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Meta-analyses of the incidence and prevalence of schizophrenia: conceptual and methodological issues

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Abstract
While meta-analytic techniques are routine in the synthesis of data from randomized controlled trials, there are no clear guidelines on how best to summarize frequency data such as incidence and prevalence estimates. Based on data from two recent systematic reviews of the incidence and prevalence of schizophrenia, this paper explores some of the conceptual and methodological issues related to the meta-analyses of frequency estimates in epidemiology. Because variations in the incidence and prevalence of disorders such as schizophrenia can be informative, there is a case against collapsing data into one pooled estimate. Variations in frequency estimates can be displayed graphically, or summarized with quantiles around measures of central tendency. If pooled estimated are of interest, then researchers need to be aware that studies based on large samples will leverage greater weight on the pooled value. Based on systematic reviews of the incidence and prevalence of schizophrenia, we explore if these and related issues are of practical concern. When used with appropriate caution, meta-analysis can complement the synthesis of frequency data in epidemiology; however, researchers interested in variation should not rely on meta-analysis alone. Copyright © 2008 John Wiley & Sons, Ltd.

Key words: schizophrenia, systematic review, meta-analysis, incidence, prevalence, epidemiology

Introduction

Systematic reviews replace the subjectivity of traditional narrative reviews with rigorous, transparent and unbiased methodology for locating studies and extracting data (Egger et al., 1997). While many systematic reviews utilize meta-analytic techniques to summarize the data, this is not always the case (Dickersin, 2002). Systematic reviews without data pooling are recommended where data are not suitable for combining (e.g. wide variation in design, exposure, and outcomes) (Ioannidis and Lau, 1999).

In spite of the widespread use of meta-analyses, there is relatively little discussion on the strengths and weaknesses of these techniques for summarizing frequency measures such as incidence and prevalence estimates (Dickersin, 2002). Recently our group published two systematic reviews on the incidence (McGrath et al., 2004) and prevalence (Saha et al., 2005) of schizophrenia. In the original publications we chose not to meta-analyse the data, but presented the readers with graphs displaying the distribution of the estimates. In the text of the original paper, we presented key quantiles that demarcated features of the graphical distributions (see Figure 1) and provided several measures of central tendency (e.g. median, mean). For example, based on the distribution of all rates for the incidence of schizophrenia in persons, the median rate was 15.2 per 100 000, the mean rate was 23.7 per 100 000, and the 10% and 90% quantiles were 7.7 and 43.0 per 100 000, respectively. The difference between the median and mean

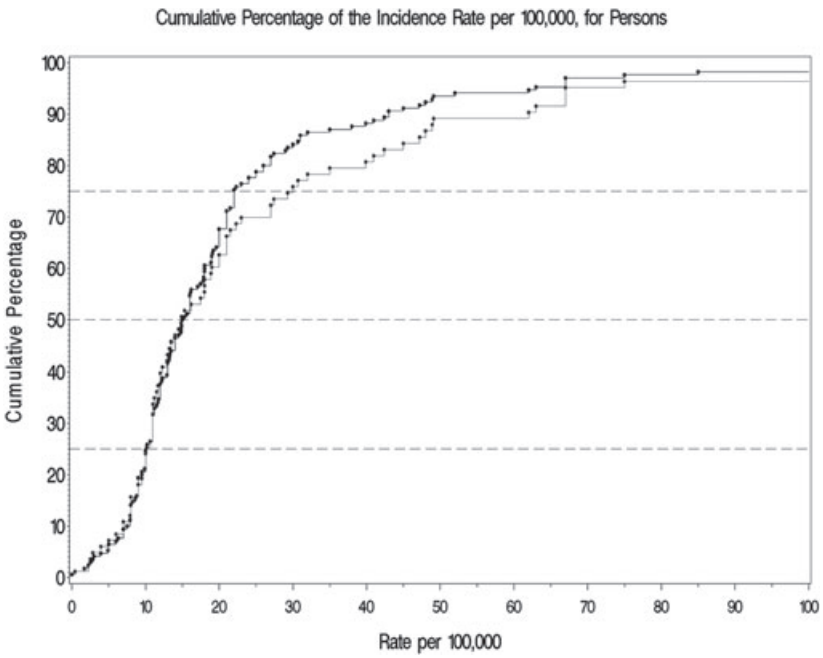

Figure 1. Cumulative plots of the incidence of schizophrenia per 100 000 persons by 'all studies' shown in black versus 'SE subset' shown in grey (i.e. studies with reported or imputed standard errors).

values indicates that the distribution of rates is skewed, while the 10% to 90% range shows that the central portion of the distribution varies over a five-fold range. In presenting the data in this fashion we accorded every rate equal value, despite the fact that the sample sizes of the contributing studies varied widely. Based on the guiding assumption that incidence rates vary widely for most diseases, we sought to preserve and report variation in the data. We were not interested in a single, pooled value – an exercise in reductionism that sacrifices potentially informative variation.

Practical issues in the meta-analysis of frequency data

Apart from conceptual issues related to the benefits of 'pooling' versus 'not pooling', there are several practical issues that need to be addressed. Firstly, those interested in meta-analysis need to reflect on issues related to heterogeneity. Heterogeneity refers to the underlying distribution of the data, and should not be confused with the range or the variability of the data (e.g. data can be homogeneous but have a very wide range). If data contributing to a meta-analysis are significantly heterogeneous, then the standard errors (SEs) or confidence limits given for the pooled estimate (effect) do not adequately reflect the variability of the underlying data (Greenland, 1998). There are several techniques now available for the formal assessment of heterogeneity in pooled data [e.g. Cochran *Q* statistic, I^2 statistic (Higgins et al., 2003)]. Researchers have used meta-regression techniques in order to identify potential sources of heterogeneity (Higgins and Thompson, 2002; Petitti, 2001).

With respect to schizophrenia, researchers have previously noted that frequency estimates from observational studies are heterogeneous (Aleman et al., 2003; Cantor-Graae and Selten, 2005; Goldner et al., 2002). Disease frequencies in schizophrenia epidemiology vary widely between sites due to variations in population characteristics, and differences in exposure levels (Kraemer et al., 1998). In these circumstances, a cumulative distribution plot may be the most informative way to present the data. These distributions can be inspected for factors such as the density of estimates underpinning various segments (e.g. data rich versus data sparse), skewness, the presence of outliers, and the width of the distribution. Such distributions can also be scrutinized in planned sensitivity analyses, and thus

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be used to explore potential sources of heterogeneity. For example, in our previous publication, we detected significant differences in the distribution of rates when sorted according to sex, migrant status and urbanicity of setting (McGrath et al., 2004).

Apart from the conceptual issues about combining heterogeneous data, one of the most frustrating aspects for systematic reviewers is the inadequate reporting of frequency estimates. In order to pool data, the SE for each estimate is required to weight the estimate. In our review of the incidence of schizophrenia (McGrath et al., 2004), only 5% of studies reported SEs for their corresponding rates. We were able to infer SEs for another 40% of studies where exact data on the numerator, denominator and duration of recruitment were available (however, derived SEs can not take into account age and sex adjustments). As a consequence, pooled estimates for systematic reviews have to be based on the 'subset' of studies, which may introduce systematic biases (Clarke and Stewart, 1994).

There is also a lack of guidance on how best to combine frequency estimates drawn from sites with different background population size. When pooling data for meta-analysis, study weight is computed from the reciprocal of the squared SE. Frequency measures drawn from larger populations will have smaller SEs. Thus, when entered into a meta-analysis along with studies based on smaller populations, standard meta-analysis allows studies based on larger background populations to exert greater influence on the pooled estimate (Flather et al., 1997; Greenland, 1998). Various methods have been proposed to deal with such sample size biases in meta-analysis. In order to counteract small study bias, some authors have suggested that small studies be excluded (Kraemer et al., 1998). For example, Goldner and colleagues (2002) included only studies with denominator populations of 450 or more for the meta-analysis of the incidence and prevalence studies. Conversely, in order to reduce the influence of studies based on large populations, Aleman and colleagues (2003) and Cantor-Graae and Selten (2005) used an arbitrary cut-off that 'capped' the sample size of studies included in their meta-analyses. Larger sample sizes do generally provide greater precision, and where a fixed effect size is predicted, this feature can be exploited in funnel plots in order to explore publication bias (Greenland, 1998).

The meta-analyses of the incidence and prevalence of schizophrenia

Leaving aside the technical aspects of pooling data, does it actually make much difference when data are summarized with conventional meta-analyses versus more descriptive approaches (e.g. median of a distribution)? For example, a recent systematic review of mortality in schizophrenia (Saha et al., 2007) found that the two measures were remarkably similar (e.g. median estimate = 2.58, meta-analysis pooled estimate = 2.50). We had the opportunity to compare methods of summarizing data based on two previously published systematic reviews of the incidence and prevalence of schizophrenia. Full details of the study methodology and citations for the included studies are available elsewhere (McGrath et al., 2004; Saha et al., 2005).

In order to explore potential biases related to the presence or absence of SEs, we prepared cumulative plots that showed the distributions for 'all studies' as well as those with published or derived SEs ('SE subset'). For the main comparison, we used 'combined' prevalence estimates based on four different prevalence estimate types (point, period, lifetime, and Not Otherwise Specified). Lifetime Morbid Risk (LMR) was reported separately. For studies with sufficient information to calculate SEs, a random-effects model was used for meta-analysis (Aleman et al., 2003; Goldner et al., 2002). Random-effects models are preferred to fixed-effects models because epidemiological frequency measures in schizophrenia are known to vary widely between sites due to variations in population characteristics, and differences in risk factors and exposure levels (Berkey et al., 1995; Berlin, 1995). All analyses were undertaken for persons (i.e. males and females combined) using macros written in SAS 9.1 (SAS Institute Inc., Cary, North Carolina, USA).

Figure 1 and Table 1 show the distribution of the incidence rates for 'all studies', and for the 'SE subset' with corresponding quantiles and moments for persons. The 'SE subset' data are also presented in Figure 2, along with the pooled estimated. While the median incidence rate for 'all studies' versus the 'SE subset' where comparable (15.2 versus 14.9 per 100 000 respectively), the pooled estimated based on the 'SE subset' was higher 21.9 per 100 000 [95% confidence interval (CI) = 19.4–24.4] (Figure 2). Cochran's Q confirmed that the data were significantly heterogeneous (Q = 360.24, df = 82, $p < 0.001$), indicating that

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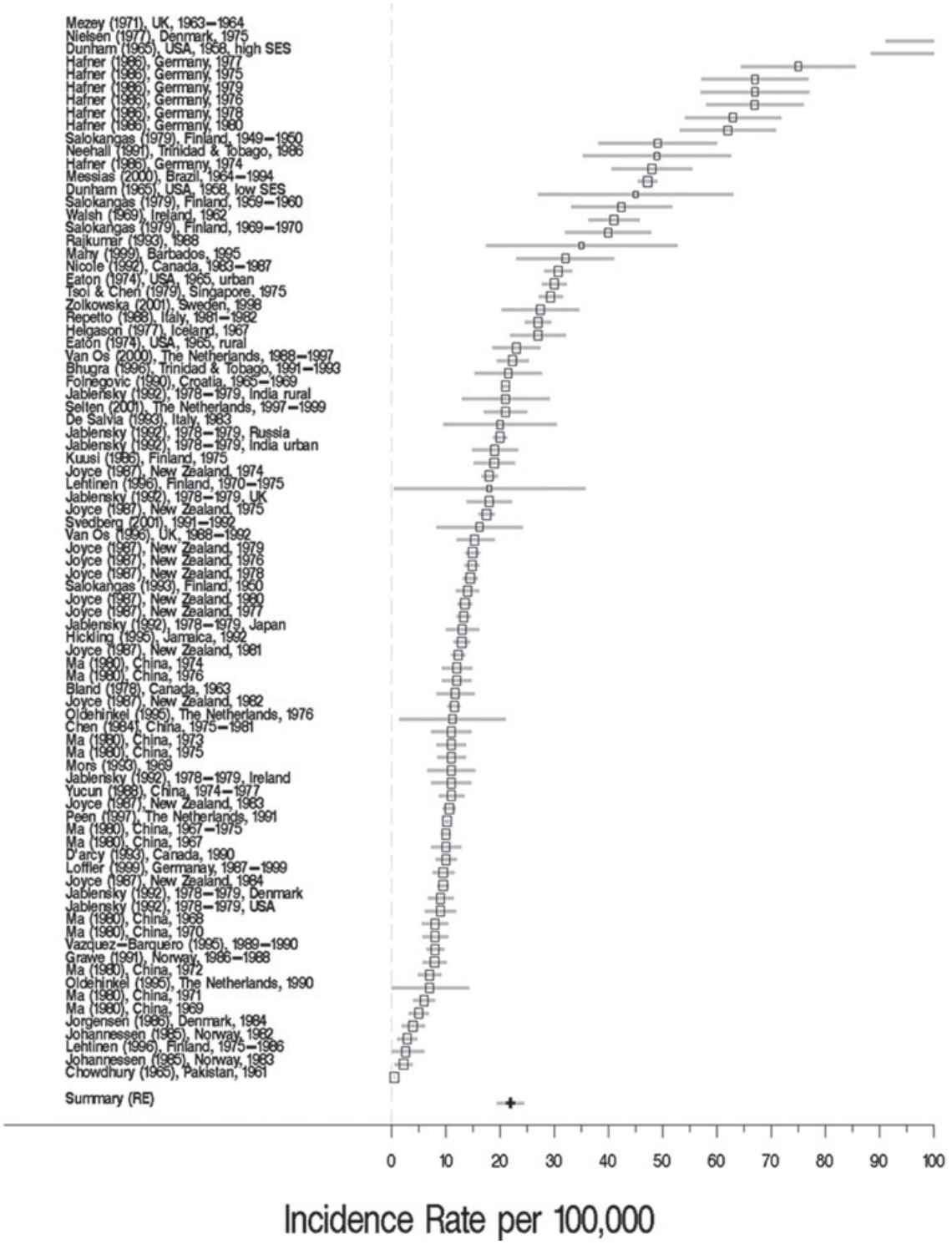

Figure 2. Forest plot of the 'SE subset' incidence of schizophrenia per 100 000 persons (studies with reported or 'imputed' SEs). The highest estimates are truncated in this figure.

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interpretation of the CIs requires caution. Because the median rate for the 'SE subset' was lower than 'all studies', the higher value found by meta-analysis suggests the influence of factors related to study size/study weights.

Figure 3 and Table 1 show that the distribution of the prevalence estimates for 'all studies', and for the 'SE subset' were broadly comparable. The median prevalence for 'all studies' was 3.3 per 1000, and for the 'SE subset' was 3.4 per 1000. Figure 4 shows the meta-analysis of the 'SE subset'. The pooled estimate for the 'subset' of prevalence studies was 4.2 (95% CI = 3.7–4.7), however, as with the incidence rates, the prevalence estimates were significantly heterogeneous ($Q = 295.2$, $df = 81$, $p < 0.001$). The pooled estimates (and 95% CI) for the individual prevalence types were 3.9 (3.2–4.7), 4.4 (3.3–5.4), 4.7 (3.6–5.9) per 1000 persons for point, period, and lifetime, respectively. In contrast to the median values we previously published (Saha et al., 2005), the pooled estimate values reflect the expectation that lifetime estimates should exceed period estimates, and that period estimates should exceed point estimates. The pooled estimate (and 95% CI) for LMR for persons was 9.5 (7.9–11.1) per 1000 (based on 11 estimates). The pooled estimated was higher than the median value, but lower than the mean previously published (median and mean 7.2 and 11.89 per 1000, respectively). In summary, the values derived from the meta-analysis of prevalence estimates are broadly comparable with the median values previously published.

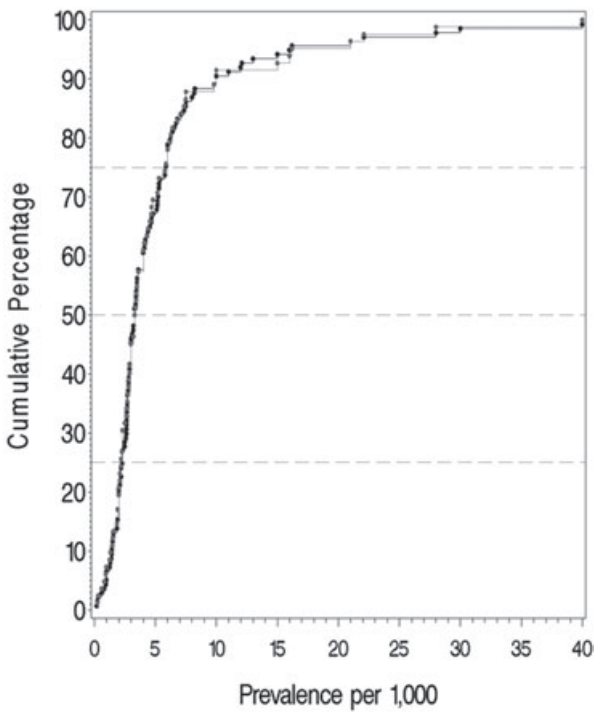

Figure 3. Cumulative plots of the prevalence of schizophrenia per 1000 persons by 'all studies' versus 'SE subset' shown in grey (i.e. studies with reported or imputed SEs).

Conclusions and recommendations

Epidemiologists seek to identify variation between sites and across time. Researchers can 'grain traction' on such gradients (McGrath, 2003) and generate candidate risk factors related to etiology or course of illness. We found five-fold variations in the incidence of schizophrenia (McGrath et al., 2004), and four- to seven-fold variations in the prevalence of schizophrenia between sites (Saha et al., 2005). In this respect, distribution plots with medians and quantiles are superior to traditional meta-analyses approaches for the assessment of variation.

Table 1. Quantiles and moments of 'all studies' and 'SE subset' of studies for incidence rates per 100 000 and prevalence estimates per 1000 persons

	n (rates/ estimates)	10%	Median	90%	Mean	SD
Incidence						
'All studies'	55 (170)	7.7	15.2	43.0	23.7	30.3
'SE subset'	43 (83)	7.0	14.9	62.0	28.2	41.1
Prevalence						
'All studies'	85 (136)	1.4	3.3	10.0	5.4	6.8
'SE subset'	63 (82)	1.5	3.4	10.0	5.3	6.8

Note: *n*, number of studies, SD, standard deviation.

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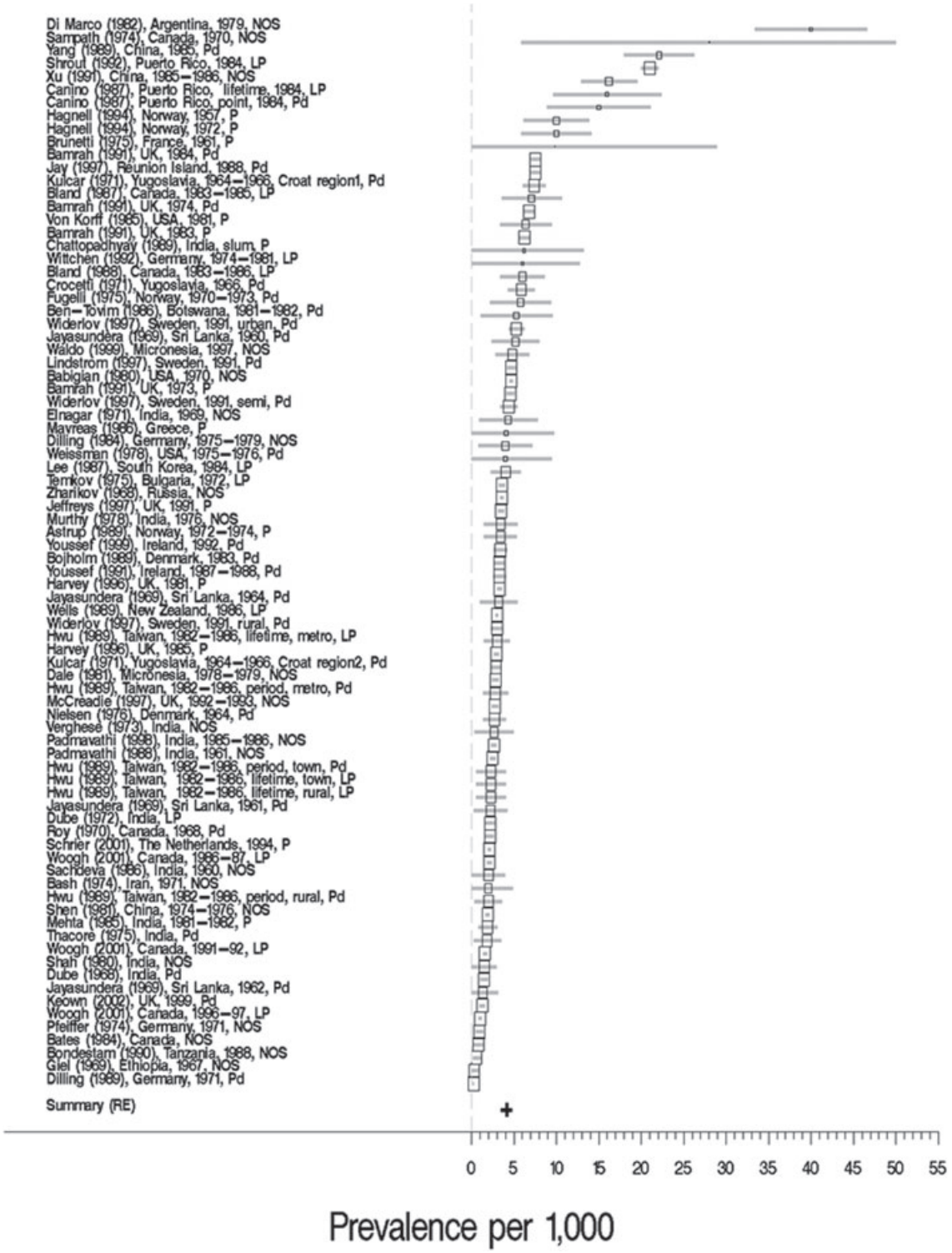

Figure 4. Forest plot of the prevalence of schizophrenia per 1000 persons for the 'SE subset' (studies with reported or 'imputed' SEs). LP = Lifetime prevalence, P = point prevalence, Pd = period prevalence, NOS = not otherwise stated prevalence.

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The synthesis of incidence and prevalence data has been critical for the evaluation of disease burden measures such as the Disability-Adjusted Life Year (DALY), a metric increasingly relied on for the prioritization of health care and service planning (Murray et al., 1994). If researchers do choose to pool data by meta-analyses (e.g. to provide a summary estimate for a group of nations), they should alert the reader about how they dealt with the issue of weighting studies of different sizes. Regardless of which methods future systematic reviewers use to summarize incidence and prevalence estimates, the quality of reporting of the primary studies needs to be addressed. Guidelines for the reporting of observational data from epidemiological studies are now available [e.g. MOOSE: Meta-analysis of Observational Studies in Epidemiology) (Stroup et al., 2000)].

The application of systematic reviews has provided fresh perspectives on the epidemiological landscape of schizophrenia (McGrath, 2006; Saha et al., 2007). By considering the strengths and weaknesses of the different methods available to summarize data from systematic reviews, we can be better equipped to draw inferences from this complex but informative data.

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