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A Systematic Review and Meta-Analysis of Recovery in Schizophrenia

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Objective: **Our primary aims were (*a*) to identify the proportion of individuals with schizophrenia and related psychoses who met recovery criteria based on both clinical and social domains and (*b*) to examine if recovery was associated with factors such as gender, economic index of sites, and selected design features of the study. We also examined if the proportions who met our definition of recovery had changed over time.** ***Method:*** **A comprehensive search strategy was used to identify potential studies, and data were extracted for those that met inclusion criteria. The proportion who met our recovery criteria (improvements in *both* clinical and social domains and evidence that improvements in at least 1 of these 2 domains had persisted for at least 2 years) was extracted from each study. Meta-regression techniques were used to explore the association between the recovery proportions and the selected variables.** ***Results:*** **We identified 50 studies with data suitable for inclusion. The median proportion (25%–75% quantiles) who met our recovery criteria was 13.5% (8.1%–20.0%). Studies from sites in countries with poorer economic status had higher recovery proportions. However, there were no statistically significant differences when the estimates were stratified according to sex, midpoint of intake period, strictness of the diagnostic criteria, duration of follow-up, or other design features.** ***Conclusions:*** **Based on the best available data, approximately, 1 in 7 individuals with schizophrenia met our criteria for recovery. Despite major changes in treatment options in recent decades, the proportion of recovered cases has not increased.**

Key words: schizophrenia/psychosis/recovery/outcome studies/prognosis/epidemiology

It is widely accepted that a proportion of individuals who develop schizophrenia have a favorable prognosis. Symptoms can abate over time, and a proportion of those with schizophrenia attain good outcomes on a range of clinical and functional outcomes (eg, education, employment, and relationships). The precise proportion of cases that have favorable outcomes is less clearly understood. To a large degree, this relates to uncertainty about how to measure multifaceted outcomes such as "recovery." Considering how much research attention has been allocated to exploring the *onset of psychosis* (eg, prodrome and early psychosis), it is appropriate that a comparable degree of research scrutiny also be accorded to the *recovery of psychosis.*[1] With respect to the remission of clinical symptoms, operationalizable criteria are now available.[2–4] However, symptom profiles are only one component of the many facets of recovery. Many consumer-based groups conceptualize recovery as a *personal* journey (ie, a subjectively evaluated process dealing with symptoms over time) rather than a defined point *outcome* (completely recovered vs persistent illness).[5] In contrast to most clinical symptoms, outcomes related to recovery do not lend themselves to simple, reliable metrics.[6,7]

Regardless of the ongoing debate around how to define and measure recovery,[3] we argue that there is a strong case to continue to explore clinical and functional outcomes of schizophrenia from an epidemiological perspective. In recent years, systematic reviews of the incidence,[8] prevalence,[9] and mortality of schizophrenia[10] have been published. Of the 4 key epidemiologic indicators required to understand the dynamics of disorders such as schizophrenia in a population (incidence, prevalence, remission/

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recovery, and mortality), recovery remains the most poorly understood. Clearly, the proportion of individuals who recover over a given period is more than 0% and (sadly) appears to be substantially less than 100%. Can we identify a range of values that encompass the best available estimates of recovery?

Several scholarly narrative reviews of outcome of schizophrenia have been published over recent decades.[11–14] While the definitions of *remission* and *recovery* have been the subject of a systematic review,[3] to the best of our knowledge, only 3 studies have examined the empirical data on "good outcomes" in schizophrenia using systematic reviews and/or meta-analytic techniques.[15–17]

According to a meta-analysis by Hegarty et al,[15] based of 320 studies published between 1895 and 1992, approximately 40% of schizophrenia patients were considered as having a good outcome. However, this review did not apply a minimum duration for good outcome, and it was acknowledged that the included studies used widely different methods to allocate subjects to the good outcome category. So, subjects showing either an improvement of symptoms or good social functioning may have been rated as having good outcome. Hegarty et al[15] found that studies using broad non-Kraepelinian diagnostic criteria had higher recovery percentages compared with Kraepelinian criteria, but the length of follow-up did not affect the proportion of recovery. Worryingly, this review noted that the proportion of patients with good outcome had not improved in recent decades. More recently, a systematic review by Menezes et al[16] of the outcome studies of first-episode psychosis was published. This review (based on 37 studies) concluded that 42% of patients had a good outcome. However, good outcome in this review did not require both good clinical and social/functional outcomes, and there was no requirement for good outcome status to have persisted for a certain period of time. This review was exclusively based on first-episode cases, with prospective follow-up for at least 6 months, though most samples had been followed-up for only a relatively short period (mean duration of follow-up was 35.1 months). Despite these caveats, the 2 systematic reviews reported remarkably similar proportions with good outcome (42% and 40%).

Warner[17] analyzed 114 follow-up studies (published between 1904 and 2000) to examine recovery in schizophrenia. He defined recovery as complete recovery (loss of psychotic symptoms and return to pre-illness level of functioning) or social recovery (economic and residential independence and low social disruption). No criterion for persistence of recovery was used. According to this analysis, 11%–33% were completely recovered and 22%–53% were socially recovered. Consistent with the findings of Hegarty et al,[15] with respect to changes in outcomes over time, Warner[17] reported that recovery rates had not increased over time.

Menezes and colleagues[16] recommended that multidimensional definitions should be used in future studies for outcome in psychosis. Other commentators have suggested that such multidimensional measures should include at least 2 domains—one related to clinical remission and another related to broader social functioning outcome.[18,19] Additionally, persistence of good outcome (indicating recovery) for a minimum of 2 years has been suggested.[18] Setting a duration criterion for persistent recovery does not exclude the possibility of relapses or continued recovery beyond that time. Mindful that not all outcome studies provide data on 2 or more domains and even fewer would share the same rating scales, we sought to collate the primary literature that reported outcome estimates based on these 2 domains. Previous reviews and original studies have often focused on cross-sectional outcomes, without any duration criteria. In this study, we will use the term *recovery* to describe very good outcome that considers both clinical and social/functional dimensions and includes a duration criteria of at least 2 years for at least 1 of these measures.

The broad objective of this study was to undertake a systematic review and meta-analysis of original studies reporting proportions of individuals with schizophrenia and related psychoses who met our predefined recovery criteria. Our primary aims were to identify the proportions of individuals who met our recovery criteria and to examine the nature of the distribution of these estimates (eg, median, mean estimate, and range).

We also examined potential sources of heterogeneity in the estimates in order to address selected research questions. For example, while narrative reviews have generally suggested that woman have better outcomes compared with men,[20] this issue was not addressed in the 3 previous systematic reviews. In recent years, there has been debate about the links between better clinical outcomes in schizophrenia and studies from sites with lower economic indices (often dichotomized to as "developing" or "developed" nations).[21,22] For example, Menezes et al[16] found better prognosis for samples from "developing country of origin." They also found an association between the methodological features of the study design and outcomes (eg, better outcome in studies with poorer representativeness and thus in studies with poorer quality). In light of the systematic reviews that have reported an association between reduced duration of untreated psychosis and better outcomes,[16,23,24] one might also predict that outcomes should have *improved* over time. In recent decades there has been increased focus on the detection and prompt treatment of early psychosis, which might result in better clinical outcomes.[25–27] Thus, optimistic researchers might predict that recovery proportions should improve over time as we continually attempt to improve treatments and service delivery. However, 2 earlier systematic reviews[15,17] found that the proportion of good outcomes had *not improved over time*—indeed there was evidence that estimates of good outcomes had declined in more recent studies. The

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lack of change in good outcomes over time is a finding that requires careful ongoing surveillance by the research community. We had the opportunity to reexamine this issue in this systematic review. Finally, we also wished to explore if a number of other design issues have an impact on recovery proportions (eg, first-episode status, narrow Kraepelinian definitions of schizophrenia, duration of follow-up, and study-quality score).

Mindful that the primary studies included in the review may not have been designed to examine these particular issues, our a priori hypotheses were the following:

1. A greater proportion of women with schizophrenia and related psychoses would meet recovery criteria compared with men.
2. The proportion of cases who recover will not have changed over time.
3. A greater proportion of cases from studies from sites with poorer economic indices would meet recovery criteria compared with sites with richer economic indices.
4. Recovery is more prevalent in first-episode samples compared with general samples.
5. Recovery is more prevalent in samples using non-Kraepelinian vs Kraepelinian diagnostic system.
6. Recovery is more prevalent in samples with longer duration of follow-up compared with shorter follow-up.
7. Recovery is more prevalent in studies with lower quality scores.

Methods

Data Collection

We applied the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines for systematic reviews and meta-analyses.[28] For data collection, we searched original articles reporting outcomes in individuals with diagnoses of schizophrenia and related psychoses. In order to locate potentially suitable studies, we conducted several searches using 6 electronic databases (last search completed in October 2011): PsycINFO (1840 onwards), Pubmed (1950 onwards), the ISI Web of Science (1900 onwards), Elsevier Science Direct (1823 onwards), EBSCOhost´s Academic Search Premier (1975 onwards), and CINAHL (1981 onwards). No language, publication date, or publication status restrictions were imposed. As a title search, the following search strategy was used: "schizo* or psychotic or psychos*s" and "recovery or remission or outcome* or course or prognosis or longitudinal or follow-up." The second search in abstracts included keywords "schizophrenia" and "recovery or remission." Articles were also searched manually and, if required and when it was feasible, authors were contacted directly for unpublished data and additional information.

All abstracts were independently analyzed by 2 authors (EJ and JMi). Then, after exclusion of irrelevant abstracts, all remaining articles were critically inspected by 2 authors (EJ and JMi). For studies that met inclusion criteria, a third investigator (PJ) independently extracted the salient data while checking data accuracy. When a disagreement occurred related to data extraction, this was resolved by consensus. In keeping with related systematic reviews of schizophrenia epidemiology,[8–10] an ad hoc quality score was devised (higher scores indicated better quality and/or better reporting of the study: see online supplementary material Appendix 1. All included studies were ranked based on total quality scores. Information on all the collected data from the selected studies is presented in the online supplementary material Appendix 2.

Definition of Recovery

We attempted to assess recovery as objectively as possible. Thus, we did not solely rely on the results (eg, based on definition of "recovery" or "complete remission" or "functional recovery") presented by the authors of original articles. When deciding the recovery criteria, we acknowledged the recommendations of using multidimensional definitions,[16] including at least 2 domains, one related to clinical remission and another related to broader social functioning outcome,[18,19] and persistence of good outcome for a minimum of 2 years.[18] For our definition of recovery, we required that the individuals should have been recovered both clinically and socially. Additionally, the improvements in at least 1 of the clinical or social outcomes should have persisted for at least 2 years, and there should be currently at most mild symptoms (ie, symptomatic remission, eg, studies reporting only "no hospitalization" as an index of clinical recovery were excluded). This definition is more stringent than the most widely used consensus measure of remission (which required only 6 months of continuous abatement of symptoms).[2] For example, a study that presents proportion of individuals (*a*) having no episode of treatment in 2 years and (*b*) having a Global Assessment of Function (GAF) ≥61 would be considered to describe recovery for our purposes; because both social/functional and clinical measures have been used, good clinical outcome have lasted for at least 2 years, and the definition also includes symptoms (included in the GAF). Other examples of recovery definitions include: "Living independently for 2 years, no psychiatric hospitalization in 5 years, and currently clinically in full remission, psychosocial functioning in normal range, and no/low antipsychotic medication" and "Remission for a minimum of 24 months, employed or active and taking care of home." All the recovery definitions of included samples are presented in online supplementary material table 1. In studies where information on both outcomes was not readily apparent, we extracted the data from texts and tables in order to satisfy our recovery criteria.

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Study Selection

The articles included into the analyses were required to meet each of the following criteria:

1. The sample included at least 80% individuals with schizophrenia, schizophreniform, schizoaffective or delusional disorder (ie, broadly defined schizophrenia).
2. The subjects were not selected a priori for good or poor outcome.
3. The sample size of 15 or more.
4. The outcomes included measures for both clinical (eg, symptom rating scales and use of hospital treatment) *and* social/functional dimensions (eg, occupational capacity, scales measuring functioning, or occupational capacity), and there should be currently at most mild symptoms (ie, symptomatic remission).
5. At least 1 of either clinical or social/functional recovery status should have persisted for at least 2 years (data collected prospectively or retrospectively).
6. Only observational (naturalistic) studies were included. While many intervention studies report clinical outcomes, the representativeness of these samples may vary widely according to the specific trial inclusion criteria. Thus, a large number of randomized controlled trials were excluded.
7. The majority of subjects had onset after 16 years of age (ie, studies reporting the outcome of childhood-onset schizophrenia were excluded).
8. Where multiple papers were available on the same or overlapping cohorts, we selected 1 representative paper with the largest sample size.

Details of the excluded studies are available from the authors on request, and some examples are presented in the online supplementary material Appendix 3.

Statistical Methods

Recovery estimates were summarized with mean, SD, median, and interquantile (25%–75%) range (IQR) and were displayed in forest plots. Based on the known heterogeneity of other schizophrenia frequency measures[29] and based on the results of previous systematic reviews,[16] we expected that the estimates of recovery proportions would also vary substantially between studies. Thus, we used random effects models in order to pool overall estimates of proportions. In the random effects analysis, each study was weighted by the inverse of its variance and the between-studies variance.[30] In order to explore if particular studies influenced the random weighted mean, we also undertook an "influence analyses," where the effect of 1 study on overall estimate was studied by excluding 1 study at a time.[31]

Standard meta-regression techniques[31] were used to explore the influence of the selected variables on recovery estimates. In order to describe recovery in studies with different durations of follow-up, we derived the *annual recovery rate* by dividing the proportion of those who met the recovery criteria by the number of years of follow-up.[32] Concerning the impact of *gender* on recovery, we first compared the pooled proportions for male-only vs female-only based estimates. In addition, for studies that present both male and female proportions, we calculated odds ratios from the recovery proportions. For the analysis related to *change over time*, we examined the studies when ranked according to the year at the midpoint of the data collection period, using the same year categories as was employed by Warner.[17] For the comparisons by *site economic index*, we used per capita income statistic as recommended by Cohen et al.[22] "Economic index of the country of the sites" was based on per capita income statistics of World Bank for year 1988 (data.worldbank.org). The income classes were divided by the units of international dollars: Low-income economies ($1005 or less) or lower middle-income economies ($1006–$3975) vs upper middle-income economies ($3976 to $12,275) vs high-income economies ($12,276 or more). *First–episode samples* were compared with *general* samples, and *length of follow-up* was estimated (2–5 years, over 5–10 years, over 10–15 years, and over 15 years). We also analyzed the *strictness of diagnostic criteria* (Kraepelinian vs non-Kraepelinian systems) on recovery percentage. Kraepelinian diagnostic systems (narrow/strict system, where diagnosis is often considered as an indicator for poor long-term prognosis) included DSM-III (Diagnostic and Statistical Manual of Mental Disorders, 3rd edition), DSM-III-R, DSM-IV, Feighner, Kraepelin, Langfeldt, and Statistical Manual of National Committee for Mental Hygiene. Non-Kraepelinian diagnostic systems included Bleuler, DSM-II, ICD-8 (International Classification of Diseases, version 8), ICD-9, ICD-10, Leonhard, Mayer-Gross, Research Diagnostic Criteria, and Schneider.[15] The analysis based on *the quality score* was conducted by comparing the top (ie, indicating higher quality studies and/or better reporting) vs bottom half of studies when the studies were ranked on descending total quality score (see online supplementary material Appendix 1).

By way of post-hoc analyses, we also examined the influence of (*a*) World Health Organization (*WHO*) *vs non-WHO studies*, (*b*) the influence of the *origin of the sample* (discharge cohorts, admission cohorts, general population, or cohorts including both outpatients and inpatients), and (*c*) *strictness of the recovery criterion.* The strictness of recovery criterion was analyzed in several ways. We designated a strictness score for the definition of recovery in each of the included original studies. In deciding the strictness score, 100 indicated the most strict definition and 0 the loosest definition. We first scored clinical dimension of the recovery definition and then the social definition and then calculated the mean of these (ie, *the strictness of the recovery criterion*) for each original studies. The recovery percentage was then analyzed in studies above and below the median strictness score. Additionally, recovery percentage was analyzed in samples where

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recovery was lasting for 2–5 years vs recovery lasting for over 5 years, among samples where clinical recovery had lasted for at least 2 years and among samples where social/functional recovery had lasted for at least 2 years.

We explored the heterogeneity of the studies with the I^2 statistic (with 95% CI). This statistic is a recommended transformation of the Q statistic. Values of I^2 range from 0% to 100%, reflecting the proportion of the total variation across studies beyond chance. The value of 25% describes low, 50% moderate, and 75% high heterogeneity.[33] The analyses were done with STATA 9.[34]

Results

The electronic database searches identified 5647 unique records. After further screening, we identified 917 potential records. Figure 1 shows the PRISMA flow diagram that details the filtering process of potential studies. From these, 37 articles or books met all our criteria and were included in the systematic review. These 37 articles or books included altogether 50 discrete samples, including 13 samples from the WHO incidence and prevalence cohorts (including also unpublished data from Dr Kim Hopper) and 7 samples found from manual search. In total, these studies included 8994 discrete individuals and were derived from 20 different countries.

Supplementary material table 1 summarizes key features of the included studies' study design, sample characteristics, the location where the study was conducted, diagnostic system, length of the follow-up, criteria for recovery, and recovery estimates. The citations for these articles are included in the online supplementary material Appendix 4.

For persons (males and females combined), we identified 50 estimates. The distribution of these estimates is shown in figure 2. Based on this distribution, the median recovery estimate was 13.5% (mean: 16.4%) with the IQR between 8.1% and 20.0%. The distribution was densely underpinned with estimates in its central 75% portion and was left-skewed (ie, some studies reported very high estimates). The mean estimates changed only slightly in the "influence analyses," when 1 study was dropped at a time (for these analyses, the estimates ranged between 15.5% and 16.7%). As expected, we confirmed that estimates

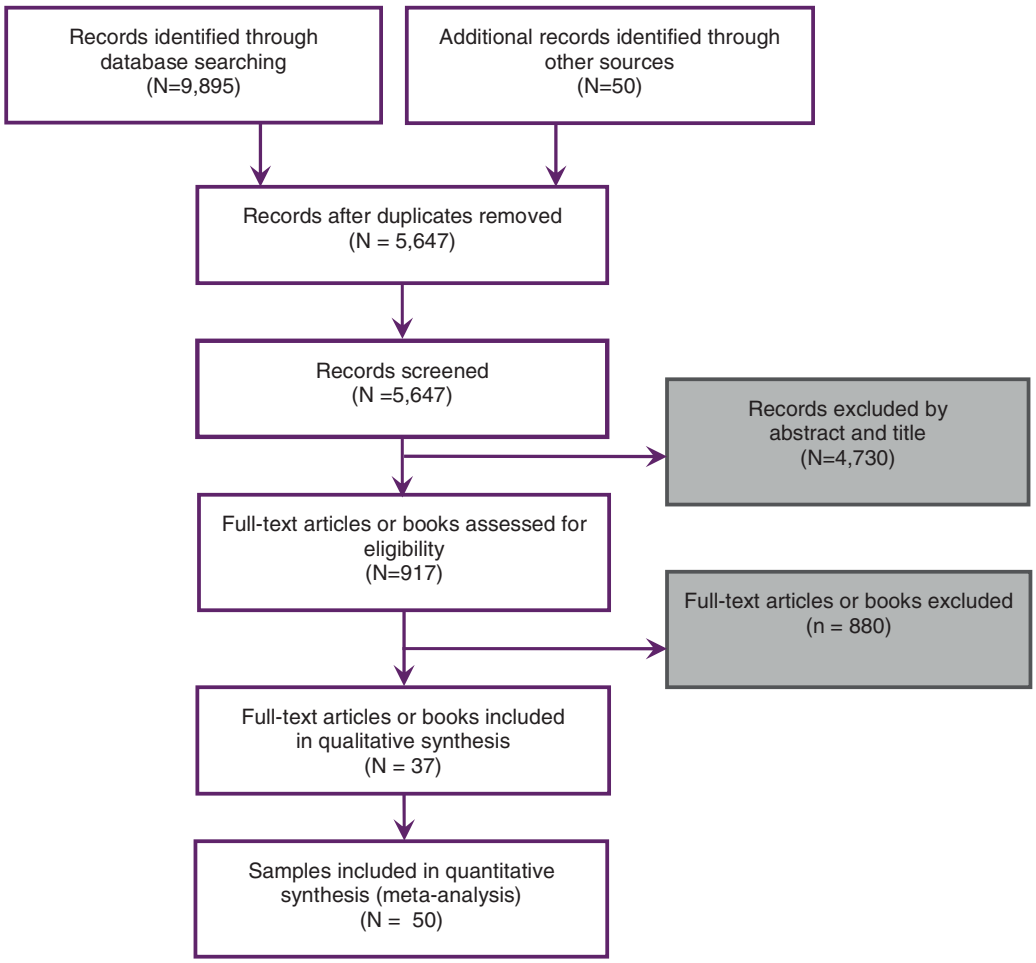

Fig. 1. Flow diagram of the selection of studies of recovery in schizophrenia.

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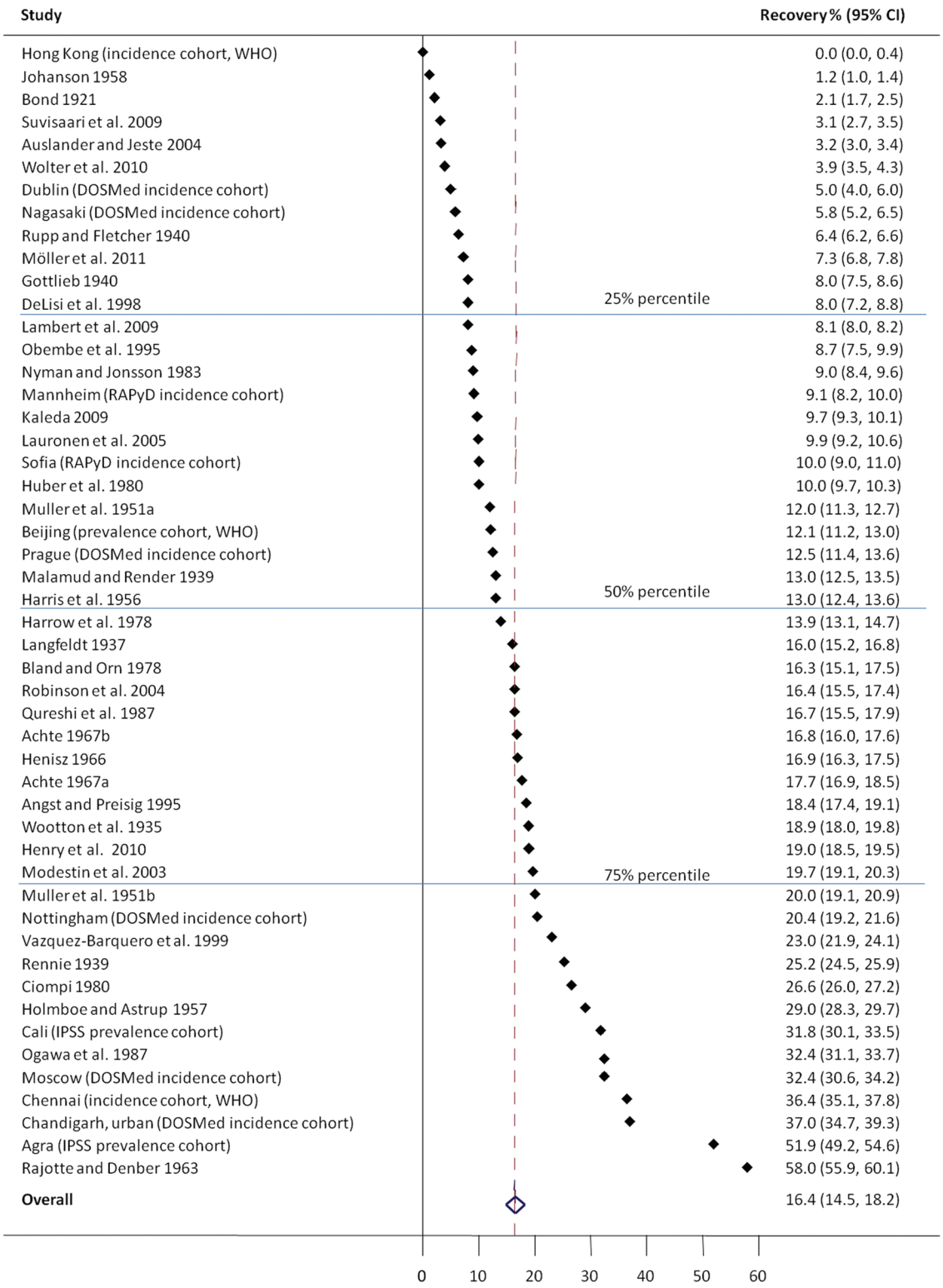

Fig. 2. Recovery percentage for included studies.

from the included studies were highly heterogeneous (I^2 = 99.8%; Q = 38 000, P < .001). The median annual recovery rate was 1.4% per annum (IQR: 0.7%–2.6%). With this annual recovery percentage, over 10 years approximately 14% would be expected to recover.

For sex-specific estimates (12 studies for males; 12 studies for females), the median recovery estimate for males was 12.9% (IQR: 10.0%–19.4%), while for females the median recovery estimate was 12.1% (IQR: 7.5%–29.0%; table 1). Only 10 studies reported recovery percentage

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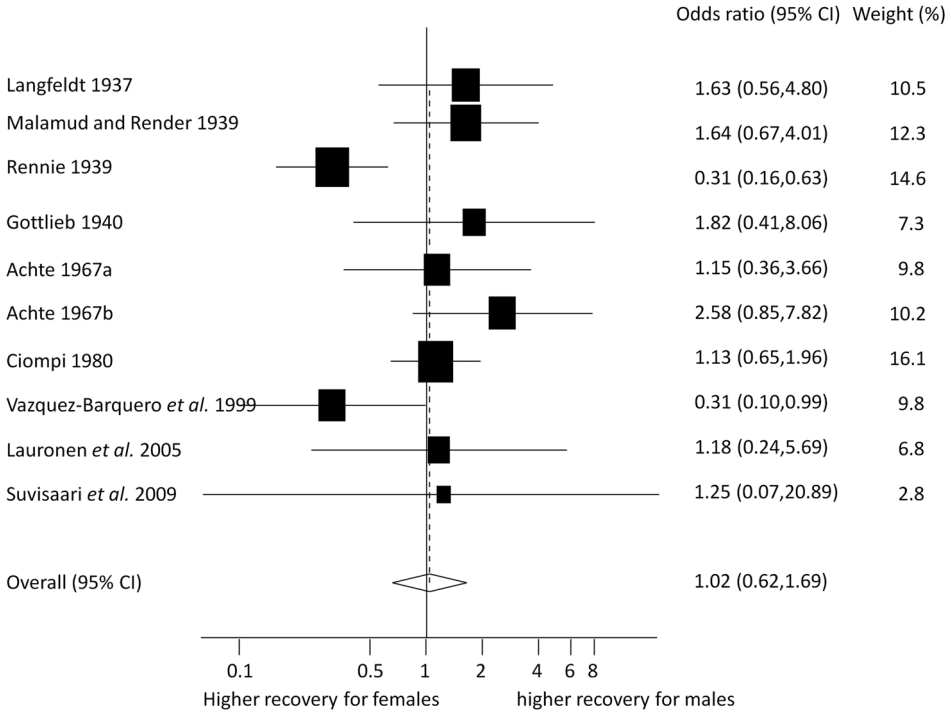

Fig. 3. Odds ratios for gender differences in original studies.

by gender, and for these studies, the OR for gender was calculated (figure 3). Eight out of 11 studies reported slightly higher recovery estimate for males, while 3 studies showed higher recovery for females, and 2 of these studies showed clearly better recovery for females; overall, there was no statistically significant difference between sexes (OR: 1.02, 95% CI: 0.62,1.69, $P = .939$).

When ranked according to the year at the midpoint of the data collection period using the same year categories as was employed by Warner,[17] the median recovery was 13.0% in studies with midpoint before 1941, 17.7% in studies between 1941 and 1955, 16.9% in 1956–1975, 9.9% in 1976–1995, and 6.0% in studies after 1996 ($P = .704$; table 1).

Compared with countries with high and upper middle income, recovery estimate was significantly higher in low or lower middle-income countries (medians 13.0% in high income countries, 12.1% in upper-middle, and 36.4% in low or lower middle-income countries) ($t = 2{,}93$, $P = .005$; table 1). When this analysis was adjusted by the middle point of the collecting of the study, the difference remained statistically significant ($t = -3.86$, $P < .001$). When WHO studies were excluded from the crude analyses, the median recovery percentages were 15.0% ($n = 34$), 9.7% ($n = 1$), and 12.7% ($n = 2$), respectively, ($t = 0.48$, $P = .632$).

The recovery estimate was numerically but not significantly lower in studies using Kraepelinian diagnostic system (median 9.0%) compared with non-Kraepelinian samples (12.5%) ($P = .396$; table 1). There were no significant differences in recovery when studies were classified according to first-episode studies vs general intake ($P = .857$), origin of the sample ($P = .802$), duration of follow-up ($P = .369$), being a WHO study vs not ($P = .185$), and quality score ($P = .792$; table 1).

When the estimates were ranked according to the strictness of the recovery criteria, the recovery percentage in studies in the lower half, ie, less strict criteria ($n = 25$) was 13.0% (IQR: 8.1%–23.0%), while studies with stricter criteria ($n = 25$) had a median recovery proportion of 13.9% (IQR: 8.7–19.0%) ($t = -1.15$, $P = .254$). The score for strictness of the definition of recovery is presented for each study in online supplementary material table 1. In 39 studies where only the clinical recovery criteria has lasted for at least 2 years, the median recovery was 13.0% (8.1–25.2%), whereas in 3 studies where only the social/functional recovery has lasted for at least 2 years, recovery was 19.0% (16.3–19.7%). In 8 studies where both clinical and social/functional recovery have lasted at least 2 years, recovery was 13.1% (7.7–16.8%). The chances of recovery are quite similar in studies where the required duration for clinical or functional recovery is under 5 years (median recovery 13.2%, IQR: 8.4%–24.1%; $n = 28$) vs over 5 years (14.7%, 7.3%–18.4%; $n = 22$).

Discussion

Based on the best available data, the median proportion of individuals with schizophrenia who met our recovery criteria was 13.5%. Despite reasonable concerns about how best to assess recovery, and the well-appreciated

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Table 1. Recovery Percentages in Subpopulations

	Number of Studies	Median%[a]	IQR[b]	Statistical Test[c]
Sex	24			t = 1.08, P = .293
Males	12	12.9	10.0–19.4	—
Females	12	12.1	7.5–29.0	—
Midpoint of the collection of the sample[d]	48			t = −0.38, P = .704
Before 1941	11	13.0	6.4–20.0	—
1941–1955	5	17.7	13.0–19.7	—
1956–1975	11	16.9	16.3–32.4	—
1976–1995	19	9.9	5.8–19.0	—
After 1996	2	6.0	3.9–8.1	—
Economic index of the site[e]	50			t = −2.93, **P = .005**
Low or lower-middle	5	36.4	16.7–37.0	—
Upper-middle	5	12.1	10.0–31.8	—
High	40	13.0	7.7–19.0	—
First-episode vs not first-episode samples	46			t = −0.18, P = .857
First-episode sample	30	16.6	9.0–20.4	—
Not first-episode sample	16	11.1	6.0–22.5	—
Origin of the sample	46			t = 0.25, P = .802
Discharge cohort	6	15.3	13.0–32.4	—
Admission cohort	24	14.5	8.4–18.7	—
Cohort including out- and inpatients or general population	16	12.3	7.5–26.1	—
Length of follow-up	50			t = 0.91, P = .369
2–5 y	13	13.9	8.1–17.7	—
>5–10 y	9	10.0	8.0–16.0	—
>10–15 y	15	16.3	9.1–29.0	—
>15 y	13	18.4	9.7–26.6	—
Diagnostic criteria[f]	33			t = 0.86, P = .396
Kraepelinian	12	9.0	4.8–17.3	—
Non-Kraepelinian	21	12.5	9.1–31.8	—
WHO study	50			t = 1.34, P = .185
Yes	13	12.5	9.1–32.4	—
No	37	13.9	8.1–18.9	—
Quality of the study	50			t = 0.27, P = .792
Quality score < median	23	16.0	9.0–18.9	—
Quality score ≥ median	27	12.5	8.0–23.0	—

Note: Statistically significant P-values are in bold.
[a]Median weighted by sample size.
[b]IQR, inter quartile range.
[c]Metaregression, t-test.
[d]Classified as in Warner (2004).
[e]Income classes: low-income economies ($1005 or less) or lower middle-income economies ($1006–$3975) vs upper middle-income economies ($3976–$12,275) vs high-income economies ($12,276 or more) (data.worldbank.org).
[f]Kraepelinian: DSM-III, DSM-III-R, DSM-IV, Feighner, Kraepelin, Langfeldt, Statistical Manual of National Committee for Mental Hygiene; Non-Kraepelinian: Bleuler, DSM-II, ICD-8, ICD-9, ICD-10, Leonhard, Mayer-Gross, Research Diagnostic Criteria, Schneider.

heterogeneity in the estimates, we found that median values for recovery were unexpectedly stable, with no statistically significant difference according to sex, time of the data collection, duration of follow-up, first-episode status, origin of the sample, and quality of the study. Our estimates were lower than those reported for "good outcome" in previous systematic reviews.[17] This probably reflects the more stringent criteria used in our definition of recovery (including both clinical and functional dimension and the requirement that the recovery should have lasted for at least 2 years). We report, for the first time to our knowledge, data on the annual recovery rate for schizophrenia—the median estimate was 1.4%. Put simply, this suggests that for every 100 individuals with schizophrenia, 1 or 2 individuals per year would meet the recovery-related criteria, and approximately 14% would be expected to recover over 10 years.

Concerning the planned analyses, we found that studies from low-income nations had higher proportions who met recovery criteria. However, it should be noted that only 5 estimates were available from lower income sites, and 3 of these studies were based on the influential WHO studies that underpinned the earlier hypotheses related to outcome and developed-nation status.[35–37] If treatment

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influences clinical outcomes, and if access to treatment varies between nations according to economic factors, then it seems reasonable to expect that outcomes would vary between these sites. However, there are concerns about the interpretation of the WHO studies (related to dropout and mortality rates).[22] Recent report from SOHO (Schizophrenia Outpatient Health Outcome), including 10 studies from Western Europe and 27 studies from 4 different continents, suggests that clinical remission was significantly lower in Europe compared with other regions, but this difference was not found for functional remission.[38] More research from the developing world will help resolve these issues, and in this context, it is gratifying to see more high quality outcome studies now emerging from these sites.[38,39]

In the meta-analysis of Hegarty et al[15] studies, using broad non-Kraepelinian criteria showed better outcomes than those using narrow Kraepelinian criteria. We did not find clear support for this finding.

Apart from the finding related to economic index of the countries of the sites, the other analyses reveal that the median values were fairly stable—the median estimates for each of the different comparisons listed in table 1 only ranged from 6.0% to 18.4%. Overall, the distributions are wide, with the central 50% of the estimates ranging from 8.1% to 19.9% (figure 2). Measurement error would contribute to this imprecision. However, it cannot be ruled out that the "true" underlying estimates do actually vary between sites and across time. This imprecision is consistent with systematic reviews on related epidemiological measures such as incidence, prevalence, and mortality.[29]

Somewhat surprisingly, we did not find statistically significant difference in the estimates of recovery between males and females. This issue has not been studied in earlier meta-analyses,[15–17] while a recent review[20] identified better prognosis for females. Our analysis, based on a reasonable number of studies, does not support this finding.

Consistent with the previous systematic reviews,[15,17] we found no evidence to suggest that recovery outcomes have improved over time. There appear to be numerical differences over time in outcome in schizophrenia, but our sample size lacked sufficient power to demonstrate statistical significance. Indeed, recent decades had lower numerical proportions of subjects who met our recovery criteria. This is a sobering finding—despite major changes in the delivery of care to people with schizophrenia (eg, deinstitutionalization, antipsychotic medications, psychosocial interventions, and early psychosis services), the proportion of those who met recovery criteria have not improved over time. However, the studies in this meta-analysis are naturalistic, and we do not know what kind of treatment the patients received. Thus conclusions about the effect of treatments are not possible.

The strictness of recovery definition had surprisingly little effect on recovery percentage in this sample. Because recovery is such a multidimensional concept, we encourage researchers to explore the data provided in the online supplementary material table 1 according to definitions of interest.

Strengths and Limitations of the Study

There are several important caveats related to this review. We did not have language restrictions. However, our search language was English, so we may have missed some old, non-English publications. Although we consider our definition of recovery justifiable (when considering the lack of consensus on the definition), we acknowledge that our definition of recovery resulted in studies with various outcomes (eg, number of criteria included, and duration of sustained recovery) being compared. However, there were still some consistency in the criteria in included studies (in online supplementary material table 1): Most studies required that the clinical recovery should have lasted for at least 2 years, with the exception of 3 studies (Bland and Orn 1978, Modestin et al. 2003, and Henry et al. 2010, in online supplementary material table 1) that required the duration of social/functional recovery for at least for 2 years and had no such duration criteria for clinical outcome. In addition, we acknowledge that the field remains in a state of flux with respect to the conceptual validity of recovery.[5] However, the research community has long been aware of the substantial heterogeneity in the diagnostic criteria for schizophrenia, thus it should not come as a surprise that measures related to the assessment of recovery for schizophrenia would be similarly heterogeneous. Additionally, it seems that our results are quite similar to those recently presented by Cuyun Carter et al,[40] who found that 10% of 1635 patients with schizophrenia in a national multisite observational study had sustained favorable long-term outcome (ie, were rated to be in the "best health state" cluster). The development of consensus criteria for complete recovery and social/functional recovery will be important guides for future research, as has already been the case for symptomatic remission.[2] With respect to the annual recovery rate, it should be noted that this derived estimate assumes that the chance of recovery is evenly distributed across time—this may not be the case.[1] It should be noted that our inclusion criteria resulted in the exclusion of studies that may still be informative with respect to recovery (eg, treatment studies). Future systematic reviews may wish to specifically examine recovery in treatment studies and stratify estimates based on the intake criteria, as well as the interventions.

The strength of this review was the comprehensive search strategy: we searched several electronic databases and also contacted researchers in the field. In addition, we also considered the definition of recovery critically. We did not rely on estimates of "recovery" or "remission" presented by the authors of original articles, but objectively sought from the article the number of patients

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meeting our recovery criteria. All the studies were given a "quality score" in order to explore the impact of methodological issues on the estimates. In the statistical analyses, we used meta-regression techniques to explore the influence of variables of interest.

This study has provided the best available estimates of recovery in schizophrenia. According to these criteria, the proportion of individuals with schizophrenia and related psychoses who met recovery is 13.5% and appears not to have increased across time. We found no evidence to suggest that we are "getting better" at getting our patients better. These findings provide a challenge for the research community to develop more effective and more widely available treatments for those with schizophrenia.

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Supplementary Material

Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org.

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