Psychological Medicine (2014), **44**, 9–16. © Cambridge University Press 2012
doi:10.1017/S0033291712002796

REVIEW ARTICLE

Systematic review and collaborative recalculation of 133 693 incident cases of schizophrenia

M. van der Werf[1], M. Hanssen[1,2], S. Köhler[1], M. Verkaaik[2], F. R. Verhey[1], RISE Investigators†, R. van Winkel[1], J. van Os[1,3]* and J. Allardyce[1]

[1] *Department of Psychiatry and Psychology, School of Mental Health and Neuroscience, Maastricht University Medical Centre, Maastricht, The Netherlands*

[2] *Regional Centre for Ambulant Mental Health Maastricht, Maastricht, The Netherlands*

[3] *Department of Psychosis Studies, Institute of Psychiatry, King's College London, King's Health Partners, London, UK*

Background. This systematic review and collaborative recalculation was set up to recalculate schizophrenia incidence rates from previously published studies by age and sex.

Method. PubMed, EMBASE and PsycINFO databases were searched (January 1950 to December 2009) for schizophrenia incidence studies. Numerator and population data were extracted by age, sex and, if possible, study period. Original data were requested from the authors to calculate age- and sex-specific incidence rates. Incidence rate ratios (IRRs) with their 95% confidence intervals (CIs) were computed by age and sex from negative binomial regression models.

Results. Forty-three independent samples met inclusion criteria, yielding 133 693 incident cases of schizophrenia for analysis. Men had a 1.15-fold (95% CI 1.00–1.31) greater risk of schizophrenia than women. In men, incidence peaked at age 20–29 years (median rate 4.15/10 000 person-years, IRR 2.61, 95% CI 1.74–3.92). In women, incidence peaked at age 20–29 (median rate 1.71/10 000 person-years, IRR 2.34, 95% CI 1.66–3.28) and 30–39 years (median rate 1.24/10 000 person-years, IRR 2.25, 95% CI 1.55–3.28). This peak was followed by an age–incidence decline up to age 60 years that was stronger in men than in women ($\chi^2 = 57.90$, $p < 0.001$). The relative risk of schizophrenia was greater in men up to age 39 years and this reversed to a greater relative risk in women over the age groups 50–70 years. No evidence for a second incidence peak in middle-aged women was found.

Conclusions. Robust sex differences exist in the distribution of schizophrenia risk across the age span, suggesting differential susceptibility to schizophrenia for men and women at different stages of life.

Received 28 October 2011; Revised 27 October 2012; Accepted 6 November 2012; First published online 19 December 2012

Key words: Age at onset, age–sex interaction, epidemiology, incidence, schizophrenia.

Introduction

Although the incidence of schizophrenia peaks in adolescence and early adulthood (Weinberger, 1987; Häfner *et al*. 1993*a*), the risk of psychosis extends well beyond this period, with sex seemingly modifying the age–incidence relationship (Angermeyer & Kuhn, 1988). To date, the best data suggest that onset in males peaks steeply in the late teens and early twenties, with rates remaining relatively constant at a lower level thereafter, whereas in females the initial peak is later, with a second smaller increase in incidence in middle age (Häfner *et al*. 1993*a*) and possibly a third peak around 65 years of age (Häfner *et al*. 1989). Although the sex difference in age of onset for schizophrenia is a well-replicated finding (Häfner *et al*. 1989; Hambrecht *et al*. 1992; Jablensky *et al*. 1992), it attenuates when known risk factors such as family history (Esterberg *et al*. 2010), pregnancy and birth complications (Kirov *et al*. 1996), paternal age (Rosenfield *et al*. 2010) and marital status (Jablensky & Cole, 1997) are adjusted for in statistical analyses (Aleman *et al*. 2003), and may even be absent in developing countries (Venkatesh *et al*. 2008). Furthermore, the observed age-of-onset distribution is influenced by study methodology such as arbitrary age cut-offs (excluding patients with late onset disproportionately excludes female patients; Castle *et al*. 1993) and different diagnostic definitions (applying more stringent diagnostic classification systems excludes more young women; Castle *et al*. 1993). This makes cross-study comparisons difficult. Understanding the functional form of the age-of-onset curve can potentially provide important pointers for aetiological research. Therefore, we conducted a systematic review and collaborative

* Address for correspondence: J. van Os, Department of Psychiatry and Neuropsychology, Maastricht University, PO Box 616 (location VIJV), 6200 MD, Maastricht, The Netherlands.
(Email: j.vanos@maastrichtuniversity.nl)

† The RISE Investigators are listed in the Appendix.

recalculation of incidence of schizophrenia by age and sex, across the entire life course (as suggested by Jablensky, 2003) using data extracted directly from published papers, raw individual-level data (centrally reorganized and combined) or rates supplied by the authors of incidence studies, published between 1950 and 2009.

Method

Search strategy and study selection

The design of the systematic review and meta-analysis was based on recommendations from the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group (Stroup *et al*. 2000). Two independent investigators (M.W. and M.H.) searched the electronic bibliographic databases PubMed, Medline/EMBASE and PsycINFO for studies published between January 1950 and December 2009. The broad key words 'epidemiology' and 'schizophrenia' OR 'psychosis' were chosen to identify as many potentially relevant studies as possible. Additionally, to reduce the likelihood of missing published data, references from the electronically identified papers, review articles, book chapters and previously published systematic reviews of incidence studies were examined (Aleman *et al*. 2003; McGrath *et al*. 2004) and forwards and backwards citation tracking was carried out using the Web of Science. Finally, experts in the field of psychosis epidemiology were contacted for missing publications and unpublished data. Studies were selected using the following inclusion criteria: (1) contained original incidence data for schizophrenia disorder defined by a standardized diagnostic classification system, (2) age- and sex-specific incidence data were present in the primary publication or in data available from the authors, (3) published between 1950 and 2009 and (4) written in English, Dutch or German. Studies with strict age cut-offs were excluded as they are likely to distort risk ratios by sex (for details see online Supplementary Table S2). Studies were included in the systematic review by consensus (M.W., M.H., J.A.).

Data extraction

Data were extracted systematically by one researcher (M.W.) and validated by investigators (M.H., S.K., J.A.). A database was compiled by independent catchment area-defined samples (rather than by published papers) and the numerator and population data (in person-years) were extracted by age, sex and study period. Age–incidence data were first extracted according to the consensus statement made by (Howard *et al*. 2000), using early (age <40 years: EOS), late (age 40–59 years: LOS) and very late onset (age $\geqslant 60$ years: VLOS) schizophrenia age groups. Data presented in different age formats were assigned to the appropriate age category. In the second approach, numerator and population data were extracted and re-calculated centrally by 10-year age bands. Information about the source population and methodological characteristics were extracted at the sample level. Each sample was classified as rural, mixed or urban, based on combined information about population density estimates and the proportion of people living in urbanized areas (World Bank, 2010). Samples were further categorized into developing or developed countries according to the World Health Organization (WHO) Human Development Index of countries (United Nations, 2009). Methodological characteristics included (i) sampling frame (hospital admission or first contact with psychiatric service), (ii) case ascertainment (clinical, systematic or interview) and (iii) diagnostic classification system [DSM (APA, 1980, 1987, 1994); ICD (WHO, 1955, 1965, 1977, 1992); RDC (Spitzer *et al*. 1978) and others]. When multiple classification systems were used, ICD rates were used instead of DSM because ICD has used a consistently broad definition throughout recent revisions. Schizophreniform disorder was included when studies used DSM criteria. Schizo-affective disorder and paranoid disorders in the elderly (i.e. paraphrenia) were not included. Authors were contacted to ensure accuracy of data and to provide original data when insufficient information to calculate age- and sex-specific incidence rates was present in the published papers.

Statistical analyses

First, a descriptive synthesis of incidence rates was completed using information from all studies with data stratified by EOS, LOS and VLOS age groups (analysis 1). The distribution of incidence rates was presented by age, sex and female-to-male incidence rate ratio (IRR_{F-M}) estimates showing mean, median (a better indicator of incidence in the case of non-normality) and 25–75% interquartile range (IQR) values (a better measure of dispersion without taking into consideration the more extreme values). Additionally, the distribution of incidence rates by population and methodological characteristics was explored.

Next, multivariable analyses were conducted on the subset of catchment area samples with numerator and dominator stratified by sex and 10-year age bands (analysis 2), to allow estimation of adjusted age–sex associations. As Poisson regression models showed significant level-1 overdispersion (which can cause standard errors to be biased downwards), a series of

https://doi.org/10.1017/S0033291712002796 Published online by Cambridge University Press

random intercept negative binomial regression models (NBRMs) were fitted to estimate IRRs, with the natural log of the raw incidence rates as the dependent variable and age group and pertinent sample and methodological characteristics (sampling frame, case ascertainment and diagnostic classification system) as independent variables. Non-linear age by sex associations were modelled by adding an interaction term. Robust standard errors were calculated using the sandwich estimator.

Studies were not formally weighted by sample size, as is common practice in pooling of randomized controlled trials. In observational studies, however, smaller studies often use more thorough case ascertainment and case verification whereas larger studies are often drawn from national databases with less rigorous case verification. Alternatively, the IRR estimates were adjusted for study sample size in the NBRM and the effect of sample size was further evaluated by repeating the analysis on a subset of larger samples (>100 cases).

Finally, to examine potential bias from studies using arbitrary age criteria, the analyses were repeated on samples from studies with no age restriction. Sampling bias due to data variability across the different selection stages was explored by contrasting sample characteristics of included and excluded studies. All statistical analyses were conducted using Stata version 11 (StataCorp, 2009).

Results

The initial electronic search identified 11 307 citations; further appraisal of the title and abstract using the inclusion criteria resulted in 329 full articles being reviewed. Ninety-one studies derived from 44 non-overlapping samples met inclusion criteria for the initial analyses. One study (Bijl *et al*. 2002) contributed significantly to methodological heterogeneity because of a study design incomparability and it was therefore excluded, leaving a set of 43 independent incidence samples for further analyses. The characteristics of the included studies (organized by sample) are presented in online Supplementary Table S1. Excluded articles and their justification for exclusion are presented as a supplementary list (online Supplementary Table S2). Included studies and those excluded due to insufficient data were similar with regard to sample characteristics, total number of cases and population size (data available upon request to the authors).

Descriptive synthesis (*analysis 1*)

The first set of analyses was based on all 43 samples, providing 1021 effect sizes and 133 693 cases of schizophrenia. The pooled median incidence rate for schizophrenia was 18.3 per 10 0000 person-years, with an almost threefold difference between catchment area samples from the lowest and highest reported rates (IQR 10.9–28.9). Incidence declined strongly with increasing age (Table 1). The overall incidence was higher in men than in women. However, the male preponderance in the EOS group ($IRR_{F–M}$ 0.55, IQR 0.45–0.74) was absent in the LOS group ($IRR_{F–M}$ 1.16, IQR 0.93–1.63), whereas in the VLOS group there was a higher relative risk for females ($IRR_{F–M}$ 1.55, IQR 0.92–2.19). The incidence by sample characteristics over the EOS, LOS and VLOS groups is also presented in Table 1. Rates tended to be lower in samples based on diagnostic interview methods and first contacts, and in samples conducted after 1990, in rural areas and in developing countries.

Systematic recalculation (*analysis 2*)

The second set of analyses was based on the subset of 33 non-overlapping samples with data stratified by sex and 10-year age bands, providing 604 effect sizes and 63 550 incident cases of schizophrenia.

In the fully adjusted model, younger age (IRR 1.25, 95% CI 1.17–1.34), male sex (IRR 1.15, 95% CI 1.00–1.31) and urbanicity (IRR 1.75, 95% CI 1.13–2.71) were associated with higher incidence rates whereas time period and methodological characteristics were not. Figure 1 shows the crude age- and sex-specific incidence rates. A negative interaction between sex and age was apparent in the crude ($\chi^2=76.32$, $p<0.001$) and fully adjusted model ($\chi^2=57.90$, $p<0.001$). In the fully adjusted model there was a significantly stronger overall age–incidence decline in males (IRR 0.71, 95% CI 0.66–0.77) compared to females (IRR 0.89, 95% CI 0.83–0.96). Table 2 presents the unadjusted and adjusted age IRRs by sex, using the youngest age group as the reference (<20 years). Male incidence peaked at age 20–29 years (IRR 2.61, 95% CI 1.74–3.92). The incidence peak in women was less sharp and distributed over age bands 20–29 (IRR 2.34, 95% CI 1.66–3.28) and 30–39 years (IRR 2.25, 95% CI 1.55–3.28). After the initial peak, incidence rates declined continuously, levelling off to a non-significant risk difference by 60 years of age. Finally, the relative risk of schizophrenia remained higher in males up to age 39, was equivalent for males and females between ages 40 and 49, and then reversed, with females having a higher risk in the 50–70-year age groups (Table 2).

Restricting the analyses to samples from studies that had no age restriction criteria ($n=20$) or a minimum sample size of 100 cases ($n=22$) yielded similar patterns of risk by age and sex to the analyses using all the data. Finally, the samples used in analysis 2 had

https://doi.org/10.1017/S0033291712002796 Published online by Cambridge University Press

Table 1. *Distribution of incidence rates stratified by sex, age and sample characteristics*[a]

	All ages		EOS		LOS		VLOS	
Sample characteristic	*n*	Median (IQR)	*n*	Median (IQR)	*n*	Median (IQR)	*n*	Median (IQR)
Age group								
Total	43	1.83 (1.09–2.89)	43	2.47 (1.54–3.61)	43	1.22 (0.70–2.17)	33	0.59 (0.30–1.27)
Men	37	1.70 (1.31–3.50)	37	2.62 (1.66–4.47)	36	0.88 (0.62–2.24)	27	0.46 (0.15–0.90)
Women	37	1.30 (0.71–2.60)	37	1.60 (0.81–2.45)	36	0.97 (0.69–2.53)	28	0.79 (0.35–1.43)
Period								
Before 1970	12	1.53 (0.81–2.61)	12	2.83 (1.27–4.63)	12	1.29 (0.68–2.18)	9	0.96 (0.42–1.53)
1970–1980	18	1.41 (0.83–2.74)	18	2.10 (1.41–3.42)	18	1.40 (0.83–2.71)	12	0.76 (0.43–1.13)
1990 and beyond	19	0.97 (0.46–2.09)	19	1.95 (1.09–2.76)	19	0.80 (0.35–1.21)	16	0.40 (0.26–0.88)
Diagnostic classification								
DSM	10	1.57 (0.60–2.61)	10	2.48 (1.63–3.56)	10	1.39 (0.60–2.17)	4	0.40 (0.35–0.60)
ICD	27	1.55 (0.73–3.06)	27	2.47 (1.56–4.11)	27	1.30 (0.71–3.06)	22	0.75 (0.35–1.30)
Case ascertainment								
Clinical	27	1.54 (0.74–3.09)	27	2.47 (1.53–4.31)	27	1.37 (0.85–2.99)	21	0.88 (0.37–1.53)
Systematic	5	1.25 (0.71–3.03)	5	3.03 (1.66–3.56)	5	0.79 (0.71–1.56)	4	0.47 (0.28–0.92)
Interview	12	1.13 (0.30–1.93)	12	1.93 (1.45–2.95)	12	0.71 (0.25–1.44)	8	0.35 (0.03–0.59)
Sample frame								
Admission	20	1.54 (0.72–3.49)	20	3.49 (1.39–4.96)	20	1.23 (0.86–3.06)	14	0.61 (0.45–1.30)
Contact	23	1.37 (0.60–2.16)	23	1.93 (1.63–3.14)	23	1.05 (0.54–1.75)	18	0.59 (0.23–1.25)
Urban level								
Rural	8	1.02 (0.35–1.90)	8	1.92 (1.14–3.30)	8	1.17 (0.50–1.70)	7	0.35 (0.22–0.60)
Urban	35	1.54 (0.71–2.99)	35	2.47 (1.56–4.09)	35	1.22 (0.70–2.61)	26	0.75 (0.40–1.53)
Human Development Index								
Developing	4	1.21 (0.89–1.93)	4	1.73 (1.21–2.20)	4	1.13 (0.65–1.69)	1	0.03 (N.A.)
Developed	39	1.49 (0.68–3.00)	39	2.76 (1.56–4.09)	39	1.23 (0.70–2.61)	32	0.60 (0.35–1.30)

EOS, Early-onset schizophrenia (age <40 years); LOS, late-onset schizophrenia (age 40–59 years: LOS); VLOS, very-late-onset schizophrenia (age ⩾60 years); IQR, interquartile range; N.A., not applicable.

[a] All rates are presented as number of cases per 10 000 person-years.

similar incidence rates by age and sex as those used for analysis 1, suggesting that sampling bias due to data availability is unlikely to have occurred (results available upon request).

Discussion

This systematic review and recalculation of primary incidence data demonstrates substantial stratification in the risk of schizophrenia by age and sex that is not explained by confounding due to known underlying differences in the population structure or characteristics of the study samples. As expected, the risk of schizophrenia rose steeply from (pre-)adolescence, reaching a peak in early adulthood. This initial increase in incidence was followed by a gradual decline to age 60 years, after which the incidence rates levelled off.

Marked sex differences in morbid risk were apparent over the life course, with lifetime risk 1.15 times higher in men than in women, a figure slightly lower

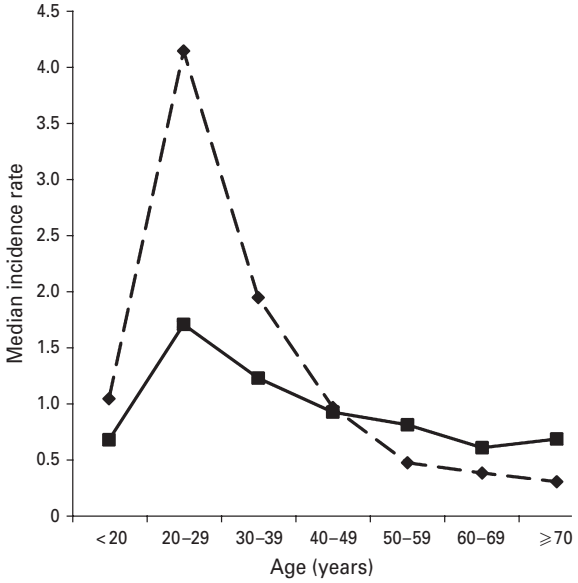

Fig. 1. Estimated age- and sex-specific median incidence rates (per 10 000 person-years): —■—, women; – –◆– –, men.

https://doi.org/10.1017/S0033291712002796 Published online by Cambridge University Press

Table 2. *Age- and sex-specific incidence rates of schizophrenia (per 10 000 person-years)*

Age (years)	Median crude rate	Crude IRR (95% CI)	Adjusted IRR[a] (95% CI)
Men			
<20	1.05	[1] reference	[1] reference
20–29	4.15	2.76 (1.90–4.01)	2.61 (1.74–3.92)
30–39	1.96	1.67 (1.10–2.53)	1.49 (0.94–2.36)
40–49	0.98	0.95 (0.57–1.58)	0.81 (0.47–1.41)
50–59	0.48	0.60 (0.34–1.06)	0.51 (0.28–0.91)
60–69	0.39	0.35 (0.21–0.59)	0.32 (0.18–0.54)
⩾70	0.31	0.39 (0.21–0.72)	0.37 (0.20–0.69)
Women			
<20	0.69	[1] reference	[1] reference
20–29	1.71	2.42 (1.78–3.29)	2.34 (1.66–3.28)
30–39	1.24	2.41 (1.71–3.38)	2.25 (1.55–3.28)
40–49	0.94	1.99 (1.35–2.96)	1.82 (1.19–2.77)
50–59	0.82	1.60 (1.03–2.47)	1.43 (0.90–2.29)
60–69	0.62	0.95 (0.61–1.50)	0.90 (0.54–1.48)
⩾70	0.69	1.00 (0.60–1.66)	0.97 (0.55–1.71)
Female-to-male IRR[b]			
<20		0.56 (0.43–0.72)	0.53 (0.41–0.69)
20–29		0.49 (0.43–0.56)	0.47 (0.41–0.54)
30–39		0.81 (0.71–0.91)	0.80 (0.71–0.91)
40–49		1.17 (0.98–1.40)	1.18 (0.99–1.41)
50–59		1.50 (1.23–1.82)	1.50 (1.25–1.80)
60–69		1.51 (1.15–1.97)	1.50 (1.13–1.99)
⩾70		1.42 (1.00–2.02)	1.38 (0.93–2.05)

IRR, Incidence rate ratio; CI, confidence interval.

[a] Adjusted for study period (in 10-year groups: <1960, 1960–1969, 1970–1979, 1980–1989, 1990–1999 and ⩾2000), population (study sample size) and methodological characteristics (sampling frame, case ascertainment and diagnostic classification system).

[b] IRR <1 indicates higher relative risk in men and IRR >1 indicates higher relative risk in women.

than those reported previously in a systematic review (McGrath *et al*. 2004) and a meta-analysis (Aleman *et al*. 2003). The initial high peak in men was followed by a dramatic drop in incidence rates around age 30. Women, on the contrary, showed a lower, broader incidence curve followed by a slower decline in risk over the age span. The slower decline of incidence rates for schizophrenia in women with increasing age resulted in a small but significant female excess of new cases in middle and old age. Finally, the study did not find a discrete second incidence peak in middle-aged women.

Incidence of schizophrenia over the age span

The results are in line with previous work suggesting that schizophrenia is principally a disorder of early adulthood but does present throughout the lifespan, with males having an earlier age of onset (on average) and slightly higher lifetime morbid risk compared to females. Several plausible hypotheses have been developed to explain the age–sex association related to, for example, prenatal development and differential exposure to gonadal hormones in men (Murray *et al*. 1992; Raz *et al*. 1994; Seeman, 1996). Similarly, the prevalence of pregnancy and birth complications, which are recognized candidate risk factors for schizophrenia, may be more common among males than females (Clarke & O'Callaghan, 2003). In women, the onset of schizophrenia may be delayed by the neuroprotective effects of oestrogen, which is postulated to have an antipsychotic effect during adolescence (Häfner *et al*. 1993*b*; Seeman, 1996).

These analyses failed to show a discrete second peak in middle-aged women (Häfner *et al*. 1993*b*; Castle *et al*. 1995). It is possible that a brief perimenopausal spike in incidence was not found as a consequence of the relatively broad 10-year age bands used in the present statistical models. However, *post-hoc* analyses on the subset of samples for whom 5-year age bands were available showed no second peak in middle-aged women.

The age-of-onset profile demonstrated in this study is consistent with complex causal pathways involving additive and interactive psychosocial, neural or hormonal protective factors (or lack of risk factors) in the context of pathoplastic normal or pathological age-related processes that impact on a milder or absent neurodevelopmental vulnerability (Vahia *et al*. 2010). Culturally and socially determined sex differences such as greater levels of social integration, better pre-morbid functioning and greater likelihood of marriage in women may act as protective factors, delaying the age at onset (Jablensky & Cole, 1997; Morgan et al. 2008).

Risk for schizophrenia and the environment

Although not the primary aim of this meta-analysis, the risk of schizophrenia was lower in rural areas than in urban conurbations. This is a replicated epidemiological finding in Western-based studies; however, the explanation for this urban excess remains elusive (Kelly *et al*. 2010) and data were not available in this study to investigate this further.

Methodological considerations

Through strong collaborative working we have had comprehensive access to international data from published incidence studies, allowing the systematic recalculation of age- and sex-specific rates for schizophrenia using raw primary data. The review

https://doi.org/10.1017/S0033291712002796 Published online by Cambridge University Press

process followed the MOOSE guidelines closely, ensuring a thorough search for incidence data and a standardized data extraction process. This study principally used individual participant-level data provided by primary researchers that were then used to centrally generate rate-level data using the same age strata across all samples. This approach has many advantages over the formal aggregate meta-analysis approach (Riley *et al*. 2010). For a minority of catchment area samples, this was unnecessary as the appropriate age- and sex-specific rates had been published previously or were available from the original investigators.

Although collaborative recalculation of primary data is a strong methodology, the results should be interpreted in light of several design limitations. First, different studies used different definitions for age of onset. Age at first hospitalization is often criticized as proxy of true age of psychosis onset because significant between-person variability in duration of untreated psychosis may cause differences in first contact with mental health services. However, the latter have repeatedly been found to be strongly correlated (DeLisi, 1992; Häfner *et al*. 1993*a*; Walker & Lewine, 1993). As such, age at first hospitalization has been shown to represent a valid index in estimating age-at-onset effects. Second, although individual-level data were available for age, sex and study period, this was not the case for other characteristics such as level of urbanicity or social fragmentation; therefore we did not explore additional sources of heterogeneity in the age and sex distribution of schizophrenia as this would be vulnerable to cross-level inferential bias. Third, no formal rating for study design was carried out, which may have contributed to a better understanding of methodological variation. However, although some reliable checklists and scales have been developed to assess the quality of trial data (Shea *et al*. 2007), defining quality for observational studies is psychometrically challenging and often highly subjective (Stroup *et al*. 2000). Fourth, estimations of risk for schizophrenia in the elderly are probably underestimations of true risk because of a seeming reluctance in clinicians to diagnose schizophrenia in the elderly (Harris & Jeste, 1988). In addition, many of the included studies excluded subjects older than 65 years, and in ICD-9, schizophrenia and schizophrenia-like illness with late onset may have been diagnosed as 'paranoid psychosis' in some countries. Hence, the 1.17-fold greater risk of schizophrenia in men compared to women found in this analysis should be interpreted in light of this, and may represent an overestimation. Limited data are available from developing countries. Only nine (of which four were included and five excluded because of limited data availability) samples were collected in developing countries. The findings, therefore, may not be generalizable to developing countries, particularly because sex differences may show a different distribution by age in these countries (Gangadhar *et al*. 2002). Finally, the number of studies that had to be excluded was relatively large (see online Supplementary Table S2), including a total of 74 studies that might have contained useful data for this meta-analysis. Although this could have affected the results and conclusions slightly, we consider that the calculations were based on sufficiently large numbers to guarantee robustness of the results. Furthermore, although not all published data were available in sufficient detail to be included in the central recalculation, studies that were excluded showed similar study and population characteristics, making systematic bias less likely.

Conclusions

The establishment of age- and sex-specific incidence rates for schizophrenia is of great importance for mental health service development; detailing the timing of schizophrenia onset reveals a window of opportunity for possible early detection and preventive strategies. The results further highlight the fact that a small, but not negligible, proportion of individuals develop schizophrenia after age 60 years. These numbers are likely to rise significantly, with the first of the post-war 'baby-boom' generation reaching 65 years of age by the end of 2010 (Jeste *et al*. 1999). The concept of prevention should therefore not only be restricted to adolescents but also be applied to middle-aged and elderly persons (Lebowitz & Pearson, 2000).

Appendix. Research Initiative into Schizophrenia Epidemiology (RISE) Investigators

M. van der Werf, S. Köhler, J. Allardyce, J. van Os, M. Hanssen, F. Verhey, I. Lynge, J.-P. Selten, J.-D. Blom, N. Veen, C. Verheyde-Zeyl, J. Geddes, M. Goldacre, D. G. R. Yeates, N. Nixon, V. Adjacic, W. Rössler, P. Baldwin, J. Waddington, J. Kirkbride, C. Morgan, P. Dazzan, R. Murray, P. B. Jones, G. Doody, G. Harrison, J. Leff, J. W. Coid, P. Fearon, J. E. Andersen, T. Hynnekleiv, R. McCreadie, H. Gilmour, P. Menezes, G. Smith, W. Iacono, A. Thorup, C. Pedersen, H. Häfner, W. an der Heiden, F. Hickling, J. Peen, J. Dekker, R. de Graaf, W. Veling, W. Hoek, M. Bogren, J. Boydell, D. Castle, E. Mitford, J. Brewin, M. Goldacre, N. Takei and F. Ammaddeo.

https://doi.org/10.1017/S0033291712002796 Published online by Cambridge University Press

Supplementary material

For supplementary material accompanying this paper visit http://dx.doi.org/10.1017/S0033291712002796.

Declaration of Interest

Jim van Os has received unrestricted investigator-led research grants or recompense for presenting his research from Eli Lilly, Bristol-Myers Squibb, Lundbeck, Organon, Janssen-Cilag, GlaxoSmithKline, AstraZeneca, Pfizer and Servier, companies that have an interest in the treatment of psychosis.

References

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

Angermeyer MC, Kuhn L (1988). Gender differences in age at onset of schizophrenia. An overview. *European Archives of Psychiatry and Neurological Sciences* **237**, 351–364.

APA (1980). *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edn (DSM-III). American Psychiatric Association: Washington, DC.

APA (1987). *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edn, revised (DSM-III-R). American Psychiatric Association: Washington, DC.

APA (1994). *Diagnostic and Statistical Manual of Mental Disorders*, 4th edn (DSM-IV). American Psychiatric Association: Washington, DC.

Bijl RV, de Graaf R, Ravelli A, Smit F, Vollebergh WAM (2002). Gender and age-specific first incidence of DSM-III-R psychiatric disorders in the general population. Results from the Netherlands Mental Health Survey and Incidence Study (NEMESIS). *Social Psychiatry and Psychiatric Epidemiology* **37**, 372–379.

Castle DJ, Abel K, Takei N, Murray RM (1995). Gender differences in schizophrenia: hormonal effect or subtypes? *Schizophrenia Bulletin* **21**, 1–12.

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

Clarke M, O'Callaghan E (2003). First-episode studies in schizophrenia. In *The Epidemiology of Schizophrenia* (ed. R. M. Murray, P. B. Jones, E. Susser, J. van Os and M. E. Cannon), pp. 148–166. Cambridge University Press: Cambridge.

DeLisi LE (1992). The significance of age of onset for schizophrenia. *Schizophrenia Bulletin* **18**, 209–215.

Esterberg ML, Trotman HD, Holtzman C, Compton MT, Walker EF (2010). The impact of a family history of psychosis on age-at-onset and positive and negative symptoms of schizophrenia: a meta-analysis. *Schizophrenia Research* **120**, 121–130.

Gangadhar BN, Selvan CP, Subbakrishna DK, Janakiramaiah N (2002). Age-at-onset and schizophrenia: reversed gender effect. *Acta Psychiatrica Scandinavica* **105**, 317–319.

Häfner H, Maurer K, Löffler W, Riecher-Rössler A (1993*a*). The influence of age and sex on the onset and early course of schizophrenia. *British Journal of Psychiatry* **162**, 80–86.

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

Häfner H, Riecher-Rössler A, an der Heiden W, Maurer K, Fätkenheuer B, Löffler W (1993*b*). 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, Häfner H, Sartorius N (1992). Transnational stability of gender differences in schizophrenia? An analysis based on the WHO study on determinants of outcome of severe mental disorders. *European Archives of Psychiatry and Clinical Neuroscience* **242**, 6–12.

Harris MJ, Jeste DV (1988). Late-onset schizophrenia: an overview. *Schizophrenia Bulletin* **14**, 39–55.

Howard R, Rabins PV, Seeman MV, Jeste DV (2000). Late-onset schizophrenia and very-late-onset schizophrenia-like psychosis: an international consensus. The International Late-Onset Schizophrenia Group. *American Journal of Psychiatry* **157**, 172–178.

Jablensky A (2003). Schizophrenia: the epidemiological horizon. In *Schizophrenia*, 2nd edn (ed. S. R. Hirsch and D. R. Weinberger), pp. 203–231. Blackwell Science: Oxford.

Jablensky A, Cole SW (1997). Is the earlier age at onset of schizophrenia in males a confounded finding? Results from a cross-cultural investigation. *British Journal of Psychiatry* **170**, 234–240.

Jablensky A, Sartorius N, Ernberg G, Anker M, Korten A, Cooper JE, Day R, Bertelsen A (1992). Schizophrenia: manifestations, incidence and course in different cultures. A World Health Organization ten-country study. *Psychological Medicine. Monograph Supplement* **20**, 1–97.

Jeste DV, Alexopoulos GS, Bartels SJ, Cummings JL, Gallo JJ, Gottlieb GL, Halpain MC, Palmer BW, Patterson TL, Reynolds 3rd CF, Lebowitz BD (1999). Consensus statement on the upcoming crisis in geriatric mental health: research agenda for the next 2 decades. *Archives of General Psychiatry* **56**, 848–853.

Kelly BD, O'Callaghan E, Waddington JL, Feeney L, Browne S, Scully PJ, Clarke M, Quinn JF, McTigue O, Morgan MG, Kinsella A, Larkin C (2010). Schizophrenia and the city: a review of literature and prospective study of psychosis and urbanicity in Ireland. *Schizophrenia Research* **116**, 75–89.

Kirov G, Jones PB, Harvey I, Lewis SW, Toone BK, Rifkin L, Sham P, Murray RM (1996). Do obstetric complications cause the earlier age at onset in male than female schizophrenics? *Schizophrenia Research* **20**, 117–124.

Lebowitz BD, Pearson JL (2000). Intervention research in psychosis: prevention trials. *Schizophrenia Bulletin* **26**, 543–549.

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.

Morgan VA, Castle DJ, Jablensky AV (2008). Do women express and experience psychosis differently from men? Epidemiological evidence from the Australian National Study of Low Prevalence (Psychotic) Disorders. *Australian and New Zealand Journal of Psychiatry* **42**, 74–82.

Murray RM, O'Callaghan E, Castle DJ, Lewis SW (1992). A neurodevelopmental approach to the classification of schizophrenia. *Schizophrenia Bulletin* **18**, 319–332.

Raz S, Goldstein R, Hopkins TL, Lauterbach MD, Shah F, Porter CL (1994). Sex differences in early vulnerability to cerebral injury and their neurodevelopmental implications. *Psychobiology* **22**, 244–253.

Riley RD, Lambert PC, Abo-Zaid G (2010). Meta-analysis of individual participant data: rationale, conduct, and reporting. *British Medical Journal* **340**, c221.

Rosenfield PJ, Kleinhaus K, Opler M, Perrin M, Learned N, Goetz R, Stanford A, Messinger J, Harkavy-Friedman J, Malaspina D (2010). Later paternal age and sex differences in schizophrenia symptoms. *Schizophrenia Research* **116**, 191–195.

Seeman MV (1996). The role of estrogen in schizophrenia. *Journal of Psychiatry and Neuroscience* **21**, 123–127.

Shea B, Dube C, Moher D (2007). Assessing the quality of reports for systematic reviews: the QUOROM statement compared to other tools. In *Systematic Reviews in Health Care: Meta-Analysis in Context* (ed. M. Egger, G. D. Smith and D. G. Altman), pp. 122–139. BMJ Books: London.

Spitzer RL, Endicott J, Robins E (1978). Research diagnostic criteria: rationale and reliability. *Archives of General Psychiatry* **35**, 773–782.

StataCorp (2009). *STATA Statistical Software: Release 11.0*. Stata Corporation: College Station, TX.

Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB (2000). Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *Journal of the American Medical Association* **283**, 2008–2012.

United Nations (2009). *Human Development Report 2009. Overcoming Barriers: Human Mobility and Development* (http://hdr.undp.org/en/media/HDR_2009_EN_Complete.pdf). United Nations Development Programme.

Vahia IV, Palmer BW, Depp C, Fellows I, Golshan S, Kraemer HC, Jeste DV (2010). Is late-onset schizophrenia a subtype of schizophrenia? *Acta Psychiatrica Scandinavica* **122**, 414–426.

Venkatesh BK, Thirthalli J, Naveen MN, Kishorekumar KV, Arunachala U, Venkatasubramanian G, Subbakrishna DK, Gangadhar BN (2008). Sex difference in age of onset of schizophrenia: findings from a community-based study in India. *World Psychiatry* **7**, 173–176.

Walker EF, Lewine RR (1993). Sampling biases in studies of gender and schizophrenia. *Schizophrenia Bulletin* **19**, 1–7; discussion 9–14.

Weinberger DR (1987). Implications of normal brain development for the pathogenesis of schizophrenia. *Archives of General Psychiatry* **44**, 660–669.

WHO (1955). *International Classification of Diseases, Seventh Revision* (*ICD-7*). World Health Organization: Geneva, Switzerland.

WHO (1965). *International Classification of Diseases, Eight Revision* (*ICD-8*). World Health Organization: Geneva, Switzerland.

WHO (1977). *International Classification of Diseases, Ninth Revision* (*ICD-9*). World Health Organization: Geneva, Switzerland.

WHO (1992). *International Classification of Diseases, 10th Revision* (*ICD-10*). World Health Organization: Geneva, Switzerland.

World Bank (2010). *World Development Indicators* (*2010*) (http://data.worldbank.org/sites/default/files/wdi-final.pdf).