ORIGINAL ARTICLE

A Population-Based Study of Shared Genetic Variation Between Premorbid IQ and Psychosis Among Male Twin Pairs and Sibling Pairs From Sweden

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Context: The strong association between lower IQ and risk for psychosis has led to the suggestion that the search for genes influencing cognition may provide a useful strategy for examining the genetic origins of psychosis. However, research in this area has generally used designs in which twin pairs are selected by case status and with assessment of IQ after the onset of psychosis rather than longitudinal population-based samples.

Objective: To examine the relationship and shared genetic origin between premorbid IQ and psychotic disorders in a longitudinal population-based cohort.

Design: Genetically informative longitudinal study.

Setting: Population-based cohort in Sweden.

Participants: Individuals were identified from the population-based Swedish Multi-Generation Register and consisted of male sibling (n=369 960), monozygotic twin (n=1986), and dizygotic twin (n=2253) pairs born between January 1951 and December 1976. Their IQs were measured during compulsory military conscription.

Main Outcome Measure: Individuals having a subsequent diagnosis of psychosis were identified via the Swedish National Hospital Discharge Register.

Results: Heritability estimates for IQ and psychosis were similar to previous estimates, approximately 69% and 56%, respectively. However, the phenotypic correlation between IQ and psychosis was only −0.11, of which 91% was due to shared genetic influences. The proportion of genetic variance for psychosis shared with that for IQ was approximately 7%.

Conclusions: Using IQ as a phenotype to identify genes that have an important role in the genetic origin of schizophrenia is unlikely to be a successful strategy. The low correlation seen in this study between premorbid IQ and psychosis vs the higher correlations reported in the literature with postmorbid IQ suggests the correlation between these phenotypes has more to do with the influence that the onset of psychosis has on cognitive functioning than with shared genetic origin.

Arch Gen Psychiatry. 2012;69(5):460-466

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THERE IS CLEAR EVIDENCE FOR a genetic component to schizophrenia.[1] Recent findings from genomic investigations provide strong evidence that a combination of common single-nucleotide polymorphisms and rare genomic copy number variants confers risk for the disorder.[2] To date, only a small proportion of the genetic variance has been accounted for by specific risk variants, and the biologic pathways through which genetic risk is mediated are yet to be identified. Many putative risk genes for schizophrenia identified through positional and candidate gene approaches seem to influence synaptogenesis or myelination[3-5] or directly influence glutamatergic function.[6] Deficits in these processes in animal models lead to detrimental cognitive effects, and associations between some of these genes and cognitive ability in humans have been reported.[7]

A strong association between lower IQ and subsequently increased risk for schizophrenia has been consistently reported.[8,9] However, it is unknown to what extent this association is causal or is a consequence of common environmental influences or pleiotropic influences of genetic variants that lead to both lower IQ and increased risk for psychosis.[10] Evidence that a substantial proportion of genetic variation for schizophrenia is shared with that for IQ (a phenotype that is also highly heritable,[11,12]) would indicate a complementary approach to identifying genes for schizophrenia might be to focus on genes influencing cognition. Given that cognition is a universally measurable trait, adequately sized genome-wide studies of this phenotype should be easy

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to conduct. In contrast, even collaborative genome-wide association studies of schizophrenia are modest in size given the effect size of common risk variants believed to be influencing disease risk.[2]

Two studies[13,14] examined shared genetic influences across IQ and schizophrenia, with one study using a subset of the sample reported in the other study. In their initial article, Toulopoulou et al[14] reported that the correlation between these 2 phenotypes was high (–0.75) and that approximately 90% of this was due to common additive genetic influences. Most important, they reported that more than 50% of the genetic component for schizophrenia could be explained by factors that also influence cognition. In the subsequent study,[13] the correlation between these 2 phenotypes was lower (–0.38), but 89% of this was estimated to be due to common additive genetic influences.

Neither of these 2 studies[13,14] was based on a population-based sample but on samples of twin pairs selected for schizophrenia and control twin pairs identified from existing voluntary registers, local advertising, and community sources. A limitation of using such a design is that model parameters for schizophrenia could not be estimated directly but were fixed based on the estimates from meta-analyses of schizophrenia heritability studies. This approach is an efficient method for addressing the lack of power in twin analyses for rare disease outcomes, such as schizophrenia, but if the estimates from the meta-analyses do not apply to the population from which the twins are sampled, this could potentially bias the estimates of covariance between IQ and schizophrenia attributed to genetic or environmental influences.

Population-based research in this area is scarce. Therefore, we aimed to examine the extent to which any genetic component for schizophrenia was shared with a genetic component for intelligence as measured by premorbid the IQ in a population-based sample that included sibling pairs and twin pairs.

METHODS

SAMPLE

The Swedish Multi-Generation Register (MGR) includes all individuals in Sweden born from January 1932 onward who were alive and residing in Sweden on January 1960 or later. This study used data from men identified through the MGR born between January 1951 and December 1976. Twin pairs were identified in which a male sibling was recorded as being born on the same day. Zygosity was identified by linkage to the Swedish Twin Registry[15] and the Swedish Young Male Twins Study.[16] A full description of zygosity assignments was previously published.[17] In total, 1986 monozygotic (MZ) male twin pairs and 2253 dizygotic (DZ) male twin pairs were identified in this manner. Among other eligible men included in the MGR, a male full sibling (FS) was also identified using family relationship information recorded in the registry. To minimize potential differences in the family environment, only pairs of male siblings born within 5 years of each other were included. In total, 369 960 sibling pairs were identified in this manner. This study was approved by the ethical review board in Stockholm, Sweden.

MEASURES

Cognition

Premorbid IQ was measured at the military conscription examination (mandatory by law for all young male Swedish citizens) between January 1969 and December 1994. Only men with a severe handicap or a chronic disease were exempted from the conscription examination. The IQ was measured at a mean (SD) age of 18.3 (0.6) years. The IQ test consists of the following 4 subtests: a logical test, a verbal test, a spatial test, and a technical test.[18] The global IQ score was standardized against the entire population to follow a gaussian distribution between 1 and 9, with a mean (SD) of 5 (2). Our study population had a mean (SD) global IQ of 5.2 (1.9).

Psychosis

The Swedish National Hospital Discharge Register has covered virtually all inpatient care for psychiatric disorders since January 1973, except for admissions in a few counties during some of the early years of data collection.[19] Admissions were coded according to the *International Classification of Diseases* (*ICD*) revisions 8, 9, or 10. We extracted data on psychiatric admissions from January 1969 to December 31, 2004. Our primary outcomes, defined a priori to maximize statistical power, were clinical diagnoses of all nonaffective psychoses and affective psychoses. Nonaffective psychoses were identified by *ICD-8* and *ICD-9* codes 291.3, 295, 297.0, 297.1, 297.9, 298.3, and 298.9; *ICD-8* codes 291.2 and 299; *ICD-9* codes 297.2, 297.3, 297.8, 298.4, and 298.8; and *ICD-10* codes F10-F19 (subsections n.5 and n.7), F20, and F22-F29. Affective psychoses were identified by *ICD-9* codes 296.04, 296.14, 296.24, 296.34, 296.44, 296.54, and 296.64 and by *ICD-10* codes F30.2, F31.2, F31.5, F32.3, and F33.3. Schizophrenia diagnoses have been shown to have good validity,[20,21] although to date this has not been studied for other psychoses. Individuals who were diagnosed as having a psychosis before or within 1 year after conscription were excluded from the analysis to ensure IQ was assessed before the onset of schizophrenia.

STATISTICAL ANALYSIS

Initial analyses were conducted to examine whether IQ and psychosis were associated. Because each twin and sibling are part of a twin-sibling pair, data were treated as equivalent to a 2-stage cluster design, with pairs as the primary sampling unit,[22] using a commercially available survey analysis program (STATA release 9; StataCorp LP). The polychoric and tetrachoric correlations were calculated using this software.

GENETIC ANALYSIS

Twin and sibling data allowed us to estimate the relative contribution of genetic and environmental influences to the liability for psychosis. The quantitative genetic modeling method is based on comparisons of MZ twins, who share 100% of their genes in common, with DZ twins and FS pairs, who share on average 50% of their genes. Therefore, for genetically influenced behavior, we would expect greater similarity among MZ pairs than among DZ and FS pairs. In the basic ACE model, variation is assumed to arise from the following 3 sources: (1) additive genetic influences, (2) common environmental influences, and (3) unique environmental influences. Common environmental influences serve to make twins or siblings more similar to one another, while unique environmental influences tend to make the individuals in twin or sibling pairs less similar.[23]

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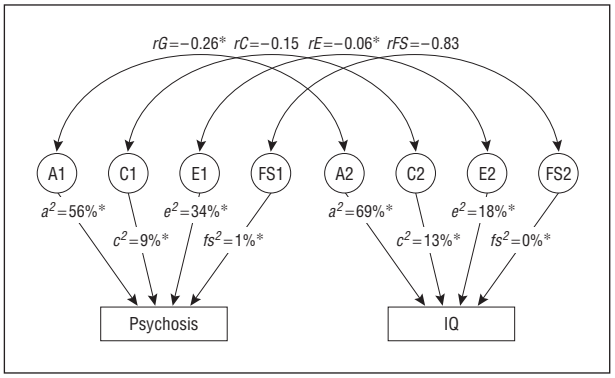

Figure. Correlated factors model (within-sibling only). Asterisk indicates a significant pathway. Additive genetic, common environment, unique environment, and sibling-specific contributions to psychosis and IQ are indicated by A1, C1, E1, and FS1, respectively, and by A2, C2, E2, and FS2, respectively. *rG*, *rC*, *rE*, and *rFS* represent the correlations between additive genetic, common environment, unique environment, and sibling-specific contributions, respectively, to psychosis and IQ. For ease of presentation, one member of a sibling pair is shown; if both sibling pairs were included, no between-sibling pair correlations for unique environment and sibling-specific contributions would be modeled (because these factors do not explain the covariance between sibling pairs). Similarly, models showing monozygotic and dizygotic twins would not include a sibling-specific contribution.

It is conceivable that there may be greater variance between siblings than between twin pairs because there may be greater exposure to different environmental influences due to their not being born at the same time (eg, different peer groups, etc). Within this sample, there is some evidence of an additional source of variance among siblings alone for other phenotypic measures, including weight and body mass index[17] and IQ (on a scale of 1-9, MZ and DZ variance is 3.6, and sibling variance is 3.7). By fitting an additional sibling-specific variance component to the variance part of the sibling variance and covariance model, it is possible to test this.[17] It is equivalent to an additional unique environment component that is specific to siblings (ie, does not explain the covariance between sibling pairs), and this was included in the model. By including a sibling-specific variance component and standardizing the estimate of all 4 sources of variance to 1, this gives an indication of the importance of the overall variance seen among siblings (the largest group in the sample) for each of the sources.

Because the presence or absence of psychosis is a binary variable, a threshold model was used whereby the underlying liability for each variable is considered as normally, or approximately normally, distributed among the population. This model assumes that psychosis will only manifest if an individual's position on the liability distribution for that behavior is above a certain liability threshold.[24]

Genetic analyses using a structural equation modeling approach and full-information maximum-likelihood estimation with raw ordinal data were performed using statistical modeling software (Mx; Medical College of Virginia).[25] The IQ was recorded as a 9-category ordinal variable; however, because the presence of psychosis was uncommon, IQ categories were condensed into low, medium, and high (corresponding to IQ categories 1-3, 4-6, and 7-9, respectively) to ensure all IQ categories had sufficient individuals having psychosis within them.

It is possible that there are fewer common environmental influences on siblings who are born further apart, violating the equal environments assumption. In addition, older individuals are more likely to have been diagnosed as having a psychosis. Therefore an age and age gap correction was used that adjusts the threshold for each twin-sibling according to his age and age gap on the distribution of liability for psychosis or IQ.[26] Thresholds were constrained to be equal across MZ and DZ pairs but were estimated separately for sibling pairs within the model.

BIVARIATE GENETIC ANALYSIS

In bivariate analyses, we tested whether genetic, environmental, and sibling-specific influences on psychosis were correlated with those influencing IQ score. A bivariate structural equation model was fitted to the data (**Figure**). It gives the estimates of the genetic (*rG* in the figure), common environment (*rC*), unique environment (*rE*), and sibling-specific (*rFS*) correlation between the 2 variables of interest. These correlations reflect the size of the relationship between the underlying factors but are independent of the size of the estimates of genetic and environmental influences on the variables of interest. As such, it is possible for large correlations to explain only a small amount of the covariation between 2 traits.

One method to address this is to combine information from the correlations (*rG*, *rC*, *rE*, and *rFS*) with the relevant heritability and environmental estimates (additive genetic [a^2], common environmental [c^2], unique environmental [e^2], and sibling-specific [fs^2] influences in the Figure) for the 2 traits.[14] This allows the calculation of the contributions of genetic, common environment, unique environment, and sibling-specific influences to the total phenotypic correlation. Although this approach makes no specific assumptions about the direction of effect, as a method it explains the contribution of different shared influences to the overall correlation between factors and allows us to address our first question: what proportion of the phenotypic correlation between IQ and psychosis can be attributed to genetic influences?

However, this approach does not address the slightly different issue of the importance of shared influences in explaining the underlying origin of psychosis. By subtracting rG^2 from 1, we are able to estimate the proportion of genetic influences specific to psychosis,[14] allowing us to address our second question: of the genetic factors influencing psychosis, what proportion is specific to psychosis and what proportion is due to factors that also influence IQ?

RESULTS

DESCRIPTIVE FINDINGS

The total sample consisted of 747 257 individuals. Full information (ie, information on IQ and psychosis) was available for 607 169 individuals. Of these, 6117 (1.01%; 95% CI, 0.98%-1.03%) were diagnosed as having a psychosis (**Table 1**). The distributions of individuals in the groups with low, medium, and high IQ were 33.9%, 40.6%, and 25.5%, respectively (**Table 2**).

The relationship between premorbid IQ and psychosis was examined using logistic regression analysis. A negative relationship was observed between the variables; individuals with medium IQ were approximately 50% less likely to be diagnosed as having psychosis than those with low IQ (odds ratio [OR], 0.52; 95% CI, 0.49-0.55), and those with high IQ were approximately 60% less likely (OR, 0.39; 95% CI, 0.36-0.42) ($P<.001$ for both).

Age and age gap between pairs were significantly correlated with IQ and psychosis ($P<.05$ for both). However, this is probably because of the many individuals in the sample, and correlations were small (range of polyserial correlations, −0.05 to −0.07), except for the relationship between age and psychosis ($r=0.20$).

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Table 1. Descriptive Summary of Individuals Included in the Study

Psychosis	Monozygotic Pairs	Dizygotic Pairs	Sibling Pairs	Total	Mean (SD)	
					Age, y	IQ[a]
Any	**25**	**55**	**6037**	**6117**	42.9 (7.9)	4.3 (2.1)
Nonaffective	22	50	5588	**5660**	43.0 (7.8)	4.2 (2.1)
Affective	3	5	449	**457**	41.7 (9.0)	4.7 (1.9)
None	3354	3849	593 849	**601 052**	36.9 (10.1)	5.2 (1.9)
Total	**3379**	**3904**	**599 886**	**607 169**	37.0 (10.1)	5.2 (1.9)

[a] On a scale of 1 to 9.

GENETIC MODEL FITTING

Correlations

The polychoric and tetrachoric correlations within trait and between trait for the MZ, DZ, and sibling pairs indicate an important genetic component in the origin of IQ and psychosis (**Table 3**). The crosstwin and cross-trait correlations suggest genes and environment have a role in the shared etiology of IQ and psychosis. However, the polychoric correlation between IQ and psychosis was small ($r = -0.17$, $P < .05$). When calculated as part of the structural equation modeling analysis using the entire sample (including those with missing data) and controlling for age and age gap between sibling pairs, this decreased marginally to an r value of −0.11.

Bivariate Analysis

Genetic components were important for IQ and for psychosis, accounting for approximately two-thirds of the variability of these phenotypes (**Table 4**). Unique environment and, to a lesser extent, common environment were moderately important for IQ, whereas sibling-specific influences were negligible. For psychosis, unique environment was moderately important, and common environment was less so. There was a moderately important sibling-specific influence, suggesting that factors relating to the differences in experience between siblings also affect psychosis. The estimates for IQ were precise, whereas there was greater uncertainty in the estimates for psychosis, as reflected in wider CIs. The crosstrait correlations (rG, rC, rE, and rFS) were negative, indicating that factors leading to higher IQ lead to decreased liability for psychosis.

PHENOTYPIC CORRELATION

The genetic, common environment, unique environment, and sibling-specific contributions to the phenotypic correlation between IQ and psychosis ($r = -0.11$) were 0.10, −0.02, −0.04, and −0.00, respectively. Genetic influences account for the largest proportion of the phenotypic correlation (−0.10/−0.11 = 90.9%).

PROPORTION OF GENETIC VARIANCE FOR PSYCHOSIS INDEPENDENT OF IQ

Because the genetic correlation is small ($rG = 0.26$), most of the genetic origin of psychosis can be thought of as separate from the genetic origin of IQ. Approximately 93.2% ($1 - [0.26^2]$) of the 0.56 heritability estimate for psychosis is independent of premorbid IQ, and approximately 6.8% is shared, suggesting most genes influencing the 2 traits are independent. A similar picture is seen for common and unique environmental influences, with 97.8% and 99.6%, respectively, of the underlying origin of psychosis being independent of IQ.

Table 2. Individuals With Low, Medium, and High IQ by Psychosis Status[a]

Psychosis	No. (%)		
	Low IQ	Medium IQ	High IQ
Monozygotic Pairs			
No (n = 3354)	1151 (34.3)	1365 (40.7)	838 (25.0)
Yes (n = 25)	11 (44.0)	9 (36.0)	5 (20.0)
Dizygotic Pairs			
No (n = 3849)	1479 (38.4)	1497 (38.9)	873 (22.7)
Yes (n = 55)	24 (45.5)	26 (47.3)	5 (9.1)
Sibling Pairs			
No (n = 593 849)	199 996 (33.7)	241 503 (40.7)	152 350 (25.7)
Yes (n = 6037)	3234 (53.6)	1902 (31.5)	901 (14.9)

[a] On a scale of 1 to 9, low, medium, and high IQ correspond to 1 to 3, 4 to 6, and 7 to 9, respectively.

SENSITIVITY ANALYSIS

Of 6117 individuals having a psychosis diagnosis, 5660 (0.9% of the 607 169 cohort) were diagnosed as having nonaffective psychosis, and 457 (0.1% of the 607 169 cohort) were diagnosed as having affective psychosis. Lower IQ was associated with increased risk for nonaffective psychosis (OR per IQ category, 0.56; 95% CI, 0.54-0.59) and for affective psychosis (OR, 0.72; 95% CI, 0.64-0.81) ($P < .001$ for both). Because it is possible that the relationship with premorbid IQ is different for those who subsequently develop affective psychosis vs schizophrenia or other nonaffective psychoses, we repeated our analysis among individuals having an outcome of nonaffective psychosis only. Results were similar in this sensitivity analysis (the phenotypic correlation was −0.07, of which approximately 80% could be attributed to genetic influences, and rG was 0.15), although the estimates were less precise.

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Table 3. Within-Trait and Between-Trait Correlations for Monozygotic Pairs, Dizygotic Pairs, and Sibling Pairs

	Correlation (95% CI)			
	Twin-Sibling 1		Twin-Sibling 2	
Variable	Psychosis	IQ	Psychosis	IQ
Monozygotic Pairs				
Twin 1				
Psychosis	. . .	−0.10 (−0.25 to 0.00)	0.82 (0.50 to 0.99)	−0.07 (−0.25 to 0.00)
IQ	. . .	. . .	−0.16 (−0.25 to 0.00)	0.83 (0.80 to 0.85)
Twin 2				
Psychosis	. . .	. . .	. . .	−0.08 (−0.30 to 0.00)
IQ	. . .	. . .	. . .	. . .
Dizygotic Pairs				
Twin 1				
Psychosis	. . .	−0.20 (−0.22 to −0.15)	0.57 (0.35 to 0.72)	−0.08 (−0.20 to 0.00)
IQ	. . .	. . .	−0.03 (−0.20 to 0.00)	0.55 (0.52 to 0.59)
Twin 2				
Psychosis	. . .	. . .	. . .	−0.10 (−0.20 to 0.00)
IQ	. . .	. . .	. . .	. . .
Sibling Pairs				
Sibling 1				
Psychosis	. . .	−0.17 (−0.18 to −0.16)	0.36 (0.34 to 0.39)	−0.06 (−0.07 to −0.05)
IQ	. . .	. . .	−0.09 (−0.11 to −0.07)	0.47 (0.46 to 0.48)
Sibling 2				
Psychosis	. . .	. . .	. . .	−0.18 (−0.19 to −0.16)
IQ	. . .	. . .	. . .	. . .

Table 4. Estimates From the Bivariate Genetic Analysis[a]

Variable	Correlation (95% CI)
Psychosis	
a^2	0.56 (0.51 to 0.61)
c^2	0.09 (0.00 to 0.16)
e^2	0.34 (0.27 to 0.41)
fs^2	0.01 (0.00 to 0.50)
IQ	
a^2	0.69 (0.67 to 0.72)
c^2	0.13 (0.10 to 0.14)
e^2	0.18 (0.17 to 0.19)
fs^2	0.00 (0.00 to 0.01)
Crosstrait	
rG	−0.26 (−0.37 to −0.08)
rC	−0.15 (−0.32 to 0.00)
rE	−0.06 (−0.33 to −0.01)
rFS	−0.83 (−1.00 to 0.99)

Abbreviations: a^2, additive genetic; c^2, common environmental; e^2, unique environmental; fs^2, sibling specific; *rC*, common environment; *rE*, unique environment; *rFS*, sibling specific; *rG*, additive genetic.

[a]Model fit statistics are as follows: −2log likelihood = 0.137E + 07, *df* = 1 354 411, and Akaike information criterion = 0.134E + 07.

COMMENT

In this study, we observed high heritability for IQ and for psychosis in the univariate analyses. Common and unique environmental influences were also important but explained less variation than additive genetic influences for both phenotypes. Unique environmental influences were particularly important for psychosis. These findings are consistent with previous literature on these phenotypes.[27-29]

We also observed a strongly significant association between premorbid IQ and psychosis, although the correlation between them was small (r=−0.11) and substantially lower than −0.38 or −0.60 reported in 2 previous studies.[13,14] In itself, this strongly suggests that shared etiological factors between IQ and psychosis are much less important than previously thought. Our results from the bivariate structural equation modeling indicated that genetic influences account for about 91% of this phenotypic correlation, similar to that reported by Toulopoulou et al,[14] whereby more than 90% of the correlation was explained by genetic influences.

When considering whether identifying genes that influence IQ is likely to be a fruitful approach to understanding psychosis, what is most important is the proportion of genetic influences on psychosis that are shared with IQ. The genetic correlation between IQ and psychosis in our study was low (rG=0.26), while the proportion of genetic variance for psychosis shared with that for IQ was 6.8% and even at the uppermost limit of the 95% CI was less than 13%.

On the basis of results from 2 studies, Toulopoulou et al[13,14] suggest the search for genes that influence IQ could potentially also be fruitful for identifying genes that influence psychosis. Based on the correlations alone, our findings from a population-based sample indicate this is not the case. Results from our genetic modeling also fail to support this view. Because a small proportion of genetic risk for psychosis is shared with IQ, using IQ as a phenotype to identify genes that have an important role in the genetic origin of schizophrenia is unlikely to be a successful strategy. Reduced cognitive function is a core feature of schizophrenia, being associated with in-

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creased incidence, greater impaired function, and poorer prognosis; therefore, greater understanding about the etiology of cognition may increase our understanding of the etiology of schizophrenia.[8,30] However, as indicated by our findings, focusing on IQ as a phenotype for genetic studies will identify a small proportion of genetic variants that influence risk for schizophrenia and as a strategy is likely to have a limited contribution to our understanding of the genetic origin of psychosis.

There are several possible reasons why our findings and subsequent conclusions are at odds with those of Toulopoulou et al.[13,14] In our study, IQ was assessed before the onset of psychosis, whereas IQ in their studies was measured after the onset of schizophrenia. Although IQ is generally considered a stable construct, there is accumulating evidence that a reduction in IQ may occur before or around the onset of psychosis.[8,31,32] Therefore, investigations that measure IQ after the onset of illness are likely to find stronger associations with schizophrenia than those in which premorbid IQ is assessed and may overestimate the likely extent to which shared genetic variation contributes to both phenotypes.

Furthermore, because our study was based on a longitudinal population-based sample, it was possible for us to use directly estimated parameters rather than ones based on the estimates from heritability meta-analyses, which could under some circumstances potentially bias the estimates of covariance between IQ and schizophrenia attributed to genetic or environmental influences. Similarly, selection bias (eg, arising relative to exclusion criteria in the selection of nonaffected twin pairs) is of greater concern in selected designs where twin pairs are identified on the basis of case status than in population-based longitudinal designs, although this is unlikely to account for the large difference in results observed between our study and the studies by Toulopoulou and colleagues.[13,14]

Another possible reason for the disparity of our findings vs those by Toulopoulou et al is that we examined a broader outcome of nonaffective and affective psychoses as our primary outcome. We decided a priori to group all psychotic disorders together to maximize power. It is possible that the genetic relationship between IQ and schizophrenia is different from that between IQ and other psychoses. There is some evidence that the relationship with premorbid IQ may be different for bipolar disorder compared with that for schizophrenia.[9,33] Therefore, we conducted an analysis restricted to individuals with nonaffective psychosis only. This produced no substantive difference in our results, suggesting that the difference in selection of outcomes examined is unlikely to be an adequate explanation for the different conclusions between our study and those by Toulopoulou et al. Moreover, most investigations indicate the relationship between premorbid IQ and other nonaffective psychoses is similar to that for schizophrenia,[9,34] while there is increasing evidence that genetic variation for schizophrenia overlaps to some extent with that for other psychotic disorders.[35,36]

It is possible that shared genetic factors influence both IQ and schizophrenia in individuals with schizophrenia and their relatives. However, these factors would contribute minimally to variation in IQ within the general population.

Finally, the modeled data in our analyses were standardized to 1 to explain the variance in siblings. To be directly comparable with twin studies, only the estimates of those factors involved in explaining the twins' variance and covariance would need to be standardized. However, because the contribution of the sibling-specific variance component to the overall variance within IQ and psychosis (and particularly between IQ and psychosis) is minimal, this is unlikely to have a large material effect on the comparability of our results.

To our knowledge, this is the first longitudinal study to examine the shared genetic contribution between premorbid IQ and psychosis, and further such studies are required. A major strength of our study is that it is population based and is likely to have complete data for diagnoses of psychotic disorders. However, results need to be interpreted in the context that, even with the large sample available, few twins with psychotic disorders were identified. The low numbers raise issues about the power of the analysis; nevertheless, the estimated CIs were narrow.

The equal environments assumption is less likely to hold true for sibling pairs compared with MZ and DZ twin pairs, although we included sibling-specific influences in our model. We also adjusted for the possible influence of the age gap present between siblings within a pair, and we limited our selection of siblings to those with a maximum 5-year age gap to further reduce the potential violation of this assumption.

In conclusion, although genetic factors are influential in the shared origin between premorbid IQ and psychosis, the importance of this relationship may have been overestimated. A strategy of using IQ as a phenotype to identify genes that have an important role in the genetic origin of schizophrenia is likely to have a limited contribution to understanding the genetic origin of psychosis.

Submitted for Publication: March 29, 2011; final revision received September 19, 2011; accepted October 7, 2011.
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Author Contributions: Dr Zammit takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Fowler, Zammit, Owen, and Rasmussen had full access to all the data in the study and approved the final manuscript.
Financial Disclosure: Drs Zammit and Owen received contributions from pharmaceutical companies as honoraria for talks.
Funding/Support: Dr Zammit was funded through a Clinician Scientist Award from the National Assembly for Wales.
Role of the Sponsor: The National Assembly for Wales had no role in the design of the study, data collection, analysis, or manuscript preparation.

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