Journal of Affective Disorders 273 (2020) 524–531

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Prevalence of comorbid depression in schizophrenia: A meta-analysis of observational studies

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ARTICLE INFO

Keywords:
Schizophrenia
Depression
Prevalence
Meta-analysis

ABSTRACT

Introduction: Comorbid depressive symptoms (depression thereafter) often occur in schizophrenia and are associated with negative outcomes. This meta-analysis estimated the prevalence of comorbid depression and its associated factors in schizophrenia.

Methods: Both international (PubMed, EMBASE, PsycINFO, and Web of Science) and Chinese (WANFANG and CNKI) databases were systematically searched. Studies with data on the prevalence of comorbid depression in schizophrenia measured with the Calgary Depression Scale for Schizophrenia (CDSS) were included. Random-effects models were used in all analyses.

Results: Fifty-three studies covering 9,879 patients were included. The pooled prevalence of comorbid depression was 28.6% (95%CI: 25.3%-32.2%). Subgroup analyses revealed that studies examining inpatients, being published in Chinese language, or those with lower CDSS cut-od values reported higher depression rates. Meta-regression analyses indicated that the rate of depression was positively associated with publication year, proportion of males, mean age, and severity of psychotic symptoms, and negatively associated with illness duration and study quality.

Conclusion: Comorbid depression is common in schizophrenia. Due to its negative impact on patients' quality of life and prognosis, regular screening and effective treatment for comorbid depression should be implemented in patients with schizophrenia.

1. Introduction

Comorbid depressive symptoms (depression thereafter) are present in all phases of schizophrenia (Naguy, 2018; Upthegrove, 2009) and correlated with higher risk of suicide (Ayesa-Arriola et al., 2015; Bagaric et al., 2013; Li et al., 2018), polypharmacy (Lako et al., 2012b), worse psychosocial functioning (Schennach-Wolff et al., 2011), and poorer quality of life (Alessandrini et al., 2016; Sim et al., 2004), and functional outcomes (Conley et al., 2007). Because comorbid depression is often under-diagnosed in schizophrenia, patients may not receive appropriate treatment (Lako et al., 2012b; Majadas et al., 2012; Upthegrove et al., 2017).

Elucidating the pattern of comorbid depression and its correlates in schizophrenia could benefit the management and prognosis of affected patients. The prevalence of comorbid depression varies greatly across studies; for instance, one study (Dai et al., 2018) found the rate of depression measured with the 17-item Hamilton Depression Rating Scale (HAMD-17) in schizophrenia inpatients was 54.6%, while the corresponding figures were 12.9% when using the Present State Examination (PSE) (Barnes et al., 1989) and 31% in outpatients with the Calgary Depression Scale for Schizophrenia (CDSS) (Majadas et al., 2012). Discrepancies between these studies could be partially due to

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https://doi.org/10.1016/j.jad.2020.04.056
Received 9 October 2019; Received in revised form 10 March 2020; Accepted 27 April 2020
Available online 12 May 2020

different study settings, the severity of psychotic symptoms, and assessment instruments.

Several scales have been used to assess comorbid depression in schizophrenia including generic ones, such as the HAMD and PSE, that have not been validated in schizophrenia and they are not as sensitive as schizophrenia-specific measures, such as the CDSS. The 9-item CDSS was developed to identify comorbid depression in schizophrenia; its total score ranges from 9 to 27 with a higher total score indicating more severe depression. The CDSS has satisfactory psychometric properties and has been widely used (Lako et al., 2012a; Scholes and Martin, 2013). Different CDSS cutoff values have been applied in research and clinical practice: a total score of ≥5 (Hani et al., 2016), ≥6 (Chang et al., 2015), ≥7 (Fountoulakis et al., 2017), >7 (Thomas et al., 2014), or ≥12 (Üçok et al., 2013).

The frequency of depression in schizophrenia ranges from 7% to 75% (Siris, 2000). The lack of a systematic literature search and the use of different depression measures may have contributed to the highly variable results and obscure conclusions about comorbidity rates. To date, no meta-analyses or systematic reviews have been published using schizophrenia-specific measures on comorbid depression. To address this gap, a meta-analysis of observational studies was performed on the prevalence and moderating factors of comorbid depression measured by the CDSS in schizophrenia.

2. Method

2.1. Search strategy

The principle of Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) was followed. Both international (PubMed, EMBASE, PsycINFO, and Web of Science) and Chinese (WANFANG and CNKI) databases were searched systematically and independently by two authors (WL and YY) from their inception until February 27th, 2019. The following key search terms were used: 'schizophrenia', 'schizophrenic disorder', 'disorder, schizophrenic', 'Disorders, Schizophrenic', 'schizophrenic disorders', 'dementia praecox', 'Calgary Depression Scale for Schizophrenia', and 'CDSS'. Additional publications were hand-searched from reference lists of relevant reviews and publications. The research protocol was predefined and registered with the International Prospective Register of Systematic Reviews (PROSPERO: CRD42019135031).

2.2. Study criteria and selection

Studies that fulfilled the following criteria were included: (1) patients diagnosed with schizophrenia according to international or local diagnostic criteria, such as 3rd, 4th and 5th Revisions of the Diagnostic and Statistical Manual of Mental Disorders (DSM; DSM-3, DSM-4, and DSM-5) (American Psychiatric Association, 1980, 1994, 2013), the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) (World Health Organization, 1992), and the Chinese Classification of Mental Disorders, 3rd Revision (CCMD-3) (Psychosis Branch of Chinese Medical Association, 2001). The diagnostic criteria for schizophrenia in CCMD-3 and ICD-10 are almost the same (Chen, 2002), with high consistency (Phillips, 2001); (2) reporting prevalence of comorbid depression as measured using the CDSS with validated cutoff values; (3) peer-reviewed articles published in English or Chinese language. Studies conducted on special populations (e.g., older patients or those at high risk of suicide) (Depp et al., 2011; Lindenmayer et al., 2003; Lippi et al., 2009), case studies, and commentaries were excluded.

The literature search and selection of studies were independently performed by the same two authors (WL and YY). Eligibility of studies was determined by reading full texts of articles after screening their titles and abstracts. Any disagreements were settled by consulting the corresponding author (YTX). If multiple studies were published based on the same dataset, only those with a larger sample size were included. Therefore, some relevant studies were not included (Andrianarisoa et al., 2017; Ayesa-Arriola et al., 2014; Fond et al., 2016; Grover et al., 2018; Maggini et al., 2004; Rey et al., 2017). Additional information from the included studies was obtained by contacting first or corresponding authors by email.

2.3. Data extraction

The same two authors (WL and YY) independently extracted data including the study and patients' characteristics, the prevalence of depression, and the CDSS cut-off values, using a data collection form. Only baseline data were extracted from prospective cohort studies.

2.4. Quality assessment

Study quality was independently rated by two authors (WL and YY) using a quality assessment instrument for epidemiological studies (Parker, 2008). The assessment covered the following 6 domains: definition and representativeness of targeted population, sampling methods, response rate, definition of outcome variable, and validation of assessment instrument. Higher total scores reflected better study quality.

2.5. Statistics

Data analyses were conducted with the Comprehensive Meta-Analysis Program, Version 2.0 (CMA 2.0) (http://www.meta-analysis.com/). Considering variable demographic characteristics and sampling methods across studies, the random-effects model was applied to estimate the pooled prevalence of depression. The logit transformation was used in the CMA 2.0 to calculate the prevalence of depression in each study. The I^2 statistic was used to test heterogeneity; I^2 values > 50% were regarded as indication of high heterogeneity (Higgins et al., 2003). Potential sources of heterogeneity were examined by subgroup, meta-regression and sensitivity analyses. Subgroup analyses were conducted for categorical variables including publication language (Chinese vs. English), country (China vs. other countries), national economic level (high-income countries vs. middle-income countries) (Worldbank, 2017), study site (multicenter vs. single site), sampling method (consecutive vs. purposive vs. random sampling), sample size (<124 vs. ≥124; dichotomized using the median split), CDSS cut-off value (studies with cut off value of "≥ x" were grouped with those "> x-1"), diagnosis (schizophrenia alone vs. schizophrenia and other related psychotic disorders), type of patients (inpatient vs. outpatient vs. community), and phase of schizophrenia (acute vs. other stages). Meta-regression analyses were conducted for continuous variables: publication year, proportion of males, mean age, mean duration of illness, quality assessment score, and the Positive and Negative Symptom Scale (PANSS) total and subscale scores. Sensitivity analyses were carried out by removing each study one by one to examine the consistency of the primary results (Higgins and Green, 2011). Publication bias was tested via Funnel plots and Begg's rank test (Begg and Berlin, 1988). Level of significance was set as $P<0.5$ (two-tailed).

3. Results

3.1. Study characteristics

Study selection procedure is shown in Fig. 1. Fifty-three studies (8 in Chinese and 45 in English) involving 9,879 schizophrenia patients published between 1999 and 2018 were included in the meta-analysis. Study characteristics are presented in Supplementary Table 1. Sample sizes ranged from 39 to 1,427 with a median of 124. The mean age of patients ranged from 24.5 to 53.7 years with a median of 35.9 years. Illness duration ranged from 1.86 to 26.09 years (median = 11.86

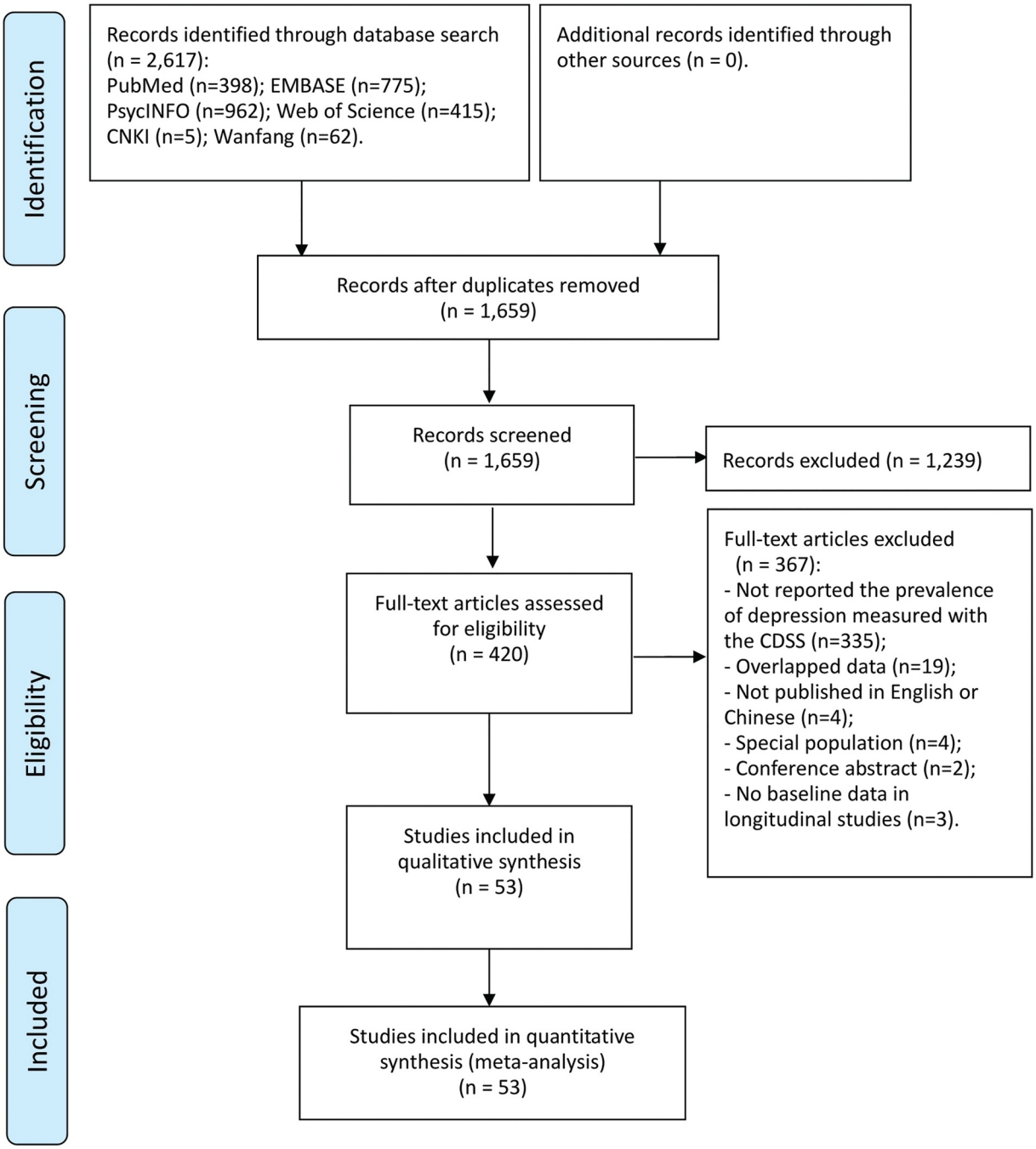

Fig. 1. PRISMA flow chart.

years). The DSM-IV and its text version were the most used diagnostic criteria (n = 39). CDSS cutoff values of >4/≥5 (n = 6), >5/≥6 (n = 17), >6/≥7 (n = 23), >7 (n = 2), and >11/≥12 (n = 4) were applied in the included studies. Study quality scores ranged between 3 and 6; 46 studies (86.8%) were rated as 4 or 5 (Supplementary Table 2).

3.2. Prevalence of comorbid depression

The pooled prevalence of comorbid depression in schizophrenia was 28.6% (95%CI: 25.3%-32.2%, $I^2 = 92.30\%$); rates ranged from 4.6% (95%CI: 2.3%-8.9%) (Fountoulakis et al., 2017) to 65.1% (95%CI: 60.1%-69.8%) (Peitl et al., 2016) (Fig. 2).

3.3. Subgroup and meta-regression analyses

Table 1 displays the results of subgroup analyses. Inpatients presented with a significantly higher prevalence of depression than outpatients and community-dwelling patients ($P = 0.014$). Studies using the cut off value of > 11 reported the lowest depression rate (15.0%, 95%CI: 10.6%-20.8%, $I^2 = 42.29\%$) while studies with the cut-off of > 4 had the highest rate (32.3%, 95%CI: 25.8%-39.5%, $I^2 = 77.44\%$) ($P = 0.001$). Studies published in Chinese language reported higher prevalence than those in English language (P = 0.038).

Meta-regression analyses revealed that publication year ($\beta = 0.022$, $P < 0.001$), proportion of males ($\beta = 0.015$, $P < 0.001$), mean age ($\beta = 0.009$, $P = 0.026$), and PANSS total ($\beta = 0.030$, $P < 0.001$) and all subscale scores (positive symptoms: $\beta = 0.047$, $P < 0.001$; negative

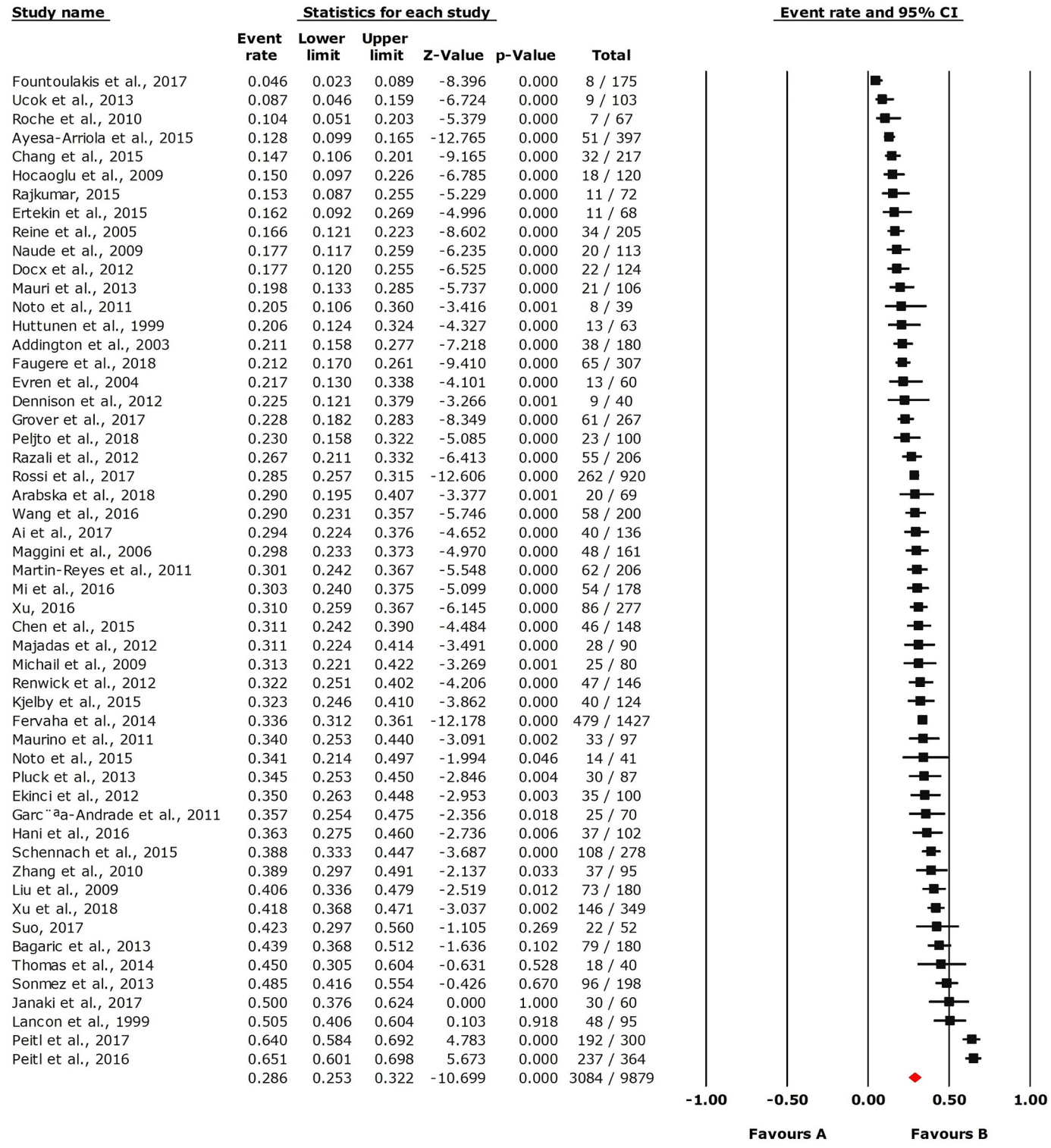

Fig. 2. Prevalence of depression in schizophrenia.

symptoms: $\beta = 0.080$, $P < 0.001$; general psychopathology: $\beta = 0.047$, $P < 0.001$) were positively associated with the prevalence of comorbid depression (Table 2). Duration of illness ($\beta = -0.069$, $P < 0.001$) and study quality ($\beta = -0.206$, $P < 0.001$) were negatively associated with depression rates (Table 2).

3.4. Sensitivity analysis and publication bias

The primary results did not change significantly after studies were removed one by one from the analysis. The Begg's test ($z = 2.201$, $P = 0.027$) and funnel plot analysis revealed publication bias (Supplementary Fig. 1).

4. Discussion

To the best of our knowledge, this was the first meta-analysis that estimated the prevalence of comorbid depression in schizophrenia. The 28.6% (95%CI: 25.3%-32.2%) comorbid depression is a similar figure

Table 1
Subgroup analyses of rate of depression in schizophrenia.

Subgroups	Categories (number of studies)	Rate of depression (%)	95% CI		Events	Sample size	I^2 (%)	*P* (within subgroup)	Q (*P* across subgroups)
Language of publication	Chinese (8)	33.2	29.9	36.8	416	1,266	39.95	0.112	4.30 (0.038)
	English (45)	27.6	23.9	31.7	2,668	8,613	93.37	<0.001	
Country	China (10)	32.2	27.0	37.9	594	1,832	83.23	<0.001	1.73 (0.188)
	Other countries (43)	27.7	23.8	31.9	2,490	8,047	93.23	<0.001	
Income	High-income (27)	27.1	23.5	31.1	1,635	5,748	88.69	<0.001	0.77 (0.380)
	Middle-income^ (26)	30.2	24.7	36.4	1,449	4,131	93.80	<0.001	
Study Site	Multicenter (17)	26.1	21.8	30.9	1,332	4,618	90.29	<0.001	0.61 (0.436)
	Single site (29)	28.7	24.1	33.8	1,314	4,244	91.22	<0.001	
Sampling method	Consecutive (15)	27.4	23.1	32.1	619	2,135	80.81	<0.001	2.26 (0.322)
	Purposive (1)	22.8	18.2	28.3	61	267	-	-	
	Random (3)	31.4	18.2	48.5	98	329	86.11	0.001	
Sample size*	<124 (26)	27.5	23.2	32.2	565	2,029	79.59	<0.001	0.43 (0.511)
	≥124 (27)	29.7	25.1	34.8	2,519	7,850	95.21	<0.001	
CDSS cut-off	>4/≥5 (6)	32.3	25.8	39.5	311	897	77.44	<0.001	17.60 (0.001)
	>5/≥6 (17)	29.7	25.9	33.8	994	3,381	82.11	<0.001	
	>6/≥7 (23)	29.0	23.0	35.9	1,647	4,960	95.38	<0.001	
	>7 (2)	31.2	13.2	57.5	56	220	89.24	0.002	
	>11 or ≥12 (4)	15.0	10.6	20.8	51	351	42.29	0.158	
Diagnosis	Schizophrenia (38)	29.0	25.1	33.3	2,508	7,758	92.98	<0.001	0.14 (0.705)
	Schizophrenia and other related psychotic disorders (15)	27.6	21.7	34.3	576	2,121	89.51	<0.001	
Illness phase	Acute (5)	31.0	22.2	41.3	235	671	84.01	<0.001	0.61 (0.738)
	Other status# (18)	29.8	22.5	38.2	1,043	3,022	95.19	<0.001	
	Mixed (5)	25.0	15.2	38.2	153	605	89.24	<0.001	
Patient type	Inpatients (16)	35.5	28.2	43.5	1,045	2,538	93.53	<0.001	10.67 (0.014)
	Outpatients (11)	25.8	21.8	30.2	668	2,517	79.21	<0.001	
	Community (1)	26.7	21.1	33.2	55	206	-	-	
	Mixed (16)	20.5	15.9	26.0	456	2,246	87.55	<0.001	

Abbreviation: CI: confidential interval.
^ Containing upper middle-income and lower middle-income countries.
* Grouped by median sample size
# Including patients at stages of schizophrenia: chronic, stable, remitted, and residual.

Table 2
Meta-regression of rate of depression in schizophrenia.

Moderators	Number of studies	Slope	Intercept	P
Publication year	53	0.022	-46.032	<0.001
Proportion of males (%)	51	0.015	-1.737	<0.001
Mean age (year)	48	0.009	-1.066	0.026
Duration of illness (year)	23	-0.069	0.244	<0.001
Quality score	53	-0.206	0.175	<0.001
Positive and Negative Symptom Scale (PANSS)				
Total score	22	0.030	-2.959	<0.001
Positive scale	24	0.047	-1.496	<0.001
Negative scale	23	0.080	-2.277	<0.001
General psychopathology scale	20	0.047	-2.424	<0.001

to the modal rate (25%) found in a previous review (Siris, 2000). Comorbid depression can have different expressions in schizophrenia: it may be related to positive symptoms in the acute phase and can remit with antipsychotic treatment (Bustamante et al., 1994; Emsley et al., 1999; Koreen et al., 1993), particularly with atypical antipsychotics (Leucht et al., 2009), or overlaps with negative symptoms in the post-psychotic or chronic phase (Majadas et al., 2012; Rabany et al., 2013). Still, depression could be present through all phases of schizophrenia as an independent and significant symptom dimension (Arabska et al., 2018; Grover et al., 2018; Upthegrove et al., 2017). As expected, in this meta-analysis depression rate was positively associated with positive, negative and general psychopathology scales of the PANSS. In addition, some studies found associations between comorbid depression, extra-pyramidal symptoms (EPS) and use of antipsychotics medications (Gebhardt et al., 2008; Siris, 2000; Weng et al., 2019), which however still needs further replications, because both EPS and depressive symptoms could be the phenotype of schizophrenia and side effects of antipsychotic medications (Majadas et al., 2012; Weng et al., 2019).

Gender difference in schizophrenia has been extensively studied (Mendrek and Mancini-Marïe, 2016), but the association between comorbid depression and gender is still unclear. Significantly higher depression rates in male patients were found in some studies (Geddes et al., 1994; Hambrecht et al., 1992), while others have reported higher risk among female patients (Goldstein and Link, 1988) or no gender differences (Shtasel et al., 1992). This meta-analysis found that male patients were more likely to suffer from comorbid depression. Apart from gender, rates of comorbid depression increased with age. Stressful life events, such as chronic medical conditions and heavy occupational stress, are more common in older people, which could increase the risk of comorbid depression (Katon, 2011; Meader et al., 2011). Schizophrenia patients face higher risk of chronic diseases with increasing age due to poverty, self-neglect and long-term use of psychotropic medications (Fischer and Buchanan, 2017). In addition, work-related stress often increases in schizophrenia patients because of severe occupational dysfunction and social isolation (American Psychiatric Association, 2013), both of which could increase the likelihood of comorbid depression with age as found in this meta-analysis.

Longer illness duration has a negative impact on cognitive deficits and social functioning in schizophrenia (Altamura et al., 2015) and is associated with higher level of self-stigma (Vrbova et al., 2016), poorer insight (Carroll et al., 1999), and demoralization (Cavelti et al., 2012), which, in turn, may raise the risk for comorbid depression (Belvederi Murri et al., 2015; Dai et al., 2018; Hill et al., 2019; López-Moríñigo et al., 2014; Majadas et al., 2012; Rapaport et al., 2002; Vidovic et al., 2016; Wang et al., 2019; Xu et al., 2018). Contrary to these findings, in this meta-analysis, longer illness duration was related to lower rates of comorbid depression. It is plausible that patients with shorter illness duration are at higher risk for comorbid depression

because they have not yet adapted to negative psychosocial outcomes caused by schizophrenia.

Meta-regression analysis revealed higher rates of comorbid depression in more recent studies. This trend could be partly due to the heightened attention and recognition of comorbid depression and its negative outcomes by health professionals, patients, and their relatives (Halbreich et al., 2019; Upthegrove et al., 2017). As a result, patients with comorbid depression may be more willing to seek help from mental health services (Picco et al., 2018). Inpatients were also more likely to suffer from comorbid depression than other types of patients. Most hospitalized schizophrenia patients experience relapse and more severe psychiatric symptoms, which could be associated with an increased likelihood of comorbid depression (Geddes et al., 1994; Kessler and Lev-Ran, 2019; Siris, 2000). Studies published in Chinese reported a higher depression rate than those published in English. Six of the 8 studies in Chinese included inpatients, 1 study covered outpatients, and another comprised both in- and outpatients. Compared to outpatients, inpatients are more likely to present severe psychiatric symptoms and comorbid depression. Comorbid depression rate was also associated with different CDSS cutoff values. As expected, studies using a lower cutoff value reported a higher prevalence of depression, except for the two with a cut-off of 7, probably due to the small number of studies. Similar to other meta-analyses of epidemiological studies (Cao et al., 2017; Li et al., 2019; Zeng et al., 2019), higher rates of comorbid depression were related to lower study quality in this study. Findings of poor-quality studies are unreliable since they examined less representative samples and lower response rates.

The strengths of this meta-analysis are the large number of included studies, the cumulative sample size of 9,879 patients, and the selection of studies based on the CDSS, a schizophrenia-specific measure of depression. However, several limitations should be acknowledged. First, most studies were conducted in middle/high-income countries, which limits the generalizability of the findings to low-income countries. Second, factors related to comorbid depression in schizophrenia, for instance, the impact of substance misuse and clinical management, could not be explored due to insufficient reporting of these data. Third, highly variable comorbidity rates were observed even with applying a schizophrenia-specific depression instrument. Some authors have concluded that high heterogeneity is unavoidable in meta-analysis of epidemiological studies (Li et al., 2016; Long et al., 2014; Winsper et al., 2013). Moderator analyses in this study have attempted to identify patient characteristics and methodological factors that could account for differing depression comorbidity estimates in the literature. Fourth, due to logistical reasons, only studies published in English and Chinese were searched. Fifth, apart from validated cutoff values, certain statistical methods based on means and SDs of CDSS (http://onlinestatbook.com/2/calculators/normal.html) (Furukawa et al., 2005) could generate prevalence of comorbid depression. However, this meta-analysis only included studies reporting prevalence of comorbid depression calculated using validated CDSS cutoff values.

In conclusion, this meta-analysis confirmed that comorbid depression is common in schizophrenia and identified several factors that are related to the frequency of comorbidity. Considering the negative effects of depression on the patients' wellbeing and prognosis, routine screening, and pharmacological (Gregory et al., 2017; Leucht et al., 2009) and psychosocial interventions (Donde et al., 2018) should be considered for patients with schizophrenia.

Role of funding

The study was supported by the National Science and Technology Major Project for investigational new drug (2018ZX09201-014), the Beijing Municipal Science & Technology Commission (No. Z181100001518005), and the University of Macau (MYRG2019-00066-FHS).

CRediT authorship contribution statement

Wen Li: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Writing - original draft. **Yuan Yang:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Writing - original draft. **Feng-Rong An:** Formal analysis, Funding acquisition, Investigation, Project administration. **Ling Zhang:** Funding acquisition, Project administration. **Gabor S. Ungvari:** Writing - review & editing. **Todd Jackson:** Writing - original draft. **Zhen Yuan:** Investigation. **Yu-Tao Xiang:** Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Supervision.

Declaration of Competing Interest

The authors declare that they have no conflicts of interest concerning this paper.

Acknowledgments

None.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2020.04.056.

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