Gender difference in age at onset of schizophrenia: a meta-analysis

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Psychological Medicine / Volume 43 / Issue 01 / January 2013, pp 155 - 167
DOI: 10.1017/S003329171200089X, Published online: 08 May 2012

Link to this article: http://journals.cambridge.org/abstract_S003329171200089X

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Gender difference in age at onset of schizophrenia: a meta-analysis

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Background. Most studies reporting the gender difference in age at onset of schizophrenia show an earlier onset in males, but vary considerably in their estimates of the difference. This may be due to variations in study design, setting and diagnostic criteria. In particular, several studies conducted in developing countries have found no difference or a reversed effect whereby females have an earlier onset. The aim of the study was to investigate gender differences in age at onset, and the impact of study design and setting on estimates thereof.

Method. Study methods were a systematic literature search, meta-analysis and meta-regression.

Results. A total of 46 studies with 29218 males and 19402 females fulfilled the inclusion criteria and were entered into a meta-analysis. A random-effects model gave a pooled estimate of the gender difference of 1.07 years (95% confidence interval 0.21–1.93) for age at first admission of schizophrenia, with males having earlier onset. The gender difference in age at onset was not significantly different between developed and developing countries. Studies using Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria showed a significantly greater gender difference in age at onset than studies using International Classification of Diseases (ICD) criteria, the latter showing no difference.

Conclusions. The gender difference in age of onset in schizophrenia is smaller than previously thought, and appears absent in studies using ICD. There is no evidence that the gender difference differs between developed and developing countries.

Received 20 June 2011; Revised 21 March 2012; Accepted 26 March 2012; First published online 8 May 2012

Key words: Age at onset, gender difference, schizophrenia.

Introduction

Emil Kraepelin (1909–1915) was the first of many researchers to suggest that men develop schizophrenia at a younger age than women. Subsequent studies addressing this gender difference in age at onset have reported findings which vary considerably; in some studies the difference is as great as 5 years (Gureje & Bamidele, 1998), and in others it is absent (Murthy et al., 1998; Gangadhar et al., 2002). Thus, in a review of 53 studies, Angermeyer & Kuhn (1988) reported that the majority of studies found an earlier onset in men, but in five studies, especially those from developing countries, there was no difference between the genders. More recently, three studies in India produced anomalous results. Subbakrishna et al. (2001) and Murthy et al. (1998) failed to find any gender difference while Gangadhar et al. (2002) found an earlier onset in females. These findings have led to speculation that the gender effect is absent or reversed in developing countries (Gangadhar et al., 2002).

The variations may reflect the wide variety of definitions of age at onset. Some studies have used the first admission, some the first consultation, while others have taken the first symptom or first positive symptom. If males and females differ in their duration of untreated psychosis, or present to services at different stages of their illness, then different definitions of onset should give rise to variations in the gender difference.

A further issue is that diagnostic criteria for schizophrenia have different thresholds for length of illness. For example, the Diagnostic and Statistical Manual of Mental Disorders (DSM), Third Edition (DSM-III), Third Edition Revised (DSM-III-R) and Fourth Edition (DSM-IV) have a 6-month duration criterion while the International Classification of
Diseases (ICD), Tenth Revision (ICD-10) requires only 1-month duration. Thus, briefer forms of psychosis are excluded by the DSM criteria for schizophrenia, but classified as schizophrenia in the ICD. This may be of relevance to the gender difference reported by different studies, as age at onset may vary with the severity and duration of psychosis (Castle et al. 1998).

No recent review has systematically reviewed the published studies on gender differences in age at onset in schizophrenia, and attempted to take into account variations in the design, methodology, and the sample selected. The present meta-analysis systematically reviews the studies published between 1987 and 2009, to obtain pooled estimates of gender difference based on these studies, and to ascertain factors that may influence it.

Method

Data sources

Ovid Medline and Web of Science databases were searched between 1987 and 2009 with the keywords ‘age at onset and gender (or sex) and schizophrenia’. In addition, references were cross-checked from recent review articles related to the subject. Where relevant data were not available in the publication, the authors were contacted and the information requested.

Study selection

Only those articles or reports fulfilling the following criteria were included:

1. Mean age at onset for schizophrenia (alone or with other psychosis) and standard deviation (S.D.) reported separately in males and females.
2. Studies using ICD (version 9 or later) or DSM (version III or later).
3. Studies published in English, in a peer-reviewed, indexed scientific journal.
4. Age at onset defined as either age at first symptom, age at first positive symptom, age at first consultation or treatment, or age at first admission.
5. Study not limited to extreme age groups such as under 18 years or over 65 years.

Exclusion criteria were as follows:

1. Part of or the entire sample overlapped with a different publication that was already included. In such instances, the most inclusive study was used, and where this was not clear, the authors were contacted for clarification.
2. The study was limited to childhood- and adolescent-onset psychosis or to cases with late onset (≥45 years).

Data extraction

A total of 553 studies were identified and their abstracts screened. Where the abstract suggested that the study might contain relevant data, the paper was scrutinized. So, 46 studies were found to meet our criteria for inclusion.

Table A1 (see Appendix) shows summary data for the included studies. Where studies reported age at onset in more than one sample, each estimate was entered separately. For example, Stöber et al. (1998) reported separate data for periodic and systemic catatonia. These data were entered as separate estimates, namely Stöber a 1998 and Stöber b 1998.

Publication bias

Possible publication bias was investigated informally by means of a funnel plot (Everitt, 2003).

Meta-analysis procedure

Initial inspection of the studies revealed that the absolute age of onset varied considerably between studies, depending on the setting and inclusion criteria of the studies. However, the difference in age of onset between men and women was much more homogeneous. Therefore, the metric that we used in all our analyses was the age of onset in males minus the age at onset in females. Thus, negative numbers indicated an earlier onset in males. All analyses were conducted in Stata Version 10 for Macintosh (StataCorp LP, USA), using the METAN (Bradburn et al. 1988) and METAREG (Harbord & Higgins, 2008) procedures. The data from the separate studies showed heterogeneity in the estimated age at onset difference for men and women (heterogeneity among all studies: χ² = 313.53, degrees of freedom = 50, p < 0.001). Furthermore, the studies were derived from a wide range of populations, using different definitions of age of onset and schizophrenia. Consequently a random-effects model was used to obtain a combined estimate and confidence interval (CI) of the gender difference in age at onset.

We conducted separate meta-analyses to obtain pooled estimates of gender difference in age at onset for studies using the following definitions of age at onset: (1) age at first symptom; (2) age at first positive symptom; (3) age at first consultation; and (4) age at first admission.

We also combined studies with the above definitions of age at onset for schizophrenia to obtain a pooled estimate of the gender difference. We then performed a further meta-analysis, where we relaxed the diagnostic criteria to include schizo-affective disorder and other non-affective psychoses. For this...
analysis, we took age at first admission as the
definition of age at onset, since this was the most
frequently reported definition.

Meta-regression

Meta-regression was used to assess whether the diag-
nostic system used (DSM versus ICD) or the level
of development of the host country influenced the
gender differences in age at onset (any of the four
above definitions used) for schizophrenia. The Human
Development Index (HDI; United Nations, 2001) was
used to classify countries into developing (HDI 2 and 3
categories) and developed (HDI 1 category) countries.

Results

Assessment of publication bias

The funnel plot shown in Fig. A1 (see Appendix) is
based on all studies reporting results for schizo-
phrenia, regardless of the definition of age of onset. It
is symmetrical about the line of estimated effect,
demonstrating that publication bias is unlikely to be
present.

Meta-analyses

I. Analyses for different definitions of age at onset

Age at first symptom in schizophrenia. A total of 17 esti-
mates from 16 separate studies were included in this
meta-analysis with a total sample size of 2609 males
and 2016 females. Fig. 1 shows the forest plot with
weighted effect size and 95% CI for each study. The
weighted mean difference (WMD) in age of onset was
−1.63 (95% CI −2.76 to −0.49), meaning that males
had an earlier age at onset of 1.63 years.

Age at first positive symptom in schizophrenia. This meta-
analysis included nine estimates from eight separate
studies. The total sample consisted of 786 males and
573 females. Fig. 2 gives the forest plot with details
of this meta-analysis. Males had an earlier onset
by 1.43 years, with a WMD of −1.43 (95% CI −2.61
to −0.25).

Age at first consultation in schizophrenia. Fig. 3 gives the
forest plot with weighted effect sizes and 95% CI for
each individual study included in this meta-analysis.
A total of 13 estimates from 12 studies were included
in this meta-analysis examining the gender difference
in age at first consultation in schizophrenia. The total
sample size consisted of 1633 males and 1126 females.
The overall WMD was −1.22, suggesting an earlier
onset in males by 1.22 years. However, the 95% CI
included zero (−2.49 to 0.06).

Age at first admission in schizophrenia. In this meta-
analysis, 23 different estimates from 16 studies were
included. The total sample size consisted of 17946
males and 11743 females. Fig. 4 shows the forest plot
for this meta-analysis. The WMD was −1.07 (95% CI −1.93
to −0.21), indicating an earlier onset in males
by 1.07 years.

II. Analysis for any definition for age at onset

in schizophrenia

As the above meta-analysis showed an earlier age at
onset in males compared with females, all the studies
from the above four meta-analysis were combined in a separate meta-analysis. For each study, age at first symptom was used where reported. Otherwise, age at first positive symptom was used. If neither was reported, age at first consultation was used, and if none of the above was reported, then age of first admission was used. Fig. 5 gives the forest plot for the gender difference in age at onset of schizophrenia with any of the above four definitions for age at onset considered. A total of 30 estimates from 22 studies were included. The sample size consisted of 25684 males and 16802 females. This showed an earlier onset in males, with a WMD of $-1.49$ years (95% CI $-2.07$ to $-0.92$).

### III. Age at first admission in non-affective psychoses

All the above meta-analyses examined gender difference in age at onset in schizophrenia. A further meta-analysis was conducted to examine the gender difference in age at onset in studies which included a broader group of disorders including schizo-affective disorders and all other non-affective psychoses. We used first admission, as this was the most frequently reported definition of onset. Fig. A2 (see Appendix) gives the forest plot for the results of this meta-analysis. A total of 30 estimates from 22 studies were included. The sample size consisted of 25684 males and 16802 females. The overall effect size was
Meta-regression analyses were conducted to examine the effect of two variables—diagnostic system used and developed/developing country status. Meta-regression was based on the meta-analysis of studies including any definition for age at onset of schizophrenia (see Fig. 5), adjusting for definition of age at onset in the analysis.

**Diagnostic system used**

A total of 48 estimates from 40 studies were included in this analysis. For ICD studies alone, the gender difference was non-significant, at −0.309 (95% CI −1.229 to 0.611, \(p = 0.510\)), while for DSM studies it was −1.92 (95% CI −2.483 to −1.356, \(p < 0.001\)). The meta-regression showed that the gender difference in age of onset was significantly greater under DSM criteria than ICD, adjusted for definition of age of onset (WMD = −1.93, 95% CI −3.11 to −0.75, \(p = 0.001\)).

**Developed versus developing country**

The host countries of the studies were categorized according to the HDI into developed or developing countries. A total of 49 estimates from 40 studies were included in this analysis. The results showed no evidence of any difference in gender difference in age of onset between developing and developed countries (WMD adjusted for definition of onset = 1.68, 95% CI −1.41 to 1.75, \(p = 0.835\)). The gender difference in developing countries was −1.54 (95% CI −2.85 to −0.23, \(p = 0.021\)), and in developed countries was −1.43 (95% CI −2.11 to −0.77, \(p < 0.001\)).

**Discussion**

Our results confirm a gender difference in the age at onset of schizophrenia, with an earlier age at onset in males. When all definitions for age at onset in schizophrenia are combined, males have an earlier onset by 1.49 years. The gender difference in age at onset is larger for age at onset of first symptom or positive symptom as compared with age at first consultation or admission (1.07 years). It is known that many patients have psychotic symptoms for some years before accessing services, and it is possible that the duration of time from the first symptoms to the first access to services is related to the patients’ gender (Salokangas et al. 2003). We found the greatest gender difference (1.63 years) when ‘age at first symptom’ was used to define the age at onset of schizophrenia, and the smallest gender difference for age at first consultation (1.22 years) and age at first admission (1.07 years). This suggests that males may have a more insidious onset...
and males may be overrepresented (Thorup 2007). Hospitalized cases may be more severe or disturbed, or use registers that record hospital admissions. These advantages are related to women with psychosis, with longer duration of untreated psychosis, than females.

There are some potential biases to consider. First, the majority of the studies are based on hospital patients or use registers that record hospital admissions. These hospitalized cases may be more severe or disturbed, and males may be overrepresented compared to females. Second, although we only included studies in working-age adults, there were some variations in lower and upper age limits of the studies, which may have influenced the size of the gender differences; for example, a study with an older upper limit may have included an excess of late-onset females.

The ascertainment of age at onset may not always have been accurate. For example, one study from South India (Murthy et al. 1998) describes the difficulties in ascertaining the age at onset in their sample in Bangalore, India. In patients who did not have date of birth records, assessment was made with information from family members using circumstantial evidence such as festivals or important national events. This highlights the difficulty in ascertaining age or age at onset in certain populations.

While we attempted to subdivide the studies according to the definition of onset used, this was not always straightforward. For example, one study defined age of onset as ‘age at first symptom’ but later stated that this was ‘the age at which symptoms such as delusions, hallucinations, excitability or aggressive behaviour, catatonia, etc began’. The definition from this study was entered as ‘age at first symptom’.

Furthermore, the point at which one begins to consider the presence of positive symptoms may be somewhat subjective, especially if clear cut hallucinations or delusions are not present. The demarcation of prodrome from onset of psychosis is also subjective, and may vary widely between clinicians. Gender differences in the ability to conceal symptoms may lead to earlier diagnosis in one gender than the other.

It has been demonstrated in previous studies that women have a second peak in incidence of psychosis.

Fig. 5. Forest plot for gender difference in age (years) at onset (any definition) of schizophrenia. For full details of study names, see Table A1 in the Appendix. WMD, Weighted mean difference; CI, confidence interval.
schizophrenia in later life, albeit much smaller than the peak in the early twenties (Thorup et al. 2007a).

The estimate ‘mean age at onset’ does not take this into account and may produce skewed mean age at onset to the right for females. There is a suggestion that earlier-onset schizophrenia may be a different variant to later-onset cases (Kleinhaus et al. 2011). There is a need for further studies to examine gender differences in different age brackets.

In this meta-analysis, the gender difference is larger when a broader group of non-affective psychoses is included, with males being admitted 1.37 years earlier than females, compared with 1.07 years in schizophrenia. This broad group of psychoses included schizophrenia, schizo-affective disorders and other non-affective psychoses. The larger gender difference in age at onset in this group may be related to the inclusion of schizo-affective disorders. Studies of bipolar disorder have found a significant earlier onset in men, both for first depression and first mania (Viguera et al. 2001). A study of bipolar I disorder, in the suburbs of London, found that men had an earlier onset by 8.3 years (Viguera et al. 2001; Raymont et al. 2003), whilst a first-onset study in inner London over 35 years (Kennedy et al. 2005) showed that men had an earlier mean onset of bipolar disorder and mania by 4.4 and 5.1 years, respectively.

The results of the meta-regression for diagnostic criteria demonstrate that the diagnostic criteria used have a large impact on the gender difference in age of onset. Indeed, studies using ICD failed to show any gender difference in age of onset. Unlike ICD, DSM-III, DSM-III-R and DSM-IV require the existence of symptoms for a 6-month period for the diagnosis of schizophrenia. Our results imply that cases of a longer duration may show a greater gender difference in age of onset. Castle and colleagues showed that the application of criteria which define a severe form of schizophrenia (DSM criteria as compared with ICD criteria) excludes more females, and results in an overall male excess, especially in those with age at onset less than 25 years (Castle et al. 1998).

The results of the meta-regression demonstrate that the development index of the country has no effect on the gender difference in age at onset of core schizophrenia. This finding demonstrates the value of meta-analysis in addressing epidemiological questions. Many of the studies from developing countries that were included in the meta-analysis showed an earlier age of onset for males, but the fact that this difference was not significant in individual studies was sometimes interpreted by the authors as evidence for absence of gender difference, and as a result a narrative has developed in the literature suggesting that the gender difference may be absent in developing countries. In fact, the main difference between the developed and developing studies in this meta-analysis was that the latter were more heterogeneous: the estimate of between-study variance, $r^2$, was 2.46 in the developed countries, but 4.63 in developing countries.

Three studies from developing countries included in the meta-regression found an earlier age at onset in females than males (Thara et al. 1994; Gangadhar et al. 2002; Kebede et al. 2003). However, the remaining seven studies from developing countries showed the expected earlier age at onset in males. The studies from developing countries had relatively small sample sizes. There is a need for larger studies from developing countries examining the gender difference in age at onset.

**Limitations**

Two databases, Ovid Medline and Web of Science, were used for literature searches. Personal communication from authors was sought for any clarification of data required. However, unpublished data or articles published in languages other than English were not included. This study did not examine gender differences in childhood-onset or late-onset schizophrenia. We were also not able to study the role of important confounders such as family history of schizophrenia, pre-morbid personality and obstetric complications as insufficient data were available. Lastly, our search covered only peer-reviewed journals. Although we cross-checked citations from individual papers, we may have missed some papers published in languages other than English and/or in non-peer-reviewed journals.

**Conclusions**

This meta-analysis shows a gender difference in age at onset of schizophrenia, with a small earlier age at onset in males. This difference is not specific to schizophrenia but is present in all non-affective psychosis. The gender difference was absent in studies using ICD-10 criteria but appeared confined to studies using DSM criteria, and was present to the same extent in studies from developed and developing countries. There is a need for large studies from developing countries to examine the gender difference in age at onset and factors influencing it. Further studies are required to examine the influence of confounding factors, such as family history of schizophrenia, pre-morbid personality and obstetric complications on gender differences in age at onset of schizophrenia.
Acknowledgements
This study was partly funded by the National Institute for Health Research (NIHR) Biomedical Research Centre for Mental Health at King’s College London and South London and Maudsley NHS Foundation Trust.

Declaration of Interest
None.

References


### Appendix

**Fig. A1.** Funnel plot with pseudo 95% confidence limits for studies using any definition of age of onset of schizophrenia (studies included in Fig. 5). s.e., Standard error; WMD, weighted mean difference.

**Fig. A2.** Forest plot for gender difference in age (years) at first admission for any non-affective psychoses. For full details of study names, see Table A1. WMD, Weighted mean difference; CI, confidence interval.
<table>
<thead>
<tr>
<th>Study and reference</th>
<th>Year</th>
<th>Subjects, n</th>
<th>Age at first symptom, years</th>
<th>Age at first positive symptom, years</th>
<th>Age at first consultation, years</th>
<th>Age at first admission, years</th>
<th>Diagnostic criteria</th>
<th>Breadth of psychoses</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albus (Albus et al. 1994)</td>
<td>1994</td>
<td>106</td>
<td>25 (9)</td>
<td></td>
<td>91</td>
<td>30 (12)</td>
<td>DSM-III-R</td>
<td>Narrow</td>
<td>1</td>
</tr>
<tr>
<td>Barrett a (Barrett et al. 2005)</td>
<td>2005</td>
<td>119</td>
<td>30.6 (13.0)</td>
<td>20.20 (4.19)</td>
<td>21.10 (4.90)</td>
<td>37</td>
<td>23.44 (5.86)</td>
<td>DSM-III-R</td>
<td>Narrow</td>
</tr>
<tr>
<td>Barrett b (Barrett et al. 2005)</td>
<td>2005</td>
<td>100</td>
<td>34 (14.3)</td>
<td></td>
<td>91</td>
<td>31 (13.9)</td>
<td>ICD-10</td>
<td>Narrow</td>
<td>1</td>
</tr>
<tr>
<td>Björck (Valög Björck et al. 2000)</td>
<td>2000</td>
<td>30</td>
<td>24.2 (5)</td>
<td>20</td>
<td></td>
<td>24.7 (5)</td>
<td>ICD-10</td>
<td>Broad</td>
<td>2</td>
</tr>
<tr>
<td>Cohen (Cohen et al. 1999)</td>
<td>1999</td>
<td>45</td>
<td>18.6 (5.9)</td>
<td>24.2 (5.0)</td>
<td>24.6 (4.75)</td>
<td>35</td>
<td>19.9 (5.9)</td>
<td>DSM-III-R</td>
<td>Broad</td>
</tr>
<tr>
<td>Dernovsek (Dernovsek &amp; Tavcar, 1999)</td>
<td>1999</td>
<td>100</td>
<td>27.8 (10.7)</td>
<td>100</td>
<td></td>
<td>32 (11.1)</td>
<td>DSM-III-R</td>
<td>Narrow</td>
<td>1</td>
</tr>
<tr>
<td>Dernovsek (Dernovsek &amp; Tavcar, 1999)</td>
<td>2000</td>
<td>34</td>
<td>22.39 (4.91)</td>
<td></td>
<td>27</td>
<td>26.88 (6.58)</td>
<td>DSM-III-R</td>
<td>Narrow</td>
<td>1</td>
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<tr>
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<td>45</td>
<td>17.8 (7.8)</td>
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<td>321</td>
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<td>Narrow</td>
<td>2</td>
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<tr>
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<td>2002</td>
<td>37</td>
<td>23.5 (7.9)</td>
<td>33</td>
<td></td>
<td>23.5 (8.2)</td>
<td>ICD-10</td>
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<tr>
<td>Gangadhar b (Gangadhar et al. 2002)</td>
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<td>38</td>
<td>27.4 (8.6)</td>
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<td>20.0 (3.1)</td>
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<td>56</td>
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<td></td>
<td></td>
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<td>Narrow</td>
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<td>267</td>
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<td></td>
<td></td>
<td>21.00 (7.8)</td>
<td>ICD-10</td>
<td>Narrow</td>
<td>2</td>
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<td>1995</td>
<td>86</td>
<td>25.2 (6.8)</td>
<td></td>
<td>37</td>
<td>26.7 (8.1)</td>
<td>DSM-III-R</td>
<td>Narrow</td>
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<td>Kirkbride (Kirkbride et al. 2006)</td>
<td>2006</td>
<td>333</td>
<td>29.6 (10.22)</td>
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<td>235</td>
<td>32.6 (10.88)</td>
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<td>1996</td>
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<td>22.9 (5.8)</td>
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<td>23.2 (7.0)</td>
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<td>1996</td>
<td>28</td>
<td>24.5 (6.9)</td>
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<td>27.5 (7.4)</td>
<td>15</td>
<td>29.7 (10.0)</td>
<td>DSM-III-R</td>
<td>Narrow</td>
</tr>
<tr>
<td>Laureillo (Laureillo et al. 1997)</td>
<td>1997</td>
<td>18</td>
<td>16.6 (3.3)</td>
<td></td>
<td>19</td>
<td>18.3 (4.9)</td>
<td>DSM-III-R</td>
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<tr>
<td>Leboyer (Leboyer et al. 1992)</td>
<td>1992</td>
<td>70</td>
<td>24 (6.5)</td>
<td></td>
<td>34</td>
<td></td>
<td>DSM-III-R</td>
<td>Narrow</td>
<td>1</td>
</tr>
<tr>
<td>Lee a (Lee et al. 2006)</td>
<td>2006</td>
<td>126</td>
<td>21.1 (5.4)</td>
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Age at onset given as mean (standard deviation).

* Breadth of psychosis: narrow = schizophrenia; broad = schizophrenia, schizo-affective disorders and all non-affective psychosis. * Country: 1 = developed country; 2 = developing country.