assumption is violated, however, genetic effects will be overestimated in both twin and extended pedigree designs. Overall, heritability estimates from twin and extended pedigree study designs are generally predicted to be similar in the absence of shared environmental effects (Docherty et al., 2015).

2.9 | Genetic analyses

Quantitative genetic analyses were performed with Sequential Oligogenic Linkage Analysis Routines (SOLAR, version 4.0.7; Almasy & Blangero, 1998) which uses maximum-likelihood variance decomposition to estimate model parameters and likelihood-ratio tests of a ½:½ mixture of a $X^2_{(1)}$ variable and a point mass at zero (Self & Liang, 1987) to evaluate their statistical significance. Using SOLAR, bivariate genetic analyses were performed in order to assess the degree to which genetic effects were correlated between two measures. The genetic correlation ($R_g$) between two traits (e.g., age of onset and negative symptoms) is estimated from the observed cross-trait, cross-relative correlations (e.g., the age of onset of individuals with schizophrenia correlated with the negative symptoms of their relatives with schizophrenia), the relatives’ degree of kinship (e.g., first degree, second degree), and the heritabilities of the traits. If a genetic correlation is significant, it suggests that the genetic effects on one trait are shared with those on a second, separate trait (e.g., pleiotropy). The statistical significance of a genetic correlation is a function of the heritability of each individual phenotype (Verhulst, 2017), meaning that if the heritability of one or both traits is low, even a large genetic correlation may not be statistically significant. Conversely, if a genetic correlation is significant, it implies that sufficient phenotypic covariation is accounted for by correlated genetic effects.

Estimates of heritabilities were also obtained for age of onset, negative symptoms, positive symptoms, cognitive functioning, and community functioning in the group of related individuals with schizophrenia. Heritability in this design is estimated by predicting the observed phenotypic covariance between relatives based on their degree of genetic relatedness, with increased genetic relatedness linearly predicting increasing phenotypic resemblance among relatives. Environmental effects are estimated as all phenotypic variance that is not attributed to genetic effects (Environmentality = 1.0 − Heritability), which also includes measurement error. To the extent that environmental effects are also linearly related with genetic resemblance (i.e., shared environmental effects), heritabilities and genetic effects will be overestimated, leading some to prefer the term “familiality” for extended pedigree designs (Kendler & Neale, 2009).

All SOLAR analyses were conducted with age and sex as covariates and using the t-distribution function, which is robust to non-normality (refer to Data S1 for more details).

2.10 | Power analyses

Based on modeling by Schork (1993), the current sample has approximately 0.80 to 0.90 power to detect a moderate genetic correlation ($R_g = 0.50$) between two traits with moderateheritabilities ($h^2 = 0.40$). Simulations in SOLAR (Almasy & Blangero, 1998) also found the sample to have satisfactory power (approximately 0.60–0.70) to detect moderate heritabilities as expected from the literature (approximately 0.50–0.60; see Power analyses section in Data S1 for details).

3 | RESULTS

3.1 | Preliminary analyses

Demographic information for the Schizophrenia group ($N = 103$) and the Control group ($N = 135$) is presented in Table 1. (As mentioned previously, the Control group is not included in the primary analyses, but is included here as a point of reference for the Schizophrenia group.) Compared to controls, individuals with schizophrenia were significantly younger, more likely to be male, had fewer years of personal education, and lower scores on the WRAT. There was no significant difference in years of parental education between the Schizophrenia group and the Control group.

The Schizophrenia group had an average age of onset of 21.53 years old ($SD = 7.75$) and an average duration of illness of 24.29 years ($SD = 13.27$). The distribution of age of onset is provided in Figure S1 and is consistent with the distributions commonly found in the age of onset literature (e.g., Welham et al., 2004). Males had an earlier mean age of onset (20.32 years old, $SD = 5.83$) than females (23.26 years old, $SD = 9.71$), although this difference was not significant ($F(1, 83) = 3.029, p = 0.086$).
The average negative symptom score based on the SANS was 1.56 (SD = 1.04) and the average positive symptom score based on the SAPS was 0.93 (SD = 0.73; Table 1). Both the SANS and the SAPS use a 0–5 Likert scale, with higher scores indicating increased symptom severity. These relatively low symptom severity scores are not unexpected considering the use of an outpatient community sample.

Within the Schizophrenia group, 91.56% of those with available data reported currently taking an antipsychotic medication, with an average chlorpromazine equivalent dosage of 938.48 (SD = 1322.42; Woods, 2003).

Table 1 also presents the cognition and community functioning factor scores for the Schizophrenia and Control groups. ANCOVAs were conducted with age and sex as covariates and there were significant overall group differences for both cognition and community functioning, with, as expected, the Schizophrenia group performing significantly more poorly than the Control group.

### Table 1  Demographic characteristics and study measures

<table>
<thead>
<tr>
<th>Demographic characteristics</th>
<th>SC</th>
<th>CTL</th>
<th>Statistic</th>
<th>df</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total N</td>
<td>103</td>
<td>135</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex % Male</td>
<td>58.3%</td>
<td>37.0%</td>
<td>10.579</td>
<td>1</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Age Mean (SD)</td>
<td>46.63 (12.54)</td>
<td>54.71 (16.75)</td>
<td>16.790</td>
<td>1, 236</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Education (years, self)</td>
<td>Mean (SD)</td>
<td>12.44 (2.72)</td>
<td>14.92 (2.43)</td>
<td>54.355</td>
<td>1, 234</td>
</tr>
<tr>
<td>Education (years, parental)</td>
<td>Mean (SD)</td>
<td>12.34 (2.90)</td>
<td>12.61 (3.02)</td>
<td>4.053</td>
<td>1, 220</td>
</tr>
<tr>
<td>WRAT Mean (SD)</td>
<td>92.44 (15.94)</td>
<td>108.34 (8.43)</td>
<td>81.136</td>
<td>1, 191</td>
<td>&lt;.001*</td>
</tr>
</tbody>
</table>

**Note:** Results of one-way ANOVAs for age and education are reported with the F statistic, and results for sex are reported with the Pearson chi-square statistic. Age and sex were entered as covariates for cognitive and community functioning only. Cognition and Community Functioning Scores were standardized based on the control group.

**Abbreviations:** CTL, Control; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; SC, Schizophrenia; WRAT, Wide Range Achievement Test.

*Parental education is the average of maternal and paternal years of education. For those individuals that were missing one, the other was substituted. Eighty-two individuals were missing both maternal and paternal education.

*See Data reduction section in Data S1 for details regarding creation of factor scores.

*Significant at p < .05.

### Table 2  Correlations and heritabilities in the Schizophrenia group

<table>
<thead>
<tr>
<th>Phenotypic correlation with Age of onset (AOO)</th>
<th>SANS</th>
<th>SAPS</th>
<th>Cognition</th>
<th>Community functioning</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of onset (AOO)</td>
<td>−0.196 (.003)*</td>
<td>−0.228 (.045)*</td>
<td>0.295 (.030)*</td>
<td>0.318 (.008)*</td>
</tr>
<tr>
<td>Genetic correlation with Age of onset (AOO)</td>
<td>−1.00 (.007)*</td>
<td>−1.00 (.296)</td>
<td>1.00 (.150)</td>
<td>1.00 (.590)</td>
</tr>
<tr>
<td>Bivariate heritability with Age of onset (AOO)</td>
<td>−0.447</td>
<td>−0.258</td>
<td>0.337</td>
<td>0.124</td>
</tr>
<tr>
<td>Environmental correlation with Age of onset (AOO)</td>
<td>1.00 (.078)</td>
<td>0.103 (.889)</td>
<td>−0.106 (.840)</td>
<td>0.248 (.388)</td>
</tr>
</tbody>
</table>

*Significant at p < .05.

The average negative symptom score based on the SANS was 1.56 (SD = 1.04) and the average positive symptom score based on the SAPS was 0.93 (SD = 0.73; Table 1). Both the SANS and the SAPS use a 0–5 Likert scale, with higher scores indicating increased symptom severity. These relatively low symptom severity scores are not unexpected considering the use of an outpatient community sample.

Within the Schizophrenia group, 91.56% of those with available data reported currently taking an antipsychotic medication, with an average chlorpromazine equivalent dosage of 938.48 (SD = 1322.42; Woods, 2003).

3.2 | Primary analyses

3.2.1 | Phenotypic correlations in schizophrenia

Within the Schizophrenia group, phenotypic correlations were calculated using SOLAR with age and sex as covariates and the data are...
presented in Table 2. As predicted, earlier age of onset was significantly associated with increased severity of negative symptoms \((R = -1.96, p = .003)\), positive symptoms \((R = -2.28, p = .045)\), poorer cognition \((R = .295, p = .030)\), and poorer community functioning \((R = .318, p = .008)\).

### 3.2.2 Correlated genetic and environmental effects between age of onset and outcomes in schizophrenia

With this key research aim, our goal was to examine if there are genetic effects shared between variation in age of onset of psychosis and our outcome measures. The genetic correlations between age of onset and outcome measures are presented in Table 2. Genetic effects explained a significant proportion of the shared variation between earlier age of onset and increased severity of negative symptoms \((R_g = -1.00, p = .007)\), and this remained significant after Bonferroni correction (i.e., corrected \(a = .05\) divided by 4 measures = 0.0125). While the genetic correlations between age of onset and positive symptoms, cognition, and community functioning were all in the predicted direction and estimated at the maximum (e.g., \(R_g = 1.00\) or \(-1.00\)), these genetic correlations were not significant, which is likely due to the low heritability of age of onset and the somewhat lower heritabilities of the individual measures (see section 3.2.3). Table 2 also presents the bivariate heritabilities, which represent the total genetic effect on the observed correlation between two traits. The bivariate heritability between age of onset and the other traits in schizophrenia was highest for negative symptoms (consistent with its significant genetic correlation), followed by cognition. In contrast, the environmental correlations between age of onset and the outcome measures were in the opposite of the predicted direction (except for community functioning), not significant, and fairly low, with the exception of the correlation between age of onset and negative symptoms.

### 3.2.3 Heritability of age of onset, symptom severity, and community and cognitive functioning in schizophrenia

Table 2 presents the heritabilities of age of onset, negative symptoms, positive symptoms, cognition, and community functioning within the Schizophrenia group. Although approximately 20% of the variation in age of onset in the sample could be attributed to genetic effects, this was not statistically significant \((p = .277)\). However, negative symptoms \((h^2 = .977, p < .001)\), positive symptoms \((h^2 = .853, p = .003)\), and cognitive functioning \((h^2 = .835, p = .013)\) were all significantly heritable. While 32% of the variance in community functioning was attributed to genetic factors, this was not significant \((p = .182)\).

### 4 DISCUSSION

Schizophrenia is a heterogeneous diagnosis both in terms of clinical presentation and genetic influences, and age of onset is among the most useful predictors of the course and severity of the disorder. Consistent with the prior literature, we found that earlier age of onset was significantly associated with increased severity of negative and positive symptoms and poorer cognitive and community functioning. Although widely observed, the causes of such correlations have been little studied and are largely unknown. To our knowledge, this study is the first to attempt to assess whether or not shared genetic effects significantly influence the correlations between age of onset and course severity. We observed a significant genetic correlation \((R_g = -1.00, p = .007)\) between earlier age of onset and increased negative symptom severity, which suggests that the genetic effects that influence age of onset are shared with those that influence negative symptom severity among individuals with schizophrenia. The genetic correlations between age of onset and positive symptoms, cognition, and community functioning were also estimated at 1.0 but were not statistically significant, presumably due to the lower than expected estimate of the heritability of age of onset coupled with the slightly lower heritabilities of the other outcome measures (as compared to the heritability of negative symptoms). As noted earlier, the statistical significance of a genetic correlation is a function of the heritability of each individual phenotype (Verhulst, 2017). Based on modeling by Schork (1993), the study should have adequate power (between approximately 0.85 and 0.925) to detect moderate genetic correlations \((0.50)\) for moderately heritable \((0.40)\) traits with the available number of relative pairs (refer to Power analyses section in Data S1 for further details). The environmental correlations between age of onset and all other outcome variables were nonsignificant and, with the exception of community functioning, not in the predicted direction; therefore, we saw limited evidence that correlated environmental effects play a meaningful role in the relationship between age of onset and other clinically relevant outcome variables.

The reported heritabilities for the symptom domains in the Schizophrenia group are also notable and contribute to the literature. Despite significant interest in the genetic effects on varying dimensions within the schizophrenia diagnosis, a limited number of studies have assessed the overall heritability of specific symptom dimensions. Our study also assessed the heritability of community functioning in schizophrenia, which remains an understudied area (for a review of the studies that assess heritabilities of cognition and community functioning in schizophrenia, see Kuo et al., 2018). Based on power analyses completed in SOLAR, this sample has adequate power \((0.65–0.81)\) to detect moderate individual heritabilities \((0.58–0.68)\) such as those predicted from the literature for age of onset, cognition, and community functioning. The sample should have modest power \((0.36–0.40)\) to detect smaller genetic effects \((0.34–0.36)\), such as those predicted from the literature for positive and negative symptoms (though the literature on the heritability of symptomatology is quite sparse and should therefore be interpreted with caution. Refer...
to Power analyses section in Data S1 for further details). In sum, the current study contributes to the limited available literature suggesting that multiple symptom domains and functional outcomes are heritable in schizophrenia. The current study also provides a valuable addition by utilizing a multiplex, extended pedigree design, rather than sibling pairs or twins to contribute to these estimates.

There are a few limitations to be cognizant of in the current study. First, our estimate of the heritability of age of onset was lower than expected based on the prior literature, which may have limited our power to detect genetic correlations. Based on our power simulations in SOLAR, the study had moderate power (0.70) to detect a heritability of 0.58, as predicted by the literature, but our estimated heritability estimate was approximately 0.20. Increased sample size and power could have improved this estimate and future studies could benefit from larger sample sizes. This lower heritability estimate could be due to the retrospective nature of our age of onset assessment (although this is standard in most studies). It is also possible that this estimate is affected by study design—heritability estimates in the literature varied widely, and the only other study that used an extended pedigree design found age of onset to be 33% heritable (Hare et al., 2010), which is similar to our estimate (even with a substantially larger sample of 717 individuals). Finally, we considered the possibility that shared environmental effects may be playing a significant role in age of onset; however, this is not supported by the prior literature (as presented in Table S1). If shared environmental effects were operating, we would generally expect higher estimates from nuclear family studies ($h^2 = .55$) than twin studies ($h^2 = .91$), but the reverse is seen.

Another limitation is that the current dataset is cross-sectional, and without longitudinal data, it is not possible to determine the causal nature of any shared genetic effects. It is unlikely that negative symptoms assessed on average 20 years post-onset could directly affect age of onset. The remaining possibilities are that (a) genetic effects on age of onset are highly correlated with genetic effects on negative symptoms (e.g., pleiotropy) or (b) genetic variation affects age of onset, which in turn has a direct causal effect on later negative symptoms. Such constraints apply to all cross-sectional studies of genetic correlations between traits.

The current study also has many strengths, including the novelty of the research question; extended pedigree sample; thorough assessment of many different aspects of symptom, cognitive, and community functioning; heritability estimates of those diverse measures of functioning; age and sex adjustments based on a matched control group, which controlled for general population but not schizophrenia-related age effects; and use of factor invariance analyses to create more accurate composite measures for our community and cognitive functioning measures.

In sum, the heterogeneity of the schizophrenia diagnosis and the predictive utility of age of onset have been of interest to researchers for decades and yet the potential causes of the relationship between age of onset and outcome are still poorly understood. To the best of our knowledge, this study was the first to examine the potential genetic relationship between age of onset and later functioning in schizophrenia. We found significant overlap of genetic variance between age of onset and negative symptoms in schizophrenia, which indicates that many of the same genetic effects that are influencing age of onset are shared with those that influence the severity of negative symptoms.

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**CONFLICT OF INTEREST**

The authors declare no potential conflict of interest.

**AUTHOR CONTRIBUTIONS**

Christie W. Musket: Conceived the presented idea, completed data analysis, and wrote the manuscript. Susan S. Kuo: Assisted with data cleaning. Petra E. Rupert: Assisted with data cleaning. Laura Almasy: Provided expertise regarding the SOLAR program and analytic approaches; designed the study and collected the data. Ruben C. Gur: Designed the study and collected the data. Konasale Prasad: Designed the study and collected the data. Joel Wood: Assisted with data management. David R. Roalf: Assisted with data management. Raquel E. Gur: Designed the study and collected the data. Vishwajit L. Nimgaonkar: Designed the study and collected the data. Michael F. Pogue-Geile: Supervised data analysis and contributed to writing the manuscript; designed the study and collected the data.

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**REFERENCES**


**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section at the end of this article.