Psychological Medicine, 2007, **37**, 479–484. © 2007 Cambridge University Press
doi:10.1017/S0033291707009944 First published online 9 February 2007 Printed in the United Kingdom

Young males have a higher risk of developing schizophrenia: a Danish register study

ANNE THORUP[1]*, BERIT LINDUM WALTOFT[2], CARSTEN B. PEDERSEN[2], PREBEN B. MORTENSEN[2] AND MERETE NORDENTOFT[1]

[1] *Department of Psychiatry, Bispebjerg Hospital, Copenhagen NV, Denmark*; [2] *National Centre for Register-based Research, University of Aarhus, Aarhus C, Denmark*

ABSTRACT

Background. Gender differences are commonly reported in schizophrenia research, especially with regard to age at onset. Few studies have reported the age- and gender-specific incidence of schizophrenia in people aged up to 71 years, and no studies have reported the cumulative incidence of schizophrenia in people aged up to 71 years.

Method. Two cohorts were established by linking data from the Danish Civil Registration System (DCRS) with data from the Danish Psychiatric Central Register (DPCR), which covers all incident cases of schizophrenia from 15 to 71 years. We estimated the gender- and age-specific incidence rates of schizophrenia for people aged up to 71 years. We also estimated the cumulative incidences.

Results. The incidence rates for males significantly exceeded those for females in the age range from 17 to 40 years. By their 72nd birthday, 1·59% of males and 1·17% of females had developed schizophrenia.

Conclusion. Male sex is a major risk factor for the development of schizophrenia.

INTRODUCTION

Gender differences in schizophrenia have frequently been reported in many different aspects of the illness, from psychopathology and prognosis to characteristics of onset and treatment response. However, many basic questions still need to be addressed.

Hafner *et al.* (1989, 1993), who contributed substantially to the available knowledge about gender differences and schizophrenia, and Hambrecht *et al.* (1993) claimed in the mid-1990s that the lifetime risk for developing schizophrenia is 1 : 1 for males and females respectively, but that the risk for women increases with increasing age. This assumption is still widely accepted and often referred to. However, on the basis of a large meta-analysis including 100 studies, McGrath *et al.* (2004) concluded that males have a 1·4-fold increased risk of developing schizophrenia compared to females. In the AESOP (Aetiology and Ethnicity of Schizophrenia and Other Psychoses) study it was also found that schizophrenia was more common in males (the incident rate ratio was 2·3) (Kirkbride *et al.* 2006). This could partly depend on diagnostic systems and tradition. For example, some clinicians may be more reluctant than others to use the diagnosis 'first-episode schizophrenia' for an 85-year-old paranoid woman.

In 1976 the Camberwell Register First Episode Study (Kendell *et al.* 1976) reported incidence rates for men and women across all ages of onset but this was a smaller study than the current one and with another purpose. The current study is the first, and one of the largest, to report the age- and gender-specific incidence of schizophrenia in people up to 71 years. Estimates were based on complete nationwide coverage of all persons admitted to hospital or treated in in-patient care. In

* Author for correspondence: Anne Thorup, M.D., Bispebjerg Hospital, Department of Psychiatry, Bispebjerg Bakke 23, DK 2400 NV, Denmark.
(Email: atv@dadlnet.dk)

https://doi.org/10.1017/S0033291707009944 Published online by Cambridge University Press

Denmark the vast majority of people with schizophrenia have either been admitted or are in in-patient care. To our knowledge this is also the first study to report unbiased estimates of the cumulative incidence of schizophrenia in people aged up to 71 years.

The aim of this study was to estimate the age- and gender-specific incidence rates of schizophrenia for people born in Denmark, and to estimate the age- and gender-specific cumulative incidence rate of schizophrenia. Incidence is defined as the number of new cases of a specific disease per 100 000 person-years in a population.

METHOD

Study population and risk period definition

In Denmark every person alive or born after 1 April 1968 is assigned a personal identification number. The Danish Civil Registration System (DCRS; Pedersen *et al.* 2006) holds information about personal identification numbers and links every person to such data as date of birth, gender, date of death, and date of emigration. The personal identification number is the unique link to individual information in all national registers.

The Danish Psychiatric Central Register (DPCR; Munk-Jørgensen & Mortensen, 1997) includes every psychiatric in-patient admission between 1 January 1970 and 31 December 2005. From 1 January 1995 this register also holds information on every out-patient attendance. Diagnosis in the period from 1 January 1970 to 31 December 1993 is coded using the ICD-8 diagnostic system, while for registration after 1 January 1994 the ICD-10 diagnostic system is used. We linked the DCRS with the DPCR using the personal identification number.

We established one cohort (the 'young cohort') by identifying every person born in Denmark from 1955 to 1990. From the DPCR we identified the first time a cohort member received a diagnosis of schizophrenia [ICD-8 (295 except 295·79) or ICD-10 (F20)], if any. Cohort members were followed from their 15th birthday until the first diagnosis of schizophrenia, death, emigration from Denmark, their 51st birthday or 31 December 2005 (whichever came first). For the 'young cohort' we have complete information about all individuals hospitalized or in out-patient care with a diagnosis of schizophrenia from their 15th to their 51st birthday.

To cover the rest of the risk period, from the 51st birthday to the 72nd birthday, we established the 'old cohort' by identifying every person born in Denmark in the period from 1934 to 1954. From the DPCR we identified the first time a cohort member received a diagnosis of schizophrenia, if any. We followed this older cohort from their 51st birthday until the first diagnosis of schizophrenia, death, emigration or 31 December 2005 (whichever came first). We expected the first registered cases of schizophrenia to represent the incident cases if they had not received a diagnosis from 1 January 1970 to 31 December 1984, thus all persons who were diagnosed before their 51st birthday were not included. Therefore, for the 'older cohort' we assume that we have complete information about all people hospitalized or in out-patient care with a diagnosis of schizophrenia from the 51st birthday and onwards. When collapsing data from the young and the older cohorts, all incident cases from the 15th to the 72nd birthday were included.

Statistical analysis

The age- and gender-specific incidence rate was calculated as the number of new cases occurring for each age and gender. To explore the age-specific incidence of schizophrenia in as much detail as possible and to minimize the risk of bias, age was categorized in 1-year intervals from the 15th to the 20th birthday and in 2-year intervals thereafter. The age- and gender-specific incidence rates were estimated using Poisson regression (Breslow & Day, 1987) in SAS version 9 (SAS Institute Inc., Cary, NC, USA).

The change in diagnostic system in Denmark in 1994 from ICD-8 to ICD-10 produced more incident cases of schizophrenia (Pedersen & Mortensen, 2001), suggesting that ICD-8 missed some cases of schizophrenia. To compensate for these changes, estimates of incidence were adjusted for calendar year, such that the estimates of incidences measured the incidences had all cohort members been followed during the use of the ICD-10 classification.

We used the estimated incidence rates to calculate the cumulative incidences (Andersen

https://doi.org/10.1017/S0033291707009944 Published online by Cambridge University Press

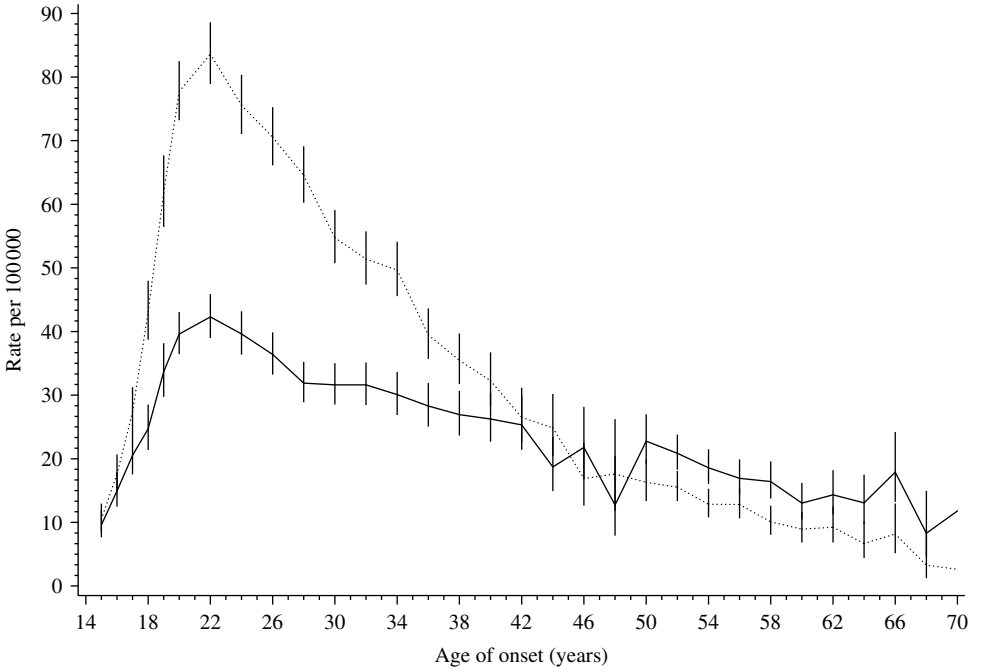


FIG. 1. Incidence rates of schizophrenia by age and gender adjusted for the changes in the diagnostic system (baseline is the ICD-10 period, 1995–2001). ——, Females; ····, males.

et al. 1993), taking into account the possibility that a person may die before receiving a diagnosis. The cumulative incidence describes, at a given age, the proportion of people in a population who have received a diagnosis earlier than the given age. These analyses were made for each gender, and both for in-patients only and for out- and in-patients.

RESULTS

Overall, 16 762 persons (6421 females and 10 341 males) developed schizophrenia during 58·0 million person-years. Of those 16 762 persons, 5633 individuals developed schizophrenia during the use of the ICD-8 classification (1970–1993) and 11 129 persons developed schizophrenia during the use of the ICD-10 classification (1994–2005).

Incidence

The incidence rates of schizophrenia varied with gender and age (Fig. 1). The incidence measures the number of new cases that occurred per 100 000 person-years at risk. Having adjusted for the diagnostic system used, these estimates measure the incidence had all cohort members been followed during the used of the ICD-10 classification (see Method section). The age-specific incidence varied by gender. In the age range from 17 to 40 years, the incidence rates for males significantly exceed those for females, while in the age groups from 50 to 68, the incidence rates for women significantly exceed those for males. For both sexes the incidence peaked at 22–23 years of age. These differences between males and females were similar for the unadjusted data and for only in-patient diagnoses.

Cumulative incidence

The age- and gender-specific cumulative incidences of schizophrenia are shown in Fig. 2. These numbers were adjusted for diagnostic changes and include both in- and out-patients. For all ages the cumulative incidence was larger for males than for females. By their 72nd birthday 1·59% [95% confidence interval (CI) 1·55–1·62] of all males and 1·17% (95% CI 1·14–1·20) of all females had developed schizophrenia.

https://doi.org/10.1017/S0033291707009944 Published online by Cambridge University Press

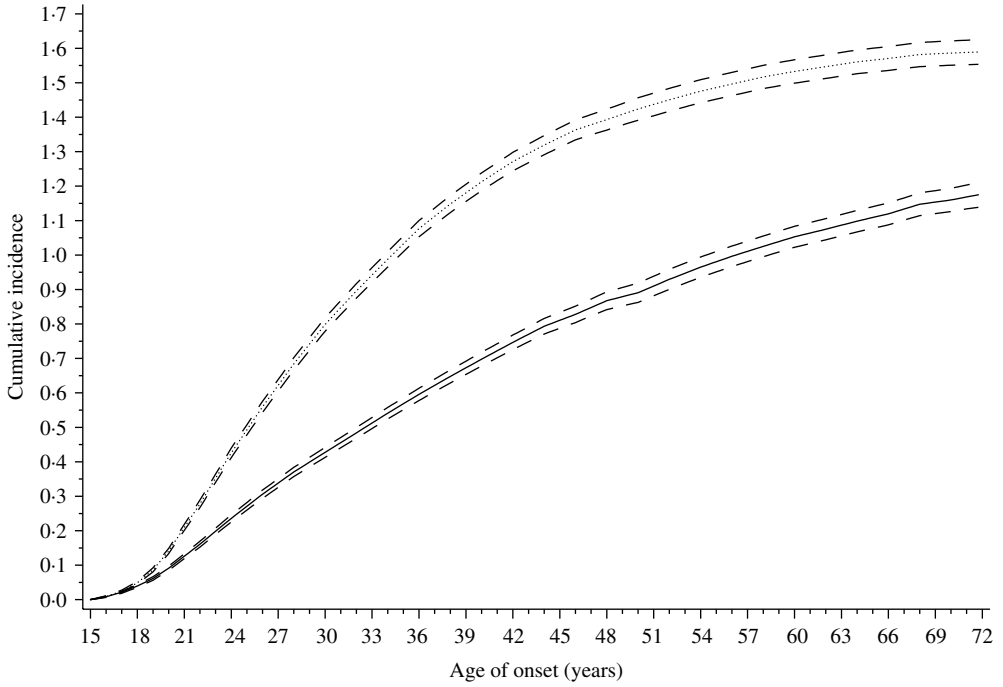


FIG. 2. Cumulated incidences of schizophrenia by age and gender in competing risk, adjusted for changes in diagnostic system. ——, Females; ····, males. The dashed lines (– – –) indicate 95% confidence intervals.

Mean age and median age

The mean age at onset for men was 29·31 (95% CI 29·12–29·51), median 26·77 (95% CI 26·59–26·95). For females the mean age was 32·78 (95% CI 32·47–33·10), median 29·08 (95% CI 28·66–29·49). However, because in this study we lacked information on the oldest incident cases of schizophrenia, our estimates of mean and median age of onset may be biased downwards.

DISCUSSION

Our data strongly indicate that the lifetime risk of developing schizophrenia is dependent on gender. We investigated two cohorts who, when the data were collapsed, had lived through the major part of the life risk period for developing schizophrenia (15–71 years of age), and found that males had the highest incidence rates from age 17 to 40, while females had the highest incidence rates from age 50 to 68. This method gives a much more detailed picture of the sex differences in onset of schizophrenia than comparing means of ages at onset. The risk period was defined as ranging from age 15 to 71 on the basis of the literature. For instance, Jablensky (Hirsch & Weinberger, 2003) states that the majority of onsets fall within the interval of 15–54 years of age. However, we extended the age range up to 71 years.

Before interpreting the results, some considerations regarding the possible bias of the results should be mentioned. Is the higher incidence among males caused by methodological bias or is it a true difference? First, we must evaluate the validity of the diagnoses and other data from the registers. To what extent do the reported incidences reflect the 'true' incidence? There are three steps before a patient is registered in the DPCR and gender bias may occur at all three steps. *Step 1*: Some patients may never apply for treatment; on some occasions this is estimated at up to 20% of all patients. Some of these may be patients with milder courses who can find a way of living with their 'special characteristics' (a majority of these might be women). Some may be the very serious cases where abuse, homelessness or criminalization prevents treatment and among whom the suicide rate is high (mostly males). However, for

https://doi.org/10.1017/S0033291707009944 Published online by Cambridge University Press

the majority of patients with schizophrenia, the disease has such a serious impact on their everyday living that the need for treatment is evident. *Step 2*: Some patients may be treated for years only by their general practitioner (GP) and thus never become registered in the DPCR. In our opinion this is a minority of cases because in Denmark we do not have a tradition of treating severe mental illness in primary health care; although in some cases GPs may be providing maintenance treatment. *Step 3* is the validity of the diagnoses. We know that the diagnosis 'schizophrenia' was applied less frequently when ICD-8 was used, and that women in particular were underdiagnosed (Castle *et al.* 1993). Physicians were more reluctant to give the diagnosis because of the poor prognosis and the stigmatizing effect implicit in the diagnosis. Although this may have changed with ICD-10, we cannot rule out the possibility that the risk of developing a poor course and being stigmatized may prevent some physicians from using the diagnosis. Aleman *et al.* (2003) mention that women may be underdiagnosed with schizophrenia at first admission, but it is also possible that males are more frequently misdiagnosed with schizophrenia, which diagnosis is then later adjusted to, for example, bipolar disorder. Cultural norms and social expectations, such as 'women are more affectionate' or 'women are more emotional', may also contribute to women being diagnosed more often with affective disorders or personality disorders (Nasser *et al.* 2002).

All these factors are theoretically sources of bias that could influence the diagnoses reported to the register and thus the estimated incidence rates. We are, however, convinced that they are of minor importance, and that the registers hold the vast majority of the patients applying for treatment for schizophrenia in Denmark.

We took into account the fact that the diagnostic system has changed during the time period that we investigated by reporting the incidence had all cohort members been followed during the use of the ICD-10 classification. The diagnostic systems and traditions may influence the number and characteristics of the patients who will meet the diagnostic criteria for schizophrenia. The narrower the diagnostic criteria used, the more women are excluded from a diagnosis of schizophrenia (Lewine *et al.* 1984; Castle *et al.* 1993). If affective or atypical symptoms are included in the diagnostic systems, more women will be diagnosed. Major changes in the treatment opportunities may also be reflected in the number of patients applying for treatment. We also included all out-patient diagnoses, which increased markedly in number after the major structural changes in the psychiatric treatment system in Denmark in the early 1980s. Out-patient diagnoses were included in the register from 1995.

In our analyses of the oldest cohort born 1934–1954, we anticipated that if an individual had not been admitted with a diagnosis of schizophrenia during the past 15 years, it meant that they would never have been diagnosed, in other words that a person with a diagnosis of schizophrenia will always be hospitalized at least once within 15 years. Although this is very likely, it may not always be the case. However, if bias was introduced, it would only affect the results concerning people aged 51 or more.

Our results confirm that the incidence rates vary a good deal over the lifetime risk period. Means and medians are also reported. We found that the mean age at onset for females is 3 years higher than that of males, as expected. Our findings of a peak in incidence for females aged 22–23 years are in contrast to the findings of the AESOP study (Kirkbride *et al.* 2004), where only a minor variation in the age-specific incidence for females was reported.

Our results are thus on some points in opposition to what Hafner and colleagues found in the ABC (Age, Beginning, Course) study and in the analyses of data from Denmark from 1976 (Hafner *et al.* 1989) and in accordance with the conclusions of McGrath *et al.* (2004) and Aleman *et al.* (2003). Our results may indicate that males develop a more severe form of the disorder, which is therefore easier to recognize and to diagnose. The possibility that schizophrenia may to a larger extent go unrecognized in women than in men, as stressed by Aleman *et al.* (2003), has not been completely ruled out. However, on the basis of our results, we conclude that male sex is a major risk factor for developing schizophrenia.

A detailed discussion of the possible reasons for this gender difference in incidence lies beyond the scope of this paper, but a few important issues should be mentioned. Some cultural

https://doi.org/10.1017/S0033291707009944 Published online by Cambridge University Press

aspects have already been mentioned, but biology is most likely to be a contributing factor.

According to the neurodevelopmental hypothesis of the origin of schizophrenia, there are special features of the male brain that make it more prone to develop structural brain abnormalities, obstetric complications and neurodevelopmental disorders such as Asperger syndrome (Castle & Murray, 1991; Kirov *et al.* 1996; Guerguerian & Lewine, 1998). Compared with women, males have higher rates of cortical atrophy and increased ventricle–brain ratios, which have been associated with cognitive impairment, poor pre-morbid adjustment and more negative symptomatology (Castle & Murray, 1991). In a review by DeLisi *et al.* (1989) aiming to answer the question 'Are gender differences in the brain relevant to pathogenesis of schizophrenia?', other important issues are described: genetic contributions, neuroendocrine disturbances and the impact of sex, growth and steroid hormones, and brain lateralization. Cowell *et al.* (1996) add to the hypotheses that hormonal and neurochemical changes during puberty may contribute to changes in neuroanatomy. In general, this field is flawed because many biological studies consist of small or unrepresentative samples with unbalanced male/female ratios (mainly excess of males; Wahl & Hunter, 1992). More gender-specific research concerning the origin of schizophrenia and, for example, gene–environment interactions is needed to explain the difference in lifetime risk for men and women.

ACKNOWLEDGEMENTS

This study was supported by the Stanley Medical Research Institute. Psychiatric epidemiological research at the National Centre for Register-based Research is in part funded through a collaborative agreement with the Centre for Basic Psychiatric Research, Psychiatric Hospital in Aarhus, Denmark.

DECLARATION OF INTEREST

None.

REFERENCES

Aleman, A., Kahn, R. S. & Selten, J. P. (2003). Sex differences in the risk of schizophrenia: evidence from meta-analysis. *Archives of General Psychiatry* **60**, 565–571.

Andersen, P. K., Borgen, Ø., Gill, R. D. & Keiding, N. (1993). *Statistical Models Based on Counting Processes*. Springer-Verlag: New York.

Breslow, N. & Day, N. (1987). *Statistical Methods in Cancer Research, Volume II: The Design and Analysis of Cohort Studies*. IARC: Lyon.

Castle, D. J. & Murray, R. M. (1991). The neurodevelopmental basis of sex differences in schizophrenia. *Psychological Medicine* **21**, 565–575.

Castle, D. J., Wessely, S. & Murray, R. M. (1993). Sex and schizophrenia: effects of diagnostic stringency, and associations with premorbid variables. *British Journal of Psychiatry* **162**, 658–664.

Cowell, P. E., Kostianovsky, D. J., Gur, R. C., Turetsky, B. I. & Gur, R. E. (1996). Sex differences in neuroanatomical and clinical correlations in schizophrenia. *American Journal of Psychiatry* **153**, 799–805.

DeLisi, L. E., Dauphinais, I. D. & Hauser, P. (1989). Gender differences in the brain: are they relevant to the pathogenesis of schizophrenia? *Comprehensive Psychiatry* **30**, 197–208.

Guerguerian, R. & Lewine, R. R. (1998). Brain torque and sex differences in schizophrenia. *Schizophrenia Research* **30**, 175–181.

Hafner, H., Riecher, A., Maurer, K., Loffler, W., Munk-Jorgensen, P. & Stromgren, E. (1989). How does gender influence age at first hospitalization for schizophrenia? A transnational case register study. *Psychological Medicine* **19**, 903–918.

Hafner, H., Riecher-Rossler, A., an der Heiden, W., Maurer, K., Fatkenheuer, B. & Loffler, W. (1993). Generating and testing a causal explanation of the gender difference in age at first onset of schizophrenia. *Psychological Medicine* **23**, 925–940.

Hambrecht, M., Maurer, K. & Hafner, H. (1993). Evidence for a gender bias in epidemiological studies of schizophrenia. *Schizophrenia Research* **8**, 223–231.

Hirsch, S. & Weinberger, D. R. (2003). *Schizophrenia* (2nd edn). Blackwell Science Ltd: Massachusetts.

Kendell, R. E., Wainwright, S., Hailey, A. & Shannon, B. (1976). The influence of childbirth on psychiatric morbidity. *Psychological Medicine* **6**, 297–302.

Kirkbride, J. B., Fearon, P., Morgan, C., Dazzan, P., Morgan, K., Tarrant, J., Lloyd, T., Holloway, J., Hutchinson, G., Leff, J. P., Mallett, R. M., Harrison, G. L., Murray, R. M. & Jones, P. B. (2006). Heterogeneity in incidence rates of schizophrenia and other psychotic syndromes: findings from the 3-center AeSOP study. *Archives of General Psychiatry* **63**, 250–258.

Kirov, G., Jones, P. B., Harvey, I., Lewis, S. W., Toone, B. K., Rifkin, L., Sham, P. & Murray, R. M. (1996). Do obstetric complications cause the earlier age at onset in male than female schizophrenics? *Schizophrenia Research* **20**, 117–124.

Lewine, R., Burbach, D. & Meltzer, H. Y. (1984). Effect of diagnostic criteria on the ratio of male to female schizophrenic patients. *American Journal of Psychiatry* **141**, 84–87.

McGrath, J., Saha, S., Welham, J., El Saadi, O., MacCauley, C. & Chant, D. (2004). A systematic review of the incidence of schizophrenia: the distribution of rates and the influence of sex, urbanicity, migrant status and methodology. *BMC Medicine* **2**, 13.

Munk-Jørgensen, P. & Mortensen, P. B. (1997). The Danish Psychiatric Central Register. *Danish Medical Bulletin* **44**, 82–84.

Nasser, E. H., Walders, N. & Jenkins, J. H. (2002). The experience of schizophrenia: what's gender got to do with it? A critical review of the current status of research on schizophrenia. *Schizophrenia Bulletin* **28**, 351–362.

Pedersen, C. B., Gøtzsche, H., Møller, J. Ø. & Mortensen, P. B. (2006). The Danish Civil Registration System – a cohort of 8 million people. *Danish Medical Bulletin* **53**, 441–449.

Pedersen, C. B. & Mortensen, P. B. (2001). Family history, place and season of birth as risk factors for schizophrenia in Denmark: a replication and reanalysis. *British Journal of Psychiatry* **179**, 46–52.

Wahl, O. F. & Hunter, J. (1992). Are gender effects being neglected in schizophrenia research? *Schizophrenia Bulletin* **18**, 313–318.

https://doi.org/10.1017/S0033291707009944 Published online by Cambridge University Press