Stratifying empiric risk of schizophrenia among first degree relatives using multiple predictors in two independent Indian samples

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Abstract

Background—Schizophrenia (SZ) has an estimated heritability of 64–88%, with the higher values based on twin studies. Conventionally, family history of psychosis is the best individual-level predictor of risk, but reliable risk estimates are unavailable for Indian populations. Genetic, environmental, and epigenetic factors are equally important and should be considered when predicting risk in 'at risk' individuals.

Objective—To estimate risk based on an Indian schizophrenia participant's family history combined with selected demographic factors.

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Methods—To incorporate variables in addition to family history, and to stratify risk, we constructed a regression equation that included demographic variables in addition to family history. The equation was tested in two independent Indian samples: (i) an initial sample of SZ participants (N = 128) with one sibling or offspring; (ii) a second, independent sample consisting of multiply affected families (N = 138 families, with two or more sibs/offspring affected with SZ).

Results—The overall estimated risk was 4.31 ± 0.27 (mean standard deviation). There were 19 (14.8%) individuals in the high risk group, 75 (58.6%) in the moderate risk and 34 (26.6%) in the above average risk (in Sample A). In the validation sample, risks were distributed as: high (45%), moderate (38%) and above average (17%). Consistent risk estimates were obtained from both samples using the regression equation.

Conclusions—Familial risk can be combined with demographic factors to estimate risk for SZ in India. If replicated, the proposed stratification of risk may be easier and more realistic for family members.

Keywords

Schizophrenia; Genetic counseling; Familial; Risk

1. Introduction

Aggregation of schizophrenia in families was studied extensively by twin and adoption studies through which genetic basis of schizophrenia came to be accepted (Gottesman et al., 1987; Sullivan et al., 2003). The mechanism of inheritance is not clear (Tandon et al., 2008). Thus the family members of schizophrenia patients are at risk for the disorder, depending, to some extent, upon the type of relationship to a proband.

Empiric risks are derived from the observed frequencies of the condition of interest in relatives of a person who has the condition (Henquet et al., 2005; Krabbendam and van Os, 2005). Empiric risks for SZ using only family history for assessing risk are available (Kendler and Zerbin-Rudin, 1996; Niemi et al., 2004; Austin and Peay, 2006), but very few considered other biological and environmental factors. Moreover, most reliable risk estimates stem from studies of Caucasian samples. How these genetic and environmental risk factors interact for predicting risk in a particular individual is uncertain (Cougnard et al., 2007), but empiric risk for SZ is well established and risk charts are available as a rough guide to genetic counselors (Gottesman, 1991). In a Danish national register study, the heritability of liability of developing schizophrenia was estimated at 0.67 (95% confidence interval (CI) 0.64–0.71) (Wray and Gottesman, 2012). The risk for SZ among first-degree relatives ranged from 6% to 13% and for second-degree relatives from 2 to 4% (Bassett et al., 2009). In a review of family studies, McGue et al. used a multifactorial threshold model to estimate that the averaged recurrence risk for confirmed plus probable diagnoses of SZ in relatives was 12.84% for offspring and 3.46% for nieces and nephews (McGue et al., 1983).

Several authors reported simple behavioral interviews for prediction among high risk populations (Johnstone et al., 2005), incorporating neurobehavioral, structural, physiological, and neurochemical brain alterations (Keshavan et al., 2004; Tandon et al.,

2012), as well as cannabis use as risk factors for developing psychosis (Dragt et al., 2010), and studying them for prevention of psychosis (Fusar-Poli et al., 2013). Shah et al. developed a formula to predict schizophrenia using familial, neurobiological, socio-environmental, cognitive and clinical data (Shah et al., 2012).

Familial risk for SZ may be modified by exposure to environmental factors such as urban living, minority status, immigration, cannabis use, season of birth, low birth weight, prenatal exposure to certain infectious agents or to trauma (Golimbet et al., 2004; Henquet et al., 2005; Krabbendam and van Os, 2005; van Os et al., 2005a, b; Veling et al., 2008; Spauwen et al., 2004). Environmental risks for psychosis may act additively in vulnerable subjects (Cougnard et al., 2007) and as a function of severity of the Index patient's (IP's) illness (Gottesman et al., 1976), the latter estimated as total length of hospitalization and outcome on follow up (Gottesman and Shields, 1966). IP is associated with increased risk among blood relatives, presumably because the overall familial risk affects both variables (Valles et al., 2000).

Older paternal age at conception of the IP has been associated with an approximate doubling of the risk for developing SZ (Wohl and Gorwood, 2007), but the rationale is uncertain. Age (risk period for SZ ranges between 15 and 55 years) – (Gottesman and Erlenmeyer-Kimling, 2001; Hafner, 2000; Hodgkinson et al., 2001), and sex (males are at 1.4 fold greater risk of SZ than females) – (McGrath et al., 2004; Selten et al., 2003) are also factors that can modify risk, e.g., a greater lifetime risk of SZ was estimated in the relatives of female than those of male patients (Goldstein et al., 1992). There is an association between urban birth, upbringing (up to the age of 15) and an increased risk of developing SZ (Kirkbride et al., 2006; Lewis et al., 1992; Mortensen et al., 1999; McGuffin and Gottesman, 1999), but the cause for the increased risk is uncertain.

Multiple psychiatric illnesses in a single family or from both paternal and maternal lineage make risk calculation more complex (Gottesman and Shields, 1976). Risk may be expressed as probability and numbers, but individuals at all levels of education experience difficulty in understanding probability and data (Kendler and Zerbin-Rudin, 1996) particularly when presented numerically (Hallowell and Richards, 1997). In view of these problems, it has been suggested that numerical information should be replaced with simple verbal categorization of risk (i.e. high, moderate or above average risk) (Gottesman and Bertelsen, 1996). Klaning et al. (2016) repeated the original twin studies in Danish population using ICD-10 diagnostic criteria and reported increased heritability and less variance attributable to environmental factors but their sample size was relatively smaller (Klaning et al., 2016). Concerns and anxiety of relatives of patients with SZ were reduced with genetic counseling that utilized available empiric risk estimates (Costain and Bassett, 2012). Stratifying risk categorically while incorporating familial and environmental risk factors should make risk more understandable. Individuals considered at high risk can be offered more intensive education to inform their decisions towards disease prevention. In addition, this can help in following up high risk individuals and ascertain which risk factors provide more predictive power (Keshavan et al., 2004). Eventually, more nuanced conversations can be held and specific issues addressed, as desired.

There are no familial risk studies in India but there is evidence that the prevalence and incidence of schizophrenia is similar across the world (Ayesa-Arriola et al., 2013); risk factors are also similar, except for contributions from infectious agents. The present study was designed to stratify the risk of schizophrenia for first degree relatives of an index patient (IP) into above average, moderate and high risk categories to make it easier for family members to understand their risk for SZ in a less abstract fashion. To do so, we applied the risk stratification process described by Scheuner and Yoon (Scheuner et al., 2004; Kendler and Zerbin-Rudin, 1996), endorsed by the US Surgeon General for stratification of risk for complex diseases (Yoon et al., 2003). We evaluated our risk analysis scheme in two samples. The first sample was clinic based, prospectively recruited and included singly affected and multiply affected families. The second, independent sample for validation comprised multiply affected families recruited in previous research studies. We predicted that if our risk prediction equations were valid, members of the second sample would be estimated to have moderate or high risk values since two or members had already been affected.

2. Methods

2.1. Sample

2.1.1. Sample A (n = 144)—Participants were recruited from Dr. Ram Manohar Lohia Hospital (RMLH), New Delhi, India. Dr. R.M.L. Hospital is a combined primary, secondary and tertiary care hospital. Thus, patients with all levels of severity can seek treatment directly. Only a relatively small number of patients are referred by other departments. Thus, RML is essentially a General Hospital Psychiatry Unit, a variety of patients seek treatment from all over Delhi and indeed, North India.

Each consecutively registered patient diagnosed with SZ in the Psychiatry Outpatient Department was referred to the research staff by their treating physician following discussions between the physician and the patient. Participation was voluntary and required written informed consent. IPs diagnosed with SZ using DSM-IV-TR criteria (and no history of substance abuse, mental retardation or neurological illness, with or without family history of SZ) and at least one healthy sibling or offspring (18–60 years of age) were eligible for inclusion. The study was approved by the Institutional Ethics Committee of PGIMER-Dr R.M.L. Hospital.

2.1.2. Sample B (retrospective) (n = 138)—Families with two affected children, or a parent and offspring 'duo' affected with SZ who had participated in our earlier studies, where complete family pedigrees were available, were included (Thomas et al., 2011). Available demographic data from the Hindi Diagnostic Interview for Genetic Studies (DIGS) and Family Interview for Genetic Studies (FIGS) (see below) were used for the regression equation.

2.2. Assessment procedures

The following interview schedules were administered to all participants (records were available for sample B):

2.2.1. Diagnostic interview for genetic studies (Deshpande et al., 1998; Nurnberger et al., 1994)—This is a comprehensive semi-structured interview schedule that includes extensive clinical as well as demographic information. The DIGS is used extensively in National Institute of Mental Health (NIMH) sponsored genetic studies and is available on the net. The DIGS was administered to IPs, healthy siblings and offspring.

2.2.2. Family interview for genetic studies (Maxwell, 1992)—This semi-structured instrument obtains information on pedigree structure and family members, their history and psychiatric symptoms across major diagnostic categories. The FIGS was administered to affected IPs and available relatives of the family to record the maximum family information. In addition to family history details the informant provided information regarding other risk factors, including paternal age at birth of the IP, age at onset, use of cannabis or other illicit substances, rural/urban residence.

2.3. Consensus diagnoses

2.3.1. Diagnoses based on DIGS interviews—The Research Associate interviewing the participants synthesized data from the DIGS, as well as collateral information obtained from relatives. This information was discussed with the principal investigator, the consultant and co-investigators. A consensus diagnosis was established using DSM IV-TR criteria. In case of disagreement, further information was obtained and the US collaborators consulted. If consensus could not be attained, the participant was not included in the analysis.

2.3.2. Diagnoses based on FIGS interviews—To determine diagnoses based on FIGS interviews with relatives, best estimate lifetime psychiatric diagnoses according to the DSM-IV-TR criteria were determined independently and then finalized in a consensus meeting. The diagnoses of psychiatric illnesses were assigned according to the information available and categorized into four groups depending on reliability as follows:

i.   i If the reported affected members were available for detailed interview, we contacted them and administered the DIGS, using this and collateral information to diagnose the illness as described above.

ii.   ii If the affected member was not available and medical records and information regarding treatment was available, the diagnosis was established using the medical records.

iii.   iii If neither personal reports nor medical records were available diagnoses were arrived at after consensus using detailed information available on FIGS checklists.

iv.   iv If a consensus diagnosis could not be achieved but the reported history indicated a serious psychiatric illness, a broad category of 'Psychiatric Illness' was assigned.

3. Risk stratification

A risk equation for stratifying risk into three groups was developed based on family history risk stratification approach of the US Centers for Disease Control and Prevention (Yoon et

al., 2002) and existing empiric risk data. In addition, we selected age of the 'at risk' individual, gender of the IP and 'at risk' individual, and paternal age at birth of the 'at risk' individual (sibling or offspring) to determine their risk. All these variables influence risk significantly but the odds ratios, i.e. the magnitude of risk varies. The gender of the 'at risk' individual was not included in the list as there were substantially fewer women in the sample; their inclusion would likely have skewed the risk estimates. Many clinic based samples have an excess of male patients, likely reflecting a referral bias, but we cannot explain the male excess among the unaffected relatives.

By using the risk numbers given in earlier studies and relationship of 'at risk' individual (see Table 1 in review by Austin and Peay (2006)) baseline numbers were assigned. Based on previous studies reported in the literature, we derived a regression equation including risk factors namely relationship and number of affected individuals, age of 'at risk' individual, paternal age at birth and gender of 'at risk' individual for susceptibility.

Next, we applied this equation to data on each of the 'at risk' individuals (the siblings and offspring of IP) to obtain an "estimate of risk of illness". The following equation was used. Equation parameters are described in Table 1.

$$Y = \beta x_1 + \beta x_2 + \beta x_3 + \beta x_4$$
$$Y = \text{Total Risk}$$
$$\beta = 1;$$

The relationship numbers for x_1 were derived from the earlier studies (Gottesman et al., 1987; Kendler et al., 1993; Sullivan et al., 2003) compiled by (Austin and Peay, 2006). In this scheme, if only one sibling is affected, the risk is estimated at 9% and is equivalent to a baseline risk of 1; if a parent is affected, the risk for offspring is 1.444 times more than that of sibling, as risk for offspring is 13% and for sibling is 9% (13/9 = 1.444). Similarly, if one sibling and one parent are affected, then the ratio is 18: 9 as risk reported in studies in such cases is 18%. Similarly if one sibling and one non-parent are affected than the ratio is 1.2.

The total risk for each case was calculated using this equation. A distribution of these 'risk estimates' was obtained for all 'at risk' individuals (siblings and offspring of cases), and individuals were stratified into 'high' (more than mean + 1 standard deviation, SD), 'moderate' (between mean + 1 SD and mean − 1 SD), and 'above average' (less than mean − 1 SD) risk categories.

3.1. Independent test of the risk equation

Sample B (validation sample), consisted of 138 multiply affected families (more than one member affected with SZ, predominantly parent/child or sibling pairs), with all information required for testing the above equation, from a group of SZ subjects recruited in our previous studies. The older member of the pair – whether the parent or a sibling – was considered to be the IP and the younger member of the pair as 'at risk' sibling/offspring for whom the risk was to be calculated. Since these individuals had already been diagnosed with

SZ, the age at onset of SZ of the nominally 'at risk' individual was taken as the chronological age for calculating risk.

4. Results

4.1. Sample A

A total of 144 families consented for participation, but four were excluded after a consensus diagnosis of bipolar disorder rather than SZ was made for the IP. Eight relatives (offspring or siblings) declined. Of the remaining 132 families, four siblings were re-examined and diagnosed with SZ. Hence these individuals were excluded from analysis.

Thus, 128 first degree relatives remained in the analysis; siblings (n = 107; male, n = 77, female, n = 30), and 21 offspring (male, n = 20, female, n = 1) (Table 2). We compared IPs of sib group and of parents group on clinical variables. Parents had significantly later age at onset (35.48 ± 9.49 vs 25.14 ± 6.75, Z = 4.43, p <0.0001). The duration of illness and GAF scores were not significantly different between parent IP and sibling IP.

There were no adopted away offspring, all offspring were under the care of affected parent where applicable.

4.2. Risk analysis

Risk was calculated based on the regression equation and 'at risk' individuals (siblings/ offspring) were stratified in three groups (high, moderate and above average). The overall estimated risk among any siblings/offspring was 4.311 ± 0.269 (mean $\pm$ standard deviation, SD). The distribution of risk is presented in Table 2. There were 19 (14.8%) individuals in the high risk group, 75 (58.6%) in the moderate risk and 34(26.6%) in the above average risk (in Sample A). Least risk was called above average risk not mild as this sample was not from normal population but a within group estimate and one person in the family was already ill.

4.3. Independent test of Risk Equation in Sample B

The equation was applied and risk calculated. In this study population individuals were stratified into high, moderate and above average risk groups based on the means calculated on sample A. Thus, 45% of at risk sibs/offspring in Sample B were classified in the high risk group and 38% in the moderate risk group. Only 17% were in the above average risk group (in Sample B). The relative excess of high risk and moderate risk individuals in this multiply affected sample, compared with sample A is consistent with the fact that sample B includes only multiply affected families and provides confidence in our equation.

In the sample B, the age at onset was earlier for IPs of affected sib group compared with IPs of affected parent group.

5. Discussion

Risk calculation is an important and fundamental component of genetic counseling. The uncertainty associated with psychiatric disorders poses challenges for genetic counselors because the current scientific knowledge cannot provide conclusive information regarding

etiology, risk, or consequences of the disorder on any given individual or family (Austin and Peay, 2006; Cougnard et al., 2007).

We attempted to stratify the first degree relatives of SZ IPs into high, moderate and above average risk categories using a statistical formula, considering not only their family history, but also additional biological factors which affect risk. The lowest named above average risk was also at higher risk than general population as one member of the family was already affected. Consistent with predictions, the majority of the individuals 'at risk' (who had in reality already fallen ill in sample B) were classified by our equation into high or moderate risk categories. If additional valid risk factors are included in the formula, more accurate estimation of risk may be possible. The simple equation can potentially be used in clinical settings to address concerns of patients and their relatives regarding marriage, propagation which depends on risk. More risk factors can be incorporated in the equation if suitable data are available.

Sample: A was recruited from a hospital which caters to a large cosmopolitan population from all across Delhi and surrounding areas. Sample B was also collected over a period of fifteen years and from all across Delhi and surrounding areas (Bhatia et al., 2008; Bhatia et al., 2012). The family history data were collected not only from IPs but also from family members who accompanied the patients.

We were constrained to use estimates from European ancestry samples in our model as there is a paucity of Indian studies. Reassuringly, the available data indicate that the prevalence and incidence of schizophrenia are similar (Ayesa-Arriola et al., 2013). The WHO cross-national study (Jablensky et al., 1992) describes comparable morbid risk data, broad (1.10%) and narrow (Catego S +) = 0.30%. for their Chandigarh Urban sample. The broad corresponds to the equivalent of "definite plus probable". However an earlier review has argued that the incidence of schizophrenia varied between sites. Prevalence was estimated as 4.0 per 1000 and lifetime morbid risk was 7.2 per 1000 (McGrath et al., 2008).

There are some other limitations in our analyses. Living in urban areas has been reported to elevate risk for SZ in contrast to rural life (Lederbogen et al., 2011). This variable was not included as all the participants in the present study were urban dwellers. As precise dates of birth could not be recalled accurately by many participants, the season of birth (birth certificates are not routine in India), which is also a suggested risk factor (Niemi et al., 2004) could not be included. As cannabis or alcohol abuse was used as exclusion criteria for the IPs, these variables were not included in the risk estimates. Risk factors such as prenatal infection and substance use could not be included as there were no reliable indicators of prenatal infection; very few at risk individuals in our sample reported abusing alcohol (consistent our inclusion criteria). Including cases with clear DSM IV diagnoses may bias the results as those who did not fulfil DSM IV criteria were excluded. Biased recall remains another potential deficiency in these data, as face to face interviews were not conducted with all the relatives reported in family history. However at risk individuals and probands were interviewed thoroughly.

As this is an initial attempt to design a model, we elected to keep it relatively simple; e.g., an additive model was invoked. We adopted an additive model since this is a preliminary attempt to categorise risk. We recognise that risks may act in a multiplicative fashion or may have complex interactions. Additional testing and refinement of this model may be useful, as there are likely to be additional variables and more complex interactions. Therefore, the model may be employed in the clinic to provide an initial assessment of risk.

In conclusion, this is a first step to describe a simple process to categorise risk for SZ in a genetic counseling and clinical framework in nations such as India. If replicated, the proposed stratification of risk may be easier for family members to understand and to consider their risk realistically. Genetic counseling, at its heart, requires empiric risk calculation. Extensive available data regarding empiric risks for genetic transmission of many disorders for offspring and siblings are available, but they do not precisely address a common question posed by relatives, "What is the chance my son or daughter will have this condition, or what is the chance my sibling might also receive this diagnosis?". At the same time, it is sometimes difficult to grasp risk in terms of just numbers. Stratifying risk may make risk more understandable after incorporating environmental risk factors.

This can be a useful estimation tool in the hands of genetic counselors for counseling families of schizophrenia patients, but further refinement of the model is necessary. For example, more risk factors and more complex interactions may need to be incorporated in order to obtain more realistic estimates. This is a preliminary study of a carefully selected sample. Although one other group was used to validate our results, this model is not ready for use in routine clinical situations. This study is first risk analysis study in South Asia. This method can be used for large epidemiological studies for further refining risks in at risk population for schizophrenia in the region.

Acknowledgments

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Table 1

Equation parametersand associated risk numbers.

Symbol in equation	Risk factor		Risk estimate
x_1	Type and number of affected members	1 sibling	**1**
		1 parent	1.444 (13/9)
		1 sibling and 1 parent	1.888 (18/9)
		1 sibling and a non-parent relative	1.2
x_2	Age of 'at risk' person	**30**	1
		<30	1.1
x_3	Paternal a age at birth	**35**	1
		<35	1.5
x_4	Gender of the affected individual	Male	**1**
		Female	**1.02**

[a](Wohl and Gorwood, 2007).

Table 2

Demographic characteristics and distribution of risk categories in both samples of at risk individuals.

	Subsample	Sample Size	Gender (M/F)	Age	Paternal age at birth of at-risk individual
Sample A	Entire Sample	128	97/31	32.44 ± 10.16	30.58 ± 9.57
	High Risk	19	11/8	27.21 ± 7.78	40.37 ± 4.63
	Moderate risk	75	65/10	29.48 ± 9.66	31.07 ± 9.48
	Above Average Risk	34	21/13	41.56 ± 5.82	24.48 ± 6.8
Sample B	Entire Sample	138	82/56	23.12 ± 6.63	32.33 ± 11.02
	High Risk	62	34/28	21.83 ± 5.15	33.25 ± 11.19
	Moderate risk	52	35/17	22.31 ± 6.07	32.1 ± 12.8
	Above Average Risk	24	13/11	24.32 ± 7.45	34.42 ± 4.66

Ages listed as mean ± standard deviation.