How Age and Gender Predict Illness Course in a First-Episode Nonaffective Psychosis Cohort

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ABSTRACT

Objective: Male gender and young age at onset of schizophrenia are traditionally associated with poor treatment outcome and often used to determine prognosis. However, many studies use nonincident samples and fail to adjust for symptom severity at onset. We hypothesized that age and gender would influence severity of presentation but would not predict outcome after adjustment for symptoms at presentation.

Method: 628 people with first-episode *ICD-9* and *DSM-IV* nonaffective psychosis from 2 historical cohorts recruited from sequential presentations in Canada and the United Kingdom (1996–1998) were assessed prospectively at presentation and over 12–18 months using the Positive and Negative Syndrome Scale (PANSS).

Results: Models of the age-at-onset distributions with 2 underlying modes at similar ages in women (ages 23 years and 47 years) and men (ages 22 years and 46 years) had relatively good fits compared to single-mode models (χ^2_1 better by 9.2 for females, 8.0 for males, both $P < .05$). At presentation, scores for negative symptoms were 1.84 points worse for males (95% CI, 1.05 to 2.58; $P < .001$) in a mixed effects model. Younger age also predicted higher negative scores at presentation (partial correlation $r = -0.18$, $P < .01$; $P < .001$ in the mixed effects model). Findings were similar for cognitive-disorganized symptoms. However, after controlling for baseline symptoms, age at onset and gender did not significantly predict subsequent symptom course in the mixed effects models.

Conclusions: Gender and age at onset are independently associated with symptoms at presentation but not with medium-term course of schizophrenia. This finding reinforces the importance of early identification and prevention of severe negative symptoms at first episode, whatever an individual's age and gender.

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Female gender and older age at onset have been suggested to predict better prognosis in schizophrenia.[1,2] This proposed association has important implications not only for gender difference in etiology but also for the treatment needs of women and men. Men tend to present with more severe negative symptoms,[3,4] higher rates of substance misuse,[3,5,6] and earlier mean age at onset,[7] although the most common age at onset is the same for women and men.[8] Many studies also report that young onset predicts worse negative and disorganized symptoms and a more malignant course.[9–11] However, the relationships between gender, age at onset, and illness course may be more complex than this basic summary suggests. To date, longitudinal evidence is limited by unmeasured confounding factors including duration of untreated psychosis and level of education.[4] Many studies with relatively small numbers lack the statistical power to examine interactions between gender, age at onset, and course of illness.[12–21] Others have neither examined this interaction nor rated symptoms at follow-up.[9,11] Some studies use nonincident samples, which are more likely to be biased toward more severe, refractory illness.[4,22–24]

Most importantly, previous studies have failed to adjust for baseline symptom severity at presentation, making it unclear whether age at onset and gender merely affect the risk of presenting with negative symptoms (which then predict poor outcome) or whether age and gender independently modify the course of the disorder after presentation. In the former case, clinicians can judge illness prognosis on the presenting symptoms alone, thus helping to provide families with information following the first episode. We aimed to model age at onset separately for females and males and then examine the interaction between age at onset, gender, and course of illness using a large, contemporaneous, incident sample to test the following hypotheses: (1) females and males have similar modes of age at onset in their early 20s; (2) males and the younger onset cases are more likely to present with worse negative and cognitive-disorganized symptoms; (3) differences at presentation, rather than gender alone, mediate gender differences in course of illness.

METHOD

Sample

We combined data from 2 large, prospectively ascertained first-episode schizophrenia cohorts recruited from Canada and the United Kingdom (1996–1998).[25–28] The cohort consisted of 628 cases (aged 14–65 years) of sequential first-episode presentations of nonaffective psychosis. Three hundred seventy-one cases (aged 14–55 years) were from a defined catchment area in Canada,

Clinical Points

- Male gender and young age at onset are traditionally associated with poor outcome in schizophrenia; however, the evidence to date has a number of limitations.
- While age and gender alter presentation, they do not appear to modify the course of illness. Only severity of a patient's symptoms at presentation offers prognostic value.
- Early recognition of patients when symptoms are less severe could have important implications for improving longer-term outcome.

and 257 cases (aged 16–65 years) were from 3 catchment areas in the United Kingdom (Liverpool, Manchester, and Nottinghamshire). The original studies were approved by Institutional Review Boards at each site. Informed consent was obtained from all participants. Canadian cases came from an early intervention service and were assigned *ICD-9* diagnosis codes of 292 (schizoaffective disorder, n = 6), 295 (schizophrenia, n = 284), 297 (delusional disorder, n = 5), and 298 (psychosis not otherwise specified, n = 76). In the United Kingdom, the cohort was recruited from consecutive presentations to in-hospital and day-hospital services in the 3 catchment areas. These patients received *DSM-IV* diagnoses of schizophreniform disorder (n = 103), schizophrenia (n = 89), schizoaffective disorder (n = 32), delusional disorder (n = 21), or psychosis not otherwise specified (n = 12). On review of the research records, cases were reassessed using *ICD-10* criteria, with proportions in the United Kingdom and Canada, respectively: schizophrenia, 75%, 78%; schizoaffective disorder, 13%, 1%; delusional disorder, 8%, 1%; and psychosis not otherwise specified, 5%, 19%.

Procedure

In the final analytic sample, gender, age at presentation, duration of untreated psychosis, level of education, and ethnicity were recorded, and symptoms were rated using the Positive and Negative Syndrome Scale (PANSS)[29] at presentation to services and at follow-up. In Canada, follow-up (at 1 year) was attempted only for the first 300 cases; of these, 202 (67%) were followed-up after attrition. In the United Kingdom, follow-up was at 18 months, and 185 of the 257 (72%) were followed up. *Baseline* refers to scores rated at presentation, and the terms *baseline* and *presentation* are used interchangeably throughout the article. Duration of untreated psychosis was defined according to an algorithm combining patient, staff, and family accounts of psychosis onset.[30,31] Age at onset of positive symptoms was defined by age at presentation minus duration of untreated psychosis, ie, the age at psychosis onset.

Analysis

Age at onset. Age at onset distribution was analyzed using SKUDRIVER and SKUMIX software.[32] Both programs are available at http://statgen.iop.kcl.ac.uk/skudriver. This software compared the fit of the incidence distribution across age at onset to models combining 1 or more normal distributions of different size and modal age, separately for each by gender. Fit of these distributional models was determined by maximum-likelihood methods, assessed by χ^2 derived from the negative logarithm of likelihood and Akaike Information Criterion (AIC, which also accounts for the parsimony of the model). *P* values were not corrected for multiple comparisons in this exploratory analysis. SKUDRIVER also allowed transformation of the age at onset distribution (using a power transform) to remove skew, which can bias estimation, simultaneously fitting the transformations and estimating means and variances for components of the resulting gaussian mixture models.[33]

Longitudinal models of outcome. Subtotals of PANSS items (see eAppendix 1) were derived from Psychotic, Negative, Cognitive (related to disorganization), Depression/Anxiety, and Hostility/Excitement dimensions, based on factors described by White et al[34] shown to fit the UK PANSS data.[35] Initial univariate analyses compared mean symptom scores between genders, and partial correlations were carried out for age at onset and symptoms, controlling for center, $\log_{10}$-transformed duration of untreated psychosis, and gender. Follow-up symptom scores were then adjusted for baseline scores to demonstrate the impact of confounding.

Logistic regression of gender, age at onset, ethnicity, and study center against dropout suggested data were "missing at random"[36] with respect to gender and age at onset. Therefore, the effect of demographic variables on PANSS scores at baseline and follow-up (apart from hostility/excitement) was assessed more definitively by fitting mixed effect models using full information maximum-likelihood using the generalized linear latent and mixed models (GLLAMMs) subroutine for STATA 11.0 (StataCorp). The models had 3 levels, visits nested within participants nested within 4 centers: 1 Canadian and 3 United Kingdom. Interaction terms were included for gender and age at onset, gender and time point (ie, follow-up rather than baseline interview), age at onset and time, and country and time. Log-transformed duration of untreated psychosis was included. Gender was examined as a source of heteroscedasticity, that is, the spread of scores being significantly different for females and males. Then the full models were reduced by removing nonsignificant terms, apart from gender and age at onset, until the overall fit of the model worsened significantly (assessed by change in χ^2). The negative subscale was transformed toward normality using the scores' natural logarithm as the outcome variable. Because of skewness in the hostility/excitement variable, it was transformed to a binary variable using the median (ie, score > 6 or not) and analyzed by general estimating equation as an alternative to the above procedure.

RESULTS

Gender Ratio of Incidence

For the whole baseline cohort, 424 (68%) were male; for the whole follow-up cohort, 376 (68%) were male: 177 (69%) in the UK cohort, 247 (67%) in the Canadian baseline cohort, and 199 (66%) of the Canadian follow-up cohort. After

Figure 1. Age at Onset by Gender for Combined Data Set

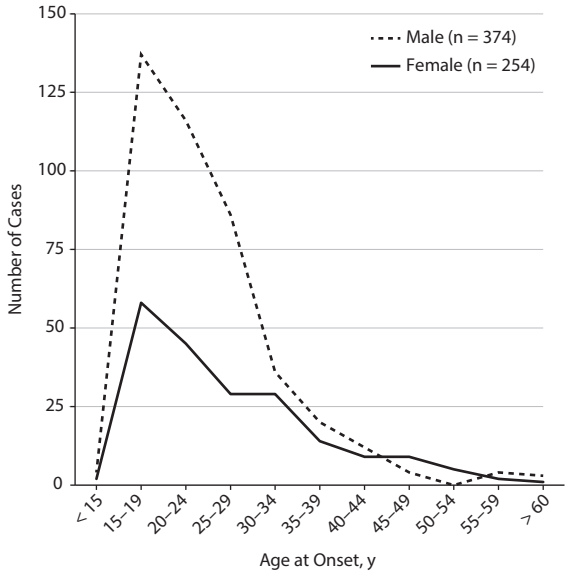


Table 1. Mean PANSS Subscale Scores by Gender

PANSS Subscale	Baseline Visit[a]	Final Visit[a]	Final Visit Adjusted for Baseline[b]
Negative			
Male	14.0*	13.0*	12.7
Female	11.4	11.2	11.9
Cognitive (related to disorganization)			
Male	11.5**	10.0*	9.9*
Female	10.6	9.1	9.3
Psychotic			
Male	15.6*	9.7	9.8
Female	14.8	9.1	9.1
Depression/Anxiety			
Male	10.3	8.0	8.1
Female	10.8	8.6	8.3
Hostility/Excitement			
Male	7.8[c]	6.1[c,]**	6.0[c]
Female	7.4	5.6	5.6

[a]Significance tested by independent *t* test, unequal variance assumed.
[b]Marginal means, adjusted by covarying for baseline score with analysis of covariance.
[c]Boot-strapped *t* test.
*$P < .05$.
**$.05 < P < .10$.
Abbreviation: PANSS = Positive and Negative Syndrome Scale.

Howard and colleagues' classification,[37] the proportion of males under the cutoff for late-onset schizophrenia (age < 40 years) was significantly higher (69%) than the proportion of males over the cutoff (48%; $P = .003$, Fisher exact test).

Age at Onset

Both distributions had a positive skew, with younger ages at onset more common than older ones for both female and male participants (see Figure 1 and Supplementary eFigure 1). Transformation to remove skew improved model fit (details available on request). Mean age at onset was 27.0 years for females (median = 24.0 years) and 24.5 years for males (median = 22.2 years).

For females, 2 components fitted better than 1 (χ^2_1 better by 9.2, $P < .05$; AIC improved from 270.3 to 265.1). Fitting 3 components improved fit only marginally: χ^2_1 improved 3.2 ($P > .05$) and AIC was 264.0. The modal ages at onset for the 2-component model were 23 years and 47 years, and for the 3-component model, 17, 27 and 44 years.

For males, 2 components also fitted better than 1 (χ^2_1 improved 8.0, $P < .05$; AIC improved from 504.9 to 500.8), but 3 components did not fit significantly better (change in χ^2_1: 2.8, $P > .05$; AIC 500.0). Modal ages at onset for the 2-component model were 22 years and 46 years.

PANSS Scores

Total PANSS scores at baseline. At presentation, on average, males had significantly more severe symptoms than females: mean (SD) male PANSS score = 73.5 (23.7); female = 68.6 (21.1); *t* test, $P = .023$. This was true in Canada (male = 63.1 [14.0]; female = 59.4 [14.6]; *t* test, $P = .040$); and the United Kingdom (male = 89.7 [17.5]; female = 85.3 [15.1]; *t* test, $P = .045$). In the United Kingdom, patients were recruited within 14 working days of admission to secondary services, 85% as inpatients, which may account for their greater severity.

PANSS subscales at baseline. PANSS subscales (see eAppendix 1) were Negative, Psychotic, Hostility/Excitement, Depression/Anxiety, and Cognitive (related to disorganization). Univariate analyses indicated that at baseline males experienced significantly more severe psychotic and negative symptoms than females, with a trend toward more severe cognitive-disorganized symptoms (Table 1).

Following adjustment for duration of untreated psychosis, age, country, and interaction terms in the mixed effects model (see the Analysis section and Table 2), males still had significantly more severe negative symptoms at presentation. After conversion from the log-transformed scores (at mean values for other baseline predictors), their Negative symptoms scores were worse by a mean 1.84 points (95% CI, 1.05 to 2.58; $P < .001$). They had a trend toward more severe Cognitive-disorganized (0.45 points; 95% CI, −0.96 to 0.06; $P = 0.086$) and Psychotic symptoms (0.52 points; 95% CI, −1.10 to 0.05; $P = .075$).

Later age at onset partially correlated with lower scores for negative, cognitive-disorganized, depression/anxiety, and hostility/excitement symptoms for females and males (Table 3). The full mixed effects model confirmed this, apart from depression/anxiety. For these symptoms, the picture was complex (Figure 2 and Table 2). Females had significantly higher mean Depression/Anxiety scores than males at presentation. Young-onset females had particularly high scores. There was an interaction between age at onset and gender, such that there was a peak in Depression/Anxiety scores for males with a middle age at onset and a reduction in older-onset males (Figure 2).

Generalized estimating equation analysis confirmed that older onset decreased the odds of high hostility/excitement

Table 2. Parameter Coefficients (B Values) and *P* Values for PANSS Subtotal Models

	ln(Negative)		Cognitive (related to disorganization)		Positive		Depression/Anxiety	
PANSS Subtotal	B	*P*	B	*P*	B	*P*	B	*P*
Time (change at follow-up)	−0.275	<.001	−3.43	<.001	−7.60	<.001	−3.10	<.001
Country × time	+0.247	<.001	+3.61	<.001	+3.01	<.001	+1.58	<.001
Age at onset	−0.007	<.001	−0.05	<.001			−0.06	.003
Gender	−0.150	<.001	*−0.45*	*.086*	*−0.52*	*.075*	+4.35	<.001
Gender × age							+0.20	.007
Gender × age^2							−0.002	.038
Age × time	*+0.004*	*.100*						
Gender × time								

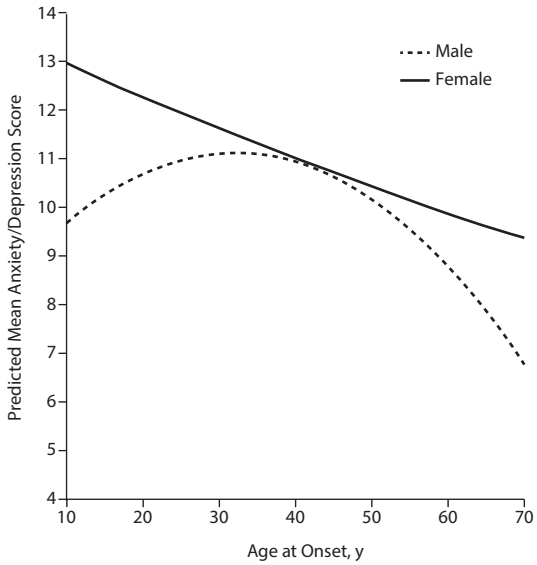
[a]Trend significant terms in italics. Blank spaces indicate that the values were nonsignificant.
Abbreviations: ln(Negative) = natural logarithm of Negative subscale score, PANSS = Positive and Negative Syndrome Scale.

Table 3. Partial Correlation of Age at Onset and PANSS Subscale Score, Controlling for Center, $\log_{10}$ Duration of Untreated Psychosis, and Gender

PANSS Subscale	Baseline Visit	Final Visit	Final Visit Adjusted for Baseline
Negative	−0.18*	−0.12*	−0.05
Cognitive (related to disorganization)	−0.15*	−0.15*	−0.10**
Psychotic	+0.03	−0.02	−0.02
Depression/Anxiety	−0.08**	−0.05	−0.04
Hostility/Excitement	−0.16*	−0.09**	−0.05

*P < .01.
**.05 < P < .10.
Abbreviation: PANSS = Positive and Negative Syndrome Scale.

Figure 2. Severity of PANSS Depression/Anxiety Subscale by Age at Onset: Predicted Mean Scores for Each Age, by Gender



Abbreviation: PANSS = Positive and Negative Syndrome Scale.

(OR = 0.982 per year increase in age at onset; 95% CI, 0.966 to 0.999), with no significant effect of gender.

Cohort at follow-up. Neither gender (P = .69) nor age at onset (P = .21) was significantly related to attrition; 68% of those followed up in each cohort were male, and median age at onset was 22.2 years for males and 26.7 for females.

PANSS scores at follow-up. At final visit, females had lower Negative and Cognitive-disorganized scores and a trend toward lower Hostility/Excitement scores (Table 1). Older age was associated with lower Negative and Cognitive-disorganized and (trend level) Hostility/Excitement scores (Table 3). However, adjustment for baseline scores removed the significance of any relationship between gender or age at onset and symptom scores, apart from a reduced, but still significant, effect of gender on cognitive disorganization (Tables 1 and 3) where males had worse scores.

Mixed effects analysis showed that all PANSS subscale scores declined significantly over follow-up (by 3.1 to 7.6 points), but scores declined from 1.5 to 3.5 points more in the United Kingdom than Canada; in each case, there was a significant country × time interaction (Supplementary eFigure 2 and Table 2). In this more rigorous analysis, there were no significant interactions between gender and age at onset and symptom course (age at onset × time *or* gender × time) for any subscale (Table 2).

In the UK data, we were able to include 3-month follow-up and to adjust the mixed effects analyses for more potential confounders: duration of untreated psychosis (weeks), years of full-time education, ethnicity (African/Caribbean, Asian, or white), and substance misuse.[38] Data included 2 follow-up points (3 and 18 months). A quadratic term modeled greater improvement during the first 3 months than between 3 and 18 months. Results remained consistent with the main analyses, except gender no longer predicted cognitive-disorganized symptoms or depression-anxiety (although older age at onset still predicted significantly lower scores for both, ie, P = .040 and P = .022, respectively). Again, there were no significant interactions of gender and age at onset or of gender and age at onset with follow-up scores.

DISCUSSION

Using one of the largest recent first-episode cohorts to date to examine the relationship between gender, age at onset, and symptom course in schizophrenia, we report 3 main findings. First, the age at onset distribution for both females and males shows 2 nearly identical modal points: in the early 20s and in middle age. Females and males showed no meaningful difference in their underlying modal age at onset (ie, 23 and 22 years, respectively), which is consistent

with previous findings[1,8,39] and supports our first hypothesis. Females and males also showed further peak onset of illness at age 46 and 47 years, respectively. However, younger-onset males outnumbered younger-onset females, whereas the reverse was true for the later-onset mode.

Our second hypothesis, that males and the younger-onset cases are more likely to present with worse negative and cognitive-disorganized symptoms, was also supported (Table 2). Overall, males showed higher total PANSS scores at baseline, with more severe negative and cognitive-disorganized symptoms but less depression/anxiety than females. These findings are similar to other reports,[1,4,6] and findings remained after adjustment for potential confounders. Independent of gender, younger age at onset was associated with more negative and cognitive-disorganized symptoms than older age at onset.

There was also a significant interaction between gender and age at onset for Depression/Anxiety scores such that, at baseline, young-onset females and middle-aged males showed highest Depression/Anxiety scores. Perhaps surprisingly, psychotic symptoms were not significantly predicted by gender or age at onset. This meant that, in older patients and females, psychotic symptoms tended to predominate because other symptoms were relatively reduced.

Finally, after adjusting for symptom severity at baseline, we report that neither gender nor age at onset modified the further course of any symptoms. That is, negative symptoms were worse in males and young patients at presentation and remained so at follow-up because neither gender nor age affected the change in scores over time. Young males without marked negative or cognitive-disorganized symptoms at presentation would not have a worse course than older or female patients with the same symptom profile; population differences between genders were due to young males more often presenting with marked symptoms, rather than a worsening of symptoms over time.

Implications for Etiology

The same modal age at incidence for females and males implies that similar mechanisms underlie psychosis onset in both. The predominance of young-onset males and older-onset females suggests that the mechanisms associated with young onset are more common in males, and those associated with older onset are more common in females. Several hypotheses have been advanced to explain gender differences in schizophrenia. Some have suggested that, in females, the neuroprotective effect of estrogen delays onset and is responsible for less severe symptoms at presentation and better long-term prognosis.[40,41] This might imply that after menopause, older females should show increased incidence and more severe illness than young females.[40] Furthermore, males should not benefit from estrogen effects, implying that there should be a gender by age-at-onset interaction for symptoms over time. Our findings do not support this hypothesis: older-onset females did not show more severe illness than younger-onset females, and age at onset had similar effects on nonaffective symptoms in females and males.

The fact that incidence was more often at young age in males than in females is consistent with the notion that different subtypes of schizophrenia are more likely to occur in one gender than another. Thus, "neurodevelopmental schizophrenia" is conceptualized as having earlier onset, having more severe cognitive-disorganized and negative symptoms, and being overrepresented in males.[39,42–44] This pattern of male predominance in early-onset schizophrenia is common to most neurodevelopmental disorders.[45] We might expect that females with a young age at onset also exhibit "neurodevelopmental schizophrenia" and therefore have the same presentation and prognosis as young-onset males (cf references 10, 39, 46). In that case, gender would have no effect on presenting symptoms after adjusting for age. However, the evidence from our study did not support this. Instead, gender differences in symptom presentation occurred across age groups, without a gender-by-age interaction (see Table 2), apart from affective symptoms, which remained more severe in females independent of age (see Figure 2).

Häfner and colleagues' study[10] included over 300 first-episode cases of schizophrenia. Comparisons with our findings are limited by some methodological differences such as use of age at first admission, rather than symptom onset, and use of broadly defined *ICD-9* caseness. Nevertheless, they also report gender differences in mean age at onset, bimodal and modal peaks for females and males that are very similar to those we observed here. Häfner et al make inferences based on the mean age difference for the genders across the distribution of onsets even though they did not transform their data to account for skewness. However, because we observe that the distribution of onset of schizophrenia is bimodal and non-normal over time, we focus on modal ages at onset (nearly identical for females and males) as well as gender differences between illness presentation at different ages.

More recent understanding of sexual dimorphism in healthy brain development has led to alternative theories about sexual dimorphism in illness risk and expression. Goldstein[47] suggested that normal sexual dimorphism in the brain might, in part, explain sexual dimorphism in both incidence and expression of schizophrenia.[24] More recent thinking takes account of the interplay between developmental stage, sex, and experience. Wong and Weickert[48] suggest that brain development, which is differentiated from conception through sex-chromosomal imprinting, interacts with specific hormonal exposure at critical periods of neurodevelopmental vulnerability. Therefore, it might be that a common mechanism driving the risk for developing schizophrenia in early adulthood in both females and males becomes differentially influenced by gender. Such influences might help to explain why females and males with schizophrenia also show the same pattern of structural brain abnormalities, but with greater severity in males.[49]

Strengths and Limitations

This study has several important strengths. First, it uses one of the largest high-quality incident schizophrenia samples that has follow-up data on cases. Second, the large size of the sample provides power to examine gender and age-at-onset interactions for illness course. Moreover, the cohort was recruited from consecutive incident service contacts using operationalized diagnostic criteria, and the methods used for longitudinal analysis were robust to missing data, making assumptions consistent with the evidence. Lastly, analyses of the UK symptom data allowed inclusion of important potential confounders unavailable for the whole data set and gave similar results to the whole.

There are, however, limitations. Both samples were identified by attendance at particular services, although, for instance, the UK SOCRATES study identified virtually all presentations to the National Health Service and hence almost all presentations.[27,28] Although SOCRATES was further limited by consent to take part in the trial, 87% consented, a higher proportion than in many epidemiologic studies.[38] Although gender differences appear similar between countries,[50,51] differences in inclusion criteria, diagnostic systems (*ICD-9* and *DSM-IV*), age limits, and services influenced differences in case characteristics between cohorts. Nevertheless, there was convergence between the distribution of diagnoses in both cohorts: 77% in Canada had *ICD*-defined schizophrenia, and 75% in the United Kingdom had *DSM*-defined schizophreniform disorder and schizophrenia. Different age limits should have affected neither the maxima of the curves underlying the age at onset distribution modeled by SKUMIX nor the relationship between gender, age-at-onset, and psychopathology in the mixed effects models. Some UK adolescents or Canadians over 40 years of age were diverted to other services. Our models adjusted for differences between services in symptoms at presentation and findings for the combined data sets, and UK data alone were consistent.

Service Implications

Male gender and younger age have traditionally been associated with poorer illness outcomes in schizophrenia. However, in this large first-episode cohort, there was no association between gender or age at onset and symptom course in the medium term after adjusting for symptom severity at presentation. This lack of association suggests that age and gender offer limited prognostic value to clinicians when attempting to determine illness course. While age and gender alter presentation (for example, females are less likely to present with severe negative and cognitive-disorganized symptoms), they do not appear to modify the course of illness. Efforts to identify individuals when symptoms are less severe could have important implications for improving longer-term outcome, which highlights the importance of early intervention services, including identification of those at ultrahigh risk of psychosis.[52–54] Similarly, efforts to reduce the duration of untreated psychosis, which has been associated with poorer outcomes,[55,56] could help improve baseline presentation and have important implications for illness course.[57]

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Supplementary material: See accompanying pages.

Database information: The UK data are owned by the UK Medical Research Council, and the Canadian data are owned by the researchers.

REFERENCES

1. Leung A, Chue P. Sex differences in schizophrenia, a review of the literature. *Acta Psychiatr Scand suppl*. 2000;401(401):3–38.
2. Ochoa S, Usall J, Cobo J, et al. Gender differences in schizophrenia and first-episode psychosis: a comprehensive literature review. *Schizophr Res Treatment*. 2012;2012:916198.
3. Thorup A, Petersen L, Jeppesen P, et al. Gender differences in young adults with first-episode schizophrenia spectrum disorders at baseline in the Danish OPUS study. *J Nerv Ment Dis*. 2007;195(5):396–405.
4. Morgan VA, Castle DJ, Jablensky AV. Do women express and experience psychosis differently from men? epidemiological evidence from the Australian National Study of Low Prevalence (Psychotic) Disorders. *Aust N Z J Psychiatry*. 2008;42(1):74–82.
5. Køster A, Lajer M, Lindhardt A, et al. Gender differences in first episode psychosis. *Soc Psychiatry Psychiatr Epidemiol*. 2008;43(12):940–946.
6. Cotton SM, Lambert M, Schimmelmann BG, et al. Gender differences in premorbid, entry, treatment, and outcome characteristics in a treated epidemiological sample of 661 patients with first episode psychosis. *Schizophr Res*. 2009;114(1–3):17–24.
7. Eranti SV, MacCabe JH, Bundy H, et al. Gender difference in age at onset of schizophrenia: a meta-analysis. *Psychol Med*. 2013;43(1):155–167.
8. Abel KM, Drake R, Goldstein JM. Sex differences in schizophrenia. *Int Rev Psychiatry*. 2010;22(5):417–428.
9. Jablensky A, Sartorius N, Ernberg G, et al. Schizophrenia: manifestations, incidence and course in different cultures: a World Health Organization ten-country study. *Psychol Med Monogr suppl*. 1992;20(1):1–97.
10. Häfner H, Maurer K, Löffler W, et al. The influence of age and sex on the onset and early course of schizophrenia. *Br J Psychiatry*. 1993;162(1):80–86.
11. Harrison G, Hopper K, Craig T, et al. Recovery from psychotic illness: a 15- and 25-year international follow-up study. *Br J Psychiatry*. 2001;178(6):506–517.
12. León CA. Clinical course and outcome of schizophrenia in Cali, Colombia. a 10-year follow-up study. *J Nerv Ment Dis*. 1989;177(10):593–606.
13. McCreadie RG, Wiles D, Grant S, et al. Scottish Schizophrenia Research Group. The Scottish first episode schizophrenia study, VII: two-year follow-up. *Acta Psychiatr Scand*. 1989;80(6):597–602.
14. Rajkumar S, Thara R. Factors affecting relapse in schizophrenia. *Schizophr Res*. 1989;2(4–5):403–409.
15. Iacono WG, Beiser M. Are males more likely than females to develop schizophrenia? *Am J Psychiatry*. 1992;149(8):1070–1074.
16. Thara R, Rajkumar S. Gender differences in schizophrenia: results of a follow-up study from India. *Schizophr Res*. 1992;7(1):65–70.
17. Vázquez-Barquero JL, Cuesta Nuñez MJ, Herrera Castanedo S, et al. Sociodemographic and clinical variables as predictors of the diagnostic characteristics of first episodes of schizophrenia. *Acta Psychiatr Scand*. 1996;94(3):149–155.
18. Wiersma D, Nienhuis FJ, Slooff CJ, et al. Natural course of schizophrenic disorders: a 15-year followup of a Dutch incidence cohort. *Schizophr Bull*. 1998;24(1):75–85.
19. Robinson D, Woerner MG, Alvir JM, et al. Predictors of relapse following response from a first episode of schizophrenia or schizoaffective disorder. *Arch Gen Psychiatry*. 1999;56(3):241–247.
20. Selten JP, Veen ND, Hoek HW, et al. Early course of schizophrenia in a representative Dutch incidence cohort. *Schizophr Res*. 2007;97(1–3):79–87.
21. Grossman LS, Harrow M, Rosen C, et al. Sex differences in schizophrenia and other psychotic disorders: a 20-year longitudinal study of psychosis and recovery. *Compr*

Psychiatry. 2008;49(6):523–529.
22. Goldstein JM, Link BG. Gender and the expression of schizophrenia. *J Psychiatr Res*. 1988;22(2):141–155.
23. Roy MA, Maziade M, Labbé A, et al. Male gender is associated with deficit schizophrenia: a meta-analysis. *Schizophr Res*. 2001;47(2–3):141–147.
24. Goldstein JM, Seidman LJ, O'Brien LM, et al. Impact of normal sexual dimorphisms on sex differences in structural brain abnormalities in schizophrenia assessed by magnetic resonance imaging. *Arch Gen Psychiatry*. 2002;59(2):154–164.
25. Addington J, Addington D. Early intervention for psychosis: the Calgary Early Psychosis Treatment and Prevention Program. CPA Bulletin (Fall). 2001;33(3):11–16.
26. Addington J, van Mastrigt S, Addington D. Patterns of premorbid functioning in first-episode psychosis: initial presentation. *Schizophr Res*. 2003;62(1–2):23–30.
27. Lewis S, Tarrier N, Haddock G, et al. Randomised controlled trial of cognitive-behavioural therapy in early schizophrenia: acute-phase outcomes. *Br J Psychiatry suppl*. 2002;43(suppl 43):s91–s97.
28. Tarrier N, Lewis S, Haddock G, et al. Cognitive-behavioural therapy in first-episode and early schizophrenia. 18-month follow-up of a randomised controlled trial. *Br J Psychiatry*. 2004;184(3):231–239.
29. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophr Bull*. 1987;13(2):261–276.
30. Drake RJ, Haley CJ, Akhtar S, et al. Causes and consequences of duration of untreated psychosis in schizophrenia. *Br J Psychiatry*. 2000;177(6):511–515.
31. Addington J, Van Mastrigt S, Addington D. Duration of untreated psychosis: impact on 2-year outcome. *Psychol Med*. 2004;34(2):277–284.
32. Maclean CJ, Morton NE, Elston RC, et al. Skewness in commingled distributions. *Biometrics*. 1976;32(3):695–699.
33. Viswanathan AC, Hitchings RA, Indar A, et al. Commingling analysis of intraocular pressure and glaucoma in an older Australian population. *Ann Hum Genet*. 2004;68(pt 5):489–497.
34. White L, Harvey PD, Opler L, et al; The PANSS Study Group. Empirical assessment of the factorial structure of clinical symptoms in schizophrenia. a multisite, multimodel evaluation of the factorial structure of the Positive and Negative Syndrome Scale. *Psychopathology*. 1997;30(5):263–274.
35. Drake RJ, Dunn G, Tarrier N, et al. The evolution of symptoms in the early course of non-affective psychosis. *Schizophr Res*. 2003;63(1–2):171–179.
36. Little RJA, Rubin DB. *Statistical Analysis with Missing Data*. New York, NY: John Wiley & Sons; 1987.
37. Howard R, Rabins PV, Seeman MV, et al; The International Late-Onset Schizophrenia Group. Late-onset schizophrenia and very-late-onset schizophrenia-like psychosis: an international consensus. *Am J Psychiatry*. 2000;157(2):172–178.
38. Drake RJ, Dunn G, Tarrier N, et al. Insight as a predictor of the outcome of first-episode nonaffective psychosis in a prospective cohort study in England. *J Clin Psychiatry*. 2007;68(1):81–86.
39. Castle DJ, Abel K, Takei N, et al. Gender differences in schizophrenia: hormonal effect or subtypes? *Schizophr Bull*. 1995;21(1):1–12.
40. Hambrecht M, Maurer K, Häfner H. Evidence for a gender bias in epidemiological studies of schizophrenia. *Schizophr Res*. 1993;8(3):223–231.
41. Riecher-Rössler A, Häfner H, Stumbaum M, et al. Can estradiol modulate schizophrenic symptomatology? *Schizophr Bull*. 1994;20(1):203–214.
42. Lewine RR. Sex differences in schizophrenia: timing or subtypes? *Psychol Bull*. 1981;90(3):432–434.
43. Murray RM. Neurodevelopmental schizophrenia: the rediscovery of dementia praecox. *Br J Psychiatry suppl*. 1994;165(25):6–12.
44. Abel KM, Castle DJ. Can estrogens account for sex differences in schizophrenia? In: Lewis-Hall F, Williams TS, Panetta JA, et al, eds. *Psychiatric Illness in Women: Emerging Treatments and Research*. 1st ed. Washington, DC: American Psychiatric Press Inc; 2002:331–347.
45. Abel KM, Allin MA. Placental programming & neurodevelopmental outcomes. In: Baker P, Sibley C, eds. *The Placenta and Neurodisability*. 3rd ed. London, UK: Mac Keith Press; 2014, In press.
46. Salokangas RK. Living situation, social network and outcome in schizophrenia: a five-year prospective follow-up study. *Acta Psychiatr Scand*. 1997;96(6):459–468.
47. Goldstein JM. Sex differences in schizophrenia: epidemiology, genetics, and the brain. *Int Rev Psychiatry*. 1997;9(4):399–408.
48. Wong J, Weickert CS. Transcriptional interaction of an estrogen receptor splice variant and ErbB4 suggests convergence in gene susceptibility pathways in schizophrenia. *J Biol Chem*. 2009;284(28):18824–18832.
49. Nopoulos P, Flaum M, Andreasen NC. Sex differences in brain morphology in schizophrenia. *Am J Psychiatry*. 1997;154(12):1648–1654.
50. Sartorius N, Jablensky A, Korten A, et al. Early manifestations and first-contact incidence of schizophrenia in different cultures. a preliminary report on the initial evaluation phase of the WHO Collaborative Study on determinants of outcome of severe mental disorders. *Psychol Med*. 1986;16(4):909–928.
51. Hambrecht M, Maurer K, Häfner H, et al. Transnational stability of gender differences in schizophrenia? an analysis based on the WHO study on determinants of outcome of severe mental disorders. *Eur Arch Psychiatry Clin Neurosci*. 1992;242(1):6–12.
52. Yung AR, Phillips LJ, Yuen HP, et al. Psychosis prediction: 12-month follow up of a high-risk ("prodromal") group. *Schizophr Res*. 2003;60(1):21–32.
53. Fusar-Poli P, Borgwardt S, Bechdolf A, et al. The psychosis high-risk state: a comprehensive state-of-the-art review. *JAMA Psychiatry*. 2013;70(1):107–120.
54. Nelson B, Yuen HP, Wood SJ, et al. Long-term follow-up of a group at ultra high risk ("prodromal") for psychosis: the PACE 400 study. *JAMA Psychiatry*. 2013;70(8):793–802.
55. Schimmelmann BG, Huber CG, Lambert M, et al. Impact of duration of untreated psychosis on pre-treatment, baseline, and outcome characteristics in an epidemiological first-episode psychosis cohort. *J Psychiatr Res*. 2008;42(12):982–990.
56. Chang WC, Tang JY, Hui CL, et al. Duration of untreated psychosis: relationship with baseline characteristics and three-year outcome in first-episode psychosis. *Psychiatry Res*. 2012;198(3):360–365.

Supplementary material follows this article.

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Supplementary Material

Article Title: How Age and Gender Predict Illness Course in a First-Episode Nonaffective Psychosis Cohort

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List of Supplementary Material for the article

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This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

eAppendix 1

PANSS subscale compositions

P (Psychotic)

P1 (Delusions), P3 (Hallucinatory behaviour), P5 (Grandiosity), G9 (Unusual thought)

Subscale range: 4-28

HE (Hostile-excited)

P4 (Agitation), P7 (Hostility), G8 (Uncooperativeness), G14 (Impulsivity)

Subscale range: 4-28

DA (Depressed-anxious)

G2 (Anxiety), G3 (Guilt), G4 (Tension), G6 (Depression)

Subscale range: 4-28

N (Negative)

N1 (Blunting), N2 (Emotional Withdrawal), N3 (Poor rapport), N4 (Social withdrawal), N6 (Lack of spontaneity), G5 (Mannerisms), G7 (Motor retardation)

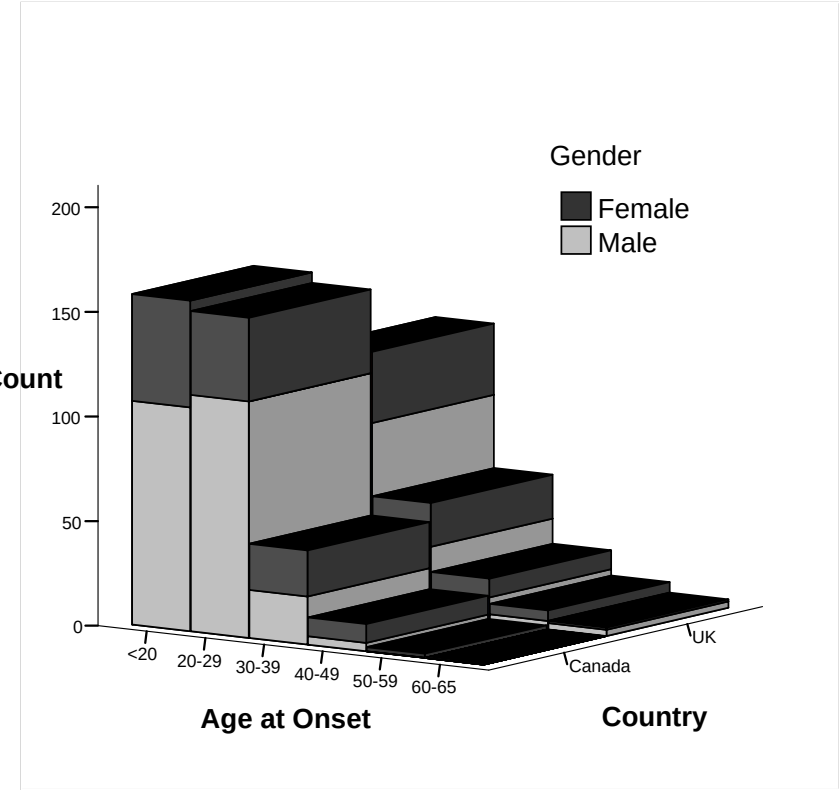
Subscale range: 7-49

C (Cognitive)

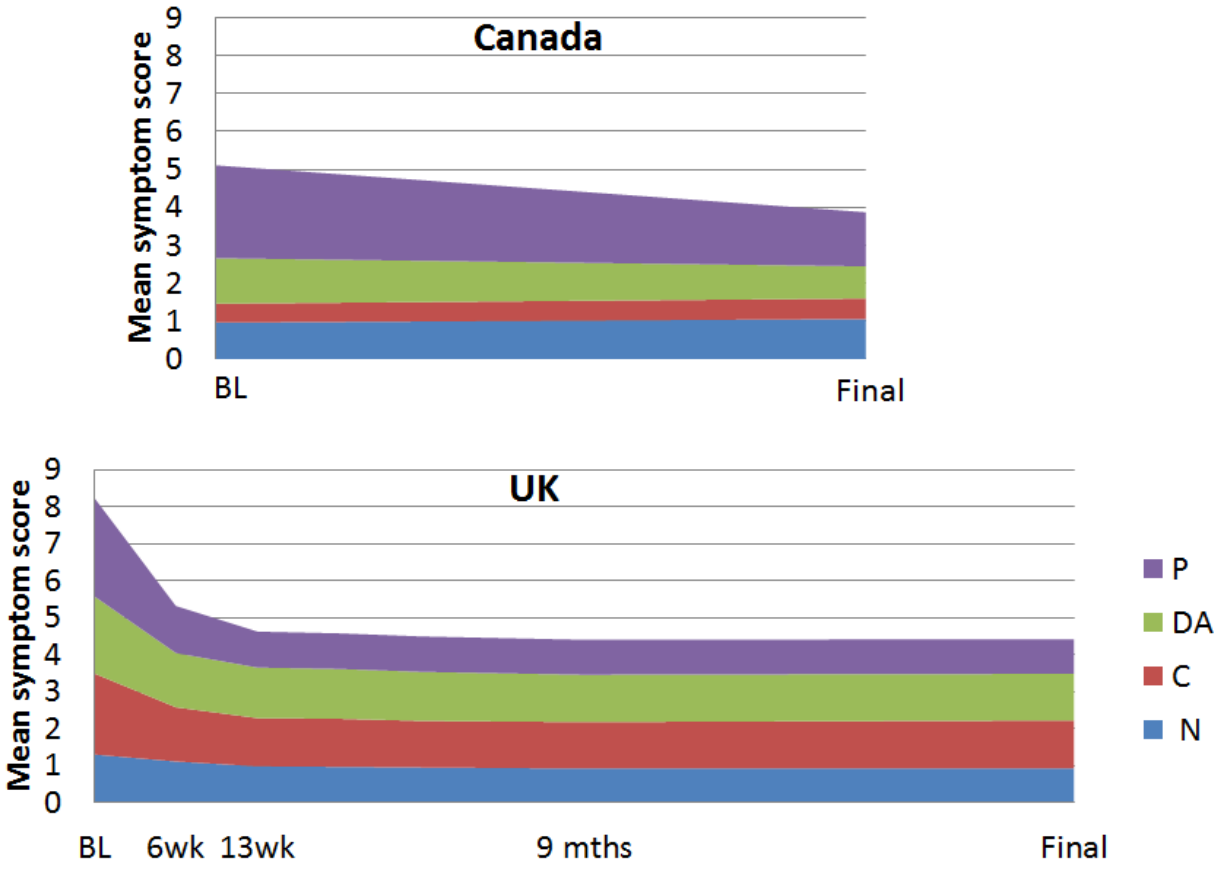
N5 (Impaired abstraction), N7 (Stereotyped thought), G11 (Attention), G13 (Disturbed volition), G15 (Preoccupation)

Subscale range: 5-35

Supplementary eFigure 1. Age-at-onset by country, stacked by gender. Total numbers for the Canadian (n=371) and UK (n=257) datasets differ.



Supplementary eFigure 2. Mean symptom score at each visit for each country. For each subscale, symptom score = (PANSS item total/number of items) – 1. [this gives a possible range of 0-6 for each subscale].



Abbreviations: BL, Baseline; C, Cognitive; DA, Depressed-anxious; Mths, Months; N, Negative; P, Positive; Wk, Weeks