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Risk Factors for Suicidality in Patients With Schizophrenia: A Systematic Review, Meta-analysis, and Meta-regression of 96 Studies

Ryan Michael Cassidy[1,6], Fang Yang[2,6], Flávio Kapczinski[3], and Ives Cavalcante Passos*[,4,5]

[1]McGovern Medical School, The University of Texas Health Science Center at Houston, Houston, TX; [2]Department of Psychiatry and Behavioral Sciences, The University of Texas Health Science Center at Houston, Houston, TX; [3]Department of Psychiatry and Behavioural Neurosciences, McMaster University, Hamilton, ON, Canada; [4]Bipolar Disorder Program and Laboratory of Molecular Psychiatry, Federal University of Rio Grande do Sul, Porto Alegre, Brazil; [5]Graduation Program in Psychiatry and Department of Psychiatry, Federal University of Rio Grande do Sul (UFRGS), Porto Alegre, Brazil

[6]These authors contributed equally to the article.

*To whom correspondence should be addressed; Federal University of Rio Grande do Sul, Avenida Ramiro Barcelos, 2350, Porto Alegre-RS 90035–903, Brazil; tel: +55-512-101-8845, fax: +55 51 33598846, e-mail: ivescp1@gmail.com

The lifetime risk of suicide and suicide attempt in patients with schizophrenia are 5% and 25%–50%, respectively. The current meta-analysis aims to determine risk factors associated with suicidality in subjects with schizophrenia. We searched Pubmed, Web of Science, EMBASE, and the reference lists of included studies. Inclusion criteria were met if an article reported a dichotomous sample of patients with schizophrenia with suicidal ideation, attempted suicide, or suicide compared to patients without. We also performed a cohort study meta-analysis as a supplemental analysis. A total of 96 studies with 80 488 participants were included in our analysis. Depressive symptoms ($P < .0001$), Positive and Negative Symptom Scale (PANSS) general score ($P < .0001$) and number of psychiatric hospitalizations ($P < .0001$) were higher in patients with suicide ideation. History of alcohol use ($P = .0001$), family history of psychiatric illness ($P < .0001$), physical comorbidity ($P < .0001$), history of depression ($P < .0001$), family history of suicide ($P < .0001$), history of drug use ($P = .0024$), history of tobacco use ($P = .0034$), being white ($P = .0022$), and depressive symptoms ($P < .0001$) were the most consistent variables associated with suicide attempts. The first two were also significant in the cohort meta-analysis. Being male ($P = .0005$), history of attempted suicide ($P < .0001$), younger age ($P = .0266$), higher intelligence quotient ($P < .0001$), poor adherence to treatment ($P < .0001$), and hopelessness ($P < .0001$) were the most consistently associated with suicide. The first three were also significant in the cohort meta-analysis. Our findings may help with future development of preventive strategies to combat suicide. Future studies may combine the above-mentioned variables by using multivariate predictive analysis techniques to objectively stratify suicidality in schizophrenia.

Key words: suicide/meta-analysis/risk factors/schizophrenia

Introduction

Suicide is the 10th leading cause of death in the United States, with 41 149 suicides in 2013 at a rate of 13/100 000 persons.[1] A total of 1.3 million individuals older than 18 attempted suicide that same year.[2] The prevalence of schizophrenia is estimated to be around 1% worldwide,[3] and a recent meta-analysis has identified a lifetime risk of suicide of 5% in this population.[4,5] It is also known that 25%–50% of patients with schizophrenia *attempt* suicide in their lifetime.[6] This represents a 50–100-fold increase in suicidality as compared to general population. However, suicide is a highly preventable event,[7] and there are preventative strategies, such as cognitive behavioral therapy and clozapine, to reduce it in patients with schizophrenia.[8]

Suicide is sometimes viewed as an extreme response to a catastrophic event, such as loss of a close relative. However, many individuals, including patients with schizophrenia, go through these kinds of stressors and yet they do not attempt suicide.[9] Consequently, a growing body of knowledge has put forward several risk factors associated with patients with schizophrenia that attempt suicide.[5,10,11] Particularly, the previous meta-analysis assessed categorical risk factors for suicide in patients with schizophrenia.[12] They analyzed 26 articles and identified 7 categorical risk factors associated with increased suicide risk, which were previous depressive disorders, previous suicide attempts,

drug misuse, agitation or motor restlessness, fear of mental disintegration, poor treatment adherence, and recent loss. Since the publication of this meta-analysis in 2005, many large scale studies evaluating schizophrenia have been published internationally. Therefore, in this study, our aim is to provide a systematic review and meta-analysis of both categorical and continuous risk factors for suicidal ideation, suicide attempts, and suicide. We will also explore sources of heterogeneity between studies using meta-regression analysis.

Methods

Guidelines

The present study was registered at PROSPERO (CRD42015027027). We utilized the guidelines described by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.[13] The PRISMA checklist we employed can be found in supplementary table 1 and the flow diagram in figure 1. Further, since we examined observational studies, we also structured our selection criteria and statistical analysis in concordance with the MOOSE guidelines for meta-analyses and systematic reviews of observational studies.[14] There are 3 methodological categories of observational studies which we chose to include: prospective and retrospective cohort studies where patients with the risk factor (in this case, schizophrenia) are followed until an outcome occurs (suicidal behavior) within a certain time frame; case-control studies, where patients are included based upon an outcome and matched by demographic characteristics to another patient without that outcome; and, cross-sectional studies, where patients with a risk factor are assessed a single time for presence of the outcome.

Search Strategy

We searched Pubmed, Web of Science and EMBASE with the following search terms: ("Schizophrenia" OR "Schizophrenias" OR "Schizophrenic Disorders" OR

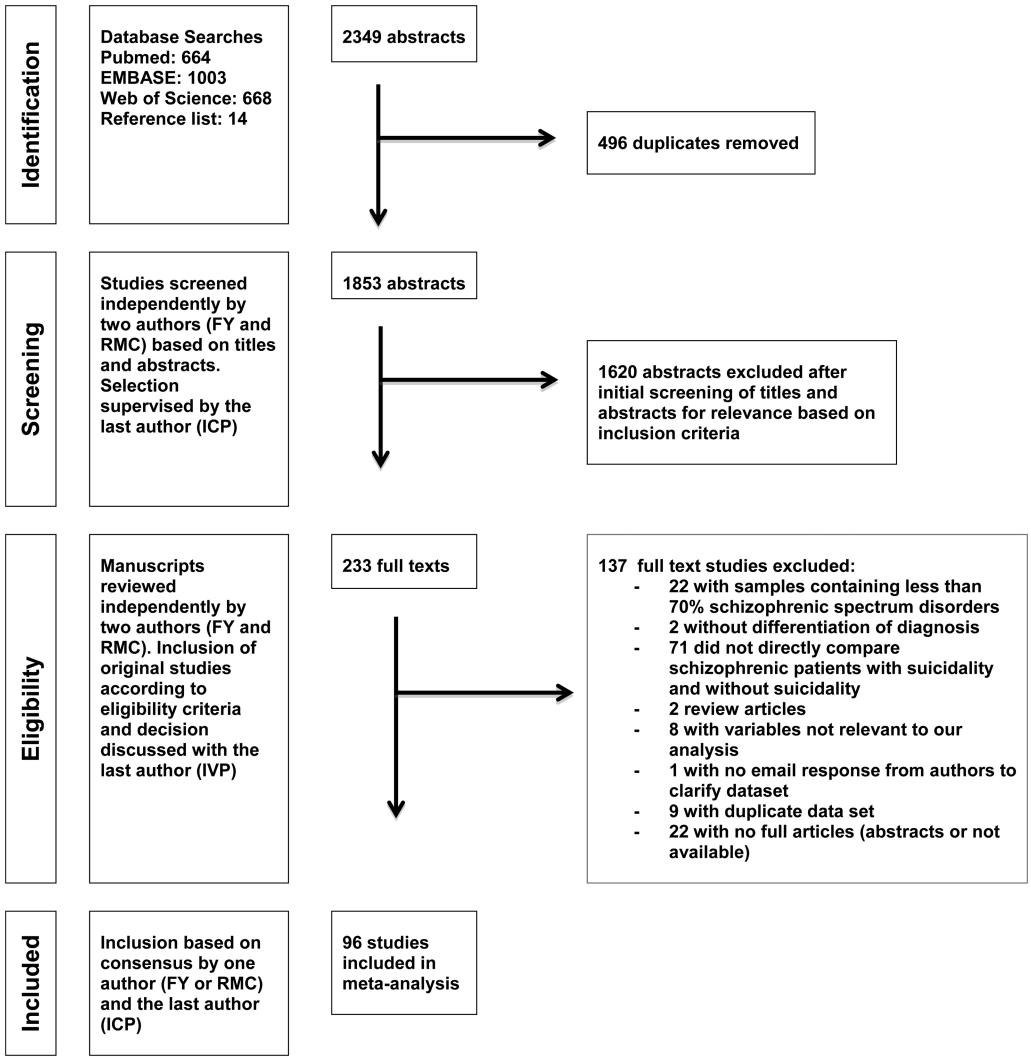

Fig. 1. Flowchart of review process and study selection.

"Schizophrenic Disorder" OR "Dementia Praecox") AND ("Suicide" OR "suicides") AND ("Risk Factors" OR "Risk Factor") from January 1, 1960 to December 18, 2016. Medical Subject Heading (MeSH) terms were used in PubMed and Emtree terms were used in Embase. These were loaded onto EndNote online to remove duplicates. We also searched the reference lists of included studies. Two researchers (R.M.C. and F.Y.) independently screened and selected titles and abstracts for full-text inclusion, with disagreements mediated by I.C.P. who made the final decision. We sought out translated versions of articles in languages which none of the authors spoke. We did not search the grey literature, due to the large dataset we predicted acquiring with the above search strategy.

Selection Criteria

Inclusion criteria were met if an article reported the following: a dichotomous sample of patients with schizophrenia with suicidality (suicidal ideation, attempted suicide, or suicide) compared to schizophrenic patients without suicidality; at least 70% of the sample had a diagnosis of schizophrenia using either International Classification of Disease or Diagnostic and Statistical Manual of Mental Disorders criteria. All 3 kinds of observational studies (cohort, cross-sectional, and case-control) were included. Review articles and studies performed on children and adolescents were excluded. If 2 or more studies reported the same risk factor within the same data set, we included only the more recent one.

Data Extraction

Each article was reviewed and the information compiled into an Excel workbook. We used the online version of EndNote to remove duplicate data. The following variables were extracted; first author; publication year; primary psychiatric diagnosis; diagnostic tool; study design; suicidality (suicidal ideation, attempted suicide, or suicide); continent; latitude of city where study was performed; number of patients in each group; sex; age; race; antipsychotic use (typical vs atypical); physical comorbidity; rural inhabitance; employment status; child status; marriage status; whether the patient lived alone; family history of suicide, psychiatric disorders, alcohol abuse, depressive symptoms, and schizophrenia; personal history of attempted suicide, suicidal ideation, depressive symptoms, alcohol abuse, tobacco use, and illicit drug use; insight; current delusions; current hallucinations; presence of flat affect; psychomotor agitation; worthlessness; hopelessness; poor compliance with treatment; aggressiveness; age of onset of illness; duration of illness; number of psychiatric hospitalizations; intelligence quotient (IQ); years of education; PANSS scores; Hamilton Depression Rating Scale (HAM-D); Beck Depression Inventory (BDI); Newcastle-Ottawa Quality Assessment Scale (NOQAS) score. For illness length, data were converted to years if reported as months. Child status was ultimately excluded as only one study reported this variable.

Authors were contacted for missing information, for mean and SD of continuous variables if they were reported as median and interquartile range, and for separated outcomes data if the study grouped 2 outcomes together (suicide ideation and suicide attempts, or suicide attempts and suicide).

Statistical Analysis

We began with meta-analysis of any risk factor which was reported in 2 or more studies, utilizing the metafor package (Version 1.9–8) in R (Version R 3.3.1) and R Studio (Version 0.99.902). A random-effects model with restricted maximum-likelihood estimator was used to synthesize the effect size across studies. This model incorporates both within-study variability and between-study variability.[15,16] The OR was used to assess the effect size for categorical risk factors because of the inclusion of case-control studies in the analysis.[15] The standardized mean difference (SMD) was used to assess the effect size for continuous risk factors.[15] SMD was calculated by use of Cohen's *d*. The significance level for this meta-analysis model was 0.05.[15] For SMD, an effect size of 0.2 is considered a low effect, whereas 0.5 a moderate effect and 0.8 or more a large effect.[17]

Heterogeneity, Bias, and Quality Assessment

Two researchers (F.Y. and R.M.C.) rated each article with the NOQAS to evaluate the risk of bias and quality of the study.[18] Disagreements in score were resolved with discussion between F.Y., R.M.C., and I.C.P. Egger's linear regression test was used to assess for asymmetry of the funnel plot in any case where 3 or more studies were included.[19] If the resulting *P* value is less than .1, we assumed asymmetry which may indicate publication bias. To account for this, we then employed the Duval and Tweedie's trim and fill method and reported whether a significant effect persists. We also used the leave-one-out function[15] for sensitivity analyses. This method consists of the removal of one study at a time from the dataset to run the meta-analysis. This analysis tests if the effect size of the meta-analysis is driven by one study. We used the Q statistic to test the existence of heterogeneity and I^2 to assess the proportion of total variability due to heterogeneity.[20] An I^2 value of about 25% could be regarded as low, about 50% as moderate, and about 75% as high.[20] We used τ^2 to estimate the total amount of heterogeneity.[20]

Meta-regression Analysis

We further explored sources of heterogeneity in studies using meta-regression analysis.[21,22] For each risk factor with a significant effect size associated with suicidality, we performed univariate meta-regression with each of

the following moderators: mean age of the total sample, mean length of illness of the total sample, region where the study was performed, study design (cross-sectional, cohort, or case-control), latitude of the city where the study was performed, and NOQAS score. To correct for repeated sampling, we employed the Knapp & Hartung adjustment.[23] When 2 or more moderators accounted for a significant amount of heterogeneity, a multivariate meta-regression with these moderators was conducted.[15] The pseudo-R^2 statistic represents the variance accounted for by the model; this indicates what percentage of all heterogeneity is accounted for by the confounding effect of the covariates. Cohort studies explore the relationship between exposure and outcome and aid in identification of causal associations. Therefore, we ran a supplemental meta-analysis only with the prospective and retrospective cohort studies in order to provide further evidence of the robustness of the risk factors identified through this meta-analysis.

Results

We included 96 studies with 80 488 participants in our analysis. Figure 1 shows the study selection process. Quality of studies and characteristics of included studies are described in supplementary table 2.

Suicide—Categorical Risk Factors

For the categorical risk factors, poor adherence to treatment ($P < .0001$), history of attempted suicide ($P < .0001$), worthlessness ($P < .0001$), hopelessness ($P < .0001$), being male ($P = .0005$), being white ($P = .0105$), history of tobacco use ($P = .0169$), and history of alcohol use ($P = .0378$) were significantly associated with patients with schizophrenia who committed suicide (table 1). Family history of alcohol use ($P = .0590$), sleep disturbance ($P = .0662$), and history of depression ($P = .0968$) trended toward significance. Table 1 shows study heterogeneity and supplementary figures 1–8 show the forest plots of significant categorical risk factors for suicide.

Egger's test revealed a publication bias for history of attempted suicide ($P = .0168$), and being white ($P = .0036$). It could not be calculated for worthlessness because only 2 studies reported these variables.[24,25] Duval and Tweedie's trim and fill method was performed on history of attempted suicide (OR = 2.73; CI: 1.96–3.81; $P < .0001$ with 5 studies estimated on the left side) and was still determined to be significant. It was performed on being white (OR = 2.98; CI: 0.87–10.23; $P = .0822$ with 2 studies on the left) and was no longer significant.

The significance of the effect size remained robust when leave-one-out models were used for poor compliance, history of attempted suicide, hopelessness, and being male. Significance testing revealed the effect size to be nonsignificant after removing 1 study history of tobacco use (supplementary table 5), any of 6 studies for history of alcohol use (supplementary table 6), 1 study for worthlessness (supplementary table 7), and 1 study for being white (supplementary table 8).

Suicide—Continuous Variables

For the continuous risk factors, IQ was higher ($P < .0001$) in patients with schizophrenia who committed suicide, illness length was shorter ($P = .0069$), and patients were younger ($P = .0266$) (table 1). Table 1 also shows study heterogeneity and supplementary figures 9–11 show the forest plots.

Egger's test revealed a potential publication bias for illness length ($P = .0304$). It could not be calculated for IQ because only 2 studies reported this variable.[26,27] Duval and Tweedie's trim and fill method results did not change the parameter estimates for illness length.

The significance of the effect size remained robust when leave-one-out models were used for IQ and illness length. Significance testing revealed the effect size to be nonsignificant after removing 1 study for age (supplementary table 9).

Suicide—Meta-regression Analysis

In our investigation of sources of heterogeneity using univariate meta-regression analyses, we found that for male gender as a risk factor, NOQAS score, region, and mean age of the total sample accounted for heterogeneity. For being male, NOQAS score negatively correlated ($b = -0.1294$, $P = .0197$), studies conducted in Asia were less associated ($b = -0.7589$, $P = .0131$), and a higher mean age of the total sample positively correlated ($b = 0.0230$, $P = .0257$) with the increased risk of suicide (supplementary table 3). The multivariate meta-regression of these moderators accounted for 100% (pseudo-R^2) of the heterogeneity ($F = 15.6286$, $P = .0036$, $k = 16$), but none of the moderators retained a significant effect on the association by themselves (supplementary table 4). Univariate meta-regression did not reveal a significant moderator effect on any other risk factor.

Attempted Suicide—Categorical Variables

For categorical risk factors, physical comorbidity ($P < .0001$), history of depression ($P < .0001$), family history of psychiatric illness ($P < .0001$), family history of suicide ($P < .0001$), history of attempted suicide ($P < .0001$), hopelessness ($P = .0001$), history of alcohol use ($P = .0001$), history of drug use ($P = .0024$), history of tobacco use ($P = .0034$), and being white ($P = .0022$) were associated with patients with schizophrenia who attempted suicide (table 2). Being male ($P = .0417$) and living alone ($P = .0338$) were found to have a reduced risk of attempted suicide (table 2). Table 2 also shows study heterogeneity and supplementary figures 12–23 show the forest plots.

Table 1. Meta-analysis of Risk Factors of Suicide in Schizophrenia

Risk Factors	Studies, *n*	Suicide, *n*	Not Suicide, *n*	Effect Size (95% CI)	*P* Value	Heterogeneity			Egger's Test: *Z* Statistic (*P* Value)
						Q Statistic (df; *P* value)	t^2	I^2	
Poor adherence[a]	4	174	205	3.01 (1.87, 4.84)	<.0001	1.6113 (3; *P* = .6568)	0	0.00%	−0.2767 (*P* = .7820)
IQ[b]	2	90	90	0.65 (0.35, 0.95)	<.0001	0.0244 (1; *P* = .8758)	0	0.00%	
History of attempted suicide[a]	24	1201	28 743	3.36 (2.49, 4.53)	<.0001	61.2695 (23; *P* < .0001	0.3177	65.21%	2.3900 (*P* = .0168)
Worthlessness[a]	2	93	5281	6.32 (2.67, 14.96)	<.0001	0.1458 (1; *P* = .7026)	0	0.00%	
Hopelessness[a]	7	261	5838	4.64 (2.24, 9.63)	<.0001	11.5576 (6; *P* = .0726)	0.4326	48.39%	1.5910 (*P* = .1116)
Male[a]	35	1625	35 097	1.34 (1.14, 1.58)	.0005	48.0013 (34; *P* = .0562)	0.0636	28.26%	0.1095 (*P* = .9128)
Illness length[b]	5	277	26 710	−2.62 (−4.52, −0.72)	.0069	284.6305 (4; *P* < .0001)	4.5249	99.08%	−2.1645 (*P* = .0304)
White[a]	6	155	959	4.95 (1.45, 16.81)	.0105	17.1912 (5; *P* = .0042)	1.2864	66.02%	2.9096 (*P* = .0036)
History of tobacco use[a]	3	260	21 496	1.40 (1.06, 1.85)	.0169	0.2050 (2; *P* = .9026)	0	0.00%	−0.2774 (*P* = .7815)
Age[b]	19	979	28 681	−0.24 (−0.45, −0.03)	.0266	116.4530 (18; *P* < .0001)	0.1712	84.72%	−0.2742 (*P* = .7840)
History of alcohol use[a]	10	607	4711	1.28 (1.01, 1.63)	.0378	13.5357 (9; *P* = .1398)	0.0051	3.25%	1.0997 (*P* = .2715)
Family history of alcohol use[a]	3	118	578	2.53 (0.97, 6.62)	.0590	2.2170 (2; *P* = .3301)	0.1106	14.77%	−1.3864 (*P* = .1656)
Sleep disturbance[a]	4	109	126	2.25 (0.95, 5.33)	.0662	4.7678 (3; *P* = .1896	0.2423	31.25%	2.1690 (*P* = .0301)
History of depression[a]	8	371	5869	2.42 (0.85, 6.84)	.0968	32.2221 (7; *P* < .0001)	1.8172	86.15%	0.1338 (*P* = .8936)
History of drug use[a]	13	739	13 228	1.18 (0.66, 2.12)	.5729	92.2153 (12; *P* < .0001)	0.8389	82.18%	1.7171 (p=0.0860)
History of suicidal ideation[a]	2	151	435	7.42 (0.53, 103.98)	.1368	5.8024 (1; *P* = .0160)	3.0463	82.77%	
Living alone[a]	12	665	4946	1.33 (0.91, 1.95)	.1426	25.1733 (11; *P* = .0086)	0.2283	58.26%	2.0218 (*P* = .0432)
Unemployed[a]	15	640	3079	1.14 (0.85, 1.55)	.3807	24.3695 (14; *P* = .0413)	0.1385	44.24%	1.1292 (*P* = .2588)
Number of psychiatric hospitalizations[b]	3	168	168	0.46 (−0.18, 1.09)	.1576	17.5211 (2; *P* = .0002)	0.2661	86.79%	0.8833 (*P* = .3771)
PANSS positive[b]	2	34	1388	−0.28 (−0.76, 0.17)	.2165	1.3262 (1; *P* = .2495]	0.0364	24.60%	
Rural[a]	2	134	361	0.68 (0.35, 1.32)	.2509	1.2781 (1; *P* = .2583)	0.0534	21.76%	
Flat affect[a]	4	128	5383	1.89 (0.55, 6.51)	.3138	17.4297 (3; *P* = .0006)	1.2827	80.89%	−0.4845 (*P* = .6281)
Black[a]	3	133	520	0.59 (0.20, 1.71)	.3300	3.0308 (2; *P* = .2197)	0.3923	39.77%	0.1797(*P* = .8574)
Physical comorbidity[a]	4	186	807	0.67 (0.25, 1.78)	.4163	8.0799 (3; *P* = .0444)	0.5754	63.12%	0.3861 (*P* = .6994)
PANSS negative[b]	2	34	1388	−0.18 (−0.61, 0.26)	.4262	1.2193 (1; *P* = .2695)	0.0252	17.99%	
Family history of depression[a]	2	96	84	1.93 (0.29, 12.72)	.4959	0.1739 (1; *P* = .6766)	0	0.00%	
Age of onset[b]	9	477	803	0.21 (−0.39, 0.82)	.4917	89.3466 (8; *P* < .0001)	0.8138	95.44%	0.6876 (*P* = .4917)
Agitation[a]	4	134	247	1.20 (0.64, 2.25)	.5752	4.4234 (3; *P* = .2192)	0.1361	32.39%	1.8045 (*P* = .0712)
Married[a]	16	753	6434	0.89 (0.61, 1.31)	.5671	34.9047 (15; *P* = .0025)	0.3128	59.36%	−0.2201 (*P* = .8258)
Delusions[a]	7	243	5956	0.99 (0.35, 2.79)	.9889	34.9338 (6; *P* < .0001)	1.5323	85.97%	3.2782 (*P* = .0010)
Family history of suicide[a]	9	476	898	1.25 (0.54, 2.89)	.6069	22.0533 (8; *P* = .0048)	0.9441	63.53%	−0.6856 (*P* = .4929)
Family history of psychiatric illness[a]	5	199	650	0.90 (0.59, 1.38)	.6183	3.4881 (4; *P* = .4797)	0	0.00%	0.1665 (*P* = .8677)
Use of typical antipsychotics[a]	3	135	5657	0.48 (0.17, 1.33)	.1591	3.8897 (2; *P* = .1430)	0.3940	48.65%	1.9015 (*P* = .0572)
Hallucinations[a]	10	457	957	1.10 (0.63, 1.91)	.7413	31.3071 (9; *P* = .0003)	0.5312	71.56%	2.9174 (*P* = .0035)
Aggression[a]	7	190	5991	0.92 (0.47, 1.83)	.8153	10.5588 (6; *P* = .1030)	0.2194	27.40%	−0.1335 (*P* = .8938)
Family history of schizophrenia[a]	6	285	1022	0.96 (0.64, 1.44)	.8317	0.7216 (5; *P* = .9818)	0	0.00%	−0.2323 (*P* = .8163)
Years of education[b]	2	134	361	−0.02 (−0.37, 0.34)	.9294	1.8531 (1; *P* = .1734)	0.0320	46.04%	

Note: df, Degrees of freedom; IQ, intelligence quotient; PANSS, Positive and Negative Symptom Scale.
[a]The effect size used was odds ratio.
[b]The effect size used was standardized mean difference.

Table 2. Meta-analysis of Risk Factors of Suicide Attempts in Schizophrenia

Risk Factors	Studies, *n*	Prior SA, *n*	No Prior SA, *n*	Effect Size (95% CI)	*P* Value	Heterogeneity			Egger's Test: *Z* Statistic (*P* Value)
						Q Statistic (*df*; *P* Value)	I^2	I^2	
History of depression[a]	3	155	334	4.13 (2.61, 6.54)	<.0001	2.2734 (2; *P* = .3209)	0.0259	13.72%	−0.6704 (*P* = .5026)
BDI score[b]	6	265	407	0.54 (0.29, 0.79)	<.0001	9.8962 (5; *P* = .0782)	0.0461	49.07%	1.2967 (*P* = .1947)
Physical comorbidity[a]	4	1264	1893	1.53 (1.27, 1.84)	<.0001	2.8652 (3; *P* = .4129)	0	0.00%	−0.3067 (*P* = .7590)
History of attempted suicide[a]	5	644	27420	3.11 (1.75, 5.54)	<.0001	22.3619 (4; *P* = .0002)	0.3434	85.44%	−3.3128 (*P* = .0009)
Number of psychiatric hospitalizations[b]	15	1279	1423	0.45 (0.30, 0.60)	<.0001	36.7025 (14; *P* = .0008)	0.0491	58.08%	2.2791 (*P* = .0227)
Family history of suicide[a]	10	373	983	2.11 (1.48, 3.02)	<.0001	8.6690 (9; *P* = .4684)	0.0251	7.45%	0.7545 (*P* = .4505)
Family history psychiatric illness[a]	11	579	1869	1.77 (1.43, 2.19); 1.64 (1.31, 2.05)	<.0001	10.7701 (10; *P* = .3757)	0.0138	9.78%	−0.0305 (*P* = .9757)
Hopelessness[a]	3	178	352	2.17 (1.46, 3.23)	.0001	1.7830 (2; *P* = .4100)	0	0.00%	−1.2856 (*P* = .1986)
History of alcohol use[a]	19	3175	3857	1.66 (1.28, 2.15)	.0001	60.5959 (18; *P* < .0001)	0.1686	59.96%	0.6753 (*P* = .4995)
Age of onset[b]	26	2775	13204	−0.14 (−0.27, −0.01)	.0397	436.9181 (25; *P* < .0001)	0.0848	81.97%	2.1643 (*P* = .0304)
Being white[a]	9	700	1214	1.46 (1.15, 1.86)	.0022	3.8877 (8; *P* = .8671)	0	000.00%	0.0212 (*P* = .9831)
History of drug use[a]	21	3292	4243	1.48 (1.15, 1.90)	.0024	72.7189 (20; *P* < .0001)	0.1733	63.02%	−1.4307 (*P* = .1525)
History of tobacco use[a]	11	1228	19111	1.38 (1.11, 1.71)	.0034	12.6102 (10; *P* = .2463)	0.0144	10.88%	0.4615 (*P* = .6444)
Living alone[a]	4	583	707	0.75 (0.58, 0.98)	.0338	0.6034 (3; *P* = .8957)	0	0.00%	−0.4714 (*P* = .6373)
Being male[a]	44	4698	34206	0.89 (0.79, 1.00)	.0417	62.5672 (43; *P* = .0272)	0.0346	29.53%	0.4676 (*P* = .6401)
PANSS positive[b]	19	1341	2275	0.12 (−0.02, 0.26)	.0967	39.6944 (18; *P* = .0023)	0.0497	56.66%	0.2668 (*P* = .7896)
Use of atypical antipsychotics[a]	5	648	1212	0.54 (0.26, 1.14)	.104	25.8973 (4; *P* < .0001)	0.5972	86.74%	0.1465(*P* = .8835)
Rural[a]	2	121	229	0.59 (0.32, 1.12)	.1084	0.0793 (1; *P* = .7782)	0	0.00%	
Family history of alcohol use[a]	2	87	197	2.43 (0.68, 8.67)	.17	0.0173 (1; *P* = .8955)	0	0.00%	
Unemployed[a]	12	1339	10197	1.09 (0.91, 1.31)	.3375	17.4750 (11; *P* = .0946)	0.0069	6.54%	−0.9679 (*P* = .3331)
Age[b]	37	3534	23755	−0.04 (−0.11, 0.04)	.3564	86.5350 (36; *P* < .0001)	0.0247	51.99%	−0.5574 (*P* = .5772)
Married[a]	16	1122	2076	1.14 (0.84, 1.56)	.4030	28.1752 (15; *P* = .0205)	0.1705	50.54%	0.4975 (*P* = 6188)
Years of education[b]	10	968	2691	−0.04 (−0.12, 0.05)	.4103	5.7718 (9; *P* = .7625)	0	0.00%	−1.7170 (*P* = .0860)
Use of typical antipsychotic[a]	5	292	915	1.27 (0.68, 2.37)	.4494	9.1816 (4; *P* = .0567)	0.2903	59.61%	1.5665 (*P* = .1172)
Insight[a]	2	104	174	0.21 (−0.38, 0.79)	.4899	5.2865 (1; *P* = .0215)	0.1434	81.08%	
Family history of depression[a]	2	87	197	1.27 (0.64, 2.53)	.4921	0.0441 (1; *P* = .8337)	0	0.00%	
PANSS negative[b]	19	1341	2275	−0.04 (−0.17, 0.09)	.5038	38.0963 (18; *P* = .0038)	0.0384	50.30%	0.4695 (*P* = .6387)
Family history of schizophrenia[a]	3	125	669	1.31 (0.53, 3.25)	.5598	4.7429 (2; *P* = .0933)	0.3216	54.71%	1.2808 (*P* = .2003)
HAM-D[b]	5	233	943	0.14 (−0.39, 0.66)	.6047	48.9028 (4; *P* < .0001)	0.3121	90.92%	0.2547 (*P* = .7990)
Being black[a]	2	75	59	1.45 (0.31, 6.78)	.6338	0.0218 (1; *P* = .8826)	0	0.00%	
Poor adherence[a]	2	101	149	0.74 (0.09, 6.09)	.7804	15.2425 (1; *P* < .0001)	2.1598	93.44%	
Delusions[a]	3	143	623	0.86 (0.14, 5.26)	.872	24.2394 (2; *P* < .0001)	2.3357	91.65%	−0.4341 (*P* = .6642)
Hallucinations[a]	2	73	543	1.10 (0.23, 5.17)	.9064	8.5531 (1; *P* = .0034)	1.1055	88.31%	
Illness length[b]	22	1962	30076	0.01 (−0.22, 0.25)	.9114	264.1502 (22; *P* < .0001)	0.2903	93.94%	0.2400 (*P* = .8103)
PANSS general[b]	10	960	766	0.00 (−0.13, 0.13)	.9855	4.8599 (9; *P* = .8489)	0	0.00%	−0.1461 (*P* = .8838)

Note: BDI, Beck Depression Inventory; df, Degrees of freedom; HAM-D, Hamilton Depression Rating Scale; PANSS, Positive and Negative Symptom Scale; SA, suicide attempt(s).

[a]The effect size used was odds ratio.

[b]The effect size used was standardized mean difference.

Egger's test revealed a potential publication bias for history of attempted suicide (P = .0009). Duval and Tweedie's trim and fill method results did not change the parameter estimates for history of attempted suicide.

By using leave-one-out models, significance testing revealed the effect size to be nonsignificant after removing one study for hopelessness (supplementary table 10), either of 2 studies for living alone (supplementary table 11) and 18 studies for being male (supplementary table 12). The significance of the effect size remained robust when leave-one-out models were used for the other risk factors.

Attempted Suicide—Continuous Variables

For continuous risk factors, number of psychiatric hospitalizations (P < .0001) and BDI score (P < .0001) were higher in patients with schizophrenia who attempted suicide, while age of onset (P = .0397) was lower (table 2). PANSS positive score trended toward significance (P = .0967). Table 2 also shows study heterogeneity and supplementary figures 24–26 show the forest plots.

Egger's test revealed a potential publication bias for number of psychiatric hospitalizations (P = .0227) and age of onset (P = .0304). Duval and Tweedie's trim and fill method results did not change the parameter estimates for number of psychiatric hospitalizations or age of onset.

In leave-one-out models, significance testing revealed the effect size to be nonsignificant after removing any of the 3 studies for age of onset (supplementary table 13). The significance of the effect size remained robust when leave-one-out model was applied for other 2 continuous factors.

Attempted Suicide—Meta-regression Analysis

In our investigation of sources of heterogeneity using univariate meta-regression analyses, we found that for physical comorbidity, the mean age of the total sample was positively associated (b = 0.1977; P = .0474) with an increased risk for suicide attempt. For family history of psychiatric disorders, studies conducted in Africa were less associated (b = −0.8841; P = .0102) and studies conducted in Oceania were more associated (b = 0.5017; P = .0477) with an increased risk of suicide attempt. For history of drug use, NOQAS score was positively associated (b = 0.1271; P = .0239) with the risk of suicide attempt. For history of tobacco use, NOQAS score was positively associated (b = 0.1328; P = .0153) with the risk of suicide attempt. For being male, studies conducted at the lower latitudes were associated (b = −0.0074; P = .0022) with an increased risk of suicide attempt (supplementary table 3). Univariate meta-regression did not reveal a significant moderator effect on any other risk factor. Multivariate meta-regression was not performed since no risk factor had more than one moderator with a significant effect.

Suicide Ideation

For the categorical risk factors, no variable was significantly associated with suicidal ideation (table 3). For the continuous risk factors, HAM-D score (P < .0001), BDI score (P < .0001), PANSS general score (P < .0001), and number of psychiatric hospitalizations (P < .0001) were higher in schizophrenic patients with suicidal ideation (table 3). A higher PANSS positive score (0.0668) trended toward significance. Table 3 also shows study heterogeneity and supplementary figures 27 and 28 show the forest plots.

Egger's test did not reveal publication bias for any risk factor.

The significance of the effect size remained robust when leave-one-out models were used for each of these variables. Univariate meta-regression did not reveal a significant moderator effect on any risk factor.

Supplemental Analysis: Meta-analysis of Cohort Studies

As cross-sectional or case-control studies only delineate the association of variables with suicidality, we further performed a supplemental meta-analysis including only cohort studies to explore potential causality. We included 6 cohort studies for attempted suicide, and 9 studies for suicide (supplementary table 14). The analyses showed that being male (P = .0003), history of suicide attempts (P = .0034), history of tobacco use (P = .0401), younger age of onset (P = .0404), shorter disease length (P = .0058), younger age (P = .0014) are predictive for suicide (supplementary table 15). For suicide attempts, predictive factors include history of attempted suicide (P < .0001), history of alcohol use (P = .0052), and family history of psychiatric illness (P = .0007) and younger age of onset (P = .0063) (supplementary table 16). Supplementary figures 29–34 show the forest plots for suicide, supplementary figures 35–38 show forest plots for suicide attempt.

Discussion

This is the first meta-analysis and meta-regression analysis of risk factors associated to suicide ideation and suicide attempts in patients with schizophrenia. It is also the first meta-analysis and meta-regression analysis of continuous risk factors associated to suicide in schizophrenia. Furthermore, we also updated a previous meta-analysis published in 2005 that assessed only categorical risk factors for suicide in patients with schizophrenia.[12] For the first time, we used strategies to explore heterogeneity and bias, namely: meta-regression, leave-one-out, Egger's test, and trim and fill and performed a separate analysis only with cohort studies.

Table 3. Meta-analysis of Risk Factors of Suicide Ideation in Schizophrenia

Risk Factors	Studies, *n*	SI, *n*	No SI, *n*	Effect Size (95% CI)	*P* Value	Heterogeneity			Egger's Test: *Z* Statistic (*P* Value)
						Q Statistic (*df*; *P* Value)	$\hat{\tau}^2$	I^2	
BDI[b]	2	33	118	1.58 (1.16, 2.01)	<.0001	0.1666 (1; .6832)	0	0.00%	
Number of psychiatric hospitalizations[a]	2	227	226	0.46 (0.27, 0.66)	<.0001	0.1688 (1; .6811)	0	0.00%	
HAM-D[b]	3	345	660	0.77 (0.63, 0.92)	<.0001	0.0223 (2; .9889)	0	0.00%	0.0148 (*P* = .9882)
PANSS general[b]	4	190	577	0.65 (0.48, 0.82)	<.0001	2.9730 (3; .3958)	0	0.01%	0.3188 (*P* = .7499)
PANSS positive[b]	5	221	678	0.26 (−0.02, 0.54)	.0668	9.0083 (4; .0609)	0.0525	55.50%	0.0038 (*P* = .9970)
Illness length[b]	4	356	695	0.15 (−0.07, 0.36)	.1808	5.9213 (3; .1155)	0.0214	47.42%	2.3354 (*P* = .0195)
PANSS negative[b]	5	221	678	0.21 (−0.14, 0.55)	.2354	10.5589 (4; .0320)	0.1026	70.85%	−0.3414 (*P* = .7328)
Age of onset[b]	4	268	211	−0.08 (−0.21, 0.06)	.2700	1.1675 (3; .7608)	0	0.00%	0.2469 (*P* = .8050)
Being male[a]	8	461	883	1.18 (0.87, 1.59)	.2838	7.4976 (7; .3790)	0.0189	9.65%	1.7901 (*P* = .0734)
Living alone[a]	2	46	144	1.44 (0.69, 3.03)	.3341	0.4343 (1; .5099)	0	0.00%	
Being white[a]	2	49	176	0.74 (0.39, 1.41)	.3632	0.8282 (1; .3628)	0	0.00%	
IQ[b]	2	311	305	0.16 (−0.20, 0.52)	.3832	4.8036 (1; .0284)	0.0524	79.18%	
Years of education[b]	4	182	622	−0.05 (−0.26, 0.17)	.6725	3.4542 (3; .3267)	0.0106	20.47%	−1.2328(*P* = .2177)
Age[b]	7	440	831	−0.03 (−0.15, 0.10)	.6837	3.3362 (6; .7656)	0	0.00%	0.4804 (*P* = .6309)
Married[a]	5	208	715	1.12 (0.78, 1.90)	.6445	4.4440 (4; .3492)	0.0567	20.01%	−0.3010 (*P* = .7634)
Unemployed[a]	3	159	539	1.06 (0.73, 1.54)	.7556	2.2037 (2; .3323)	0	0.00%	
History of suicide attempts[a]	2	145	527	0.88 (0.17, 4.51)	.8739	10.3168 (1; .0013)	1.2653	90.31%	

Note: BDI, Beck Depression Inventory; df, degrees of freedom; HAM-D, Hamilton Depression Rating Scale; IQ, intelligence quotient; PANSS, Positive and Negative Symptom Scale; SI, suicidal ideation.
[a]The effect size used was odds ratio.
[b]The effect size used was standardized mean difference.

Suicidal Ideation and Attempt

Our meta-analysis showed that some symptoms scales were associated with suicidality in patients with schizophrenia. Depressive symptoms as assessed by BDI and HAM-D scores were associated with both suicide ideation and suicide attempt. The PANSS general scale was also associated with suicide ideation. Future studies may identify more specific subscales for predicting suicide. Finally, a greater number of psychiatric hospitalizations was strongly associated with both ideation and attempts; this likely represents a more severe course of illness.

Suicide Attempt

Besides hopelessness, history of depression, history of attempted suicide, family history of psychiatric illness, family history of suicide, and being white, we found that history of alcohol, drug, and tobacco use were all associated with increased risk of suicide attempts. Tobacco use is particularly common in patients with schizophrenia, and it was reported that smoking cessation reduces depression and suicidality in patients with psychosis.[28] Two protective factors were identified for suicide attempts: living alone and being male. Living alone was usually dichotomized against a group-living or long-term care facility, so it may represent a greater functional capacity and reduced disease burden. Male as a protective factor is consistent with the "gender paradox" phenomena in suicidology, where men are less likely to attempt suicide, but more likely to use lethal suicide means.[29,30] Univariate models accounted for heterogeneity in several risk factors for suicide attempts (see "Results" section). For instance, for history of drug use and tobacco use, studies with high quality as assessed by NOQAS were more associated with an increased risk of suicide attempt.

Suicide

Three continuous risk factors, shorter illness length, younger age, and higher IQ were noted in our study to be associated with increased suicide; the first two were also significant in the cohort study. We also identified that history of tobacco use and history of alcohol use as significant risk factors for suicide, while these factors were either not tested or not significant in the prior meta-analysis for suicide.[12] We confirmed some results of the previous meta-analysis[12]: being male, history of attempted suicide, worthlessness, hopelessness, poor treatment adherence are significant risk factors of suicide in patients with schizophrenia. The first two remained significant in our cohort meta-analysis. A model composed of 3 variables (NOQAS score, region of study, and mean age of the samples) was able to explain all the heterogeneity for being male.

Most articles included in this analysis did not employ suicide risk assessment scales; when they did, often they were unique to that study and not used in any other, preventing their inclusion in our analysis. This reflects the lack of consensus on how one assesses suicidality in schizophrenia. A similar statement can be made about assessment tools for symptomatology; while we included scoring for schizophrenic symptoms, depression, and anxiety, many other scales were excluded because they were reported only within one article.

The 3 categories of suicidality described in this article had largely similar risk factors, with some notable differences. There are several reasons why this may be the case. First, there is a difference in the information available to collect in the case of suicide and suicide attempt, as most suicide studies were post-mortem psychological autopsies and things such as symptomatology scales could not be evaluated. Another reason is that these categories do seem to represent different phenomena; eg, it is well-established that women are more likely to attempt suicide, but men are more likely to commit suicide, indicating that being female is a risk factor for suicide attempt, and being male is a risk factor for suicide. One goal of our study was to highlight these differences in risk factors for each category.

Strengths and Limitations

While we cannot infer causality from this pooling and analysis of observational studies, the results of this meta-analysis have significantly strengthened and grounded the evidence for the existence of these risk factors for suicidality in schizophrenia and provides an opportunity for clinicians to employ the typical strategies targeting reduction of these risk factors with the additional benefit of reducing suicide risk. An important strength of our systematic review was the search strategy, since we have made an exhaustive effort to acquire data by contacting the authors. Thus, we were able to include a large number of papers, providing a more accurate estimate of the influence of these risk factors. In addition, we were able to perform a supplemental analysis only with cohort studies. Our study has some limitations. For the significant risk factors, high levels of between-study heterogeneity ($I^2 > 50\%$) were recorded for illness length, history of attempted suicide and age for suicide, and for history of attempted suicide, history of drug use, history of alcohol use, and number of psychiatric hospitalizations for suicide attempt. However, univariate meta-regression analysis showed that quality of the included studies assessed by NOQAS explained a large amount of heterogeneity for history of drug use. Unexplained heterogeneity could be related to genetics, presence of different subgroups, or methodological variability. For instance, evaluation of potential risk factors often took place a long time before death or attempt occurred, and these factors might have changed in the intervening period. We were also unable to examine treatments in this meta-analysis, because medication was

often referred to in general terms, such as "antipsychotics" or chlorpromazine dose equivalence. However, our meta-analysis showed that suicide risk is considerably increased in patients who adhere poorly to treatment. In addition, we could not exclude the effect of publication bias in the effect size of the following variables: illness length for suicide and history of attempted suicide and number of psychiatric hospitalizations for suicide attempt. Finally, a small number of studies may have driven the effect size observed, as the leave-one-out method demonstrated in some variables as reported in results section. Therefore, additional studies are needed for a definitive conclusion on these variables.

Conclusion

In summary, our study showed the risk factors associated with suicide ideation, suicide attempt, and suicide in patients with schizophrenia, indicating that suicidality in schizophrenia has a signature composed of several risk factors. The risk factors we identified, particularly for suicide attempts, in this population have compelling indications for clinical management. For example, effective treatment modality of substance use may be applied to reduce the risk of suicide attempts, as well as suicide in schizophrenia population. As we noted, patients with higher IQ were more vulnerable to suicide, better clinical strategies of suicide prevention may be implemented for the care of this group of patients. Further, despite the promising evidence that antipsychotic therapy may reduce suicidal risk, we found in our study a gap in the literature regarding effective reporting and cataloguing of this effect. It is likely that this is because of the relatively inconsistent use of the suicide risk-reducing antipsychotic clozapine; exposing this gap will provide impetus to use these medications as a suicide risk-reducing method when a schizophrenic patient presents with many of the risk factors detailed in our study. The difference in identified risk factors for suicide and suicide attempts necessitates further research on the biological and psychological underpinning of both processes. Future longitudinal studies examining the mechanism of how these variables are linked to suicidality might offer new insight into how to treat and prevent it. Future studies may combine these risk factors with machine learning techniques in order to objectively predict at an individual level suicide and suicide attempt in patients with schizophrenia.

Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin* online.

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Conflict of Interest

All authors report no competing interests.

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