The Role of Gender in Early and Very Early Onset of Psychotic Disorders

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Abstract

This study examines the impact of gender and very early onset on the prognosis of a psychotic disorder. **Methods:** Eighty-seven youths under 18 years of age, 36 (41%) female and 51 (59%) male, hospitalized with first-episode psychosis were investigated in a multi-site, longitudinal, retrospective follow-up cohort design. An exploratory examination of the subjects was undertaken to assess the impact of very early transition to psychosis on prognosis. Data at Time 1 (time of discharge) were retrospectively collected using a standardized questionnaire from patients' hospital records, and follow-up data at Time 2 (a minimum interval of two years post discharge) were obtained using a mailout questionnaire. Subjects were followed for at least two years (3.9±1.3 years). **Results:** Females with very early onset (<13 years) were more likely to have a poorer prognostic course and experience relapse resulting in hospital readmission than older females (13–18 years). Conversely, older males were more likely than younger males to experience relapse. Kaplan-Meier survival curves found that females were more likely to relapse than males. Breslow-Day test found that very early-onset females were more likely to relapse than younger males, older males, or older females. **Conclusions:** Findings supported by existing research indicate that very young age of onset and female gender predicted a greater chance of relapse. Poor prognosis in very early-onset females may result from a lack of the protective influence of estrogen, earlier brain maturation, or lack of development of help-seeking behaviors. More research is warranted to understand these relationships. Findings and research are outlined in order to promote the prospective investigation of these phenomena.

Key Words: Psychosis, Early Onset, Gender, Puberty, Relapse, Estrogen

Introduction

Early onset of psychotic conditions is uncommon and very early onset is even rarer. Prevalence rates for children and adolescents under 15 years of age range from 1.6 to 1.9 per 100,000 (1-4); in older adolescents, ages 15 to 18 years, the prevalence rate increases to 230 per 100,000 (4). Epidemiological research reports that males typically experience earlier onset, between the ages of 15 to 25 years, compared to an older female age of onset, between 25 to 35 years (5). Approximately 40% of males and almost 25% of females will experience onset before they turn 19 years of age (6). Research indicates that children and adolescents with psychotic disorders will experience poorer prognostic outcomes than adults, resulting in impaired social functioning, episodic symptom relapses, and readmission to hospital (7-9).

The influence of very early- and early-onset psychosis on gender has received limited scientific attention. This study reviews the existing research and investigates the prognostic effects on females if onset of the psychotic disorder occurs very early (under age thirteen), and explores why child and

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adolescent females may relapse at a greater rate than males. Several preliminary hypotheses have slowly emerged in this literature to account for the possibility that very early onset in females results in poorer outcomes, including biological, genetic, and social explanations. There is a possibility that the "estrogen effect," that is protective in adult females, is minimized or muted if onset occurs prior to puberty. In females, some researchers found that the earlier the age of menarche (first period), whether through hormonal or social influences, the later the age of first psychotic symptoms and hospitalization. Such an effect was not found in men, where the opposite trend was evident (10). According to Galdos and colleagues (11), Eggers and Bunk (12), and Hochman and Lewine (13), developmental reorganization and maturation of the brain may occur earlier in girls than boys and play a role in earlier onset. Consequently, females with early onset exhibit earlier symptoms and potentially worse prognosis.

This article presents a small exploratory study examining the association of very early onset in females and males. This investigation is first set against the backdrop of the existing research in very early- and early-onset psychosis in relation to gender, highlighting a potential alternative hypothesis and an emerging trend indicating that child and adolescent females may have poorer prognosis than males.

Background

Researchers have sought to establish a relationship between menarche and onset of psychosis. In Galdos and colleagues' chart review (11) of 97 adolescents with psychosis, 49 male and 48 female, they found a significantly younger age of onset of psychosis for females. Galdos et al. reviewed epidemiological data and found that over a thirteen-year period in England and France (1973–1986) there was a slight but nonsignificant excess of females in the 10–14 year old age group, with a highly significant change in the male to female ratio between 10–14 year olds and 15–19 year olds. This evidence suggested earlier onset in females. The authors propose an apparent trend toward an increasing proportion of females near puberty. They also found a significant relationship between menarche and onset of psychosis for females where the age of menarche was known. Galdos et al. posit the theory that schizophrenia may be related to errors in the maturational reorganization of the brain and that the reorganization or other developmental changes may allow previously latent congenital defects in neurodevelopment to become apparent. The authors also report that the protective effects of estrogen may not be established until some time after menarche and the establishment of regular cycles.

Frazier et al. (14) found no significant correlation between development of psychosis and menarche in a study of 28 adolescents (14 males and 14 females) aged 6 to 18 years with treatment refractory childhood-onset schizophrenia (COS). There was a significant relationship for females between sexual development and onset of psychosis, but it was reported to be driven by one outlier. The authors report that the effect of typical neuroleptics on pubertal development is not systematically studied. Prolactin increase related to medication may affect menarche and could possibly affect pubertal development. Frazier et al. questioned whether the equal gender ratio may be related to a treatment refractory sample.

Eggers and Bunk's study (12) found no overall gender difference in age of onset, but did find that cumulative prevalence is earlier in females, with an excess of very early onset with girls (before age 15 years), and a greater preponderance in boys aged 15 to 24 years. Generally, there is a recognized predominance of males in early-onset schizophrenia (15) with a male to female ratio of 2–2.5:1 (16). Male patterns, in comparison to female distribution patterns, reportedly start early, and their numbers steeply increase "to a pronounced peak in the age group 15 to 25 years," then steadily fall away (17).

However, Eggers and Bunk (12) found the opposite in a younger population, with a slight predominance of females (M:F–19:25). They found that those with early-onset illness before age 12 had a worse prognosis than later onset at age 12 and older (12). They found that all of the girls in the sample were psychotic by 15 years, but all of the boys by 18 years. Like Galdos et al. (11), they propose that antidopaminergic properties of estrogen may become protective from psychosis after the peak of puberty. Also, Eggers and Bunk (12) discuss neutrotrophic functions, and the possibility that "estrogens may counteract the reduction in synaptic density that takes place during late puberty and early adolescence" (p. 112); synaptic pruning may be related to the development of psychosis. Developmental changes may differ in males and females. Prenatal and perinatal neuroanatomical lesions may play a role in schizophrenia, and estrogen may have a protective effect. Girls may enter puberty earlier, and the accompanying earlier brain maturation could lead to earlier development of psychosis. Later, during adolescence, the protective neurotrophic effects of estrogen may counteract neuronal changes and synaptic pruning, but not with very early onset. In this research the focus was on a younger population, which may support the notion that younger females under the age of 15 years may have a unique and under-investigated poorer prognosis. Regardless of gender, insidious onset appears more common in younger children and is related to a worse prognosis.

Hochman and Lewine (13) investigated 68 females (mean age [M]=41.2 years, standard deviation [SD]=15.4) and found that a later age of menarche was associated with higher negative symptom scores and greater functional impairment. In contrast to Cohen et al. (10) and Galdos et al.

(11), Hochman and Lewine did not find a correlation between menarche age and onset of schizophrenia. They propose that neuroprotective effects resulting from estrogen may become evident after ovuatory cycles are well established. Contrarily, they report that heightened cortisol levels in adolescence may promote dopamine function and oppose the estrogen protectivity. They also state that estrogen protectivity may be opposed by the faster development in girls with an earlier menarche and the earlier brain changes in them during development that may precipitate onset earlier (13). They conclude that neurohormonal and significant brain changes need to be better understood.

Hafner (18) reflects the need to better understand the differences between brain development and functioning of men and women. Hafner suggests evidence that with familial schizophrenia there is no major difference in age of onset and that estrogen has less of a delay effect with those at greater genetic risk. He also indicates that prenatal and perinatal complications reduce the protective effect of estrogen.

It is important to recognize that the etiology of psychotic symptoms in children and adolescents can be difficult to determine. Psychotic symptoms in childhood and adolescence do not necessarily indicate the presence of schizophrenia or other primary psychotic disorders. Neurologic, metabolic and other general medical conditions may cause or contribute to the development of psychotic symptoms and need to be very carefully considered. Psychotic symptoms also occur in the context of prodromal or active mood disorders. Due to the overlap in symptom manifestation, it is often challenging to distinguish psychotic disorders from mood disorders with psychotic features in youth (15), resulting in 20 to 30% of adolescents being rediagnosed (19). Psychotic-like symptoms may also occur in other psychiatric disorders, such as pervasive developmental disorders or obsessive compulsive disorder.

Greater research on adults has determined a significant predictive value associated with gender, and it is accepted that females tend to have later onset of schizophrenia than males (17, 20, 21). Hafner and colleagues determined that first admission, on average, is five years earlier in males (22, 23). Research has also found that adult females experience better prognostic outcomes after first admission (21, 24). Geddes and colleagues (24) found that females had shorter total inpatient admissions and better prognosis. This finding was substantiated by secondary data analysis of 1,331 first-hospitalized patients with schizophrenia or affective disorders, which revealed that females had better outcomes (25). In examining differences among females, higher premorbid intellectual functioning was associated with improved outcomes. Conversely in males, premorbid personality traits, specifically social functioning and organizational ability, were associated with better outcomes (25). In Wieselgren and Lindstrom's study (21), females had significantly better outcomes following first admission in relation to social contacts, employment, and decreased psychotic symptoms. Other first-episode investigations concluded that females respond better to medication (21, 26).

Two adult studies found interesting associations related to poorer prognosis or onset with females. Parker and Hadzi-Pavlovic's (27) study investigated hospital readmission after 12 months in 118 patients diagnosed with schizophrenia (age range 18 to 77 years). Univariate analyses found that being female, unemployed, on social benefits and noncompliant with medication were associated with readmission. Parker and Hadzi-Pavlovic (27) recognized the contrasting nature of these findings, but concluded that "our female preponderance reflected a sample nuance, and that it is not a finding of necessarily wider relevance" (p. 162). No further details were offered. Colenda and Hamer's study (28), not specific to psychosis, of first admission to a state psychiatric hospital of 210 young adults (M=22.1 years, SD=.15 years) with various conditions initially found that nonwhite females had a higher admission rate, and white females a higher readmission rate, but this gender factor was questioned as the findings determined that 75% of these females had major mental illnesses.

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While the existing research in very early- and early-onset psychosis in relation to gender is limited, an emerging trend has developed that indicates child and early adolescent females may have poorer prognosis than males, which is the inverse relationship to that in the adult population. A number of possible explanations have been proposed to explain this phenomenon. In light of this research, the following study examined the association of very early-onset in females and males. Based on the literature, this study will investigate the following hypotheses: 1) gender influences prognosis in very-early and early-onset psychosis; and, 2) females with very early-onset psychosis have a poorer prognosis than females with early onset or males with very early or early onset. In addition, we will examine what explanations may exist for a potential gender difference and outline recommendations for further study in order to prospectively investigate this phenomenon.

Finally, this research builds upon an initial investigation that examined the relapse rate and its associated predictors for children and adolescents experiencing a first episode of psychosis, and developed a statistical risk model for prediction of time to first relapse (29). A model for relapse was developed comprised of four key risk factors, including the relationship in which female gender was associated with relapse. This study was designed to specifically examine the influence of female gender in early- and very early-onset psychosis based on the above hypotheses.

Methods

Design

Following ethics approval, participants were recruited following admission to one of six child and adolescent psychiatric inpatient units. Data on eighty-seven adolescents with a psychotic disorder or major mood disorder with psychotic features were collected using a retrospective, follow-up, longitudinal, cohort research design. Data were collected at two time points. Time 1 (T1) data were abstracted from medical records for the youths' first inpatient admissions for psychosis with hospital discharge occurring between January 1, 1999 and October 31, 2003. Time 2 (T2) data were collected by a mailed questionnaire to parents following a minimum interval of two years (M=3.9, SD=1.3) postdischarge, between April 1, 2004 and October 31, 2005.

Sample

Eligible criteria included participants under eighteen years of age at time of admission, hospitalized for their first episode of a primary psychotic disorder or a mood disorder with psychotic features, and hospitalized for a minimum of seventy-two hours. All participants received a *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* diagnosis from a child and adolescent psychiatrist during the initial index hospital admission as recorded in the medical charts. Diagnoses included psychotic disorders and mood disorders with psychosis, specifically schizophrenia, schizophreniform disorder, schizoaffective disorder, brief psychotic disorder, psychotic disorder not otherwise specified, depressive disorders with psychotic features, and bipolar disorders with psychotic features. Exclusion criteria included participants whose psychotic symptoms were due to substance use or to a general medical condition.

Participants were recruited from six child and adolescent psychiatric inpatient hospital units in Ontario, Canada. Letters introducing the study were mailed to the families and adolescents; this was followed by telephone contact to solicit participation. Two hundred and twenty-nine eligible participants were contacted: 87 (38%) families participated and returned the completed parent consent and adolescent assent forms and data collection questionnaires; 58 (25%) did not wish to participate and 84 (37%) agreed to participate, but did not return the completed instruments.

Instruments

Time 1 (T1) data were retrospectively collected using the Chart Review Data Instrument to extract available data from the hospital records of the adolescents' index admission. The Chart Review Data Instrument was developed for this study in congruence with a number of recognized methodological steps and established criteria (30, 31), including operationalizing variables in accordance with the literature and clinical and scientific experts, piloting the instrument with two independent reviewers for reliability, and the development of a set of standard protocols and a thirty-page data abstraction manual with precise guidelines for the data extraction. Reliability of the instrument was tested on a subset of cases using independent raters, and intraclass correlation coefficients (ICCs) and Kappas ranged from 0.74 to 1.00 (29). The variables gender and age each had a Kappa of 1.00 (32).

The Time 2 (T2) data questionnaire, Information Update Profile Sheet, was mailed to parents a minimum of two years following their child's index hospital admission. The questionnaire was piloted on a subset of adolescents and their parents; participants were able to complete the questionnaire without difficulty. This questionnaire collected data on whether their adolescent had been readmitted to any psychiatric inpatient hospital, admission and discharge dates, and reason for readmission since index hospitalization. Data collected in the questionnaire were compared, when possible, with medical and hospital records to confirm accuracy.

The outcome or dependent variable, relapse, was defined as readmission to an inpatient psychiatric unit for more than seventy-two hours due to a worsening or reemergence of their psychotic symptoms (27, 33). Readmissions due to social reasons, threatening behavior, or suicide risk were not counted as a relapse. There are advantages and limitations in operationalizing relapse in terms of hospital readmission. Specifically, youths experiencing relapse may be managed in outpatient settings; however, the vast proportion of children and adolescents with first-onset psychotic disorders are likely to require inpatient care (34). In addition, this marker for relapse was used due to its clear, quantifiable definition, reliability and validity in terms of describing more severe events and is common practice in research with this population (27, 35-40).

Statistical Analysis

Descriptive statistics were conducted on all variables. The data were then subjected to two statistical analyses:

Kaplan-Meier survival analysis of the association between gender and survivability, and a Breslow-Day test for homogeneity of odds ratios to determine if there were statistically significant differences between age and gender.

Survival analysis is a statistical process that focuses on how long subjects persist in a state ("survive"); in this study, the focus is participants who have not relapsed (41). This set of statistical techniques was chosen due to its ability to model time to an event where length of follow-up differs among subjects; it is suitable for smaller data sets with precisely measured events (42), and has been widely used to investigate psychotic disorders in adults (43-49).

The Breslow-Day test for homogeneity of odds ratio evaluates whether the two tables are homogenous. The Breslow-Day test examines the hypothesis that the odds ratios are equal, which in this study investigates the variability and interaction of the relationship between relapse of females and males with very early-onset psychosis (12 years of age and under) and early-onset psychosis (13–18 years of age).

Results

In the sample of 87 participants, 36 (41%) were female and 51 (59%) were male. The overall mean age at first-episode admission was 15.24 (SD=2.25). Females had a mean age of 14.73 (SD=2.33) and males a mean age of 15.60 (SD=2.14). The mean duration of untreated illness from first reported symptom to treatment was 19.8 weeks (SD=27.8). Average length of first hospitalization was 26.85 days (SD=36.6). Upon first-admission discharge, 98% of all participants had clinical follow-up, and 94% were prescribed psychiatric medication. Of the 36 female participants, 24 (67%) experienced a relapse and hospital readmission. As for the 51 males, 26 (51%) experienced a relapse and hospital readmission. Overall, 12 participants (14%) were diagnosed with very early onset (12 years old or younger) and 75 (86%) with early-onset psychosis (13–18 years of age). Six females (17%) were diagnosed with very early onset and 30 females with early-onset psychosis; 6 male (12%) participants had a diagnosis of very early onset and 45 males had early-onset psychosis.

Of the 36 female participants, two-thirds (n=24) or 67% had a relapse requiring hospital readmission by the end of the follow-up period. For the 51 male participants, approximately half (n=26) or 51% experienced a relapse during the same follow-up period. A univariate analysis using a logrank test found that gender was significantly associated at a p-value=.02 with relapse requiring hospital readmission. The Kaplan-Meier curve (see Figure 1) modeling the rate of relapse stratified for gender shows a more rapid rate of relapse in females for the first twelve months followed by a more parallel relapse rate.

The second Kaplan-Meier curve (see Figure 2) stratifies for age group and gender. This model shows that very early-onset females (age 12 and under) are the most likely group to relapse, while very early-onset males are the least likely to relapse. With the pattern of females being more likely to experience a relapse in early-onset group (13–18 years), as compared to early-onset males, the difference in the relapse curves narrowed. The logrank test finds a p-value of 0.081, which indicates that there is a trend for the difference in which females, specifically younger females, relapse sooner. Even though the p-value does not show a statistical significance, it does show a clinical trend, which we cannot ignore. This p-value is impacted by a small sample size and four groupings.

A Breslow-Day test for homogeneity of odds ratio was analyzed to further examine the variability and interaction of the relationship between relapse of females and males with very early-onset psychosis (12 years of age and under) and early-onset psychosis (13–18 years of age). Specifically

Figure 1 Kaplan-Meier Survival Curve Stratified for Gender

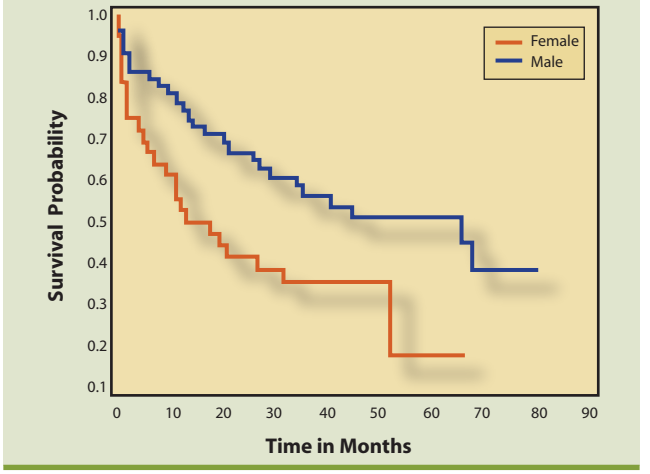
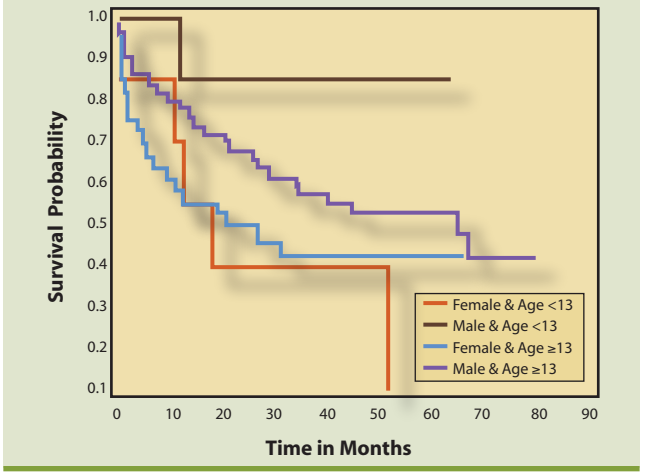


Figure 2 Kaplan-Meier Survival Curve Stratified for Age Group and Gender



the Breslow-Day test compares the odds ratio (OR) of two tables. The first two-by-two frequency table investigates females by age group (very early versus early onset) to females who relapse versus did not relapse. The second two-by-two frequency table similarly investigates males (see Tables 1 and 2).

Table 1 Breslow-Day Test Female Age Group by Relapse

Frequency Percentage (%)	Relapse	Non-Relapse	Total
<13 years	5 13.89 83.33 20.83	1 2.78 16.67 8.33	6 16.67
>13 years	19 52.78 63.33 79.17	11 30.56 36.67 91.67	30 83.33
Total	24 66.67	12 33.33	36 100

Table 2 Breslow-Day Test Male Age Group by Relapse

Frequency Percentage (%)	Relapse	Non-Relapse	Total
<13 years	1 1.96 16.67 3.85	5 9.80 83.33 20.00	6 11.76
>13 years	25 49.02 55.56 96.15	20 39.22 44.44 80.00	45 88.24
Total	26 50.98	25 49.02	51 100

The Breslow-Day test's null hypothesis is H_o: $OR_F=OR_M$. This analysis finds that the females, OR=2.89 (confidence interval [CI]=.30 to 28.07), are more likely to relapse at a younger age than males, OR=0.16 (CI=.01 to 1.48). The inverse relationship is also evident; that is, males are more likely to relapse at an older age than females. The overall test has a p-value=0.057, which, although not significant, indicates a clinical trend in which younger very early-onset females are more likely to relapse.

Discussion

Studies investigating this under-explored and uncommon phenomenon of very early-onset psychosis related to gender are confronted with a number of methodological obstacles and research limitations, and this study is no exception. The small sample size limits the power of this study. The retrospective nature of this investigation limits the analysis to variables extracted from previously recorded data in hospital records, which may produce bias. Also, there may be an overrepresentation of the most severe cases; this limitation may be minimal as most adolescents with first-onset psychotic disorders are admitted to inpatient hospital units (34). The low response rate of approximately 40% in this study is the largest limitation. In studies of first-episode schizophrenia and treatment adherence in adults with psychotic disorders or mood disorders with psychotic features, response and attrition rates are a recognized limitation (33, 50). This study's response rate is low, but in keeping within reported rates of discharged patients from inpatient psychiatric treatment programs from 31% to over 75% (51-53). While similar retrospective studies have extracted data without the subjects' permission (54), ethical boards demanded full consent from participants. So, no comparison between participating and eligible nonparticipating subjects was possible. However, this study experienced no attrition due to its retrospective follow-up design.

As this sample was comprised of hospitalized youth, it is not possible to generalize the findings. However, these exploratory findings, with some limited support in the existing research, indicate that gender does play a role in the prognosis of early-onset and very early-onset psychosis and that a subset of child and adolescent females may experience a poorer prognosis than males. In this study the total male to female ratio was 3:2, but in very early onset the ratio was 1:1. Generally, there is a recognized predominance of males in early-onset schizophrenia (15). Werry and McClellan (16) reported that most childhood-onset schizophrenia studies found a male to female ratio of 2–2.5:1. However, the 1:1 ratio may support the increased preponderance of very early-onset females found in Eggers and Bunk's (12) investigation that found an excess of very early onset with girls, and the Galdos et al. (11) study that suggested an increasing proportion of females near puberty. Similar to this study that found a ratio change between very early and early onset, Eggers and Bunk's (12) investigation likewise found a distinct change in the gender ratio from a slight excess in the female 10–14 year old group to the male-dominated 15–19 year old group. This may support the notion that younger females under the age of 15 years may have a unique and under-investigated poorer prognosis. While existing research support for increased risk to females is sparse, it is not absent.

The findings show that very early- (12 years old and younger) and early- (13 to 18 years) onset females were more likely than either very early-onset or early-onset males to relapse and require hospital readmission. This finding is not supported by research with adults, where findings between gender and functioning are mixed. While many adult investigations have found no significant association in relation to gender (7, 8, 55-58), several studies have determined

a significant predictive value associated with gender (23). In research that supports a gender effect, adult females are consistently found to experience better outcomes after first admission, and in overall prognosis, than males (21, 24). The findings of this study, however, are supported by some very-early and early-onset studies that indicate child and adolescent females have a poorer prognosis than males (11, 12).

In assessing this gender finding, a number of possibilities emerge. Females generally have a greater tendency of help-seeking behavior, and this variable may be capturing a potential social construct of gender, where females are more likely to remain engaged in treatment (59) and any deterioration of their symptoms would be detected by treating healthcare professionals. This may result in an overrepresentation of female readmission rates. However, this study found no significant association between gender and clinical treatment. Methodological limitations of individual studies, such as the limited sample size of female, older-onset participants, compared to the traditionally larger male sample composition, may have contributed to the diverse findings related to this variable. Furthermore, the epidemiologic trend that indicates males may have an earlier age of onset could be explained by a sampling bias, especially when assessing first-episode or predictive studies, where males are overrepresented in the studies.

An alternative possibility may be extended to this younger population from the growing literature on the estrogen effect. Specifically, a number of researchers have proposed in several investigations that estrogen may be a protective factor for females (11, 60-62). Estrogen may affect "serotonin receptors at neurochemical and the molecular level," and may be involved in a reduction in dopaminergic behavior by attenuating the sensitivity of central D2 receptors (17). Therefore, the estrogen effect "could mean that women are less susceptible to the presumed dopamine excess, which is central to prevailing neurotransmitter theories of schizophrenia" (61). Furthermore, this protective effect in females seems to disappear after menopause (18). A possible extension of this estrogen effect was initially forwarded by Merry and Werry (63) when they postulated that "girls may have lower estrogen, but this has not been investigated to date" (p. 280). And, as previously discussed, estrogen may have a neutrotrophic effect. Following this hypothesis, the onset of psychosis in prepubescent girls may nullify or minimize the estrogen effect that is evident in older females. Galdos et al. (11) and Hochman and Lewine (13) suggested that the protective effect of estrogen may not emerge until after the establishment of regular cycles. Similarly, Eggers and Bunk (12) noted that the estrogen effect may not become effective until puberty has reached its peak. Therefore, as evidenced by these findings, very early onset may result in females being at greater risk.

Another potential hypothesis forwarded by Oades and Schepker (64) is that females affected by psychosis may intrinsically have lower estrogen levels. While this current investigation did not measure estrogen levels or onset of puberty, a general comparative assessment may be drawn. In population studies, the average age of menarche is 12.54 years in North America (65, 66). Though it is suggested that puberty should not be defined by age (15), it readily can be extracted as a coarse measure. In this research, while the Breslow-Day test was not statistically significant with a p-value of 0.0571, a clinical trend appears to be evident. These findings clearly do not validate this hypothesis, but illuminate the need for further research.

Current findings suggest that poor prognosis in very early-onset females may result from a lack of the protective influence of estrogen or development of help-seeking behaviors, but many other explanations are possible.

There may be other possible explanations for these preliminary findings that did not emerge in this study. We need to leave room to consider other hypotheses in the biological, psychological and social domains. Gender differences may be related to variables with males that were not investigated in this study or age of onset, in the end, may turn out to have a largely genetic basis—other possible explanations could be involved. Recommendations for a prospective study to further examine this phenomenon are outlined in the conclusions.

Conclusions

This exploratory study and the existing, albeit limited, research to date have found that very young age of onset and female gender predict a greater chance of relapse. Research has begun to document a number of possible explanations for this finding, including the potential role of estrogen in prognosis and outcome. Current findings suggest that poor prognosis in very early-onset females may result from a lack of the protective influence of estrogen or lack of development of help-seeking behaviors, but many other explanations are possible. These findings suggest that the protective effects of estrogen, including antidopaminergic and neurotrophic effects, may by nullified or minimized in girls with very early onset. Some elements of earlier puberty and neurodevelopmental changes in girls may be implicated, and cognitive and social consequences are likely heightened with earlier onset.

In order to further examine this phenomenon, the following recommendations are outlined for future investiga-

tions. It is necessary to have a prospective design that follows prepubertal children exhibiting prodromal symptoms or who are at high risk of developing psychosis. Relevant data include family genetic history, detailed birth and developmental history incorporating Tanner puberty stages, detailed medical history including any history of trauma, and history of substance use. Relevant investigations including genetic testing and neuroimaging may provide valuable information. Sample size remains a problematic issue; however, this potential limitation can be addressed with a smaller number of participants in a well designed and comprehensive methodology study. Further research in the area of gender differences in neurodevelopment is highly recommended.

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References

1. Burd L, Kerbeshian J. A North Dakota prevalence study of schizophrenia presenting in childhood. J Am Acad Child Adolesc Psychiatry 1987;26(3):347-350.
2. Gillberg C. Infantile autism and other childhood psychoses in a Swedish urban region. Epidemiological aspects. J Child Psychol Psychiatry 1984;25(1):35-43.
3. Gillberg C, Steffenburg S. Outcome and prognostic factors in infantile autism and similar conditions: a population-based study of 46 cases followed through puberty. J Autism Dev Disord 1987;17(2):273-287.
4. Nylander L, Gillberg C. Screening for autism spectrum disorders in adult psychiatric out-patients: a preliminary report. Acta Psychiatr Scand 2001;103(6):428-434.
5. Hafner H, Maurer K, Loffler W, Fatkenheuer B, an der Heiden W, Riecher-Rossier A, et al. The epidemiology of early schizophrenia. Influence of age and gender on onset and early course. Br J Psychiatry Suppl 1994(23):29-38.
6. Davis DJ, Schultz CL. Grief, parenting, and schizophrenia. Soc Sci Med 1998;46(3):369-379.
7. Eaton WW, Mortensen PB, Herrman H, Freeman H, Bilker W, Burgess P, et al. Long-term course of hospitalization for schizophrenia: Part I. Risk for rehospitalization. Schizophr Bull 1992;18(2):217-228.
8. Lay B, Blanz B, Hartmann M, Schmidt MH. The psychosocial outcome of adolescent-onset schizophrenia: a 12-year followup. Schizophr Bull 2000;26(4):801-816.
9. Schmidt M, Blanz B, Dippe A, Koppe T, Lay B. Course of patients diagnosed as having schizophrenia during first episode occurring under age 18 years. Eur Arch Psychiatry Clin Neurosci 1995;245(2):93-100.
10. Cohen RZ, Seeman MV, Gotowiec A, Kopala L. Earlier puberty as a predictor of later onset of schizophrenia in women. Am J Psychiatry 1999;156(7):1059-1064.
11. Galdos PM, van Os JJ, Murray RM. Puberty and the onset of psychosis. Schizophr Res 1993;10(1):7-14.
12. Eggers C, Bunk D. The long-term course of childhood-onset schizophrenia: a 42-year followup. Schizophr Bull 1997;23(1):105-117.
13. Hochman K, Lewine RR. Age of menarche and schizophrenia onset in women. Schizophr Res 2004;69(2-3):183-188.
14. Frazier JA, Alaghband-Rad J, Jacobsen L, Lenane MC, Hamburger S, Albus K, et al. Pubertal development and onset of psychosis in childhood onset schizophrenia. Psychiatry Res 1997;70(1):1-7.
15. Werry JS, McClellan JM, Andrews LK, Ham M. Clinical features and outcome of child and adolescent schizophrenia. Schizophr Bull 1994;20(4):619-630.
16. Werry JS, McClellan JM. Predicting outcome in child and adolescent (early onset) schizophrenia and bipolar disorder. J Am Acad Child Adolesc Psychiatry 1992;31(1): 147-150.
17. Hafner H, an der Heiden W. Epidemiology of schizophrenia. Can J Psychiatry 1997;42(2):139-151.
18. Hafner H. Gender differences in schizophrenia. Psychoneuroendocrinology 2003;28(Suppl 2):17-54.
19. Kampman O, Kiviniemi P, Koivisto E, Vaananen J, Kikku N, Leinonen E, et al. Patient characteristics and diagnostic discrepancy in first-episode psychosis. Compr Psychiatry 2004;45(3):213-218.
20. Orr KGD, Castle DJ. Schizophrenia at the extremes of life. In: Murray RM, Jones PB, Susser E, Van Os J, Cannon M, editors. The epidemiology of schizophrenia. New York: Cambridge University Press; 2003. p. 167-190.
21. Wieselgren IM, Lindstrom LH. A prospective 1-5 year outcome study in first-admitted and readmitted schizophrenic patients; relationship to heredity, premorbid adjustment, duration of disease and education level at index admission and neuroleptic treatment. Acta Psychiatr Scand 1996;93(1):9-19.
22. Hafner H, Maurer K, Trendler G, an der Heiden W, Schmidt M. The early course of schizophrenia and depression. Eur Arch Psychiatry Clin Neurosci 2005;255(3):167-173.
23. Hafner H, Riecher A, Maurer K, Loffler W, Munk-Jorgensen P, Stromgren E. How does gender influence age at first hospitalization for schizophrenia? A transnational case register study. Psychol Med 1989;19(4):903-918.
24. Geddes J, Mercer G, Frith CD, MacMillan F, Owens DG, Johnstone EC. Prediction of outcome following a first episode of schizophrenia. A follow-up study of Northwick Park first episode study subjects. Br J Psychiatry 1994;165(5):664-668.
25. Rabinowitz J, Haim R, Reichenberg A, Weiser M, Kaplan Z, Davidson M, et al. Association between functioning in adolescence prior to first admission for schizophrenia and affective disorders and patterns of hospitalizations thereafter. Schizophr Res 2005;73(2-3):185-191.
26. Robinson D, Woerner MG, Alvir JM, Bilder R, Goldman R, Geisier S, et al. Predictors of relapse following response from a first episode of schizophrenia or schizoaffective disorder. Arch Gen Psychiatry 1999;56(3):241-247.
27. Parker G, Hadzi-Pavlovic D. The capacity of a measure of disability (the LSP) to predict hospital readmission in those with schizophrenia. Psychol Med 1995;25(1):157-163.
28. Colenda CC, Hamer RM. First admission young adult patients to a state hospital: relative risk for rapid readmission. Psychiatr Q 1989;60(3):227-236.
29. Gearing RE, Mian IA, Sholonsky A, et al. Developing a risk-model of time to first-relapse for children and adolescents diagnosed with psychotic disorders or mood disorders with psychotic features. J Nerv Ment Dis. In press 2008.
30. Findley TW, Daum MC. Research in physical medicine and rehabilitation. III. The chart review or how to use clinical data for exploratory retrospective studies. Am J Phys Med Rehabil 1989;68(3):150-157.
31. Gearing RE, Mian IA, Barber J, Ickowicz A. A methodology for conducting retrospective chart review research in child and adolescent psychiatry. J Can Acad Child Adolesc Psychiatry 2006;15(3):126-134.
32. Gearing RE. Developing a risk-model of time to first relapse for children and adolescents with primary psychotic disorders or mood disorders with psychotic features [dissertation]. Toronto, Canada: University of Toronto; 2007.
33. Bergen J, Hunt G, Armitage P, Bashir M. Six-month outcome following a relapse of schizophrenia. Aust N Z J Psychiatry 1998;32(6):815-822.
34. Ropcke B, Eggers C. Early-onset schizophrenia: a 15-year follow-up. Eur Child Adolesc Psychiatry 2005;14(6):341-350.
35. Birchwood M, Smith J, Macmillan F, Hogg B, Prasad R, Harvey C, et al. Predicting relapse in schizophrenia: the development and implementation of an

early signs monitoring system using patients and families as observers, a preliminary investigation. Psychol Med 1989;19(3):649-656.

36. Birchwood M, Todd P, Jackson C. Early intervention in psychosis. The critical period hypothesis. Br J Psychiatry Suppl 1998;172(33):53-59.
37. Caton CL, Goldstein JM, Serrano O, Bender R. The impact of discharge planning on chronic schizophrenic patients. Hosp Community Psychiatry 1984;35(3):255-262.
38. Davidson L, McGlashan TH. The varied outcomes of schizophrenia. Can J Psychiatry 1997;42(1):34-43.
39. Giron M, Gomez-Beneyto M. Relationship between family attitudes measured by the Semantic Differential and relapse in schizophrenia: a 2 year follow-up prospective study. Psychol Med 1995;25(2):365-371.
40. Johnstone EC, Macmillan JF, Frith CD, Benn DK, Crow TJ. Further investigation of the predictors of outcome following first schizophrenic episodes. Br J Psychiatry 1990;157:182-189. [See comment on in Br J Psychiatry 1991;158:713-714]
41. Vogt WP. Dictionary of statistics and methodology. 2nd ed. Thousand Oaks (CA): Sage Publications; 1999.
42. Allison PD. Survival analysis using SAS: a practical guide. Cary (NC): SAS Press; 1997.
43. Favre S, Huguelet MA, Vogel S, Gonzalez MA. Neuroleptic compliance in a cohort of first episode schizophrenics: A naturalistic study. European Journal of Psychiatry 1997;11(1):35-42.
44. Hogarty GE, Kornblith SJ, Greenwald D, DiBarry AL, Cooley S, Ulrich RF, et al. Three-year trials of personal therapy among schizophrenic patients living with or independent of family, I: Description of study and effects on relapse rates. Am J Psychiatry 1997;154(11):1504-1513. [See comment on in Am J Psychiatry 1999;156(2):336-337]
45. Hunt GE, Bergen J, Bashir M. Medication compliance and comorbid substance abuse in schizophrenia: impact on community survival 4 years after a relapse. Schizophr Res 2002;54(3):253-264.
46. Lieberman J, Jody D, Geisler S, Alvir J, Loebel A, Szymanski S, et al. Time course and biologic correlates of treatment response in first-episode schizophrenia. Arch Gen Psychiatry 1993;50(5):369-376.
47. Robinson DG, Woerner MG, Alvir JM, Bilder RM, Hinrichsen GA, Lieberman JA. Predictors of medication discontinuation by patients with first-episode schizophrenia and schizoaffective disorder. Schizophr Res 2002;57(2-3):209-219.
48. Scott J, Pope M. Nonadherence with mood stabilizers: prevalence and predictors. J Clin Psychiatry 2002;63(5):384-390.
49. Tohen M, Chengappa KN, Suppes T, Baker RW, Zarate CA, Bowden CL, et al. Relapse prevention in bipolar I disorder: 18-month comparison of olanzapine plus mood stabiliser v. mood stabiliser alone. Br J Psychiatry 2004;184:337-345.
50. Birchwood M, Smith J, Cochrane R. Specific and non-specific effects of educational intervention for families living with schizophrenia. A comparison of three methods. Br J Psychiatry 1992;160:806-814.
51. Olfson M, Mechanic D, Boyer CA, Hansell S. Linking inpatients with schizophrenia to outpatient care. Psychiatr Serv 1998;49(7):911-917.
52. Olfson M, Mechanic D, Hansell S, Boyer CA, Walkup J, Weiden PJ. Predicting medication noncompliance after hospital discharge among patients with schizophrenia. Psychiatr Serv 2000;51(2):216-222.
53. Pfeiffer SI. Follow-up of children and adolescents treated in psychiatric facilities: a methodology review. Psychiatr Hosp 1989;20(1):15-20.
54. Friis S, Hauff E, Island TK, Lorentzen S, Melle I, Vaglum P. The Ulleval acute ward follow-up study: a personal 7-year follow-up of patients with functional psychosis admitted to the acute ward of a catchment area. Psychopathology 1991;24(5):316-327.
55. Cannon M, Walsh E, Hollis C, Kargin M, Taylor E, Murray RM, et al. Predictors of later schizophrenia and affective psychosis among attendees at a child psychiatry department. Br J Psychiatry 2001;178:420-426.
56. Pencer A, Addington J, Addington D. Outcome of a first episode of psychosis in adolescence: a 2-year follow-up. Psychiatry Res 2005;133(1):35-43.
57. Robinson DG, Woerner MG, Alvir JM, Geisler S, Koreen A, Sheitman B, et al. Predictors of treatment response from a first episode of schizophrenia or schizoaffective disorder. Am J Psychiatry 1999;156(4):544-549. [See comment on in Am J Psychiatry 1999;156(4):501-503]
58. Whitehorn D, Richard JC, Kopala LC. Hospitalization in the first year of treatment for schizophrenia. Can J Psychiatry 2004;49(9):635-638.
59. Boyer CA, McAlpine DD, Pottick KJ, Olfson M. Identifying risk factors and key strategies in linkage to outpatient psychiatric care. Am J Psychiatry 2000;157(10):1592-1598.
60. Hafner H, Maurer K, Loffler W, an der Heiden W, Hambrecht M, Schultze-Lutter F. Modeling the early course of schizophrenia. Schizophr Bull 2003;29(2):325-340.
61. Loranger AW. Sex difference in age at onset of schizophrenia. Arch Gen Psychiatry 1984;41(2):157-161.
62. Seeman MV. Schizophrenia, gender, and affect. Can J Psychiatry 1996;41(5):263-264. [See comment on in Can J Psychiatry 1996;41(5):265-268]
63. Merry SN, Werry JS. Course and prognosis. In: Remschmidt H, editor. Schizophrenia in children and adolescents. Cambridge: Cambridge University Press; 2001. p. 268-297.
64. Oades RD, Schepker R. Serum gonadal steroid hormones in young schizophrenic patients. Psychoneuroendocrinology 1994;19(4):373-385.
65. Anderson SE, Dallal GE, Must A. Relative weight and race influence average age at menarche: results from two nationally representative surveys of US girls studied 25 years apart. Pediatrics 2003;111(4 Pt 1):844-850.
66. Towne B, Czerwinski SA, Demerath EW, Blangero J, Roche AF, Siervogel RM. Heritability of age at menarche in girls from the Fels Longitudinal Study. Am J Phys Anthropol 2005;128(1):210-219.