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Original Research

The Effect of Paternal Age on Relapse in First-Episode Schizophrenia

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Objective: Multiple etiological and prognostic factors have been implied in schizophrenia and its outcome. Advanced paternal age has been reported as a risk factor in schizophrenia. Whether this may affect schizophrenia outcome was not previously studied. We hypothesized that advanced paternal age may have a negative effect on the outcome of relapse in schizophrenia.

Method: We interviewed 191 patients with first-episode schizophrenia and their relatives for parental ages, sociodemographic factors at birth, birth rank, family history of psychotic disorders, and obstetric complications. The outcome measure was the presence of relapse at the end of the first year of treatment.

Results: In the 1-year follow-up period, 42 (22%) patients experienced 1 or more relapses. The mean paternal age was 34.62 years (SD 7.69). Patients who relapsed had significantly higher paternal age, poorer medication adherence, were female, and were hospitalized at onset, compared with patients who did not relapse. A multivariate regression analysis showed that advanced paternal age (OR 1.05, 95% CI 1.01 to 1.10), medication nonadherence (OR 2.37, 95% CI 1.12 to 4.99), and female sex (OR 2.44, 95% CI 1.14 to 5.24) independently contributed to a higher risk of relapse. Analysis between different paternal age groups found a significantly higher relapse rate with paternal age over 40.

Conclusions: Advanced paternal age is found to be modestly but significantly related to more relapses, and such an effect is the strongest at a cut-off of paternal age of 40 years or older. The effect is less likely to be mediated through less effective parental supervision or nonadherence to medication. Other possible biological mechanisms need further explorations.

L'effet de l'âge paternel sur la rechute lors du premier épisode de schizophrénie

Objectif : De multiples facteurs étiologiques et pronostiques sont impliqués dans la schizophrénie et son issue. L'âge paternel avancé a été signalé comme étant un facteur de risque de la schizophrénie, mais il n'a pas été déterminé si ce facteur peut influer sur l'issue de la schizophrénie. Nous avons émis l'hypothèse que l'âge paternel avancé peut avoir un effet négatif sur l'issue d'une rechute de la schizophrénie.

Méthode : Nous avons interviewé 191 patients au premier épisode de schizophrénie et leurs familles au sujet de l'âge des parents, des facteurs sociodémographiques à la naissance, du rang de naissance, des antécédents familiaux de troubles psychotiques, et des complications obstétriques. La mesure du résultat était la présence d'une rechute à la fin de la première année de traitement.

Résultats : Sur une période de suivi d'un an, 42 patients (22 %) ont connu 1 ou plusieurs rechutes. L'âge paternel moyen était de 34,62 ans (ET 7,69). Les patients qui rechutaient avaient un âge paternel significativement plus élevé, une mauvaise observance des médicaments, étaient de sexe féminin, et étaient hospitalisés au début de la maladie, comparativement aux patients qui ne rechutaient pas. Une analyse de régression multivariée a montré que l'âge paternel avancé (RC 1,05; IC à 95 % 1,01 à 1,10), la non-observance des médicaments (RC 2,37; IC à 95 % 1,12 à 4,99) et le sexe féminin (RC 2,44; IC à 95 % 1,14 à 5,24) contribuaient indépendamment à un risque de rechute plus élevé. L'analyse entre les différents groupes d'âge paternel a révélé un taux de rechute significativement plus élevé lorsque l'âge paternel dépassait 40 ans.

Conclusions : L'âge paternel avancé est relié modestement mais significativement à plus de rechutes, et cet effet est le plus marqué au seuil de l'âge paternel supérieur à 40 ans ou plus. Cet effet est moins probablement produit par une supervision parentale moins efficace ou la non-observance des médicaments. D'autres mécanismes biologiques possibles doivent être explorés.

The outcome of schizophrenia is subject to the influence of factors ranging from biological to psychosocial aspects.[1–3] After clinical stabilization, where positive psychotic symptoms are expected to have largely subsided, other aspects of the illness, such as relapse, become increasingly pertinent in the course of recovery.[4–7] The re-emergence of psychotic symptoms is distressing to the patients and their families,[8] and some relapses may even lead to treatment resistance.[9] In a recent meta-analytic review on 109 relapse predictors, Álvarez-Jiménez et al[10] identified medication discontinuation, persistent SUD, caregivers' critical comments, and premorbid adjustment to be significant. Further evidence within the early intervention services in different countries has also confirmed these findings.[11–13] The continual identification of predictors for relapse, especially in the early phase of the disorder, is therefore the logical next step in research.[10,14]

Studying etiological factors not only helps us to understand the illness but also suggests ways to find potential subgroups of the disorder that may affect clinical management.[15–17] Advanced paternal age has been reported as a risk factor in disease development in several birth and army cohorts,[18–22] and as a predisposing factor for a particular subtype of schizophrenia.[23–26] Interestingly, a recent meta-analysis has reported both older (30 years or older) and younger (younger than 25 years) fathers increased the risk of schizophrenia; and, in particular, younger paternal age effect was found among male but not female offspring, indicating the potential confounding effect of sex.[27]

Clinical Implications

- Advanced paternal age (particularly 40 years and older) has a negative effect on relapse following FEP, even after controlling for medication discontinuation and sex.
- Our findings raise an interesting research question of how advanced paternal age might contribute to possible biological and psychosocial mechanisms leading to relapse.

Limitations

- The exact timing of relapse was not measured.
- The relatively short follow-up period also limited the observation. Hence observation may only allow for distinction between a minority of the patients with more serious illness and those running a more benign course.
- The potential confounding variable of premorbid adjustment, caregivers' negative comments, and substance abuse were not measured.

Abbreviations

AP	antipsychotic
DUP	duration of untreated psychosis
EASY	Early Assessment Service for Young people with psychosis
FEP	first-episode psychosis
IRAOS	Interview for the Retrospective Assessment of the Onset of Schizophrenia
OC	obstetric complication
PANSS	Positive and Negative Syndrome Scale
SUD	substance use disorder

At present, many studies focus on paternal age as an etiological factor of schizophrenia. Whether paternal age has any effect on the clinical course of illness (for example, relapse) in schizophrenia has not been explored. Evidence has begun to suggest that patients with advanced paternal age have more severe psychotic symptoms after medication withdrawal.[26] The preliminary data call for a need to further examine the neurobiological factors, symptoms, treatment effects, and course of illness in patients with older fathers, which may lead to a meaningful differentiation between subtypes of the disorder.[26] Therefore, we consider paternal age to be a probable prognostic indicator adversely influencing the outcome of psychotic relapse in schizophrenia.

Examining the role of advanced paternal age in early relapse within 12 months from the start of treatment is important because this is the time when most patients would have remitted from the first episode and embarked on a rehabilitation program or resumed work and (or) study. We

therefore hypothesized that patients with older fathers have more relapses at 1-year follow-up. We speculated that any identified effect of paternal age in relapse to be unrelated to medication adherence and sex, and that the main hypothesis would still stand when potential confounding factors were considered.

Methods

Subjects

Subjects were recruited consecutively as they presented to the EASY clinics for follow-up at Queen Mary Hospital and Pamela Youde Nethersole Eastern Hospital. EASY is a specialized early intervention service for FEP patients aged younger than 26 years old.[28] Patients came from a catchment area within Hong Kong serving a population of 1.3 million. Intervention consisted of the use of low-dose APs, comprehensive outpatient and community-based care, and designated case workers working with a standardized psychoeducation program.[28] Subjects were eligible for our study if they were suffering from first-episode schizophrenia at initial presentation to the service and fulfilled the Diagnostic and Statistical Manual of Mental Disorders criteria[29] for schizophrenia on review by the end of the first year of treatment. Patients with a history of special school attendance; physical conditions, such as brain damage, delusional disorders, and substance-related psychotic disorders; or those with known SUD during the first year of treatment were excluded. Patients with significant comorbid SUD or substance-related psychotic disorders were excluded, as the rate of substance abuse among remitted FEP patients in Hong Kong is relatively low. The study was approved by the institutional review boards at each site and all participants provided written informed consent.

Assessments

Basic demographic information, including sex, age at study entry, and age at onset, was collected. In evaluation of occupational functioning, the exact nature of occupation was asked (for example, primary school teacher, account clerk, or cleaner) and categorized into professional, high-skilled, skilled, and unskilled work, student, and unemployed.

Relapse was defined by a significant deterioration in positive symptoms (delusions, hallucination, and thought disorder) that led to a change in medication treatment or hospitalization.[30] Admissions for other reasons, such as depressive episodes or suicidal attempts, were not counted as relapse if there were no deterioration in positive symptoms. Information was obtained from the subject's clinical case notes and confirmed through interview with the patient and informant. Medication adherence was estimated to be good for being adherent in more than 50% of the time in the first month of AP treatment, and poor if otherwise, according to the self-report from patients' and clinicians' judgment.

DUP was determined according to the IRAOS.[31] Subjects were assessed by trained clinicians for symptoms by the PANSS[32] at initial presentation. Interrater reliability for PANSS positive subscale, negative subscale, total score, and DUP were performed on an independent sample of 12 patients. The intraclass correlation was 0.87 for the PANSS positive subscale, 0.66 for the PANSS negative subscale, 0.76 for the PANSS total score, and 0.99 for DUP. Other information, such as diagnosis and whether hospitalized at onset, were also obtained.

Subjects underwent a structured interview for parental sociodemographic details at birth. An informant (whenever possible, the subject's mother), was interviewed for collateral information with the subject's consent. The clinical case notes were also studied as an additional source of information. Paternal and maternal age (at time of subject's birth) was obtained by directly asking the subject. Important dates, such as the world wars, were also used as reference points. Paternal and maternal occupation, and levels and years of education (excluding kindergarten) were also collected. The structured interview also recorded other details around the time of the subjects' birth, such as type of accommodation (private housing, public housing, rented housing, boat, squatter hut, or village housing).

Assessment for family history was locally adapted based on the IRAOS, as many family members may not be aware of the diagnosis of a proband. The patient and informant were asked to describe each first- and second-degree relative in detail for the interviewer, specifically for any knowledge of mood, mental, or stress-related states, and behavioural abnormalities of that person. Only people with descriptions indicative of a psychotic disorder were included. For example, an uncle described as saying he was being persecuted and hearing voices of aliens would be included. A grandmother scolding others, sleeping poorly, appearing irritable with psychiatric follow-up would not be included without further relevant description. In ambiguous cases, an exclusive approach was adopted to preserve specificity and to avoid false positives.

The Obstetric Complications Scale,[33] which has acceptable reliability by maternal recall,[34] was used for OCs. For specificity purposes only, definite rather than equivocal OCs were counted. Precipitous labour was disregarded[34,35] as it systematically occurs in multiparous births without any definite complications. Birth rank within the same biological parents was recorded along with total sibship size.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics 20.0 (IBM SPSS Inc, Armonk, NY). Descriptive statistics on sample characteristics and paternal and maternal data were reported. To test the primary hypothesis of whether advanced paternal age has an effect on relapse at 1 year, we first compared the potential variables (paternal and maternal age, sex, medication adherence, hospitalization, DUP, family history, OCs, birth rank, and sibship size) between people who relapsed and those who did not by independent *t* tests or chi-square tests. Those significant variables, with *P* values

Table 1 Patients' basic and clinical characteristics at baseline

Characteristic	Whole sample *n* = 191	Person who has not relapsed *n* = 149	Person who has relapsed *n* = 42	Tests
Sex, *n* (%)				$\chi^2 = 7.184$, *df* = 1, *P* = 0.007
Female	97 (50.8)	68 (45.6)	29 (69.0)	
Male	94 (49.2)	81 (54.4)	13 (31.0)	
Age at study entry, years, mean (SD)	23.43 (7.86)	23.60 (8.14)	22.81 (6.84)	ns
Age at onset, years, mean (SD)	22.56 (7.45)	22.79 (8.00)	21.76 (5.00)	ns
Occupation status, *n* (%)				
Unemployed	76 (39.8)	61 (40.9)	15 (35.7)	ns
Students	66 (34.6)	50 (33.6)	16 (38.1)	ns
Unskilled workers	16 (8.4)	14 (9.4)	2 (4.8)	ns
Skilled workers	26 (13.6)	20 (13.4)	6 (14.3)	ns
High-skilled workers	7 (3.7)	4 (2.7)	3 (7.1)	ns
Professional workers	0 (0.0)	0 (0.0)	0 (0.0)	
DUP, days, median (IQR)	150 (45–360)	150 (45–360)	105 (30–278)	ns
Medication compliance, *n* (%)				$\chi^2 = 5.217$, *df* = 1, *P* = 0.02
Poor	63 (33.0)	43 (28.9)	20 (47.6)	
Good	128 (67.0)	106 (71.1)	22 (52.4)	
Hospitalization at onset, *n* (%)	101 (52.9)	73 (49.0)	28 (66.7)	$\chi^2 = 4.107$, *df* = 1, *P* = 0.04
PANSS, mean (SD)				
Total score	81.07 (21.94)	82.06 (21.67)	77.23 (22.94)	ns
Positive symptoms	21.40 (5.67)	21.44 (5.47)	21.23 (6.49)	ns
Negative symptoms	16.49 (7.73)	16.63 (7.75)	15.93 (7.73)	ns
General psychopathology	38.28 (11.23)	39.03 (11.27)	35.37 (10.78)	ns

DUP = duration of untreated psychosis; ns = not significant; PANSS = positive and negative syndrome scale

of 0.05 or lower, were entered into a multivariate binary logistic regression to test for its independent predictive ability with relapse.

Results

Demographic and Clinical Data

Table 1 shows the characteristics of participants. Among the 194 eligible patients approached, 191 of them gave informed consent and were recruited into the study during a 4-month period. The sex ratio of the whole population was 94 males to 97 females, with a significantly higher proportion of males who did not relapse (54.4%) than those who did relapse (31.0%, $P = 0.007$). As expected, more patients who relapsed were hospitalized (66.7%) than those who did not relapse (49.0%, $P = 0.04$). Both groups did not differ in age at study entry, age at onset, occupational status, DUP, and positive and negative symptom scores at baseline. In general, the population had a mean age of 23.43 years (range 13 to 58, SD 7.86) and the average onset age of psychotic disorders was 22.56 years (range 13 to 56, SD 7.45). There were 76 (39.8%) patients who were unemployed and 66 (34.6%) patients who were students. Most of them had good medication adherence ($n = 128$, 67.0%). The median DUP was 150 days (interquartile range 45 to 360). All participants were diagnosed with schizophrenia.

Paternal and Maternal Data

As shown in Table 2, the mean paternal age was 34.62 years (range 17 to 62, SD 7.69), and the predominant paternal occupation was unskilled worker ($n = 91$, 47.6%). For participants' mothers, the mean maternal age was 28.52 years (range 16 to 45, SD 5.53), and most of them were housewives ($n = 90$, 47.1%) or unskilled workers ($n = 65$, 34%). Parental education was relatively low, with a mean of 7.32 years (SD 4.40) for fathers and 5.90 (SD 4.26) for mothers. One-fifth of the participants had a positive family history of psychotic disorders ($n = 37$, 19.4%). Around the time of the participants' birth, 34% of them lived in private housing.

Predicting Relapse in 1 Year

At 1-year follow-up following first-episode schizophrenia, 42 participants (22.0%) experienced 1 or more relapses, and 149 of them had no relapses (78.0%). Comparisons between people who did relapse and those who did not relapse found that higher paternal age (37.67, compared with 33.76, $t = 2.778$, $df = 60$, $P = 0.007$), poor medication adherence (47.6%, compared with 28.9%, $\chi^2 = 5.217$,

Table 2 Participants' birth and parental information

Characteristic	Whole sample *n* = 191	Person who has not relapsed *n* = 149	Person who has relapsed *n* = 42	Tests
Paternal age, years, mean (SD)	34.62 (7.69)	33.76 (7.33)	37.67 (8.25)	$t = 2.778$, $df = 60$, $P = 0.007$
Paternal occupation, *n* (%)				ns
Unemployed	0 (0.0)	0 (0.0)	0 (0.0)	
Students	1 (0.5)	1 (0.7)	0 (0.0)	
Unskilled workers	91 (47.6)	72 (48.3)	19 (45.2)	
Skilled workers	58 (30.4)	47 (31.5)	11 (26.2)	
High-skilled workers	29 (15.2)	22 (14.8)	7 (16.7)	
Professional workers	12 (6.3)	7 (4.7)	5 (11.9)	
Paternal education, years, mean (SD)	7.32 (4.40)	7.20 (4.38)	7.74 (4.49)	ns
Paternal education level, *n* (%)				ns
No formal education	21 (11.0)	18 (12.1)	3 (7.1)	
Primary	73 (38.2)	56 (37.6)	17 (40.5)	
Secondary	73 (38.2)	59 (39.6)	14 (33.3)	
Matriculation or above	24 (12.6)	16 (10.7)	8 (19.0)	
Maternal age, years, mean (SD)	28.52 (5.53)	28.15 (5.41)	29.86 (5.84)	ns
Maternal occupation, *n* (%)				ns
Unemployed	1 (0.5)	1 (0.7)	0 (0.0)	
Students	1 (0.5)	1 (0.7)	0 (0.0)	
Housewife	90 (47.1)	71 (47.7)	19 (45.2)	
Unskilled workers	65 (34)	48 (32.2)	17 (40.5)	
Skilled workers	20 (10.5)	18 (12.1)	2 (4.8)	
High-skilled workers	11 (5.8)	7 (4.7)	4 (9.5)	
Professional workers	3 (1.6)	3 (2.0)	0 (0.0)	
Maternal education, years, mean (SD)	5.90 (4.26)	5.85 (4.24)	6.10 (4.40)	ns
Maternal education level, *n* (%)				ns
No education	42 (22.0)	35 (23.5)	7 (16.7)	
Primary	73 (38.2)	54 (36.2)	19 (45.2)	
Secondary	64 (33.5)	54 (36.2)	10 (23.8)	
Matriculation or above	12 (6.3)	6 (4.0)	6 (14.3)	
Accommodation, *n* (%)				ns
Private	65 (34.0)	44 (29.5)	21 (50.0)	
Others: public, rental, squatter, boat	126 (66.0)	105 (70.5)	21 (50.0)	
Positive family history of psychotic disorders, *n* (%)	37 (19.4)	30 (20.1)	7 (16.7)	ns
Definite obstetric complications, *n* (%)	29 (15.2)	25 (16.8)	4 (9.5)	ns
Sibship size, mean (SD)	2.86 (1.56)	2.90 (1.53)	2.74 (1.68)	ns
Birth rank, mean (SD)	2.07 (1.38)	2.03 (1.30)	2.21 (1.65)	ns

ns = not significant

Table 3 Paternal age groups and relapse at 1 year

Outcome	<30 years *n* = 51	30 to 39 years *n* = 97	≥40 years *n* = 43	Total
Not relapsed at 1 year, *n* (%)	44 (86.3)	80 (82.5)	25 (58.1)	149 (78.0)
Relapsed at 1 year, *n* (%)	7 (13.7)	17 (17.5)	18 (41.9)	42 (22.0)

df = 1, *P* = 0.02), female sex (69.0%, compared with 45.6%, χ^2 = 7.184, *df* = 1, *P* = 0.007), and hospitalization at onset (66.7%, compared with 49.0%, χ^2 = 4.107, *df* = 1, *P* = 0.04) were significantly associated with relapse. However, maternal age was not significantly different between the 2 groups (29.86, compared with 28.15, *t* = 1.778, *df* = 189, *P* = 0.07). Other nonsignificant relapse predictors were family history, OCs, birth rank, sibship size, and DUP.

A logistic regression was then performed to study the independent predictive abilities of these identified factors (paternal age, medication adherence, sex, and hospitalization at onset) with relapse. In this multivariate analysis, significant predictors for relapse included higher paternal age (β = 1.05, 95% CI 1.006 to 1.103, *P* = 0.03), poor adherence (β = 2.37, 95% CI 1.122 to 4.989, *P* = 0.02), and female sex (β = 2.44, 95% CI 1.136 to 5.235, *P* = 0.02). The full model (χ^2 = 21.269, *df* = 4, *P* < 0.001) accounted for 10.5% to 16.2% of variance in relapse status, with 79.1% of the prediction correct.

To further elucidate whether a particular paternal age range was significantly associated with relapse, patients were divided into 3 groups depending on paternal age: younger than 30 years, between 30 and 39 years, and 40 years and older. We found a significant effect of advanced paternal age on 1-year relapse rate (χ^2 = 13.055, *df* = 2, *P* = 0.001) (Table 3). Post hoc chi-square tests revealed that the oldest age group (40 years and older) was significantly different from the middle group (30 to 39 years) (41.9%, compared with 17.5%, χ^2 = 9.409, *df* = 1, *P* = 0.002) and the lowest age group (younger than 30 years) (41.9%, compared with 13.7%, χ^2 = 9.460, *df* = 1, *P* = 0.002). No difference was found between the lowest and the middle paternal age groups (13.7%, compared with 17.5%; χ^2 = 0.355, *df* = 1, *P* = 0.55). A cut-off of paternal age of 40 years and older was related to more relapse.

Discussion

To our knowledge, there is no report of the effect of advanced paternal age on relapse at 1-year following the first episode of schizophrenia. Key findings were as follows: advanced paternal age modestly but significantly increased the risks of relapse; such an effect was independent of medication adherence, sex, maternal age, family history, OCs, birth rank, sibship size, and DUP; and such an effect was the strongest at a cut-off of paternal age of 40 years and older. Another finding was that the 1-year relapse rate in this sample was 22%. The result is comparable with a previous naturalistic study of first-episode schizophrenia in Hong Kong, where a relapse rate of 19% was found in the first year.[36]

To account for the paternal age effect on relapse, current knowledge on the biological and psychosocial hypotheses in explaining the development of schizophrenia has been put forward. The first of these postulations is that biological factors associated with high paternal age, for example, de novo mutation in spermatogenesis, may lead to developmental brain changes associated with an increased intrinsic biological propensity to relapse. Similar to the population-based cohort study in Sweden,[22] our research indicated that people who did not relapse and those who did relapse did not differ in terms of family history of psychotic disorder. With the influence of familial vulnerability being equal in the 2 groups, advanced paternal age effect is clearly demonstrated among people who did relapse, suggesting that de novo mutation in spermatogenesis in older fathers, especially for those 40 years and older, may contribute to higher risk of relapse.

The second postulated psychosocial hypothesis is that older parents may be less effective in supervision of the patient's adherence behaviour. If parental supervision is a key factor, we would expect a significant relation between maternal age and relapse as well. As the mother is often the key caregiver for patients with psychotic disorders,[37,38] we would expect that the relation between maternal age and relapse to be stronger than that for paternal age. The absence of such a relation in our data made this postulation unlikely. Likewise, we found that the relation between paternal age and relapse was not mediated by adherence behaviours, that is, paternal age and adherence each contribute independently to relapse. We explored if higher paternal or maternal age were related to adherence, however, no significant associations were found (*P* = 0.22 and *P* = 0.74, respectively). Our data contrasted with the second hypothesis of low parental supervision on patients' adherence behaviours leading to relapse.

In hindsight, older Chinese fathers who are usually strict and heavily involved in the discipline of their children might lead them to express a higher level of critical comments toward their ill children. As caregivers' critical comments were one of the more consistent relapse factors,[10] it is probable that critical comments is a mediating variable through which it expresses its impact on relapse. As this variable is not investigated in our study, whether the relation between advanced paternal age and relapse is mediated by more negative comments should be explored in future studies.

Our findings give further evidence to the hypothesis that a higher paternal age-related schizophrenia may represent a specific illness subtype. It has been suggested that patients born to older fathers had better treatment response in positive symptoms, irrespective of the treatment or the placebo groups.[26,39] Although generalization may be an issue, as the sample was recruited from clinical trials and in patients with very early onset schizophrenia,[39] this and our findings also hint at the important influence of advanced paternal age on different course parameters in schizophrenia. Further investigations are needed to examine whether either one or both biological and psychosocial hypotheses play a role in moderating the relation between advanced paternal age and relapse, as well as whether these relations are specific to early or late-onset schizophrenia. Another significant finding is that females

were associated with more relapses than males. The result contradicts previous findings where male sex had poorer outcomes in general and more relapses.[40,41] A potential explanation is that our female patients had a higher severity level of positive symptoms at onset ($P = 0.04$) than their male counterparts. Studies demonstrated that more severe positive symptoms at onset is predictive of relapse in recent onset psychosis.[42] Moreover, we found a doubled relapse risk among patients with poor medication adherence. The link between nonadherence and relapse in first-episode schizophrenia has been reported consistently, both in naturalistic[36,43] and in controlled studies.[30,44–46] Despite this well-replicated finding, current interventions to enhance adherence in recent-onset psychosis remain a challenge, as nonadherence is not caused by one but a multiple of factors; and no single intervention can be effective for all patients.[14] Therefore, the exploration of predictors of relapse, other than nonadherence, would be important in designing new interventions to enhance medication adherence and reduce relapse.

Limitations

There are several limitations in our study. Some potential relapse predictors, such as persistent substance abuse, caregivers' critical comments, and premorbid adjustment, were not measured. Although substance abuse may be relevant, its prevalence is relatively low in the Hong Kong population (5.5% for female and 9.3% for male in a comparable age group of 18- to 24-year-olds).[47] Here, patients with significant comorbid SUD in the past year or substance-related psychotic disorders were excluded, and thus alcohol and substance abuse were not investigated as potential predictor. Additionally, measuring the variable of critical comments may require lengthy interviews using the Camberwell Family Interview with family members of the psychiatric patient, and thus were not investigated in our study. Likewise, premorbid adjustment was not measured. However, this made the exploration of its potential role in mediating the existing finding on advanced paternal age and relapse impossible. The exact timing of relapse was not measured. We acknowledge that reliable measurement of medication adherence is a difficult empirical challenge, and the way it measures compliance in our study may not be stringent enough to fully elucidate the effect of medication compliance on relapse.[48–50] Further, the identification of relapse is now based on clinical judgment rather than measurement of symptoms, which might also weaken the strength of current findings. The relatively short follow-up period also limited the observation. Hence observation may only allow for distinction between a minority of the patients with more serious illness and those running a more benign course.

Clinical and Research Implications

Our study has furthered our understanding toward the role of paternal age in predicting psychotic relapse in first-episode schizophrenia. The finding that patients with higher paternal age (particularly at 40 years and older) had more relapses is of great clinical and research significance. The effect of advanced paternal age still holds after controlling for medication discontinuation and sex. These data need to be replicated, perhaps with a longer follow-up period. The finding raises interesting research questions about how advanced paternal age might contribute to possible biological and psychosocial mechanisms leading to relapse. Future studies should confirm whether advanced paternal age may affect the initial response to treatment in patients with psychosis and represent a subtype of schizophrenia by a wider investigation into the neurobiology, psychopathology, treatment effects, and course of illness in patients.

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References

1. Murray RM, van Os J. Predictors of outcome in schizophrenia. J Clin Psychopharmacol. 1998;18(2 Suppl 1):2S–4S.
2. Vyas NS, Hadjulis M, Vourdas A, et al. The Maudsley early onset schizophrenia study. Predictors of psychosocial outcome at 4-year follow-up. Eur Child Adolesc Psychiatry. 2007;16:465–470.
3. Emsley R, Chiliza B, Schoeman R. Predictors of long-term outcome in schizophrenia. Curr Opin Psychiatry. 2008;21:173–177.
4. McCreadie RG, Wiles D, Grant S, et al. The Scottish first episode schizophrenia study. VII. Two-year follow-up. Scottish Schizophrenia Research Group. Acta Psychiatr Scand. 1989;80:597–602.
5. Samele C, van Os J, McKenzie K, et al. Does socioeconomic status predict course and outcome in patients with psychosis? Soc Psychiatry Psychiatr. 2001;36:573–581.
6. Lehman AF, Fischer EP, Postrado L, et al. The Schizophrenia Care and Assessment Program Health Questionnaire (SCAP-HQ): an instrument to assess outcomes of schizophrenia care. Schizophr Bull. 2003;29:247–256.
7. Thara R. Twenty-year course of schizophrenia: the Madras Longitudinal Study. Can J Psychiatry. 2004;49:564–569.
8. Weiden PJ, Olfson M. Cost of relapse in schizophrenia. Schizophr Bull. 1995;21:419–429.
9. Lieberman JA. Evidence for sensitization in the early stage of schizophrenia. Eur Neuropsychopharmacol. 1996;6:155.
10. Álvarez-Jiménez M, Priede A, Hetrick SE, et al. Risk factors for relapse following treatment for first episode psychosis: a systematic review and meta-analysis of longitudinal studies. Schizophr Res. 2012;139:116–128.
11. Malla A, Norman R, Bechard-Evans L, et al. Factors influencing relapse during a 2-year follow-up of first-episode psychosis in a specialized early intervention service. Psychol Med. 2008;38:1585–1593.
12. Caseiro O, Pérez-Iglesias R, Mata I, et al. Predicting relapse after a first episode of non-affective psychosis: a three-year prospective study. J Psychiatr Res. 2012;46:1099–1105.
13. Wade D, Harrigan S, Edwards J, et al. Substance misuse in first-episode psychosis: 15-month prospective follow-up study. Br J Psychiatry. 2006;189:229–234.

14. Robinson DG. Medication adherence and relapse in recent-onset psychosis. Am J Psychiatry. 2011;168:240–242.
15. Alvir JM, Woerner MG, Gunduz H, et al. Obstetric complications predict treatment response in first-episode schizophrenia. Psychol Med. 1999;29:621–627.
16. Jarbin H, Ott Y, Von Knorring AL. Adult outcome of social function in adolescent-onset schizophrenia and affective psychosis. J Am Acad Child Adolesc Psychiatry. 2003;42:176–183.
17. Bromet EJ, Naz B, Fochtmann LJ, et al. Long-term diagnostic stability and outcome in recent first-episode cohort studies of schizophrenia. Schizophr Bull. 2005;31:639–649.
18. Malaspina D. Paternal factors and schizophrenia risk: de novo mutations and imprinting. Schizophr Bull. 2001;27:379–393.
19. Brown AS, Schaefer CA, Wyatt RJ, et al. Paternal age and risk of schizophrenia in adult offspring. Am J Psychiatry. 2002;159:1528–1533.
20. Zammit S, Allebeck P, Dalman C, et al. Paternal age and risk for schizophrenia. Br J Psychiatry. 2003;183:405–408.
21. El-Saadi O, Pedersen CB, McNeil TF, et al. Paternal and maternal age as risk factors for psychosis: findings from Denmark, Sweden and Australia. Schizophr Res. 2004;67:227–236.
22. Sipos A, Rasmussen F, Harrison G, et al. Paternal age and schizophrenia: a population based cohort study. BMJ. 2004;329(7474):1070.
23. Fletcher NA, Foley J. Parental age, genetic mutation, and cerebral palsy. J Med Genet. 1993;30:44–46.
24. Montgomery SM, Lambe M, Olsson T, et al. Parental age, family size, and risk of multiple sclerosis. Epidemiology. 2004;15:717–723.
25. Vestergaard M, Mork A, Madsen KM, et al. Paternal age and epilepsy in the offspring. Eur J Epidemiol. 2005;20:1003–1005.
26. Rosenfield PJ, Kleinhaus K, Opler M, et al. Later paternal age and sex differences in schizophrenia symptoms. Schizophr Res. 2010;116:191–195.
27. Miller B, Messias E, Miettunen J, et al. Meta-analysis of paternal age and schizophrenia risk in male versus female offspring. Schizophr Bull. 2011;37:1039–1047.
28. Chen EYH. Developing an early intervention service in Hong Kong. In: Ehmann T, MacEwam GW, Honer WG, editors. Best care in early psychosis intervention: global perspectives. New York (NY): Taylor and Francis; 2004. p 125–130.
29. American Psychiatric Association (APA). Diagnostic and statistical manual of mental disorders. 4th ed. Washington (DC): APA; 1994.
30. Chen EY, Hui CL, Lam MM, et al. Maintenance treatment with quetiapine versus discontinuation after one year of treatment in patients with remitted first episode psychosis: randomised controlled trial. BMJ. 2010;341:c4024.
31. Hafner H, Riecher-Rossler A, Hambrecht M, et al. IRAOS: an instrument for the assessment of onset and early course of shcizophrenia. Schizophr Res. 1992;6:209–223.
32. Kay SR, Fiszbein A, Opler LA. Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophr Bull. 1987;13:21–76.
33. Lewis SW, Owen MJ, Murray RM. Obstetric complications and schizophrenia: methodology and mechanisms. In: Schultz SC, Tamminga CA, editors. Schizophrenia: scientific progress. New York (NY): Oxford University Press; 1989. p 56–68.
34. O'Callaghan E, Larkin C, Waddington JL. Obstetric complications in schizophrenia and the validity of maternal recall. Psychol Med. 1990;20:89–94.
35. Smith GN, Honer WG, Kopala L, et al. Obstetric complications and severity of illness in schizophrenia. Schizophr Res. 1995;14:113–120.
36. Chen EY, Hui CL, Dunn EL, et al. A prospective 3-year longitudinal study of cognitive predictors of relapse in first-episode schizophrenic patients. Schizophr Res. 2005;77:99–104.
37. Kuipers L. Family burden in schizophrenia: implications for services. Soc Psychiatry Psychiatr Epidemiol.1993;28:207–210.
38. Glanville DN, Dixon L. Caregiver burden, family treatment approaches and service use in families of patients with schizophrenia. Isr J Psychiatry Relat Sci. 2005;42:15–22.
39. Opler M, Malaspina D, Gopal S, et al. Effect of parental age on treatment response in adolescents with schizophrenia. Schizophr Res. 2013;151:185–190.
40. Angermeyer MC, Goldstein JM, Kuehn L. Gender differences in schizophrenia: rehospitalization and community survival. Psychol Med. 1989;19:365–382.
41. Tohen M, Stoll AL, Strakowski SM, et al. The McLean First-Episode Psychosis Project: six-month recovery and recurrence outcome. Schizophr Bull. 1992;18:273–282.
42. Hides L, Dawe S, Kavanagh DJ, et al. Psychotic symptom and cannabis relapse in recent-onset psychosis. Prospective study. Br J Psychiatry. 2006;189:137–143.
43. Hui CLM, Tang JYM, Leung CM, et al. A 3-year retrospective cohort study of predictors of relapse in first-episode psychosis in Hong Kong. Aust N Z J Psychiatry. 2013;47:746–753.
44. Kane JM, Rifkin A, Quitkin F, et al. Fluphenazine vs placebo in patients with remitted, acute first-episode schizophrenia. Arch Gen Psychiatry. 1982;39:70–73.
45. Crow TJ, MacMillan JF, Johnson AL, et al. The Northwick Park Study of first episodes of schizophrenia II. A randomized controlled trial of prophylactic neuroleptic treatment. Br J Psychiatry. 1986;148:120–127.
46. Hogarty GE, Ulrich RF. The limitations of antipsychotic medication on schizophrenia relapse and adjustment and the contributions of psychosocial treatment. J Psychiatr Res. 1998;32:243–250.
47. Lau JTF, Kim JH, Tsui HY. Prevalence, health outcomes, and patterns of psychotropic substance use in a Chinese population in Hong Kong: a population-based study. Subst Use Misuse. 2005;40:187–209.
48. Agarwal MR, Sharma VK, Kishore Kumar KV, et al. Non-compliance with treatment in patients suffering from schizophrenia: a study to evaluate possible contributing factors. Int J Soc Psychiatry. 1998;44:92–106.
49. Hui CL, Chen EY, Kan C, et al. Anti-psychotics adherence among out-patients with schizophrenia in Hong Kong. Keio J Med. 2006;55:9–14.
50. Perkins DO, Johnson JL, Hamer RM, et al. Predictors of antipsychotic medication adherence in patients recovering from a first psychotic episode. Schizophr Res. 2006;83:53–63.