Online Supplementary Document

Chen and Rudan et al. Prevalence of schizophrenia in China between 1990 and 2010

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Table s1: A detailed breakdown of the results of initial search of the Chinese databases for the papers on epidemiology of schizophrenia between 1990 and 2010. (note: R1=FFZ; R2=SJM)

Table s2. The full list of studies retained for the analyses (Note: The list employs the official English translation of the journal names, journal abbreviations and paper titles as evident in the printed journal, CNKI, WanFang and other official academic databases. Wherever the official English translation of the journal names was not available, a pinyin title is used. (*indicates translation of Chinese paper titles by the authors of this manuscript for Chinese papers where official English translation is not available).

Table s3. The full list of studies retained for the analyses (Note: The list employs the official English translation of the journal names, journal abbreviations and paper titles as evident in the printed journal, CNKI, WanFang and other official academic databases.

Table s4. Distribution of studies by province/municipalities.

*Note: 1 of the prevalence studies was conducted in 7 provinces/municipalities.

Table s5. The table presents a targeted sub-analysis of the data to avoid potential differences in study design and case ascertainment between urban and rural areas. A specific comparison of prevalence of schizophrenia in urban and rural setting is presented for 10 studies that used a sample of comparable size from both urban and rural area within the same setting, and used the same study design and methods of case ascertainment.

Figure s1a-c. Meta-analysis of the retained studies to explore the effects of urban area residence, year of study and method of case finding, to explore the effects of study heterogeneity. All results are based on prevalence estimates per 1000 population (to make the graphs more presentable). In all analyses, a random effects model was used because of high heterogeneity. Results of heterogeneity are reported in the graph (I^2 and p-value). When I^2 is higher than 50% and p-value is less than 0.05, there is an evidence of heterogeneity.

Figure s1a

Figure s1b

Figure s1c

eMethods. Statistical analyses of the data.

1. Bayesian analysis to estimate the prevalence in urban and rural regions at different time points

The results here are based on a Bayesian analysis. Based on the data available, we have used a binomial logistic regression model. As we have used the same approach for all four datasets, we describe it for the lifetime urban studies.

Let y_i denote the number of cases of schizophrenia for study $i = 1, 2, \ldots$, 28 (because 28 of 42 studies contained information on urban areas and lifetime prevalence), and N_i denote the total population size. Then the model states that

$$
y_i \sim \text{Binomial}(N_i, p_i).
$$

The unknown parameters *pi* are the unknown probabilities of an individual selected at random having schizophrenia for each study. These would be modeled on the number of years since the earliest study using the logistic link. This means

$$
logit(p_i) = log\left(\frac{p_i}{1-p_i}\right) = \beta_0 + \beta_1 \times time_i,
$$

or equivalently

$$
p_i = \frac{\exp\{\beta_0 + \beta_1 \times \text{time}_i\}}{1 + \exp\{\beta_0 + \beta_1 \times \text{time}_i\}}.
$$

In this equation, time*i* is 0 for any of the studies in 1990 (in this case) and represents the number of years since 1990 and β*0* and β*1* represent unknown parameters to make inference on. The Bayesian approach allows prior knowledge (if any) to be incorporated. As we didn't have any prior knowledge, we express this lack of knowledge using independent normal distributions on β_0 and β_1 both having a huge variance of 10⁶:

$$
\beta_0 \sim \text{Normal}(0, 10^6),
$$

$$
\beta_1 \sim \text{Normal}(0, 10^6).
$$

Now using Bayes theorem, it was possible to find the joint distribution of β*0* and β*1* given the data that was observed. This is called the posterior distribution and is denoted as

$$
\Pr(\beta_0, \beta_1 | y_1, y_2, \ldots, y_{28})
$$

or as Pr(β0, β1|y) for short. Of particular interest were the marginal posterior distributions $Pr(\beta_0|y)$ and $Pr(\beta_1|y)$ which can be obtained from $Pr(\beta_0, \beta_1|y)$ by integration.

Given the marginal posterior distribution, appropriate summaries could be obtained. These could include point estimates such as the posterior mean, median or mode as well as uncertainty measures including the standard deviation and the 95% credible interval defined for $β$ ⁰ as the interval (l, u) such that

$$
Pr(l < \beta_0 < u|\mathbf{y}) = 0.95.
$$

To obtain the quantities above, it was necessary to use Markov chain Monte Carlo sampling, because the relevant marginal posterior distributions were not available in closed form. Given some initial values, this sampling scheme runs through 2 stages: the "burn in", which must be discarded, and the "post burn in" which can be retained as approximate samples from the marginal posterior distributions of interest. The relevant quantities can then be calculated on these samples.

We have used a Markov chain Monte Carlo sampler called a Gibbs sampler. Based on 3 independent chains, we found no evidence of lack of convergence after 1,000 iterations, so this part of the sample was discarded. The results in **Table S1** were based on pooling the samples from each chain after discarding 3,000 burn in samples (1,000 per chain) and leaving a total sample of 30,000 samples. We used the sample posterior median as the estimate.

It is often of interest to compare two or more competing models. There are a number of approaches to do this in a Bayesian framework. One popular approach is based on the deviance information criterion (DIC) introduced in Spiegelhalter et al. (2002). This popularity is in part due to the fact that it can be estimated from a sample from the posterior distribution. In common with other model selection criteria, it consists of a measure of fit to the data (the deviance) and a penalty on model complexity to guard against over-fitting. In comparing two or more models, the 'best' model is the one with the smallest value of the DIC. The results in **Table S2** are the difference in DIC between the model with time as a covariate and the intercept only model.

The results suggested that for studies in the 'lifetime' category, the log odds ratio for both rural and urban studies was positive. The credible intervals did not contain 0 and the deviance information criterion was lower for the model including time, implying that there was indeed an increase in probability of schizophrenia as time increases. For the studies in the 'point' category, the probability of schizophrenia in urban areas also appeared to increase over the years, but for rural areas, the credible interval included 0 and the DIC for the intercept only model was smaller, suggesting that the model stated that the probability of schizophrenia is constant in rural areas.

eMethods Table 1. Results from Bayesian analysis of schizophrenia studies. The estimate is based on the posterior median. The covariate "Year (of study)" is included as number of years since the earliest study.

eMethods Table 2. The deviance information criterion (DIC) difference relative to the intercept only model (i.e. DIC for model with year of study as a covariate - DIC for intercept only model).

Based on the samples, it was possible to estimate the probabilities of having schizophrenia in 1990, 2000 and 2010, together with a 95% credible intervals, as presented in **Table 2** in the main text. Credible intervals did not take into account the likely effect of sampling uncertainty, which - if taken into account - would slightly expand the credible interval.

2. Additional sensitivity analysis to investigate the potential effects of age and sex distribution of the study sample on the prevalence of schizophrenia

Our primary interest in this study was to explore the effects of the year of study and urban/rural residency on the prevalence of schizophrenia. We based our analysis on 42 large studies, all of which provided the information on predictor variables - year of study and urban/rural setting. Our primary analysis resulted in robust and internally consistent estimates, with narrow confidence intervals, which was expected given a very large overall sample size (2·28 million examinees).

Following the completion of our primary analysis (above), we run an additional sensitivity analysis to explore a potential bias that could have arisen from possible differences in age and sex distribution of the examinees between the samples of different studies. We did not include mean age or male-to-female ratio in the primary analysis for three reasons:

- i. We did not have complete information on age and/or sex distribution of the sample from a number of studies;
- ii. Reports on prevalence specifically by gender were available only from a handful of studies; and
- iii. Adding of additional covariates to the Bayesian analysis described above leads to large increase in the complexity of computations and demand for computer time and capacity.

We did not expect the effect of internal age-sex structure of the samples to be a major confounding factor in our study because:

- i. The samples in all studies were large (or very large) and broadly representative of the underlying population; male-to-female ratio from the samples was therefore similar to that expected in the population, which meant that the observed prevalence could not be dramatically affected by male-to-female ratio of the sample, even if there were significant differences in prevalence between two sexes;
- ii. Lifetime morbid risk for schizophrenia does not have dramatic peaks at particular ages, so it was unlikely that the mean age of the sample would be a striking predictor of the prevalence, necessitating adjustments in the observed reports before the final analysis.

We used the same analysis described above, based on the deviance information criterion (DIC) (Spiegelhalter et al., 2002), to explore the role of the mean age of the sample and the sex on the prevalence of schizophrenia in a limited sub-sample where this information was available. The results are shown in **Table S3**:

Table s3. The deviance information criterion (DIC) for full model, including the information on age of examinees (Age), year of study (YoS), urban/rural residency (Res) and gender (Sex).

The analysis shows that DIC does not increase when mean age is dropped as a predictor, meaning that mean age of the sample has no effect on the reported prevalence. However, the analysis in a sub-sample of studies where the prevalence was reported differentially by sex indicates that there are differences in prevalence by sex, with males having higher rates. However, this does not affect our population-based estimates for China, because the male-to-female ratio in our samples was comparable to the male-to-female ratio in Chinese population aged 15 years or more, to which we applied the estimates of the prevalence, meaning that no further adjustments were necessary.

eReference

Spiegelhalter DJ, Best NG, Carlin BP, van der Linde A. Bayesian measures of model complexity and fit (with discussion). *J R Stat Soc Series B Stat Methodol.* 2002;64:583-639.