Rates of Treatment Resistant Schizophrenia from First Episode Cohorts: A Systematic Review and Meta-analysis

Running title: TRS rates

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Abstract (words 249)

Background: Treatment resistant schizophrenia (TRS) is associated with high levels of functional impairment, health care usage and societal costs. Cross-sectional studies may overestimate TRS rates due to selection bias.

Aims: We therefore aimed to quantify the TRS rates using first episode cohorts to improve resource allocation and clozapine access.

Methods: We undertook a systematic review of TRS rates among people with first-episode psychosis and schizophrenia, with a minimum follow-up of 8-weeks. We searched Pubmed, PsycInfo, EMBASE, CINAHL and Cochrane and meta-analysed TRS rates from included studies.

Results: Twelve studies, half of high quality, with 11,958 subjects, were included. The rate of TRS among all first-episode cohorts was 22.8% (95%CI 19.1% to 27.0%, p<0.001), and 24.4% (95%CI 19.5% to 30.0%, p<0.001) among first-episode schizophrenia cohorts. Subgroup sensitivity analyses by location of recruitment, TRS definition, study quality, time of data collection and retrospective versus prospective data collection did not lead to statistically significant differences in heterogeneity. In a meta-regression duration of follow-up and percentage dropout did not significantly impact the overall rate of TRS. Men were 1.57 times more likely to develop TRS than women (95%CI 1.11-2.21, p=0.010).

Conclusions: Almost one quarter of people with first-episode psychosis or schizophrenia will go on to develop TRS in the early stages of treatment. When people with schizophrenia who relapse despite initial response and continuous treatment are considered, rates of TRS may be as high as one third. These high rates of TRS highlight the need for improved access to clozapine and psychosocial supports.

Keywords: Schizophrenia, Treatment Resistant Schizophrenia, Rates, Meta-Analysis, Systematic Review.

Relevance Statement

Treatment resistant schizophrenia (TRS) is associated with high levels of functional impairment, health service usage and societal costs. Quantifying rates of people with TRS to date has been challenging. Cross-sectional studies tend to overestimate the rates of TRS due to selection bias, while single site first-episode cohort studies may not be generalisable. We found TRS rates among first-episode cohorts to be 22.8% (95%CI 19.1%-27.0%), and 24.4% (95%CI 19.5%-30.0%) among first-episode schizophrenia cohorts. Men were 1.57 times more likely to develop TRS than women. These high rates of TRS highlight the need for improved access to clozapine and psychosocial supports.

1.Introduction:

Schizophrenia has a lifetime morbid prevalence of 7 per 1000 people.[1] Although antipsychotic medication is the mainstay of treatment for schizophrenia, not all patients respond to first-line antipsychotic treatment.[2] These cases of treatment resistant schizophrenia (TRS) are associated with high levels of functional impairment,[3] health care usage, societal costs,[4] and physical health comorbidity.[5]

In response, a consensus definition of TRS has been developed by the Treatment-Resistant Schizophrenia: Treatment Response and Resistance in Psychosis (TRRIP) working group. These include the following: 1) current symptoms of at least moderate severity and moderate or worse functional impairment; and 2) prior treatment with at least two different antipsychotics, each for at least 4-6 weeks minimum duration at total daily dose equivalent of at least 600 mg of chlorpromazine.[2]

The most effective medication for TRS is clozapine, with improvement in positive symptoms,[6] hospitalisations,[7] and overall mortality.[8] In most jurisdictions, clozapine use in schizophrenia is limited to patients who have had two failed trials of first-line antipsychotics.[9-11] As such, use of clozapine is sometimes regarded as a marker of TRS.

Despite the increasing attention on providing treatment and psychosocial support for people with treatment resistant schizophrenia,[12] there remains a lack of clarity as to the proportion of people with schizophrenia who are treatment resistant. Given low levels of clozapine prescribing in some jurisdictions,[9] quantifying the rates of patients with TRS could highlight the need to improve access to clozapine,[13] and increase opportunities of a clozapine trial for patients with TRS. Cross-sectional studies examining the proportion of patients with TRS may over-estimate true rate due to selection bias.[14] By contrast, longitudinal first-episode cohort studies may more accurately quantify the incidence of patients with TRS, and better inform health care service resourcing. However, first-episode cohort studies from single sites may not be generalisable, and as such need to be combined with first-episode cohorts from multiple sites.

We therefore systematically reviewed the literature to quantify the proportion of people with TRS given the recent improvements in the clarity of definition. We searched for longitudinal cohort studies of people with first-episode psychosis, and identified what proportion met criteria for TRS at follow up. We then undertook a meta-analysis to quantify rates of TRS.

2. Method:

2.1 Design

This systematic review was registered with PROSPERO, an international database of prospectively registered systematic reviews (Registration number: CRD42019140958). We followed guidelines for the reporting of meta-analyses of observational studies in epidemiology (MOOSE),[15] which comprised background, search strategy, methods, results, discussion and conclusions and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[16] (Supplementary Table 7 PRISMA Checklist)

2.2 Search Strategy

We searched Pubmed, PsycInfo, EMBASE, CINAHL and the Cochrane Database from inception to the date of data extraction (13 December 2020) using the following terms: Schizophrenia, Psychosis, Psychotic Disorder, Refractory, Refractoriness, Treatment Resistant, Treatment Resistance, Clinical Remission, Symptomatic Remission, Clinical Response, Clozapine, First, Age at Onset. The full Pubmed search strategy is provided in Supplementary Table 1. Key researchers were contacted regarding unpublished datasets.

The studies identified through the electronic search were then reviewed at abstract and title level by two authors (BB and KY). These titles were then reviewed at full text level by two of four authors (SO, SS, BB and KY). The results of the full text search were verified by a third member of the research team (DS) and any discrepancies were resolved through discussion with the entire review team. Reference lists were hand searched to identify any potential additional articles.

2.3 Inclusion Criteria

In order to be included in the systematic review and subsequent meta-analyses, studies were required to meet the following criteria:

1. Cohort studies of individuals with First-Episode Psychosis (FEP) or First-Episode Schizophrenia (FES) who were diagnosed according to DSM-4/5 or ICD-10 Classification
2. The presence of a clear definition of treatment resistance consistent with TRRIP Working Group's standardised definition[2]
3. The presence of longitudinal information on pharmacological interventions
4. Reports on the proportion of the FEP/FES population who were followed up prospectively and went on to develop a treatment-resistant form of the illness.
5. The study had at least 8-weeks follow up.

Papers were excluded if there was greater than 75% overlap of the included datasets with another paper. Where multiple papers had >75% overlap of datasets, the paper that had the TRS definition most aligned to the TRRIP guidelines was selected, while papers with longer duration of the cohort follow-up, and papers using the largest sub-sample of the cohort were used preferentially.

Exclusion Criteria:

Studies were excluded if the study population had already been exposed to previous anti-psychotic treatment prior to entry into the cohort, and if substance-induced psychosis could not be excluded at time of follow up. Study designs that did not specifically capture all sequential first-episode patients, such as cross-sectional or randomised controlled trials, were excluded as it could not be ascertained if the criteria for participation in these studies constituted a selection bias.

2.4 Data Extraction

Two authors (BB and KY) independently extracted data which was validated by another two authors (SO and SS) from the research team. The primary outcome measure was the proportion of the original cohort with TRS diagnosis at follow-up. If data on multiple TRS definitions were provided within the same study, the data for the TRS definition most aligned to the TRRIP guidelines was used. We extracted the following data: total sample size at baseline; total sample size at follow-up; number of individuals with TRS at follow-up; percentage of individuals who dropped out or were lost to duration of follow-up in months; years in which the majority of the study data was collected (grouped to prior to/after the year 2000); country in which the study was conducted; alignment of definition of TRS to TRRIP guidelines; mean age of the cohort; proportion of male individuals in the cohort; whether the cohort studied were from an inpatient or community setting; whether data collection was prospective or retrospective; and whether there was involuntary mental health treatment during the study.

2.5 Study Quality

We used a modified version of The Newcastle-Ottawa Scale (NOS) to assess the quality of included non-randomised studies (Supplementary Table 4 Modified Newcastle-Ottawa Scale). The scale assesses the quality in several domains including sample representativeness and size, loss to follow up and ascertainment of diagnosis of schizophrenia. The quality of descriptive statistics, which included reporting of population demographics (e.g. age, sex) and measures of dispersion (e.g. standard deviation, standard error, range), were also assessed. Studies were assessed as low risk of bias and high strength of reporting (≥3 points) or high risk of bias and low strength of reporting (<3 points).

2.6 Statistical Analysis

The primary outcome was the event rate, defined as number of people diagnosed with treatment resistant schizophrenia among all subjects at follow-up. Meta-analyses were conducted using Comprehensive Meta-Analysis (Version 3.3). Given the observational nature of primary studies and expected high rates of heterogeneity, a random effects model was used for all the analyses.

2.7 Subgroup and Sensitivity Analysis and Meta-Regression

Subgroup analyses were undertaken on location of recruitment (community, inpatient or both), definition of TRS, diagnostic criteria (first-episode psychosis (FEP) vs first-episode schizophrenia (FES)), study quality, time period of the majority of data collection (dichotomised as before versus after the year 2000, corresponding to the publication of DSM-IV-TR[17]) and study design (retrospective versus prospective cohort study). Studies with overlapping datasets were selectively excluded to assess impact on overall results. Comparisons of subgroup heterogeneity were undertaken using mixed effects analysis.[18] Sensitivity analysis was undertaken to study the effect of only including studies of higher quality, and meta-regression of the effect of covariates including duration of follow up and percentage dropout.

The risk ratio of rates of TRS between males and females was calculated using a random effects meta-analysis using Revman (Version 5.3.5).

2.8 Publication Bias

We explored publication bias using funnel plot asymmetry testing for statistical significance with both Kendall's Tau and Egger's regression, where low p values suggest publication bias, when meta-analyses included ten or more studies.[19]

3. Results

3.1 Study Selection:

We identified 8273 unique articles in the search of databases. We excluded 8061 at title and abstract level. 212 articles were reviewed at full text level, with 12 studies meeting criteria for inclusion,[20-32] of which one was an unpublished dataset.[29] No additional studies were identified through hand search. (Supplementary Figure 1 PRISMA Flow Diagram and Supplementary Table 6 Excluded Studies)

3.2 Study Characteristics

The studies were from Canada (2), Denmark (1), England (2), Japan (1), Turkey (1), India (1), Brazil (1), United States (1), Ireland (1) alongside 2 studies that had multiple international locations (Table 1 Included Studies).

These studies covered a total of 11,958 subjects. Sample size ranged from 70 to 7749 participants. The proportion of study participants who were male was 61.9% (SD 10.4%). Median duration of follow up was 26 months (range 2 to 120 months). Two studies recruited from community sites, two from inpatient units, and eight from a combination of community and inpatient. Nine studies undertook the majority of data collection after the year 2000.

Nine cohorts comprised participants with first-episode schizophrenia while three were of first-episode psychosis participants. Definitions of TRS were relatively homogeneous, with nine studies using criteria aligned with the TRRIP guidelines. Nine studies used prospective data collection, with the other three being collected retrospectively. Only two studies provided data on involuntary treatment status,[21, 32] precluding meaningful sensitivity analysis on this variable.

3.3 Risk of bias within studies

Six studies were rated as being of high quality. (Supplementary Table 5 Assessment of Quality). The main concern regarding was study quality was the relatively high dropout rate (mean 24.2%, SD 19.1%).

3.4 Synthesis of Results.

Using data from 12 studies, the overall rate of TRS was 22.8% (95%CI 19.1% to 27.0%, $p<0.001$, I^2 91.8%) (Table 2 Rates of TRS and Figure 1 Forest Plot of TRS). The rates of TRS were significantly lower in FEP cohorts compared to FES cohorts (17.8% vs 24.4%, $p=0.046$). (Table 2 Rates of TRS)

There was no statistically significant difference in subgroup heterogeneity for recruitment location, TRS definition, time period of recruitment, study quality or prospective versus retrospective data collection (Table 2).

Meta-regression by duration of follow up and percentage dropout did not statistically significantly impact the overall result. (Supplementary Table 2 Meta Regression).

Eight studies provided usable data to compare rates of TRS between males and females. Men were 1.57 times more likely to develop TRS than women (95%CI 1.11 to 2.21, p=0.010, I^2=74%). (Figure 2 Rates of TRS by Sex)

3.5 Risk of Bias Across Studies

There was no evidence of significant risk of publication bias with Kendall's tau or Egger's regression (Supplementary Table 3 Risk of Bias).

4. Discussion

This study is the first to quantify rates of treatment resistant schizophrenia from first-episode cohorts using meta-analysis. We found that the rate of TRS was 22.8%, rising to 24.4% when only FES cohorts were included. The higher rate of TRS among FES vs FEP cohorts is not unexpected, as TRS requires a diagnosis of schizophrenia, while FEP cohorts included participants with diagnoses other than schizophrenia. Differences in definition of TRS did not impact the overall rate of TRS.

Men were one and a half times as likely as women to develop TRS. This is in keeping with previous findings that men are one and a half times more likely to develop schizophrenia than women.[33] There is a sex difference in age of onset of schizophrenia, with men being diagnosed at a younger age.[34]

The findings of this study may underestimate the true level of clinically relevant treatment resistance. Whilst the majority of those with TRS demonstrate resistance from onset of illness, between 16 and 30% have been shown to develop treatment resistance at a later stage of illness, following an initial period of treatment response.[21, 26] This has been shown to occur on average 5 years following illness onset,[21] and thus may have been underreported by the two thirds of studies which had periods of follow up less than 5 years. Additionally, the TRIPP definition of TRS may not account for those who initially respond to antipsychotic treatment, but go on to develop psychosis relapse despite ongoing maintenance antipsychotic treatment.[35] Studies have shown that around 20-30% of those prescribed long-acting injectable antipsychotics, following an initial symptom resolution will develop a later treatment resistance.[36-38] There is emerging evidence that patients with breakthrough psychosis symptoms despite antipsychotic maintenance medication share a similar pathology as those with TRS and clinically will require similar management options such as clozapine consideration.[35] Given the studies included in this analysis were first-episode cohorts, the true rate of TRS may be as high as one in three in longer-term patients.

These findings highlight the need for ongoing monitoring of psychotic symptoms and psychosocial functioning among people with first-episode psychosis. Early identification of people with first-episode schizophrenia who fail to respond to first or second antipsychotic trials can assist in timely provision of evidence-based treatments for TRS such as clozapine [6, 7].

While clozapine remains the most effective and efficacious medication for TRS, access to clozapine remains poor, ranging from between one-fifth to one-half.[9] Barriers include a lack of experience among prescribers and the absence of specialised clozapine clinics.[13] The high rates of TRS in our study suggest the need to improve access to clozapine in this population.

Pharmacological interventions for TRS form only one part of the treatment strategy. Multidisciplinary interventions including CBT,[39] and psychosocial interventions such as personalised support delivered by support workers,[40] and supported accommodation [41] are

also needed. People with TRS have an increased risk of physical health comorbidity, which should be addressed through lifestyle interventions including diet, exercise and improved access to primary and tertiary health care services.[5]

Our study had several limitations. There were high rates of dropouts in the cohort studies included in our meta-analysis, and it is unclear whether those who dropped out of the included cohorts were more or less likely to develop TRS. This may mean that we may have over- or under-estimated the true rate of TRS. Reassuringly, when we undertook meta-regression by percentage dropout in the included studies, there was no statistically significant difference in the overall rate of TRS. Similarly, meta-regression by duration of follow-up did not significantly alter the rate of TRS. Definitions of TRS varied between studies, but when we undertook sensitivity analysis by definition of TRS, the overall rate remained stable. Although many studies provided information on dose and duration of medication trials, there was a lack of data on other factors which may influence treatment response, including medication trial adherence and comorbid substance abuse. Insufficient data was available to undertake sub-analyses of specific antipsychotics used, nor on route of administration. There was limited data on provision of psycho-social interventions. Only two studies commented on whether patients were voluntary or involuntary, making sub-analysis by voluntary status impractical. Our analysis had a high level of heterogeneity and as such should be treated with caution. Exploration by subgroup was unable to identify key factors driving heterogeneity.

In conclusion, a substantial proportion of people with schizophrenia have treatment resistant illness, with almost one quarter of participants with first-episode schizophrenia having TRS. The true rate of TRS may be as high as a third if people who develop breakthrough psychotic symptoms following initial response are considered. As with schizophrenia more generally, men are more likely to develop TRS. Given the low rates of clozapine use among people with TRS, there needs to be increased efforts to improve access to clozapine and psychosocial supports among patients with TRS.

Declarations
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Author contributions
DS collaboratively conceived of the study with SO and SS with input from all authors. DS, SO, SS, OY, BB and SK developed the search terms. SO, SS, OY and BB conducted the searches and data extraction with support from DS and SK. DS undertook the data analysis collaboratively with SO and SS with support from OY, BB and SK. DS, SO and SS collaboratively wrote the first draft of the manuscript. All authors contributed to the editing of the manuscript.

Table Legends

Table 1. Included Studies

* Two trials of antipsychotics at adequate dose and duration, aligned to Treatment Response and Resistance In Psychosis (TRRIP) working group
FEP – First-Episode Psychosis
FES – First-Episode Schizophrenia

Table 2 Rates of TRS

TRRIP = Treatment Response And Resistance In Psychosis guidelines
FEP = First-Episode Psychosis
FES = First-Episode Schizophrenia

Figure 1 Forest Plot of TRS

Figure 2. Rates of TRS by Sex

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Table 1: Included Studies

Author Year	Country	Participants at inception	Participants with TRS at endpoint	Loss to follow up (%)	Length of cohort follow up (months)	% male	Standard definition of TRS*	Type of cohort
Agid et al 2011	Canada	287	50	15.0%	2	74	Yes	FES Prospective
Demjaha et al 2017	England	557	74	42.0%	120	58	Yes	FES Prospective
Doyle et al 2017	Ireland	171	28	28.1%	120	58	No (Treatment with clozapine as marker for TRS)	FEP Retrospecti ve
Johnson et al 2012	India	131	30	27.5%	60	55	Yes	FES Prospective
Kahn et al 2018	Europe	446	40	27.8%	2.5	70	No (half of participants had only 1 trial an antipsychotic)	FES Prospective
Lally et al 2016	England	283	81	15.2%	60	68	No (Treatment with clozapine as marker for TRS in subset)	FES Prospective
Lieberman et al 1993	United States	219	8	68.0%	28	56	Yes	FES Prospective
Malla et al 2006	Canada	114	19	6.1%	24	77	Yes	FEP Prospective
Smart et al 2019	Europe	2449	392	0.0%	12	61	No (Treatment with clozapine as marker for TRS in subset)	FEP Prospective

Ucok et al 2016	Turkey	187	28	43.9%	≥24	55	Yes	FES Prospective
Wimberley et al 2016	Denmark	8624	1703	10.1%	108	62	No (Treatment with clozapine as marker for TRS in subset)	FES Retrospective
Yoshimura et al 2019	Japan	160	60	18.1%	2	41	Yes	FES Retrospective

* Two trials of antipsychotics at adequate dose and duration, aligned to Treatment Response and Resistance In Psychosis (TRRIP) working group

FEP – First Episode Psychosis

FES – First Episode Schizophrenia

Table 2 Rates of TRS

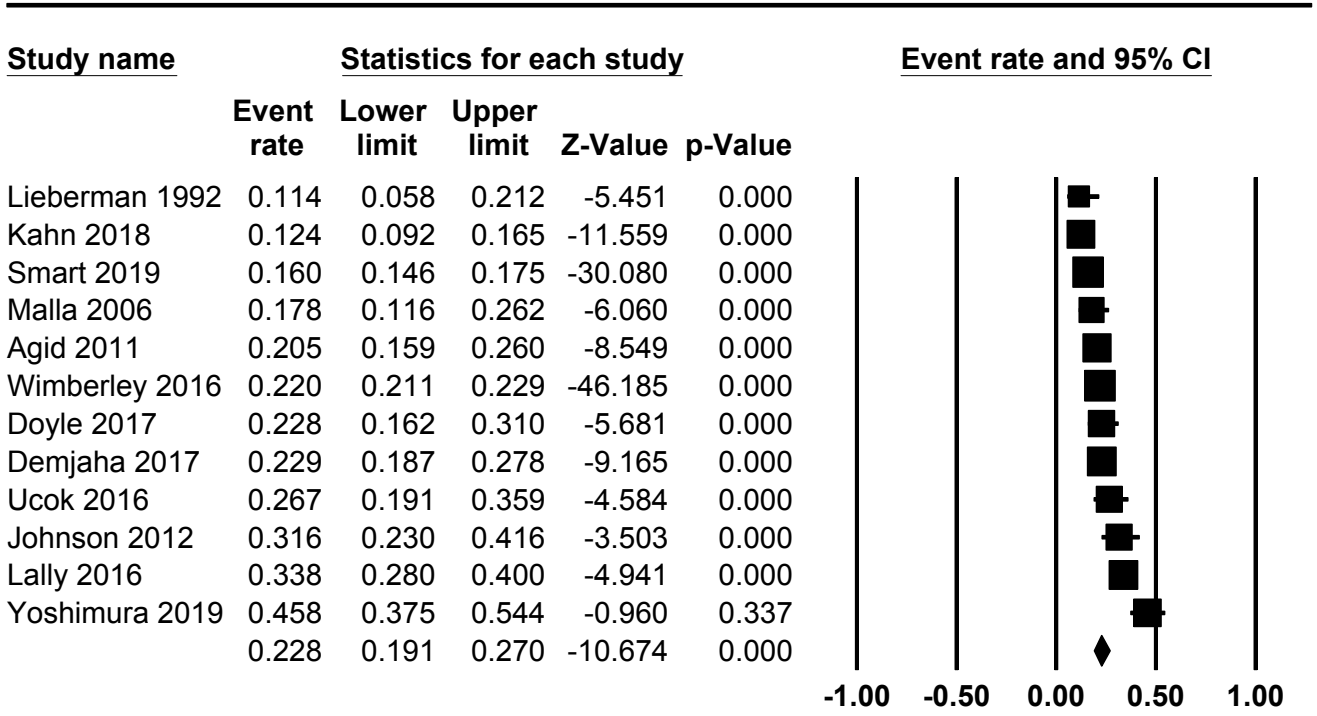
Subgroup	Number of studies	Rate of TRS	95% CI	p-value	I^2	Between subgroup comparison	
						Q-Value (df)	p-value
All	12	22.8%	19.1% to 27.0%	<0.001	91.8%		
Recruitment site							
Community	2	22.8%	17.5% to 29.2%	<0.001	37.7%	0.173 (2)	0.917
Inpatient	2	25.4%	5.1% to 68.2%	0.251	95.1%		
Mixed	8	21.5%	17.8% to 25.8%	<0.001	91.8%		
TRS definition							
TRRIP aligned	7	24.6%	18.1% to 32.7%	<0.001	86.0%	0.881 (1)	0.348
TRRIP non-aligned	5	20.5%	16.0% to 25.9%	<0.001	94.8%		
Time period							
Before 2000	3	20.4%	15.9% to 25.9%	<0.001	54.0%	0.718 (1)	0.397
After 2000	9	24.0%	18.0% to 31.3%	<0.001	93.5%		
Study Quality							
Low	6	24.8%	16.7% to 35.2%	<0.001	87.7%	0.602 (1)	0.438
High	6	20.9%	16.8% to 25.6%	<0.001	93.6%		
Type of Cohort							
FEP	3	17.8%	14.3% to 22.0%	<0.001	50.0%	9.984 (1)	0.046
FES	9	24.4%	19.5% to 30.0%	<0.001	84.0%		
Data Collection							
Prospective	9	20.8%	16.2% to 26.3%	<0.001	89.3%	1.335 (1)	0.248
Retrospective	3	29.1%	17.1% to 44.9%	0.011	94.8%		

TRRIP = Treatment Response And Resistance In Psychosis guidelines

FEP = First Episode Psychosis

FES = First Episode Schizophrenia

Figure 1 Forest Plot of TRS



Rate of TRS

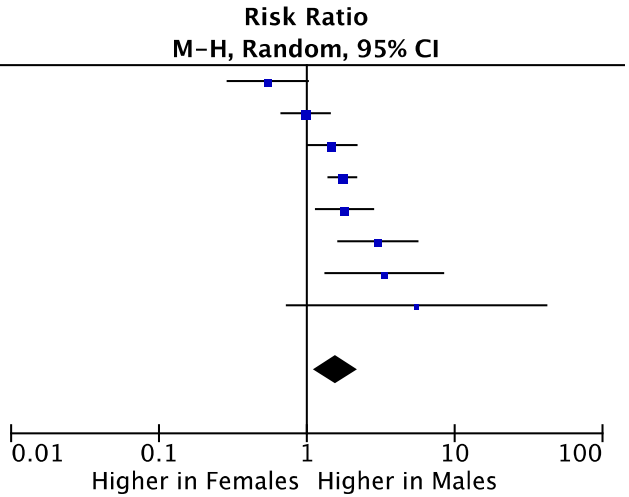
Figure 2. Rates of TRS by Sex

Study or Subgroup	Weight	Risk Ratio M-H, Random, 95% CI
Johnson 2012	12.0%	0.54 [0.29, 1.01]
Lally 2016	16.1%	0.98 [0.67, 1.43]
Yoshimura 2019	15.9%	1.48 [1.00, 2.17]
Smart 2020	18.4%	1.74 [1.40, 2.16]
Demjaha 2017	14.9%	1.80 [1.15, 2.81]
Ucok 2016	12.1%	3.02 [1.63, 5.59]
Doyle 2017	8.2%	3.35 [1.34, 8.38]
Lieberman 1993	2.5%	5.54 [0.73, 41.76]
Total (95% CI)	**100.0%**	**1.57 [1.11, 2.21]**

Total events

Heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 27.07$, df = 7 (P = 0.0003); $I^2 = 74\%$

Test for overall effect: Z = 2.58 (P = 0.010)



Supplementary Table 7 PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7

Supplementary Table 7 PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 1 and Figure 1
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	9
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11
FUNDING			

Supplementary Table 7 PRISMA 2009 Checklist

Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	12

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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