Schizophrenia Bulletin
doi:10.1093/schbul/sbx157

Prevalence of Catatonia and Its Moderators in Clinical Samples: Results from a Meta-analysis and Meta-regression Analysis

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Catatonia is an independent syndrome that co-occurs with several mental and medical conditions. We performed a systematic literature review in PubMed/Scopus until February 2017 and meta-analyzed studies reporting catatonia prevalence. Across 74 studies (cross-sectional = 32, longitudinal = 26, retrospective = 16) providing data collected from 1935 to 2017 across all continents, mean catatonia prevalence was 9.0% (k = 80, n = 110 764; 95% CI = 6.9–11.7, I^2 = 98%, publication bias P < .01), decreasing to 7.8% (k = 19, n = 7612, 95% CI = 7–8.7, I^2 = 38.9%) in a subgroup with low heterogeneity. Catatonia prevalence was 23.9% (k = 8, n = 1168, 95% CI = 10–46.9, I^2 = 96%) in patients undergoing ECT/having elevated creatinine phosphokinase. Excluding ECT samples, the catatonia prevalence was 8.1% (k = 72, n = 109 606, 95% CI = 6.1–10.5, I^2 = 98%, publication bias P < .01), with sensitivity analyses demonstrating that country of study origin (P < .001), treatment setting (P = .003), main underlying condition (P < .001), and sample size (P < .001)moderated catatonia prevalence, being highest in Uganda (48.5%, k = 1) and lowest in Mexico (1.9%, 95% CI = 0.4–8.8, I^2 = 67%, k = 2), highest in nonpsychiatric out- or inpatient services (15.8%, 95% CI = 8.1–28.4, I^2 = 97%, k = 15)and lowest in psychiatric outpatients services (3.2%, 95% CI = 1.7–6.1, I^2 = 50%, k = 3), highest in presence of medical or neurological illness with no comorbid psychiatric condition (20.6%, 95% CI = 11.5–34.2, I^2 = 95%, k = 10)and lowest in mixed psychiatric samples (5.7%, 95% CI = 4.2–7.7, I^2 =98%, k = 43), highest in studies with sample sizes <100 (20.7%, 95% CI = 12.8–31.6, I^2 = 90%, k = 17) and lowest in studies with sample sizes >1000 (2.3%, 95% CI = 1.3–3.9, I^2 = 99%, k = 16). Meta-regression showed that smaller sample size (P < .01) and less major depressive disorder (P = .02) moderated higher catatonia prevalence. Year of data collection did not significantly moderate the results. *Results* from this first meta-analysis of catatonia frequencies across time and disorders suggest that catatonia is an epidemiologically and clinically relevant condition that occurs throughout several mental and medical conditions, whose prevalence has not decreased over time and does not seem to depend on different rating scales/criteria. However, results were highly heterogeneous, calling for a cautious interpretation.

Key words: catatonia/meta-analysis/DSM5/severe mental illness/prevalence

Introduction

Catatonia is a complex psychopathological and clinical condition.[1] The difficulties in the clinical diagnosis, conceptualization, and management of catatonia have been described as "the catatonic dilemma."[2,3] Clinical manifestations of catatonia are extremely heterogeneous and at least 40 separate signs of catatonia have been described,[4] making recognition challenging with frequent misdiagnoses.[5]

The nosological conceptualization of catatonia ranges from the original concept catatonia as an independent syndrome as per Kahlbaum and Heckers, to the inclusion of catatonia into Kraepelin's nomenclature of dementia praecox (although he acknowledged Kahlbaum's theory, but coming to different nosology though), which influenced various diagnostic classifications to include a catatonia subtype of schizophrenia.[6] Despite Bleuler's assimilation of catatonia as a feature of schizophrenia, and despite DSM-III and -IV including the subtype of catatonic schizophrenia, which each ignored Taylor and Abrams's reports describing a high frequency of catatonia in bipolar disorder (BD) rather than schizophrenia, the literature as well as DSM-5 gradually, but only partially,[6,7] acknowledged Kahlbaum's and Hecker's original categorization of catatonia as an independent syndrome.[8,9]

In recent years, catatonia has accrued renewed interest in clinical research, as shown by an exponentially growing number of published studies (from a total of 1660 hits with "catatonia" search in PubMed from database inception until 2000, 546 from 2000 to 2010, and 738 just between 2010 and May 2017). Some authors[10–15] proposed refined criteria to identify catatonia as a self-standing syndrome with its core clinical features that can be addressed by effective therapies, such as benzodiazepines (BDZs) and electroconvulsive treatment (ECT).[1] However, international classification systems of psychiatric diseases have only partially accepted these proposals. In 2013, the Diagnostic and Statistical Manual of Psychiatric Disorders (DSM5)[16] classified catatonia not as separate syndrome but as a "specifier," which may occur among virtually all psychiatric disorders (mainly neurodevelopmental, psychotic, and mood disorders) as well as medical conditions and which may be associated to drug treatments (mainly antipsychotics). However, a change toward catatonia as an independent syndrome has been considered, but not made yet.[9]

Due to the fact that theoretical frameworks, nosological concepts, and rating scales/criteria used to diagnose catatonia have changed across time, and since pharmacological treatments for a wide range of nonpsychotic conditions shifted from mainly first-generation antipsychotics (FGAs) to second-generation antipsychotics (SGAs) that are associated with less extrapyramidal symptoms (with EPS being a risk factor for catatonia),[17,18] it may be expected and has been described that the epidemiology of catatonia may have decreased over time.[19,20]

However, data on time trends are scarce and isolated and the prevalence of catatonia likely varies based on several factors, including the specific population and sampling frame, underlying diagnoses, definition of catatonia, country/continent of study origin, and time of the study, which may also be related to differences in specific medication and dosing patterns of antipsychotics.

Recent studies have reported that the prevalence of catatonia rates is around 10% among acute psychiatric inpatients,[10,21] with apparently different prevalence ranges according to the underlying or comorbid condition, ie, 4%–67% for schizophrenia, 14%–71% for mood disorders, and 4%–46% for medical conditions.

As an additional complication, however, is that catatonia definitions vary according to the number, duration, definition, and severity of signs and symptoms, with different criteria having been used in different studies. Moreover, there are several different rating scales or catatonia criteria definitions that have been proposed to detect and measure catatonic symptomatology. A recent narrative review of different catatonia scales which have been used/developed in the last 3 decades[22] identified the following: Modified Rogers Scale (MRS) in 1991,[23,24] Rogers Catatonia Scale revised (RCS) in 1996,[25] Bush–Francis Catatonia Rating Scale (BFCRS) in 1996,[4] Northoff Catatonia Rating Scale (NCRS) in 1999,[26] and the Catatonia Rating Scales in 2000.[27] In addition, Carrol also proposed the Kanner Scale in 2000.[28] Furthermore, frequencies of catatonia measured with these different rating scales may differ substantially (range: 3.4% to 10.3%).[29] Despite the heterogeneous nature and theoretical background of the above-mentioned rating scales, which could raise the concern about the validity of the measured clinical syndrome, they have all shown high sensitivity/specificity.

Moreover, some studies have reported changes in rates of catatonic schizophrenia during different time periods at single sites,[19,30] suggesting that at least catatonic schizophrenia may have become less common during the course of the 20th century. However, this supposedly decreased incidence may be influenced by several factors, including the selection of the type and dose regimen of FGAs or SGAs, to rating scales/criteria used to diagnose catatonia, or likelihood of misdiagnoses (secondary to neuroleptic malignant syndrome or rapid BDZ/anti-parkinsonian agent discontinuation), which has not been systematically and quantitatively assessed.[13,31]

Since the epidemiology of catatonia remains poorly investigated and has not been systematically evaluated, we conducted a systematic review and meta-analysis plus moderator analysis of the prevalence of catatonia and of potential moderators.

Methods

Search Strategy and Study Selection

This systematic review adhered to the MOOSE guidelines[32] and PRISMA statement.[33]

Four authors divided into two pairs (GP, AG, BR, LM) independently searched PubMed, and Scopus from database inception until February 11, 2017, using the following search terms: ("catatonia" [MeSH Terms] OR "catatonia" [All Fields]) OR ("catatonia" [MeSH Terms]

OR "catatonia" [All Fields] OR "catatonic" [All Fields]). We also checked the reference list of included articles and of relevant reviews. Studies were deemed eligible if they reported the prevalence of catatonia, or data allowing to compute it, in a psychiatric or medical clinical sample, with data gathered after 1935.

Data Extraction

Four authors divided into two pairs (GP, AG, BR, LM) independently extracted data, using a predetermined extraction form, including: catatonia prevalence (or variables needed to compute it), author, year of publication, year of data collection, country/continent of data collection, study design, setting, demographic characteristics, underlying main condition, employed catatonia rating scale used to diagnose catatonia, and percentage of subjects diagnosed with schizophrenia, major depressive disorder (MDD), BD, or other primary diagnoses, and prescription of FGAs or SGAs.

Quality Assessment

Two authors (BR, MS) independently assessed the quality of included studies with the Newcastle-Ottawa Scale (NOS), with a score of ≤5 (out of 9) indicating high risk of bias.[34]

Meta-analysis

Due to the anticipated heterogeneity, we utilized a random effects meta-analysis and calculated pooled prevalence and 95% confidence intervals (CIs) with comprehensive meta-analysis (CMA, version 3). Heterogeneity was assessed with the Cochrane Q and I^2 statistics for each analysis.[35] We conducted meta-regression analyses with CMA for outcomes with high heterogeneity ($I^2 > 50\%$ and/or $P < .05$) and reported by ≥4 studies to investigate potential moderators of the observed catatonia prevalence. We conducted sensitivity analyses according to country, continent, rating scale/criteria used to define catatonia, treatment setting (nonpsychiatric out- or inpatient units, psychiatric inpatient units or psychiatric outpatients services), period of data collection, main underlying/co-morbid clinical condition (specific psychiatric diagnosis, or absence of any psychiatric condition, ie, medical/neurological condition) and quality of the study (post hoc, using the NOS score >5 as the threshold for high quality studies). We also investigated the following moderators: sample size, year of data collection, mean age, percentage of males, percent of subjects with schizophrenia, with mood disorders, with MDD, with BD, taking antipsychotics (FGAs and/or SGAs).

Publication bias was assessed via visual inspection of funnel plots and with the Begg–Mazumdar Kendall's tau[36] and Egger bias test.[37] In case that publication bias was suspected, we calculated the trim and fill adjusted analysis[38] to remove the most extreme small studies from the positive side of the funnel plot, and recalculated the effect size at each iteration until the funnel plot was symmetric around the (new/adjusted) effect size.

Whenever studies reported more than one prevalence result, providing frequencies for different catatonia criteria/rating scales, we averaged the frequencies to yield one single prevalence result for these studies and avoid double counting of subjects in the main analyses.

Given the fact that studies restricted to patients undergoing ECT or those with elevated levels of creatinine phosphokinase (CPK) inherently contain a selection bias toward higher catatonia prevalence in these enriched samples, we reported outcomes separately in these studies and the remaining ones not restricting their samples in this way. Thereafter, we conducted a comprehensive series of subgroup analyses or sensitivity analyses, adding also treatment setting (nonpsychiatric in- or outpatient services and psychiatric in- and outpatient units or services) and subgroups of studies with ascending numbers of included patients (as we found that sample size had a significant effect on the catatonia prevalence (ie, $n \geq 100$, $n \geq 200$, $n \geq 300$, $n \geq 500$, $n \geq 750$, $n \geq 1000$) in order to find possible explanations of the high observed heterogeneity. Finally, we trimmed down the same number of studies on both sides of the catatonia point prevalence of the studies not focusing on ECT/elevated CPK samples in an ascending fashion until we had a final study sample without significant heterogeneity, reporting this *post hoc* exploratory result in comparison to the overall prevalence to provide a benchmark of a nonheterogeneous catatonia prevalence estimate not influenced by outliers with overly high or low results, assessing the range and robustness of our primary findings.

Results

Search Results

Out of initial 4089 hits in PubMed and Scopus after duplicate removal, 3813 studies were excluded after title/abstract reading. Full text articles of 276 studies were assessed, with further exclusion of 201 studies due to several reasons specified in figure 1. Finally, we included 73 studies that provided data about the prevalence of catatonia.[20,21,26,29,39–107]

Characteristics of Included Studies

All included studies' main features are reported in table 1.

We included 73 studies with a total population of 110 559 subjects from 99 individual samples. Studies were conducted across all continents, with median year of data collection ranging from 1935 to 2017. The majority of studies, 55, included psychiatric inpatients, 7 described patients undergoing ECT, 4 studies provided data from psychiatric consultation services, 4 involved outpatients,

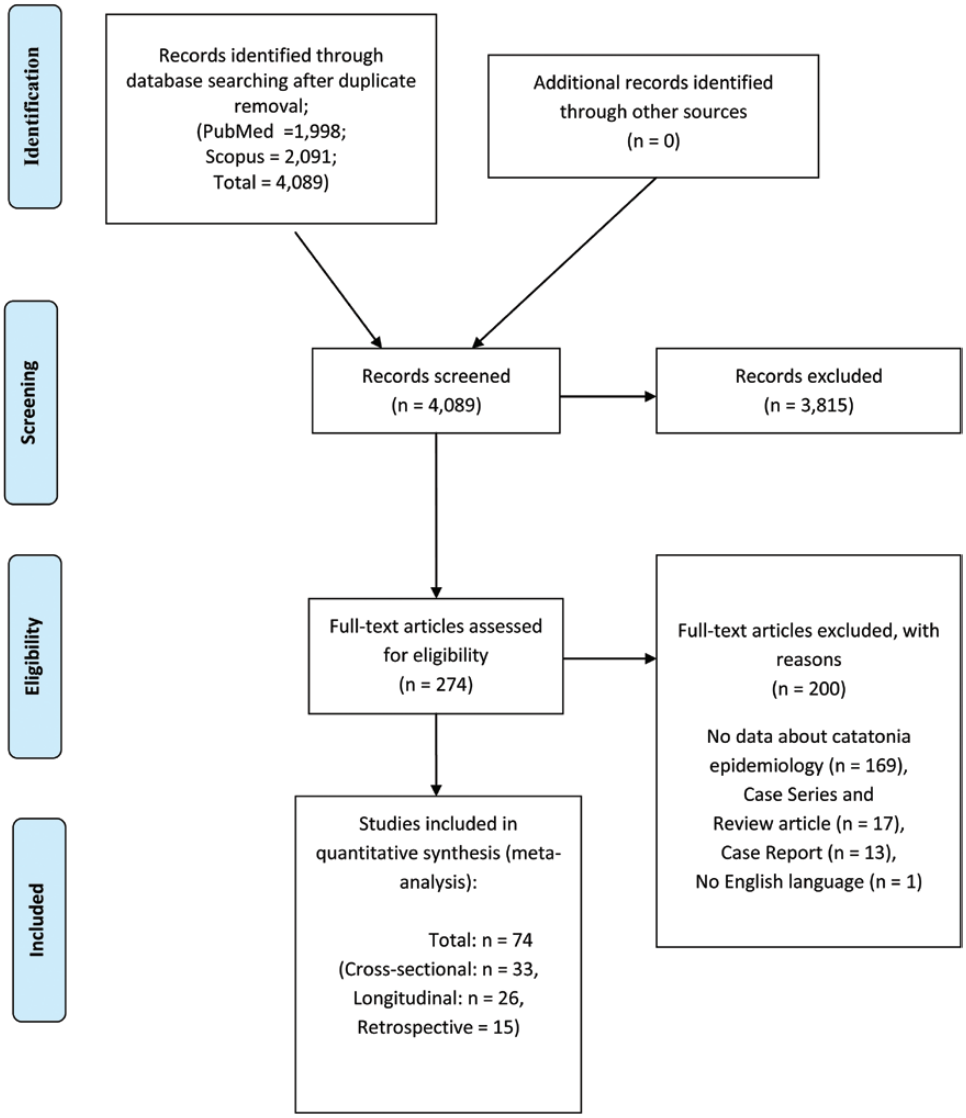

Fig. 1. PRISMA flowchart.

while 3 studies included medical inpatients. The populations included subjects with several psychiatric conditions in 36 studies, while the sample was limited to patients diagnosed with schizophrenia in 26 studies, BD in 4 studies, autism in 2 studies, and postpartum psychosis in a single study. A comorbid medical or neurological condition was present in 26 studies. Catatonia was defined according to Bush-Francis scales (k = 25), DSM-any version (k = 24), ICD-any version (k = 11), Lohr's criteria (k = 7), Rosebush's criteria (k = 7), Catatonia Rating Scales (k = 4), Leonhard's criteria (k = 4), Northoff's criteria (k = 3), Modified Rogers Scale (k = 3), Catatonia Scale Instrument (k = 2), Fink and Taylor's criteria (k = 2), Bleuler's criteria (k = 2), or Carrol's criteria (k = 1), while no validated tool was used in 11 studies. Europe was the most represented continent (k = 40), followed by Asia (k = 19), North America (k = 7), Africa (k = 3), Oceania (k = 2), and South America (k = 2). The design of the study was cross-sectional (k = 32), longitudinal prospective (k = 26), or retrospective (k = 15). The mean Newcastle-Ottawa scale quality score across all studies was 5.6 ± 1.5 (out of a range from 1–9), indicating medium risk of bias.

Meta-analysis of Catatonia Prevalence, Publication Bias, Heterogeneity in the Whole Sample

Results of meta-analysis are reported in detail in table 2.

The overall pooled catatonia prevalence across 80 samples from 74 studies (some studies reported results from samples in different countries or time periods) and 110 774 individuals was 9.0% (95% CI = 6.9–11.7, I^2 = 98%). Heterogeneity was high (I^2 = 98%, P < .0001). Publication bias was present according to Egger's test (5.18, P < .01) and visual funnel plot inspection (figure 2), and results increased to 12.6%

Table 1. Study, Sample and Catatonia Definition Characteristics of Included Studies (Organized by Median Year of Data Collection)

Study	NOS scale Quality	Country	Region	Median Year of Data Collection	Sample Size	Study	Age	Population	Psychiatric Diagnosis	Medical, Neurologic, or Intellectual Disability Comorbidity	Catatonia Definition
Baran et al[39]	3	Hungary	Europe	1935	23	LG	AD	Psychiatric inpatients, ECT	Mixed	N	ICD-10
Flekkoy[40]	4	Norway	Europe	1956	72	CS	AD	Psychiatric inpatients	SCZ	N	Study-defined criteria
*Guggenheim and Babigian[41]	6	USA	North America	1963	39475	CS	AD	Psychiatric inpatients	Mixed, SCZ	N	Study-defined criteria
Kimura et al[42]	4	Japan	Asia	1967	173	LG	C/A	Psychiatric outpatients	SCZ	N	Study-defined criteria
Kleinhaus et al[43]	8	Israel	Asia	1970	568	LG	AD	Psychiatric inpatients	SCZ	N	ICD-10
Petho et al[44]	8	Hungary	Europe	1971	276	LG	AD	Psychiatric inpatients	Mixed	N	Leonhard's criteria
Bland[45]	4	USA	North America	1972	1556	CS	AD	Psychiatric inpatients	SCZ	N	ICD-8
Scharfetter[46]	6	Switzerland	Europe	1973	140	LG	AD	Psychiatric inpatients	SCZ	N	ICD
Serban[47]	6	USA	North America	1975	641	CS	AD	Psychiatric inpatients	SCZ	N	DSM-II
Tsoi[48]	4	Singapore	Asia	1975	423	CS	AD	Psychiatric inpatients	SCZ	N	ICD-9 + Bleuler
Strian and Klicpera[49]	6	Germany	Europe	1976	225	LG	AD	Psychiatric inpatients	SCZ	N	ICD
Ihezue and Kumaraswamy[50]	7	Nigeria	Africa	1978	204	LG	AD	Psychiatric inpatients	SCZ	N	Study-defined criteria
Beckmann et al[51]	6	Germany	Europe	1992	749	CS	AD	Psychiatric inpatients and outpatients	SCZ	N	Leonhard's criteria
Northoff et al[52]	6	Germany	Europe	1992	1143	CS	AD	Psychiatric inpatients	Mixed	Y	Rosebush + Lohr and Wiesniwski
Beratis et al[53]	5	Greece	Europe	1993	374	R	AD	Psychiatric inpatients	SCZ	N	DSM-III
Wing and Shah[54]	6	UK	Europe	1994	506	CS	AD	Psychiatric inpatients and outpatients	Autism	N	Study-defined criteria
Northoff et al[26]	9	Germany	Europe	1994	1259	CS	AD	Psychiatric inpatients	Mixed	N	Rosebush + Lohr and Wiesniwski
Peralta et al[55]	8	Spain	Europe	1994	272	CS	AD	Psychiatric inpatients	Mixed	N	DSM-III + AMDP
Lee[56]	6	Australia	Oceania	1994	802	R	AD	Psychiatric inpatients	Mixed	Y	Rosebush + Lohr and Wisenewski + CRS + CSI

Table 1. *Continued*

Study	NOS scale Quality	Country	Region	Median Year of Data Collection	Sample Size	Study	Age	Population	Psychiatric Diagnosis	Medical, Neurologic, or Intellectual Disability Comorbidity	Catatonia Definition
*Stein et al[57]	5	Israel	Asia	1994	81	R	AD, C/A	Psychiatric inpatients, ECT	Mixed	N	DSM-III, IV
Lykouras et al[58]	7	Greece	Europe	1995	120	CS	AD	Psychiatric inpatients	Mixed	Y	DSM-IV
*Stompe et al[59]	7	Austria	Europe	1996	254	CS	AD	Psychiatric inpatients	SCZ	N	DSM-IV, ICD-10, Leonhard's criteria, Bleuler's definition
Bush et al[4]	8	USA	North America	1996	215	R	AD	Psychiatric inpatients	Mixed	N	BFCSI
Bräunig et al[60]	6	Germany	Europe	1997	61	CS	AD	Psychiatric inpatients	BD	N	Braunig criteria
Northoff et al[61]	8	Germany	Europe	1997	385	CS	AD	Psychiatric inpatients	Mixed	N	BFCRS, Lohr Criteria, Rosebush, Northoff Catatonia Scale
Lee[62]	5	Australia	Oceania	1997	1392	LG	AD	Psychiatric inpatients	Mixed	Y	Rosebush + Lohr and Wisenewsky
Raffin et al[63]	6	France	Europe	1997	5532	LG	C/A	Psychiatric inpatients	Mixed	Y	BFCRS
Conca et al[64]	7	Austria	Europe	1998	354	LG	AD	Psychiatric inpatients	Mixed	N	ICD-10 + AMDP
Northoff et al[65]	5	Germany	Europe	1998	500	CS	AD	Psychiatric inpatients	Mixed	N	BFCRS, Lohr Criteria, Rosebush, Northoff Catatonia Scale
Cohen et al[66]	6	France	Europe	1998	4976	LG	C/A	Psychiatric inpatients	Mixed	Y	BFCRS
Krüger et al[67]	7	Germany	Europe	1999	76	CS	AD	Psychiatric inpatients	SCZ	N	CRS
Koch et al[68]	5	USA	North America	1999	16	R	AD	Medical and psychiatric inpatients, with elevated CPK	Mixed	Y	DSM-IV, BFCRS
Bark et al[69]	9	Germany	Europe	2000	276	CS	AD	Psychiatric inpatients	SCZ	N	BFCRS, Lohr Criteria, Rosebush, Northoff Catatonia Scale
Stöber[70]	7	Germany	Europe	2000	749	CS	AD	Psychiatric inpatients and outpatients	SCZ	N	Leonhard's criteria

Table 1. *Continued*

Study	NOS scale Quality	Country	Region	Median Year of Data Collection	Sample Size	Study	Age	Population	Psychiatric Diagnosis	Medical, Neurologic, or Intellectual Disability Comorbidity	Catatonia Definition
Tuerlings et al[71]	1	Netherlands	Europe	2000	285	R	AD	Psychiatric inpatients, ECT	Mixed	Y	DSM-IV
Peralta and Cuesta[72]	6	Spain	Europe	2001	187	CS	AD	Psychiatric inpatients	SCZ	N	Modified Rogers Scale
Consoli et al[73]	6	France	Europe	2001	5532	LG	C/A	Psychiatric inpatients	Mixed	N	BFCRS
Gazdag et al[74]	6	Hungary	Europe	2001	43	R	AD	Psychiatric inpatients, ECT	SCZ	N	Study-defined criteria
Krüger et al[75]	5	Germany	Europe	2002	99	CS	AD	Psychiatric inpatients	BD	N	CRS
Ungvari et al[76]	8	China	Asia	2003	225	CS	AD	Psychiatric inpatients	SCZ	N	BFCRS
Suzuki et al[77]	6	Japan	Asia	2004	51	LG	AD	Psychiatric inpatients	SCZ	N	DSM IV
Benarous et al[78]	9	France	Europe	2004	6463	LG	C/A	Psychiatric inpatients	Mixed	Y	PCRS (from BFCRS)
Narayanaswamy et al[79]	6	India	Asia	2005	7474	LG	AD	Psychiatric inpatients	Mixed	N	DSM-IV
Grover et al[80]	5	India	Asia	2005	25	R	C/A	Psychiatric inpatients, receiving ECT	Mixed	Y	BFCRS
Cavanna et al[81]	5	UK	Europe	2005	55	CS	AD	Medical outpatients	None	Y	BFCRS, BFCSI
*Chalasani et al[82]	6	UK, India	North America, Asia	2006	208	CS	AD	Psychiatric inpatients	Mixed	Y	DSM-IV, CSI, Morrison
Dutt et al[83]	5	India	Asia	2006	1056	LG	AD	Psychiatric inpatients	Mixed	Y	BFCRS
Ghaziuddin et al[84]	2	USA	North America	2006	101	R	C/A	Psychiatric inpatients	Mixed	Y	Study-defined criteria
Sayegh and Reid[85]	5	UK	Europe	2007	453	LG	AD	Psychiatric inpatients	Mixed	Y	Modified Rogers scale
Cottencin et al[86]	5	France	Europe	2007	656	LG	AD	Medical inpatients, consultation	Mixed	Y	Carrol
Mustafa et al[87]	5	Kuwait	Asia	2008	729	R	AD	Psychiatric inpatients	Mixed	N	ICD-10
Kruse et al[88]	4	USA	North America	2008	32	R	AD	Medical and psychiatric inpatients	Mixed	Y	Study-defined criteria
Yoshimura et al[89]	5	Japan	Asia	2009	450	R	AD	Psychiatric inpatients	SCZ	N	DSM-IV, BFCRS
Peralta et al[90]	4	Spain	Europe	2009	200	LG	AD	Psychiatric inpatients	SCZ	N	DSM-IV
Peralta et al[91]	6	Spain	Europe	2009	200	LG	AD	Psychiatric inpatients	SCZ	N	Modified Rogers scale

Table 1. *Continued*

Study	NOS scale Quality	Country	Region	Median Year of Data Collection	Sample Size	Study	Age	Population	Psychiatric Diagnosis	Medical, Neurologic, or Intellectual Disability Comorbidity	Catatonia Definition
Benzoni et al[92]	6	Italy	Europe	2009	264	LG	AD	Psychiatric inpatients, ECT	Mixed	Y	DSM-IV
Zahid and Ohaeri[93]	4	Kuwait	Asia	2009	130	CS	AD	Psychiatric outpatients	SCZ	N	ICD-10
Guinchat et al[94]	4	France	Europe	2010	58	R	C/A	Psychiatric inpatients	Autism	Y	Study-defined criteria
Menard et al[95]	6	France	Europe	2010	15	LG	C/A	Psychiatric inpatients	Mixed	N	BFCRS
Grover et al[21]	4	India	Asia	2011	201	LG	AD	Psychiatric inpatients	Mixed	N	BFCSI
Medda et al[96]	6	Italy	Europe	2011	447	CS	AD	Psychiatric inpatients, ECT	BD	N	DSM-V
Takahashi et al[97]	5	Japan, Korea, Taiwan	Asia	2011	324	LG	AD	Psychiatric outpatients	SCZ	N	DSM-IV
*Grover et al[98]	5	India	Asia	2012	205	CS	AD	Medical inpatients, consultation	None	Y	DSM5, BFCSI, BFCRS, Fink and Taylor
*Jaimes-Albornoz et al[99]	4	Spain	Europe	2012	348	CS	AD, E	Medical inpatients, consultation	None	Y	DSM-IV, BFCSI, Fink and Taylor's criteria
Nahar et al[100]	6	India	Asia	2013	200	R	AD	Psychiatric inpatients, postpartum psychosis	Postpartum psychosis	N	BFCRS
*Sarkar et al[29]	5	France	Europe	2013	87	CS	AD	Psychiatric inpatients	Mixed	N	DSM-5, ICD-10, BFCRS, BFCSI, CRS.
Ishida et al[101]	6	Japan	Asia	2013	911	R	AD	Psychiatric inpatients, involuntarily admitted	Mixed	Y	BFCSI
Kakooza et al[102]	6	Uganda	Africa	2013	33	CS	C/A	Medical inpatients	None	Y	BFCRS
Valencia et al[103]	5	Mexico	South America	2014	168	CS	AD	Psychiatric inpatients	SCZ	N	DSM-IV
Espinola-Nadurille et al[104]	9	Mexico	South America	2014	2044	LG	AD	Medical and psychiatric inpatients	Mixed	Y	DSM-5, BFCRS, BFCSI
Rajkumar[105]	6	India	Asia	2016	66	CS	AD	Psychiatric inpatients	BD	N	Study-defined criteria.
*Kaelle et al[106]	5	Australia	Oceania	2014	108	CS	E	Medical inpatients, consultation	Mixed	Y	BFCSI, BFCRS

Table 1. *Continued*

Study	NOS scale Quality	Country	Region	Median Year of Data Collection	Sample Size	Study	Age	Population	Psychiatric Diagnosis	Medical, Neurologic, or Intellectual Disability Comorbidity	Catatonia Definition
*Usman et al[107]	5	Nigeria	Africa	1984, 2004	13968	LG	AD	Psychiatric inpatients	Mixed	N	DSM-IV, BFCSI
*Van der Heijden et al[20]	5	Netherlands	Europe	1985, 1995, 1998, 2002	2805	R	AD	Psychiatric inpatients	SCZ	N	DSM-III
Total: 74 studies	Mean 5.7 (1.5)	40 Europe, 19 Asia, 8 North America, 3 Africa, 2 Oceania, 2 South America		From 1935 to 2016	110,774	32 CS, 26 LG, 16R	63 adults, 11 children/ adolescents, 2 elderly	55 psychiatric inpatients, 4 psychiatric consultation, 7 ECT treated patients,1 elevated CPK, 4 outpatients, 3 medical inpatients	37 mixed, 26 SCZ, 4 BD, 2 autism, 4 none, 1 postpartum psychosis	48 no, 26 yes	25 Bush-Francis scales, 24 DSM, 11 ICD, 11 no validated tool, 7 Lohr, 7 Rosebush, 4 CRS, 4 Leonhard's criteria, 3 Northoff, 3 Modified Rogers Scale, 2 CSI, 2 Fink and Taylor, 2 Bleuler, 1 Carrol

Note: AD, adults, BD, bipolar disorder; BFCRS: Bush-Francis catatonia rating scale; BFCSI: Bush-Francis catatonia screening instrument; C/A, children/adolescents; CPK, creatinine phosphokinase; CRS, catatonia rating scale; CS, cross-sectional; DSM, Diagnostic and statistical manual; E, elderly; ECT, electroconvulsive therapy; ICD, International classification of diseases; LG, longitudinal; PCRS, pediatric catatonia rating scale; R, retrospective; SCZ, schizophrenia. Asterisk indicates more than one sample in the study, or catatonia defined according to more than one definition.

Table 2. Meta-analysis of Prevalence of Catatonia in Psychiatric and Medical Patients

Subgroup/Moderator	Number of Samples	Number of Participants	Prevalence (%)	95% Confidence Interval (CI)		I^2 (%)
				Lower 95% CI	Upper 95% CI	
Catatonia (main analysis)	**80**	**110 774**	**9.0**	6.9	11.7	98
Catatonia (low heterogeneity subgroup)	**19**	**7612**	**7.8**	7.0	8.7	39
Catatonia (ECT/elevated CPK subgroup)	**8**	**1168**	**23.9**	10.0	46.9	96
Catatonia (no ECT/elevated CPK subgroup)	**72**	**109 606**	**8.1**	6.1	10.5	98
Sensitivity analyses excluding patients undergoing ECT (based on 92 of 100 samples, from 72 of 80 studies)						
Continent (between continent *P* value = .30)						
North America	8	50 130	**11.1**	5.0	22.7	99
Asia	22	14 113	**10.0**	6.3	15.4	98
Europe	52	37 303	**8.3**	6.0	11.2	97
Oceania	4	2410	**7.1**	5.8	8.8	32
Africa	4	28 173	**5.9**	0.1	31.7	99
South America	2	2212	**1.9**	0.4	8.8	67
Country[a] (between country *P* value *P* < .001)						
Uganda	1	33	**48.5**	NA	NA	NA
China	1	225	**32.0**	NA	NA	NA
Switzerland	1	140	**27.1**	NA	NA	NA
UK	6	1326	**19.9**	8.8	38.9	96
Hungary	1	276	**19.6**	15.3	24.7	NA
Singapore	1	423	**16.8**	NA	NA	NA
Austria	5	1370	**12.1**	8.1	17.6	86
India	12	10 129	**11.2**	5.2	22.6	98
USA	8	50 130	**11.1**	5.0	22.7	99
Spain	9	1631	**10.7**	8.2	13.8	69
Germany	11	5522	**8.2**	4.5	14.5	97
Israel	1	568	**7.6**	5.7	10.1	NA
Japan	5	1909	**7.6**	4.5	12.6	87
Australia	4	2410	**7.1**	5.8	8.8	32
Netherlands	4	2805	**6.9**	3.0	15.0	96
Norway	1	72	**5.6**	NA	NA	NA
Kuwait	2	859	**4.9**	3.2	7.6	22
Greece	2	494	**3.9**	2.5	6.	NA
France	12	23 667	**3.6**	2.1	6.2	95
Nigeria	3	28 140	**2.5**	0.3	17.7	99
Mexico	2	2212	**1.9**	0.4	8.8	67
Rating scale/criteria used to diagnose catatonia (between group *P* value = .13)						
Other	23	9430	**11.9**	8.7	16.1	96
ICD	10	4466	**10.6**	7.6	14.5	92
Study-defined	10	48 781	**10.2**	5.0	19.6	99
BFCSI	8	1968	**9,7**	7.0	13.3	77
BFCRS	16	25 648	**7.4**	3.2	16.1	99
DSM	25	44 048	**5.4**	3.3	8.6	98
Period of study conduct (between group *P* value = .13)						
Before 1970	5	48 382	**5.4**	2.0	13.6	99
1970–1980	7	3465	**13.6**	9.2	19.6	93
1980–1990	2	14 880	**2.4**	0.2	21.7	99
1990–2000	26	22 537	**6.9**	4.6	10.3	98
2001–2010	29	39 087	**10.4**	6.3	16.7	98
After 2010	23	5990	**9.0**	5.9	13.3	95
Age group (between group *P* value = .38)						
Adults (>18 years old)	78	106 006	**9.0**	7.0	11.4	98
Elderly (>65 years old)	5	552	**8.5**	6.4	11.	0
Children/adolescents	9	22 883	**4.9**	2.1	11.0	98
Risk of bias (between group *P* value = .85)						
NOS ≤ 5	45	42 202	**8.6**	5.9	12.3	98
NOS > 5	47	92 139	**8.2**	6.0	11.2	99

Table 2. *Continued*

Subgroup/Moderator	Number of Samples	Number of Participants	Prevalence (%)	95% Confidence Interval (CI)		I^2 (%)
				Lower 95% CI	Upper 95% CI	
Main condition[a] (between group *P* value < .001)						
Medical or neurological illness	10	1480	**20.6**	11.5	34.2	95
Bipolar disorder	3	226	**20.1**	9.6	37.3	94
Postpartum psychosis	1	200	**20.0**	NA	NA	NA
Autism	2	564	**11.1**	3.0	33.5	93
Schizophrenia	33	20 276	**9.8**	8.0	12.0	95
Mixed	43	111 595	**5.7**	4.2	7.7	98
Treatment setting[a] (between group *P* value = .003)						
Nonpsychiatric out- or inpatient units	15	4412	**15.8**	8.1	28.4	97
Psychiatric inpatients units	74	129 302	**7.7**	6.0	9.9	99
Psychiatric outpatients services	3	627	**3.2**	1.7	6.1	50
Sample size[a] (between group *P* value < .001)						
<100	17	1069	**20.7**	12.8	31.6	90
≥100	19	2324	**10.9**	8.2	14.3	80
≥200	21	4766	**12.9**	9.7	17	93
≥300	4	1437	**4.4**	1.3	13.7	95
≥400	3	1326	**11.1**	7.0	17.3	88
≥500	12	8424	**6.1**	4.2	9.0	96
≥1000	16	114 995	**2.3**	1.3	3.9	99

Note: Bold values indicates maini analyses.
[a]Country, treatment setting, main underlying condition, and sample size influenced results.

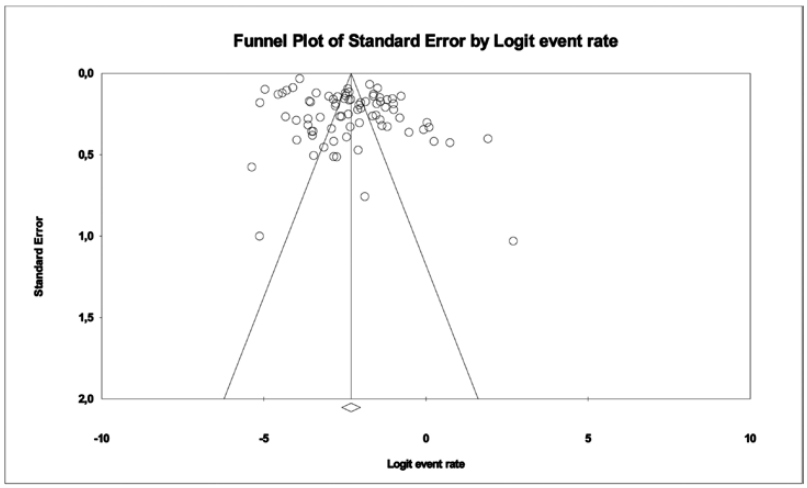

Fig. 2. Funnel plot of meta-analysis of catatonia prevalence in whole included clinical populations (80 samples from 74 studies).

(95% CI = 9.1–17.4) after employing the trim and fill procedure and trimming 12 studies.

Meta-analysis of Catatonia Prevalence, Publication Bias, Heterogeneity, and Categorical Sensitivity Analysis Without Studies Selecting Patients Undergoing ECT or With Elevated CPK Levels

After exclusion of patients undergoing ECT/having elevated CPK, across 72 samples and 109 606 subjects the pooled catatonia prevalence was 8.1% (95% CI = 6.1–10.5). Heterogeneity was high (I^2 = 98%). Publication bias was evident according to Egger's test (intercept 4.8, $P < .01$) and visual funnel plot inspection (supplementary figure 1), and the adjusted point estimate increased after trim and fill analysis (11 studies trimmed) to a catatonia prevalence of 11.3% (95% CI = 8.2–15.3).

In subgroup and sensitivity analyses of studies without ECT/elevated CPK samples the following significant moderators of catatonia prevalence were identified: country ($P < .001$), ranging from Mexico (1.9%, 95% CI = 0.4–8.8, I^2 = 67%, k = 2) to Uganda (48.5%, 95%

CI = NA, I^2 = NA, k = 1); main underlying condition (P < .001), ranging from mixed psychiatric samples (5.7%, 95% CI = 4.2–7.7, I^2 = 98%, k = 43) to medical or neurological illness with no comorbid psychiatric condition (20.6%, 95% CI = 11.5–34.2, I^2 = 95%, k = 10); treatment setting (P = .003), ranging from psychiatric outpatient services (3.2%, 95% CI = 1.7–6.1, I^2 = 50%, k = 3) to nonpsychiatric/medical out- or inpatient services (15.8%, 95% CI = 8.1–28.4, I^2 = 97%, k = 15); sample size (P < .001), ranging from studies with sample sizes >1000 (2.3%, 95% CI = 1.3–3.9, I^2 = 99%, k = 16) to sample sizes <100 (20.7%, 95% CI = 12.8–31.6, I^2 = 90%, k = 17).

In contrast, the following variables did not significantly moderate catatonia prevalence: continent (P = .30), ranging from South America (1.9%, 95% CI = 0.4–8.8, I^2 = 67%, k = 2) to North America (11.1%, 95% CI = 5.0–22.7, I^2 = 99%, k = 8); rating scale/criteria (P = .13), ranging from DSM criteria (5.4%, 95% CI = 3.3–8.6, I^2 = 98%, k = 25) to studies using other than ICD, DSM, BFCSI, BFCRS, or study defined diagnostic criteria (11.9%, 95% CI = 8.7–16.1, I^2 = 96%, k = 23); time of data collection (P = .13), ranging from 1980 to 1990 (2.4%, 95% CI = 0.2–21.7, I^2 = 99%, k = 2) to 1970–1980 (13.6%, 95% CI = 9.2–19.6, I^2 = 93%, k = 7); age group (P = .38), ranging from children/adolescents (4.9%, 95% CI = 2.1–11, I^2 = 98%, k = 9) to adults (9.0%, 95% CI = 7.0–11.4, I^2 = 98%, k = 78).

Meta-regression Analysis of Potential Continuous Variable Moderators, in Samples Without Patients Undergoing ECT/Elevated CPK

The only significant continuous moderator variables of greater catatonia prevalence in the entire sample were smaller sample size (P < .001), and lower percentage of patients with MDD (P = .02) (table 3) Moreover, in the subgroup of studies including patients with conditions other than schizophrenia (k = 65), smaller sample size moderated higher prevalence (P < .001).

Meta-analysis of Catatonia Prevalence, Publication Bias, Heterogeneity in Studies Selecting Patients Undergoing ECT or with Elevated CPK Levels

The overall pooled catatonia prevalence across 8 samples and 1168 subjects was 23.9% (95% CI = 10–46.9, I^2 = 96%). Heterogeneity was high (I^2 = 96%, P < .0001). Publication bias was not evident according to Egger's test (intercept 7.2, P = .18) or visual funnel plot inspection (supplementary figure 2).

Meta-analysis of Catatonia Prevalence in a Restricted Sample of Studies to Yield Low Heterogeneity

After visual inspection of funnel plot of non-ECT subgroup meta-analysis, we progressively excluded outlying studies with highest and lowest values until the pooled catatonia prevalence estimate had low heterogeneity with an I^2 < 50%. Across 19 studies and 7612 subjects, the nonheterogeneous pooled catatonia prevalence was 7.8% (95% CI = 7–8.7, I^2 = 39%) (figure 3).

Discussion

This comprehensive meta-analysis, including 74 studies and 107 304 individuals from 99 independent samples across all continents, showed that the overall pooled, mean prevalence of catatonia was 9.2% among subjects diagnosed with a variety of psychiatric or medical conditions. Meta-regression results indicated that a lower sample size and a lower proportion of patients diagnosed with MDD significantly moderated higher catatonia prevalence in the entire sample. Finally, despite substantial heterogeneity, catatonia prevalence was not significantly affected by year of study conduct throughout a long-time span ranging from 1935 to 2017, as well as a number of varying patient, system, diagnostic, illness, and treatment variables.

Our results confirm that the catatonia syndrome is not rare among both people with severe mental illnesses and medical conditions. In fact, our findings suggest that catatonia may even be more frequent in patients with a medical condition, progressively decreasing through BD, to autism, schizophrenia, and mixed psychiatric illness, with MDD moderating lower catatonia prevalence. Prior studies suggested that comorbid medical conditions in patients with psychiatric disorders,[73] delirium[108] and in medically ill samples, especially the presence of encephalitis and seizure disorder, represented risk factors for catatonia.[109] Our finding that the catatonia prevalence was higher in BD, even more than in schizophrenia or MDD, is consistent with the prior literature,[21,82] with experts underlining the difference between schizophrenia and catatonia as 2 entities,[8,110] and the trans-diagnostic nature across mental and psychiatric conditions.[111] Moreover, although MDD has long been considered one of the conditions related to catatonia the most,[21,108,112] our meta-regression findings suggested MDD as a moderator of lower prevalence of catatonia. However, this result should be interpreted with caution and in light of the absence of "pure" MDD samples precluding isolated sensitivity analysis for this diagnostic subgroup. Furthermore, one potential explanation for the relatively lower catatonia prevalence in samples with more MDD patients may be that with the advent of SGAs for the adjunctive treatment of MDD, doses used for this indication have become much lower than previously when used for psychotic depression or when using FGAs, and the catatonia prevalence in MDD samples may be lowered via a reduced risk for extrapyramidal side effects with low-dose SGA treatment, compared with higher SGA doses when used to treat BD or schizophrenia.

Table 3. Mixed Effect Meta-regression of Moderators of Catatonia Prevalence across All Diagnoses, in Schizophrenia, and in Patients With Other Disorders than Schizophrenia (Excluding 8 Studies Restricted to Patients Undergoing Electroconvulsive Treatment or Having Elevated Creatine Phosphokinase)

	Moderator Variable	Number of Comparisons	β	95% CI		*P* value
All diagnoses	**Sample size**	**92**	**−0.000**	**−0.000**	**−0.000**	**.00009**
	Year of data collection	92	0.000	−0.009	0.027	.36
	Mean age	92	0.006	−0.011	0.024	.48
	% male	92	0.007	−0.009	0.023	.38
	% schizophrenia	92	−0.006	−0.013	0.000	.06
	% mood disorders	92	−0.005	−0.016	0.005	.36
	% SGA	15	−0.004	−0.022	0.013	.66
	% FGA	12	0.006	−0.001	0.020	.59
	%MDD	**74**	**−0.023**	**−0.045**	**−0.002**	**.02**
	%BD	74	0.000	−0.011	0.017	.65
Schizophrenia only	Sample size	33	−0.000	−0.000	0.000	.87
	Year of data collection	33	−0.000	−0.022	0.021	.93
	Mean age	33	0.000	−0.045	0.045	.99
	% male	33	−0.004	−0.034	0.026	.79
	%FGA	5	−0.003	−0.014	0.008	.58
	%SGA	10	−0.017	−0.038	0.002	.09
Other disorders than schizophrenia	**Sample size**	**59**	**−0.000**	**−0.000**	**−0.000**	**.00023**
	Year of data collection	59	0.031	−0.001	0.064	.06
	Mean age	59	0.008	−0.013	0.029	.46
	% male	59	0.009	−0.010	0.029	.35
	% mood disorders	59	−0.006	−0.021	0.009	.43
	%FGA	8	0.010	−0.007	0.028	.25
	%SGA	6	0.012	−0.001	0.025	.07

Note: BD, bipolar disorder; FGA, first-generation antipsychotic; MDD, major depressive disorder; SGA, second-generation antipsychotic; SMI, severe mental illness. Bold *P*-values: $P < .05$. Bold values indicates significant moderators.

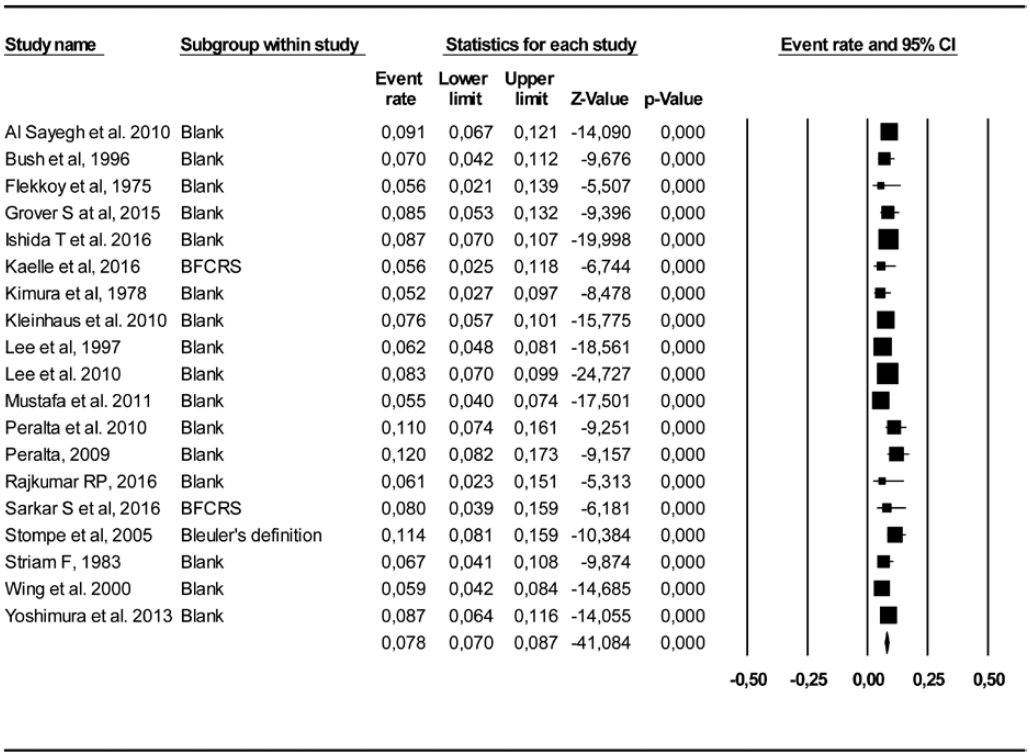

Fig. 3. Forest plot of catatonia prevalence in a subgroup of 19 studies with reduced heterogeneity ($I^2 < 50\%$).

Several limitations of the present meta-analysis need to be considered. These include the limitations of the meta-analyzed sample, such as high heterogeneity of studies, populations, and treatments, as well as assessment and diagnostic strategies for catatonia. Nevertheless, the catatonia prevalence did not seem to be significantly affected by these factors in our meta-regression or sensitivity analyses. Additional limitations that need to be considered when interpreting the results include the presence of publication bias, yet results remained similar after statistical correction for this effect. Furthermore, there was a lack of more specific longitudinal medication-related information, which would have been needed to better disentangle the relationship between antipsychotic and/or other psychotropic medication treatment and catatonia. Moreover, since it may be sometimes difficult to differentiate catatonia from severe EPS or malignant neuroleptic syndrome,[113] we cannot exclude some diagnostic imprecision. However, since all of these biases relate to all studies to a large degree and seem relatively independent of when and where the data were collected, the lack of a time trend difference in the frequency of catatonia seems to be a robust finding, withstanding the heterogeneity and potential biases inherent in the meta-analyzed database. Nevertheless, the fact that smaller sample sizes were related to higher catatonia prevalence indicates the potential of a selection bias in smaller sized studies that focused on more enriched samples for the risk and occurrence of catatonia. Thus, the prevalence estimates may be lower in population based samples, even when including patient subgroups with the diagnoses that have been associated with higher frequencies of catatonia. To address this shortcoming, large studies of representative samples are needed in order to further inform the prevalence range and moderator variables of catatonia. Additionally, under-represented countries with extreme prevalence values may have skewed our results. Moreover, no "pure" sample including only patients with MDD were available, precluding any sensitivity analysis for this pure diagnostic subgroup, and relatively few samples including BD patients, rendering the results in patients with affective disorders potentially less robust. Furthermore, the meta-analyzed data rely on published data, and unpublished results could alter the results. Hence, authors should include information on catatonia prevalence when describing their samples.[6] Moreover, we included populations affected by potentially severe comorbid conditions, such as those with underlying medical disorders, or psychiatric inpatients, or neurological conditions, such as Tourette's syndrome, or nodding syndrome, with frequent comorbid catatonic symptoms.[81,88,102] Moreover, severity of catatonia was rarely reported. Thus, our catatonia prevalence estimate in clinical population may not be representative of patients affected by milder conditions. Nevertheless, we attempted to investigate this possibility by comparing catatonia prevalence estimates in psychiatric outpatient samples (ie, a potential proxy marker of milder illness) with those in inpatient and non-psychiatric samples, finding that psychiatric outpatients had lower rates of catatonia, of 3.2%, ie, almost one third of the pooled overall catatonia prevalence, but only 3 small studies (n = 667) were available capturing such populations. Finally, we only used cross-sectional data in our analyses, thus, any causal relationship between catatonia prevalence and investigated moderators remains to be investigated in prospective studies.

Despite these limitations, this is the first comprehensive meta-analysis of the frequency and correlates of catatonia across diverse psychiatric and medical conditions that indicates that catatonia is not a disappearing clinical condition, as had been suggested before.[19,20] Overall, our data seem to confirm Kahlbaum's introduction of the concept of catatonia, around 150 years after he conceptualized it as a syndrome occurring in different psychiatric and medical conditions.[8] Since catatonia has been associated with greater illness severity in BD[60] and MDD,[25] may recur,[114] has been associated with an increased risk of suicide,[43] and may be life-threatening,[115] it deserves ongoing clinical attention. Moreover, when treated appropriately and not co-occurring with or misdiagnosed as schizophrenia,[111] eg, when managed with BDZs and/or ECT, catatonia generally has a good outcome.[116] In particular, instead of continuing antipsychotics treatment, quick relief from BDZs can actually confirm a diagnosis of catatonia and should encourage an escalation to higher doses of BDZs with a positive response in up to 80% of patients, while nonresponders should prompt referral to undergo ECT to maximize response rates.[110] In order not to miss cases with catatonia, sufficiently sensitive and specific rating scales exist.[16–23] In fact, at least according to our sensitivity analyses, the catatonia prevalences were not significantly different across rating scales used to diagnose catatonia. Thus, clinicians might feel free chose the scale/criteria they are more used to or that they find most practical. The clinical attention and regular screening for catatonia in patients with suggestive symptoms and signs is particularly relevant, as several authors have suggested that catatonia may remain under-recognized due to lack of awareness or symptomatic overlap with core motor/behavioral symptoms of autism, stuporous, negativistic, or melancholic depression, or negative and disorganized symptoms of schizophrenia.[20,117,118]

Taken together, our results suggest that beyond specific study settings, time of data collection, rating scales/criteria used to diagnose catatonia or continent, encompassing data from a wide and comprehensive range of settings and clinical conditions, catatonia is a clinically relevant condition that has remained relatively frequent as a feature of medical and psychiatric disorders, whose prevalence (different to some opinions) does not seem to have decreased over a long period of time. Risk factors appear to include underlying medical or neurological conditions. Additional, prospective cohort studies or detailed

database and register studies are needed to better understand the current prevalence and risk factors for catatonia. Moreover, additional studies are needed to describe the outcome in specific patient subgroups in response to immediate or delayed identification of catatonia as well as to different interventions.

Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin* online.

Acknowledgments

Dr Solmi, Dr stubbs, Dr Fornaro, Dr Monaco, Dr Veronese, Dr Carvalho, Dr Pigato, Dr Roiter, Dr Guaglianone, and Dr Martini have no conflict of interest. Dr Correll has been a consultant and/or advisor to or has received honoraria from: Alkermes, Allergan, Bristol-Myers Squibb, Gerson Lehrman Group, IntraCellular Therapies, Janssen/J&J, LB Pharma, Lundbeck, Medavante, Medscape, Neurocrine, Otsuka, Pfizer, Sunovion, Takeda, and Teva. He has provided expert testimony for Bristol-Myers Squibb, Janssen, and Otsuka. He served on a Data Safety Monitoring Board for Lundbeck and Pfizer. Dr Correll received grant support from Takeda.

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