

IQ and Schizophrenia in a Swedish National Sample: Their Causal Relationship and the Interaction of IQ With Genetic Risk

Kenneth S. Kendler, M.D., Henrik Ohlsson, Ph.D., Jan Sundquist, M.D., Ph.D., Kristina Sundquist, M.D., Ph.D.

Objective: The authors sought to clarify the relationship between IQ and subsequent risk for schizophrenia.

Method: IQ was assessed at ages 18–20 in 1,204,983 Swedish males born between 1951 and 1975. Schizophrenia was assessed by hospital diagnosis through 2010. Cox proportional hazards models were used to investigate future risk for schizophrenia in individuals as a function of their IQ score, and then stratified models using pairs of relatives were used to adjust for familial cluster. Finally, regression models were used to examine the interaction between IQ and genetic liability on risk for schizophrenia.

Results: IQ had a monotonic relationship with schizophrenia risk across the IQ range, with a mean increase in risk of 3.8% per 1-point decrease in IQ; this association was stronger in the lower than the higher IQ range. Co-relative control analyses showed a similar association between IQ and schizophrenia in the general population and in cousin, half-sibling, and full-sibling pairs. A robust interaction was

seen between genetic liability to schizophrenia and IQ in predicting schizophrenia risk. Genetic susceptibility for schizophrenia had a much stronger impact on risk of illness for those with low than high intelligence. The IQ-genetic liability interaction arose largely from IQ differences between close relatives.

Conclusions: IQ assessed in late adolescence is a robust risk factor for subsequent onset of schizophrenia. This association is not the result of a declining IQ associated with insidious onset. In this large, representative sample, we found no evidence for a link between genius and schizophrenia. Co-relative control analyses showed that the association between lower IQ and schizophrenia is not the result of shared familial risk factors and may be causal. The strongest effect was seen with IQ differences within families. High intelligence substantially attenuates the impact of genetic liability on the risk for schizophrenia.

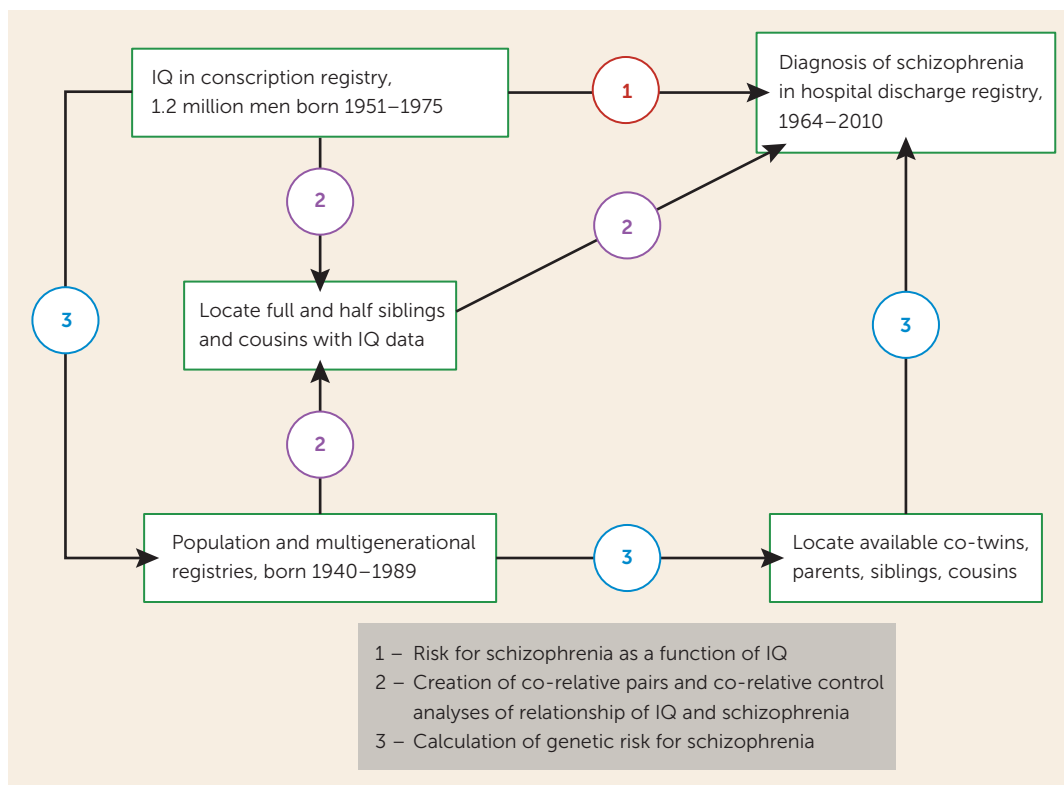
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Speculations about the nature of the relationship between IQ and severe psychiatric illness began in the early 1900s, shortly after the development of standardized intelligence tests (1, 2). A recent meta-analysis of 12 studies including over 750,000 subjects examined the prospective relationship between IQ and schizophrenia and concluded that IQ had a relatively consistent dose-response relationship with schizophrenia, with an increase in risk of ~3.7% per 1-point decrease in IQ (3). Here we undertake a further study of this question in a prospective sample larger than all the previously published studies combined.

We address four questions about the IQ-schizophrenia relationship, the first two of which attempt to refine earlier findings. First, can we confirm previous findings of an association of IQ and schizophrenia risk and rule out the possibility that this association reflects prodromal effects of an impending schizophrenic illness? Second, can we clarify, in more detail than previously possible, the nature of the “dose-response”

relationship between IQ and risk for schizophrenia? Is the association linear or nonlinear, and if nonlinear, is it stronger at lower or at higher IQs (3)? Furthermore, is the association monotonic, so that the lowest risk for schizophrenia is seen with the highest IQ? Or, as suggested by some previous analyses (3), is the function U-shaped, with the lowest risk at moderately high IQs and the highest IQ scores associated with a greater risk of illness?

We then examine two important questions about the IQ-schizophrenia association that, to our knowledge, have not been previously addressed. First, using a co-relative design (which selects pairs of relatives with discrepant risk factor exposures and examines their difference in a disease outcome), can we determine the degree to which the association between IQ and schizophrenia arises from shared familial/genetic factors or from a possible causal relationship? Second, what is the etiologic relationship between genetic liability to schizophrenia and premorbid IQ? Are these two risk factors

FIGURE 1. Key Features of the Research Design^a

^a Data were obtained from four major Swedish national registries: the Military Conscription Register, the Total Population Register, the Multi-Generation Register, and the Swedish Hospital Discharge Register. The three major analyses of this study are illustrated here. Examining the risk for schizophrenia as a function of prior IQ is accomplished by matching information from the conscription registry, via path 1, to the hospital discharge registry. Performing co-relative analyses of the relationship between IQ and schizophrenia required that we obtain male-male co-relative pairs with IQ data from the population, multigeneration, and conscription registries and then match those pairs with the discharge registry. These steps are indicated as path 2. Calculating the genetic risk for schizophrenia, which we used to jointly predict, along with IQ, the risk for schizophrenia, required the location of available co-twins, parents, siblings, and cousins of individuals from the conscription registry in the population and multigeneration registries and then matching them to the discharge registry. These steps are indicated as path 3.

additive in their effect, or do they interact? If they interact, does a high genetic liability to schizophrenia have a greater impact on those with low, or those with high IQ?

METHOD

We used data from multiple Swedish nationwide registries linked by the unique individual Swedish 10-digit personal identification number assigned at birth or immigration to all Swedish residents; identification numbers were replaced by random numbers to preserve confidentiality. As illustrated in Figure 1, the analyses reported here were largely based on four Swedish registries: the Military Conscription Register, which includes cognitive assessments for nearly all 18-year-old men in Sweden; the Total Population Register, containing annual data on family status; the Multi-Generation Register, which provides information on family relations; and the Swedish Hospital Discharge Register, which contains data on all hospitalizations in Sweden since 1964. We also used data from the Swedish Mortality Register to calculate the follow-up time in our hazard models. The Swedish military service conscription examination involves a full medical assessment that includes

cognitive function (IQ), measured by four subtests representing logical, spatial, verbal, and technical abilities. During the years covered by this study, this examination was required by law. Among all men born in Sweden, only those with serious medical conditions or disabilities were excused from the conscription examination (~4.2% of individuals). The global IQ score, derived from a summation of the four subtests, was standardized to give a Gaussian-distributed score between 1 and 9, which we translated into units of the Wechsler Adult Intelligence Scale with a mean of 100 and a standard deviation of 15.

Schizophrenia was defined in the Swedish Hospital Discharge Register as ICD8 codes 295.1, 295.2, 295.3, 295.5, and 295.6; ICD9 codes 295B, 295C, 295D, 295G, and 295X; and ICD10 codes F20.0, F20.1, F20.2, F20.3, F20.5, F20.8, and F20.9. Nonaffective psychosis was defined as ICD8 codes 295, 297, 298.2, 298.3, and 298.9; ICD9 codes 295, 297, 298C, 298E, 298W, and 298X; and ICD10 code F2. The ratio of nonaffective psychosis to schizophrenia cases in our sample was 2.14:1. We obtained ethical approval for this study from the Regional Ethical Review Board of Lund University.

The database began with all male individuals in the Swedish population born between 1951 and 1975 who were registered in

the Military Conscription Register, a total of 1,324,117 individuals. For 85,432 of these, no information was available for the IQ variable; 33,376 were missing data for the conscription examination; and 326 had a registration of schizophrenia prior to their conscription examination. In total, we investigated 1,204,983 male individuals, representing 87.2% of all male individuals born in Sweden between 1951 and 1975 who survived to age 18.

We used Cox proportional hazards models to investigate the future risk for schizophrenia in individuals as a function of their IQ score. Robust standard errors were used to adjust the 95% confidence intervals, as we had several individuals from the same family. Follow-up time in years was measured from year of conscription examination until year of first registration for schizophrenia, death, emigration, or end of follow-up (year 2010), whichever came first. In all models, we investigated the proportionality assumption. In a second step, we wanted to compare the results from the entire population with the results from a co-relative design. By means of the Swedish Multi-Generation Register, we identified all full-sibling, half-sibling, and first-cousin pairs. Using stratified Cox proportional hazards models, we performed three analyses on all full-sibling, all half-sibling, and all first-cousin pairs that did not have the same IQ score from the conscription registry, with a separate stratum for each relative pair. The co-relative design allowed us to contrast the rates of schizophrenia in relatives with different levels of IQ. The stratified Cox proportional hazards models provide a hazard ratio for IQ that is adjusted for the familial cluster and therefore accounts for an array of shared genetic and environmental factors.

To investigate the etiologic relationship between genetic liability to schizophrenia and IQ, we calculated a genetic liability score for schizophrenia. First, we calculated the morbid risk for schizophrenia for the population born between 1940 and 1989 using an abridged Weinberg age correction (4). We defined three age groups as the first, the middle two (second and third), and the fourth quartiles of the age distribution of first schizophrenia registration: <28 years, weighted 0; 28–42 years, weighted 0.5; and >42 years, weighted 1. Next, we performed a logistic regression analysis based on information from the Swedish population born between 1940 and 1989 ($N=5,646,776$) and their relatives (monozygotic twins, dizygotic twins, full siblings, half siblings, mother, father, and cousins). The model outcome variable was schizophrenia, and the predictor variable was the morbid risk of schizophrenia among the different relative types. The resulting beta weights for the genetic liability score, which followed quantitative genetic expectations, are listed in Table S1 in the data supplement that accompanies the online edition of this article. We did not use standard family history scores (5) because they pool relatives, thereby ignoring the large impact on risk of schizophrenia in specific relatives resulting from fitness effects (6, 7). We generated the beta weights in the same sample to which we applied them. While this traditionally might result in “overfitting,” this is a minimal concern when the entire population is being assessed. This model produced a predicted probability for schizophrenia ranging

between 0.36% and 79%, termed the genetic liability score. We repeated this approach to assess genetic liability to nonaffective psychosis (see Table S2 in the online data supplement).

We sought to examine the interaction between IQ and genetic liability on risk for schizophrenia. Along with Rothman et al. (8), we favor a risk difference over a risk ratio approach to this question because it adopts a public health perspective, asking whether more cases of illness will arise when individuals at low versus high disease liability from one factor (genetic risk) are exposed to low versus high levels of another factor (IQ) (9). Therefore, we analyzed interactions using an identity link function. In the first model, we estimated the interaction between IQ and genetic liability using the identity link. We then sought to investigate whether this interaction was driven by between-family or within-family IQ effects. Within each set of full siblings, we calculated the between and the within value of IQ (the between value is the mean value for each set of full siblings, and the within value is each sibling's deviation from the mean value in the sibling set). In these models, the genetic liability was averaged over all siblings within each set of siblings. We then performed a regression model using the identity link and robust standard errors, with the genetic liability score, the between-sibling-set IQ score, the within-sibling-set IQ score, and the two interaction terms: one with the between IQ score and the genetic liability score, and one with the within IQ score and the genetic liability score. We could then see if the interaction effect was due to between or within IQ effects, as the genetic liability score was held constant for all siblings within a sibling set. All statistical analyses were performed using SAS 9.3 (SAS Institute, Cary, N.C.).

RESULTS

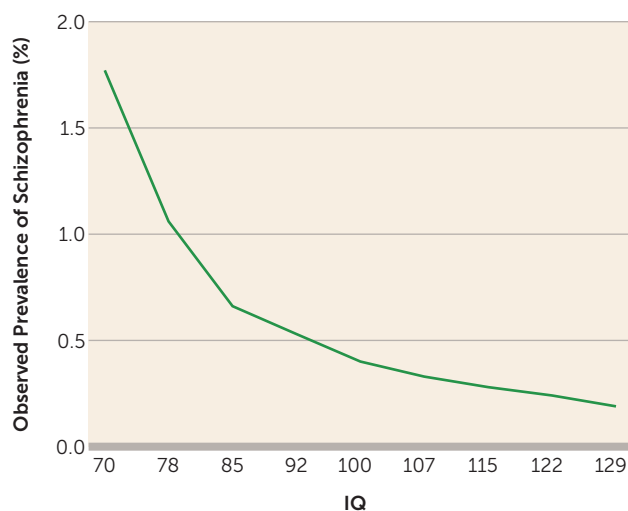
The Nature of the IQ-Schizophrenia Relationship

Our first analyses examined, in all males born between 1951 and 1975 for whom conscription registry data were available ($N=1,204,983$), whether an onset of schizophrenia was recorded in the hospital discharge registry after the conscription examination (path 1 in Figure 1). Such an onset was found in 0.49% of these individuals ($N=5,948$). The risk for schizophrenia in each of the IQ deciles declined monotonically (Figure 2), although the slope of the decline was steeper in the lower than in the higher IQ range.

A linear model fitted to these data produced a hazard ratio of 0.962 (95% CI=0.960–0.964), indicating an increase of 3.8% in risk for schizophrenia per 1-point decrease in IQ. We next added a quadratic function to capture the steeper, then more shallow, function seen in Figure 2. It was also significant, producing the following model: linear effect, hazard ratio=0.967 (95% CI=0.965–0.969); quadratic effect, hazard ratio=1.001 (95% CI=1.000–1.001).

The Possible Effect of a Prodrome

One possible mechanism for an association between IQ and schizophrenia risk would be a decline in IQ as individuals entered a prodromal state associated with an insidious onset.

FIGURE 2. Observed Prevalence of Schizophrenia as a Function of Premorbid IQ Score in a Swedish National Sample^a

^a Schizophrenia was assessed using hospital diagnoses; only onsets that occurred after IQ testing were included.

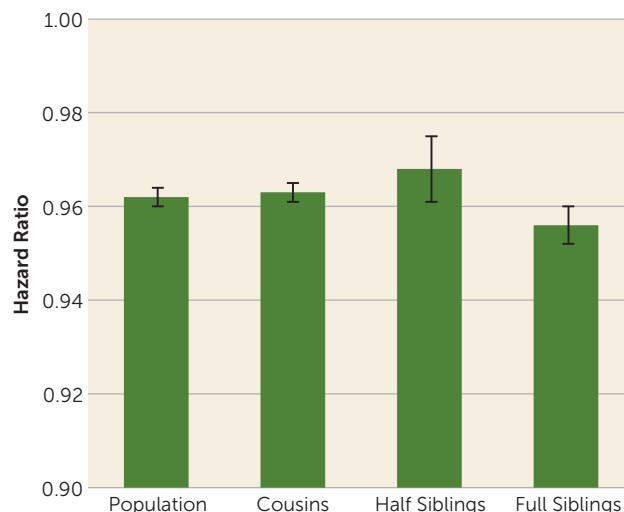
If this mechanism were important, then the IQ-schizophrenia association should decline substantially if we censored onsets of schizophrenia occurring soon after IQ testing. We repeated analyses predicting the linear risk for first-onset of schizophrenia in those who were free of recorded schizophrenia episodes during the 5-year period after administration of the IQ test (N=682, 11% of all cases). The linear association (hazard ratio=0.963, 95% CI=0.961–0.965) was nearly identical to that seen initially.

Co-Relative Analyses

For our co-relative analyses, we located male-male full-sibling, half-sibling, and cousin pairs from the population and multigenerational registries for whom IQ data were available in the conscription registry and matched them to the discharge registry (path 2 in Figure 1). For simplicity, our co-relative analyses utilized the linear model only. In our entire sample, the hazard ratio for schizophrenia was 0.962 (95% CI=0.960–0.964). As seen in Figure 3, the observed schizophrenia-IQ associations in co-relative pairs with differing IQs (that is, their IQ scores were not in the same decile) were as follows: the hazard ratio was 0.963 (95% CI=0.961–0.966) for first-cousin pairs (total N=514,692; concordant affected N=12; discordant N=3,643; concordant unaffected N=511,037); the hazard ratio was 0.968 (95% CI=0.961–0.974) for half-sibling pairs (total N=52,137; concordant affected N=3; discordant N=644; concordant unaffected N=51,490); and the hazard ratio was 0.956 (95% CI=0.952–0.960) for full-sibling pairs discordant for IQ (Total N=232,648; concordant affected N=52; discordant N=2,239; concordant unaffected N=230,357). We were unable to estimate this effect in monozygotic pairs because of the very small available sample size (six pairs discordant for both IQ and schizophrenia).

Interaction Between IQ and Genetic Liability

Using the population and multigeneration registries, we located all available co-twins, parents, full siblings, half siblings, and first

FIGURE 3. Hazard Ratios for Schizophrenia as a Function of Premorbid IQ Score, in the General Population and in First Cousins, Half Siblings, and Full Siblings Discordant for IQ Score^a

^a Within these relative pairs with differing IQs, the association between IQ and schizophrenia is as strong as that seen in the general population. Error bars indicate 95% confidence interval.

cousins of our sample and matched these individuals to the discharge registry to calculate a genetic liability score (path 3 in Figure 1), which equaled the weighted function of the risk for schizophrenia in relatives. As seen in Table 1, our regression model, implementing a risk difference approach to interactions, showed strong main effects for both IQ and genetic liability score and a robust negative interaction: -0.0019 (SE= -0.0001 ; $p<0.0001$). Figure 4 illustrates the predicted risk for schizophrenia as a function of premorbid IQ at five levels of increasing genetic liability. In the lower IQ range, large differences in risk for schizophrenia are seen in individuals with varying levels of genetic liability. However, at higher IQs, the impact of genetic liability on risk for schizophrenia decreases substantially and nearly disappears at the highest IQ level.

We repeated these analyses using a broader definition of genetic liability based on rates of nonaffective psychosis in relatives. The results were similar (Table 1), although differences in risk at the highest IQ level were somewhat greater than those seen with the narrower definition of genetic liability (see Figure S1 in the online data supplement).

Finally, we examined in full siblings (488,794 individuals from 224,003 families) the prediction of schizophrenia onset as a function of 1) genetic liability to schizophrenia, 2) a within-sibship IQ effect, 3) a between-sibship IQ effect, and 4) the interactions between genetic liability and the within- and between-sibship IQ effects. As shown in Table 2, while both interaction effects were significant, the interaction between genetic liability to schizophrenia and the within-sibship IQ effect was an order of magnitude stronger than that seen between genetic liability and the between-sibship IQ effects. These results suggest that, congruent with our findings in the co-relative analyses, the overall interaction observed in our sample between IQ and genetic liability to schizophrenia is driven

TABLE 1. Prediction of Future Risk for Schizophrenia From IQ, Genetic Liability to Schizophrenia, and Their Interaction, Using an Identity Link Function

Measure	Genetic Liability Assessed Using Schizophrenia in Relatives			Genetic Liability Assessed Using Nonaffective Psychosis in Relatives		
	Beta	SE	p	Beta	SE	p
Intercept	0.0053	0.0002	<0.0001	0.0062	0.0002	<0.0001
IQ	−0.0007	0.0001	<0.0001	−0.0006	0.0001	<0.0001
Genetic liability score	0.0174	0.0004	<0.0001	0.0147	0.0004	<0.0001
Interaction of genetic liability and IQ	−0.0019	0.0001	<0.0001	−0.0019	0.0001	<0.0001

largely by a greater pathogenic effect of genetic risk on individuals whose IQ is lower compared with their close relatives.

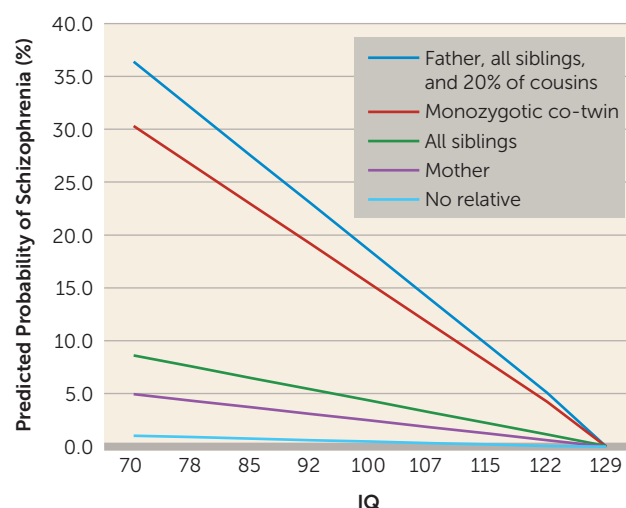
DISCUSSION

We sought in this study to address, in a nearly complete sample of Swedish males born between 1951 and 1975, four questions about the relationship between IQ as assessed in late adolescence and subsequent risk for schizophrenia. First, we sought to replicate previous findings of an association between IQ and future risk for schizophrenia. A linear hazard ratio model showed an increase in risk of onset of 3.8% per 1-point decrease in IQ. This estimate is nearly identical to the estimate of 3.7% obtained from the most recent meta-analysis (3). We also examined whether this association declined if we began our follow-up 5 years after IQ assessment, thereby eliminating most schizophrenia cases that would have been in a prodromal stage at testing. Congruent with a previous Finnish study that examined a 1-year “blocked out” interval (10), we found no change in the association with our delayed follow-up period. The observed IQ-schizophrenia association does not, to any appreciable degree, appear to result from declines in intelligence in individuals undergoing an insidious onset of schizophrenia at the time of testing.

Our second goal was to clarify, with our large sample, the nature of the “dose-response” relationship between IQ and risk for schizophrenia. Inspection of the raw data (Figure 2) revealed a monotonic relationship, beginning with a relatively steep slope in the low IQ range and then a decline in slope as IQ increased. Model fitting, consistent with results of the recent meta-analysis (3), verified these impressions, showing both a significant linear and a significant quadratic function.

In an examination of the five strongest previous studies of the IQ-schizophrenia relationship, three of the studies showed a greater risk of illness in individuals at the highest IQ levels compared with those in the moderately high IQ levels (~120) (3). A Finnish study found substantial enrichment for cases of schizophrenia among those with the highest level of academic achievement in high school (11). Such findings suggest a relationship between schizophrenia and “genius” (12–14). However, our results show no evidence for this. Risk for schizophrenia in our highest IQ category (mean IQ, 129; 0.19% of the sample) was lower than that in the next highest group (mean IQ, 122; 0.24% of the sample).

Third, we sought to clarify the nature of the association between IQ and schizophrenia. Both intelligence and

FIGURE 4. Predicted Probability of Schizophrenia as a Function of Premorbid IQ Score and Five Levels of Genetic Liability to Schizophrenia, as Predicted by Risk of Illness in Close Relatives^a

^a The five levels correspond to the following familial configurations: 1) no relatives affected with schizophrenia, 2) a mother affected, 3) all full siblings affected, 4) an affected monozygotic co-twin, and 5) a father affected, all full siblings affected, and 20% of first cousins affected.

TABLE 2. Prediction of Future Risk for Schizophrenia From Genetic Liability to Schizophrenia, a Within-Sibship Effect of IQ, a Between-Sibship Effect of IQ, and Their Interaction, Using an Identity Link Function

Measure	Between/Within Model		
	Beta	SE	p
Intercept	−0.006	0.0016	0.0003
Between-sibship effect of IQ	−0.0004	0.0003	0.2254
Within-sibship effect of IQ	0.0074	0.0012	<0.0001
Genetic liability score	0.0442	0.0043	<0.0001
Interaction (within) ^a	−0.0239	0.0032	<0.0001
Interaction (between) ^b	−0.0021	0.0008	0.0093

^a Interaction between the within-sibship effect of IQ and genetic liability to schizophrenia.

^b Interaction between the between-sibship effect of IQ and genetic liability to schizophrenia.

schizophrenia risk are strongly familial, largely because of genetic factors (15–17). Therefore, the IQ-schizophrenia association could plausibly arise because of genetic and/or familial-environment factors predisposing both to low IQ and risk for schizophrenia. This hypothesis is consistent with evidence that 1) several candidate genes for schizophrenia are associated with lower IQ (18, 19); 2) identified copy number variants increase risk both for schizophrenia and for intellectual

disability (20); 3) an exome study in schizophrenia found enrichment in intellectual disability for loss-of-function de novo mutations (21); 4) children at high genetic risk for schizophrenia were shown to have lower IQ (22); and 5) one previous twin study demonstrated a strong negative genetic correlation between IQ and schizophrenia liability (23).

Our results were inconsistent with this hypothesis. Within pairs of relatives with differing IQs, the association between intelligence and schizophrenia was as strong as in the general population. Furthermore, no trend was seen for the association to be attenuated (that is, for the hazard ratio to approach unity) in siblings who share half their genes and are typically reared together compared with that seen in cousin pairs (who share one-eighth of their genes and are rarely reared together), or compared with that seen in the general population with no control for familial influences. However, our results are broadly congruent with a previous Swedish twin-sibling analysis that reports a very modest negative genetic correlation between IQ, as assessed at conscription, and schizophrenia (24). The results of our co-relative analyses are most consistent with the hypothesis that some environmental risk factors not shared with close relatives have an impact on brain functioning in a way that both lowers IQ and predisposes to risk for schizophrenia.

Our final goal was to illuminate the nature of the joint effects of genetic liability to schizophrenia and IQ on the risk for schizophrenia. We were particularly interested in distinguishing between additive effects—where liability to schizophrenia would reflect the independent contributions of genetic risk and IQ—and an interactive model in which the impact of genetic liability to schizophrenia is moderated by IQ. If we found an interactive model, would sensitivity to genetic effects be greatest in those with low or with high IQ?

Our results robustly supported an interactive rather than the additive model for the joint effects of genetic liability and IQ on risk for schizophrenia. Furthermore, the interaction arose because individuals with low IQ were much more sensitive to the effect of genetic liability than those with high IQ. That is, high IQ substantially attenuated the impact of genetic liability on risk for schizophrenia. We extended these findings by examining a broader definition of genetic liability as assessed in relatives (nonaffective psychosis), which produced similar findings. Follow-up analyses demonstrated that, consistent with our co-relative findings, the IQ-genetic liability interaction arose largely from IQ differences between close relatives.

This is not the place for speculative theories about why the still poorly understood genetic pathways of risk for schizophrenia might be more penetrant in individuals with low intelligence than in those with high intelligence. If our results are replicated, we can provide one important clue for neuroscientists and molecular geneticists. The changes in brain function that are expressed as low or high intelligence, and that convey sensitivity or resistance to the pathogenic effects of genetic liability to schizophrenia, appear to arise environmentally and will be seen most clearly in close relatives who differ in intelligence.

We are not the first to examine the relationship between IQ assessed in Swedish conscripts and subsequent risk for schizophrenia. Gunnell et al. (25) and Zammit et al. (26) examined 109,643 and 50,087 conscripts evaluated in the periods 1990–1997 and 1969–1970, respectively. As expected, our results on the association of IQ and schizophrenia are congruent with their findings, both of which were included in the recent meta-analysis (3). The agreement between our results and those of the meta-analysis are thus slightly biased because of sample sharing, although only 9.6% of schizophrenia cases from the meta-analysis came from these two Swedish studies (3).

Limitations

These results should be interpreted in the context of five potentially important methodological limitations. First, our sample was restricted to Swedish males. Second, we required a single hospital diagnosis of schizophrenia. Two studies found, using record reviews (27) and diagnostic interviews (28), that 96% and 94% of Swedish cases with hospital diagnoses of schizophrenia, respectively, met DSM-IV criteria for schizophrenia. When we narrowed our diagnosis to require at least two hospital diagnoses, the prevalence declined to 0.37%. Neither the linear effect of IQ on schizophrenia (hazard ratio=0.962, 95% CI=0.959–0.964) nor the results of the full-sibling co-relative control analyses (hazard ratio=0.957, 95% CI=0.952–0.962) changed appreciably. Third, IQ was available only as a global score in nine categories, the uppermost with a mean of 129. Therefore, we may have failed to detect small increases in risk for schizophrenia associated with very high IQ scores or with high levels of specific cognitive abilities. Fourth, using a planned risk-difference approach (9), we observed a robust interaction in predicting schizophrenia from IQ and genetic liability. However, when these results were analyzed using a risk ratio approach, as implemented in Cox proportional hazards models, no significant interaction was found. To a first approximation, the impact of IQ and genetic liability to schizophrenia on risk for schizophrenia in this sample is the product of the two individual risks, not the sum. Fifth, diagnostic practices may differ by social class and, indirectly, by IQ. Such a bias is unlikely to explain much of the observed IQ-schizophrenia association because in this sample, IQ also strongly predicted the hazard ratio for other nonaffective psychoses (hazard ratio=0.971, 95% CI=0.969–0.972).

CONCLUSIONS

IQ as assessed in late adolescence is a robust predictor for subsequent risk for schizophrenia, and this association is not the result of a declining IQ associated with insidious onset. The nature of the association is monotonic, although it is stronger in the lower than in the higher IQ range. In our large, representative sample, we found no evidence for a link between genius and schizophrenia. Rather, the risk for schizophrenia was lowest in the group with the highest premorbid IQ. Co-relative control analyses show that the IQ-schizophrenia association does not result from shared genetic or familial-environmental

risk factors and may be causal. In a risk-difference model, a robust interaction was seen between genetic liability to schizophrenia and IQ in predicting schizophrenia risk. Genetic susceptibility for schizophrenia had a much stronger impact on risk of illness for those with a low IQ compared to those with a high IQ. This IQ-genetic liability interaction arose largely from IQ differences between close relatives.

AUTHOR AND ARTICLE INFORMATION

From the Virginia Institute for Psychiatric and Behavioral Genetics, the Department of Psychiatry, and the Department of Human and Molecular Genetics, Virginia Commonwealth University, Richmond; the Center for Primary Health Care Research, Lund University, Malmö, Sweden; and the Stanford Prevention Research Center, Stanford University School of Medicine, Stanford, Calif.

Address correspondence to Dr. Kendler (kendler@vcu.edu).

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REFERENCES

1. Aylward E, Walker E, Bettes B: Intelligence in schizophrenia: meta-analysis of the research. *Schizophr Bull* 1984; 10:430-459
2. Woodberry KA, Giuliano AJ, Seidman LJ: Premorbid IQ in schizophrenia: a meta-analytic review. *Am J Psychiatry* 2008; 165:579-587
3. Khandaker GM, Barnett JH, White IR, Jones PB: A quantitative meta-analysis of population-based studies of premorbid intelligence and schizophrenia. *Schizophr Res* 2011; 132:220-227
4. Slater E, Cowie V: *The Genetics of Mental Disorders*. London, Oxford University Press, 1971
5. Milne BJ, Moffitt TE, Crump R, Poulton R, Rutter M, Sears MR, Taylor A, Caspi A: How should we construct psychiatric family history scores? A comparison of alternative approaches from the Dunedin Family Health History Study. *Psychol Med* 2008; 38:1793-1802
6. Risch N: Estimating morbidity risks in relatives: the effect of reduced fertility. *Behav Genet* 1983; 13:441-451
7. Kendler KS, MacLean CJ: The impact of altered fitness on the risk of illness in relatives. *Genet Epidemiol* 1989; 6:481-491
8. Rothman KJ, Greenland S, Lash TL: *Modern Epidemiology*, 3rd ed. Philadelphia, Lippincott Williams & Wilkins, 2008
9. Kendler KS, Gardner CO: Interpretation of interactions: guide for the perplexed. *Br J Psychiatry* 2010; 197:170-171
10. Tiihonen J, Haukka J, Henriksson M, Cannon M, Kiesepää T, Laaksonen I, Sinivuo J, Lönnqvist J: Premorbid intellectual functioning in bipolar disorder and schizophrenia: results from a cohort study of male conscripts. *Am J Psychiatry* 2005; 162:1904-1910
11. Isohanni I, Järvelin MR, Jones P, Jokelainen J, Isohanni M: Can excellent school performance be a precursor of schizophrenia? A 28-year follow-up in the Northern Finland 1966 birth cohort. *Acta Psychiatr Scand* 1999; 100:17-26
12. Waddell C: Creativity and mental illness: is there a link? *Can J Psychiatry* 1998; 43:166-172
13. Post F: Creativity and psychopathology: a study of 291 world-famous men. *Br J Psychiatry* 1994; 165:22-34
14. Nasar S: *A Beautiful Mind*. London, Faber and Faber, 1998
15. Bouchard TJJr, McGue M: Familial studies of intelligence: a review. *Science* 1981; 212:1055-1059
16. Deary IJ, Spinath FM, Bates TC: Genetics of intelligence. *Eur J Hum Genet* 2006; 14:690-700
17. Sullivan PF, Kendler KS, Neale MC: Schizophrenia as a complex trait: evidence from a meta-analysis of twin studies. *Arch Gen Psychiatry* 2003; 60:1187-1192
18. Luciano M, Miyajima F, Lind PA, Bates TC, Horan M, Harris SE, Wright MJ, Ollier WE, Hayward C, Pendleton N, Gow AJ, Visscher PM, Starr JM, Deary IJ, Martin NG, Payton A: Variation in the dysbindin gene and normal cognitive function in three independent population samples. *Genes Brain Behav* 2009; 8:218-227
19. Harrison PJ, Weinberger DR: Schizophrenia genes, gene expression, and neuropathology: on the matter of their convergence. *Mol Psychiatry* 2005; 10:40-68, 5
20. Guilmatre A, Dubourg C, Mosca AL, Legallic S, Goldenberg A, Drouin-Garraud V, Layet V, Rosier A, Briault S, Bonnet-Brilhault F, Laumonnier F, Odent S, Le Vacon G, Joly-Helas G, David V, Bendavid C, Poinot JM, Henry C, Impallomeni C, Germano E, Tortorella G, Di Rosa G, Barthelemy C, Andres C, Faivre L, Frébourg T, Saugier Veber P, Campion D: Recurrent rearrangements in synaptic and neurodevelopmental genes and shared biologic pathways in schizophrenia, autism, and mental retardation. *Arch Gen Psychiatry* 2009; 66:947-956
21. Fromer M, Pocklington AJ, Kavanagh DH, Williams HJ, Dwyer S, Gormley P, Georgieva L, Rees E, Palta P, Ruderfer DM, Carrera N, Humphreys I, Johnson JS, Roussos P, Barker DD, Banks E, Milanova V, Grant SG, Hannon E, Rose SA, Chambert K, Mahajan M, Scolnick EM, Moran JL, Kirov G, Palotie A, McCarroll SA, Holmans P, Sklar P, Owen MJ, Purcell SM, O'Donovan MC: De novo mutations in schizophrenia implicate synaptic networks. *Nature* 2014; 506:179-184
22. Dickson H, Cullen AE, Reichenberg A, Hodgins S, Campbell DD, Morris RG, Laurens KR: Cognitive impairment among children at-risk for schizophrenia. *J Psychiatr Res* 2014; 50:92-99
23. Touloupoulou T, Picchioni M, Rijdsdijk F, Hua-Hall M, Ettinger U, Sham P, Murray R: Substantial genetic overlap between neurocognition and schizophrenia: genetic modeling in twin samples. *Arch Gen Psychiatry* 2007; 64:1348-1355
24. Fowler T, Zammit S, Owen MJ, Rasmussen F: A population-based study of shared genetic variation between premorbid IQ and psychosis among male twin pairs and sibling pairs from Sweden. *Arch Gen Psychiatry* 2012; 69:460-466
25. Gunnell D, Harrison G, Rasmussen F, Fouskakis D, Tynelius P: Associations between premorbid intellectual performance, early-life exposures: and early-onset schizophrenia: cohort study. *Br J Psychiatry* 2002; 181:298-305
26. Zammit S, Allebeck P, David AS, Dalman C, Hemmingsson T, Lundberg I, Lewis G: A longitudinal study of premorbid IQ score and risk of developing schizophrenia, bipolar disorder, severe depression, and other nonaffective psychoses. *Arch Gen Psychiatry* 2004; 61:354-360
27. Lichtenstein P, Björk C, Hultman CM, Scolnick E, Sklar P, Sullivan PF: Recurrence risks for schizophrenia in a Swedish national cohort. *Psychol Med* 2006; 36:1417-1425
28. Ekholm B, Ekholm A, Adolfsson R, Vares M, Osby U, Sedvall GC, Jönsson EG: Evaluation of diagnostic procedures in Swedish patients with schizophrenia and related psychoses. *Nord J Psychiatry* 2005; 59:457-464