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Alcohol use and suicide-related outcomes in people with a diagnosis of schizophrenia: a comprehensive systematic review and meta-analysis

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Review Article

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Abstract

Suicide is the leading cause of unnatural death among people with a diagnosis of schizophrenia. Alcohol use is a prevalent comorbid feature of schizophrenia and a modifiable risk factor for suicide. We conducted a prospectively registered (PROSPERO, CRD42022358214) systematic review and meta-analysis to quantify the relationship between alcohol use and suicide-related outcomes in schizophrenia.

We searched Medline, Embase, and PsycINFO for cross-sectional, case–control and longitudinal studies using exhaustive terms from database inception to December 2022 inclusive. Computation of odds ratios (ORs) and hazard ratios (HRs) were performed using a random-effects model with DerSimonian–Laird estimation. We also evaluated publication bias, study quality, and performed subgroup analysis and meta-regression. Fifty studies, comprising 65 samples, met eligibility criteria. Overall, alcohol use was associated with suicide (OR 1.38, 95% CI 1.21–1.58; HR = 1.32, 95% CI 1.00–1.74), attempted suicide (OR 1.69, 95% CI 1.45–1.98), and suicidal ideation (OR 1.69, 95% CI 1.22–2.34). While there was no evidence of publication bias, between-sample heterogeneity was moderate in analyses of attempted suicide ($I^2 = 39.6\%$, $p = 0.01$) and suicidal ideation ($I^2 = 56.0\%$, $p = 0.01$). Summary effects were significant in all subgroups except for longitudinal studies of attempted suicide (OR 1.60, 95% CI 0.86–3.00) and studies of suicidal ideation using gender combined samples (OR 1.63, 95% CI 0.99–2.67). Alcohol use is significantly associated with suicide-related outcomes in schizophrenia. Clinicians should routinely inquire about alcohol use in mental health services to focus preventative treatment efforts.

Introduction

Suicide is the leading cause of unnatural death among people with a diagnosis of schizophrenia (Moreno-Küstner et al., 2021). In this group, rates of suicide are almost 10 times higher than the general population (Correll et al., 2022); approximately 50% of people will attempt suicide in their lifetime (Chapman et al., 2015) and suicidal thoughts are common (Bai et al., 2021). Consequently, the reduction of suicide-related outcomes in schizophrenia remains an international public health priority (Lu et al., 2020). Several demographic, clinical, and behavioral factors have been associated with suicide in people with a diagnosis of schizophrenia. While some factors are broadly aligned with risk factors found in the general population; including male gender, age, unemployment, isolation, criminality, substance use, trauma, and access to lethal means (Favril, Yu, Uyar, Sharpe, & Fazel, 2022); others are schizophrenia-specific and relate to illness course, symptoms, and medication (Sher & Kahn, 2019).

Alcohol use is a prevalent comorbid feature of schizophrenia and a modifiable risk factor for suicide (Gut-Fayand et al., 2001). Meta-analyses have shown that approximately 25% of people with a diagnosis of schizophrenia meet criteria for alcohol use disorder (Hunt, Large, Cleary, Lai, & Saunders, 2018) and up to 50% have a dual diagnosis (Drake, 2007; Tiet & Mausbach, 2007). However, while cross-sectional and longitudinal studies have reported positive associations between alcohol use and suicide (Zaheer et al., 2020), attempted suicide (Østergaard, Nordentoft, & Hjorthøj, 2017) and suicidal ideation (Dai et al., 2022), these findings have not always been replicated (Freeman et al., 2019; Reutfors et al., 2009), and some have found relationships in the opposite direction (Hjorthøj et al., 2015; Jovanovic, Kudumija Slijepcevic, & Podlesek, 2019). Several reasons may account for this,

including between-study differences in: (1) research design; (2) assessment of alcohol use; (3) outcome variables studied (i.e. suicide/attempted suicide/suicidal ideation); (4) study quality; or (5) variance in samples according to symptom severity, age, or gender.

Furthermore, two existing meta-analyses on global risk factors for suicide and attempted suicide in schizophrenia have also reported both non-significant and significant outcomes for the effect of alcohol use, respectively (Cassidy, Yang, Kapczinski, & Passos, 2018; Hawton, Sutton, Haw, Sinclair, & Deeks, 2005). However, many methodologically sound studies have recently been published (Dai et al., 2022; Lähteenvuo et al., 2021; Olfson et al., 2021), and a large number of relevant studies were not included in previous meta-analyses, possibly due to caveats associated with title and abstract only searching (e.g. Barrett et al., 2010; Canal-Rivero *et al.* 2016; Fazel, Wolf, Palm, & Lichtenstein, 2014; Fedyszyn, Robinson, Harris, Paxton, & Francey, 2012; Fialko *et al.* 2006; Harkavy-Friedman *et al.* 1999; Leposavić, Dimitrijević, Đorđević, Leposavić, & Nikolić Balkoski, 2015; Pratt, Gooding, Johnson, Taylor, & Tarrier, 2010). Moreover, to date, there have been no attempts to meta-analyze the effects of alcohol use on suicidal ideation in those with a diagnosis of schizophrenia, despite this being a risk factor for other suicide-related outcomes (Chapman et al., 2015). It is also key for effective risk management and a viable target for intervention (Bateman, Hansen, Turkington, & Kingdon, 2007).

This paper reports on the first ever, focused, and comprehensive systematic review and meta-analysis on the relationship between alcohol use, measured categorically or continuously, of any frequency, degree, or impact, at any time point, and suicide-related outcomes (i.e. suicide, attempted suicide and suicidal ideation) in those with a diagnosis of schizophrenia. It also evaluates potential sources of heterogeneity between studies.

Method

Search strategy

A pre-registered (PROSPERO: CRD42022358214) systematic review and meta-analyses were undertaken following guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; Moher, Liberati, Tetzlaff, and Altman, 2009 – see online Supplementary Appendix A). Eligible studies were identified through: (1) an electronic literature search of three bibliographic databases including Medline (from 1946 to 2022, inclusive), PsycINFO (from 1806 to 2022, inclusive), and Embase (1974 to 2022, inclusive) (2) scrutiny of reference lists and citations of papers meeting inclusion criteria to identify studies not located in database searches (i.e. forward and backward tracking of literature); and (3) contact with authors in cases where additional information was required to compute effect sizes. Search terms included: (substance use* OR substance abuse* OR substance misuse* OR substance dependen* OR substanc* OR alcohol* OR alcohol use* OR alcohol abuse* OR alcohol misuse* OR alcohol dependen* OR addict* OR drug* OR drug use* OR drug abuse* OR drug misuse* OR drug dependence OR cannabis OR marijuana OR cocaine OR heroin OR amphetamine* OR methamphetamine* OR smoking OR tobacco OR nicotine).af AND (suicide OR suicid* OR suicidal behavio* OR self*harm*).af AND (psychosis OR psychoti* OR schizo* OR hallucinat* OR delusion* OR paranoi*).af. Medical Subject Headings (MESH) were used to further expand the results of the database search to identify all relevant studies. Duplicate records were removed electronically and manually. Broad search terms were used as initial scoping of the literature suggested that alcohol-related effects may be reported in studies that did not focus exclusively on alcohol, but substance abuse more generally.

Inclusion and validity

Longitudinal, case–control and cross-sectional studies were included if they: (1) sampled adults with a diagnosis of a schizophrenia-spectrum disorder (i.e. psychotic disorder, schizophrenia, schizoaffective disorder, delusional disorder, schizophreniform disorder), consistent with DSM-III, DSM-III-R, DSM-IV, DSM-IV-TR, DSM-5 or equivalent research diagnostic criteria [International Classification of Diseases (ICD)], or based on psychiatrist or psychologist case note review or clinical interview; (2) included a subjective or objective measure of alcohol use (i.e. self-, informant- or clinician-reported composite, dichotomous, or continuous measures of current or past alcohol use, including questionnaire, checklist or presence of alcohol diagnosis derived from case note review or clinical interview, or recording of biological markers, including blood alcohol content or urine analysis); (3) included a specific measure of suicidality (i.e. self-, informant- or clinician-reported dichotomous or continuous measures of current or past suicidal ideation, attempted suicide, or suicide); and (4) presented summary estimates of alcohol use and suicide-related outcomes sufficient to compute meta-analysis.

We excluded studies not written in the English language. We also excluded: (1) case reports, conference proceedings, and reviews; (2) studies that employed measures of non-suicidal self-injury (NSSI) given the differences between NSSI and suicidality in terms of intention, frequency, lethality, and function (Cipriano, Cella, & Cotrufo, 2017); and (3) studies that investigated adults with substance-induced psychosis, those 'at risk' of psychosis, focused on retrospective relationships between variables prior to the onset of psychosis, or reported on a combined patient sample of which less than 50% had a schizophrenia-spectrum diagnosis.

Eligibility was assessed independently by two researchers following a 2-stage procedure: title and abstract screening, and whole article screening. In the first phase, L.M. and K.H. screened all titles and abstracts independently. If either deemed a title or abstract for inclusion, this was subject to further examination in whole article screening (independent agreement: 92.5%). In the final phase, whole articles were examined to reach final decisions on inclusion (independent agreement: 98.5%). Intercoder discrepancies were resolved in consultation with a third reviewer (GH) for arbitration and consensus.

Risk of bias was assessed using a modified version of the Effective Public Health Practice Project (Thomas, Ciliska, Dobbins, & Micucci, 2004) tool for quantitative studies to enhance its relevance to the requirements of this review and akin to previous meta-analyses (Howard, Berry, & Haddock, 2022). The modified EPHPP assessed methodological quality of studies across several domains, including: (1) selection bias; (2) confounders; (3) data collection methods; (4) withdrawals / dropouts; and (5) statistical analyses; to inform a global score. Two researchers (L.M. and K.H.) independently coded each study for quality and discrepancies were discussed and resolved in consultation with a third researcher (G.H.). There was substantial agreement in global scores between coders (93.75%).

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Data extraction

All data were independently extracted by L.M. and K.H and were cross-checked to ensure accuracy. Where relevant data were missing from a study, the authors were contacted. Descriptive variables extracted included: year of study; setting (i.e. country); study methodology; sample size; age of sample; number, and age of cases/controls (if applicable); gender; population diagnoses; diagnoses measure; alcohol measure; alcohol timeframe; suicidality measure; baseline total Positive and Negative Syndrome Scale (PANSS; Kay, Fiszbein, & Opler, 1987) score (if available); and statistical information required to calculate effect sizes. Baseline total PANSS score was extracted above other measures, such as the Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1988), as it combines specific symptoms of schizophrenia and general psychopathology in one composite score.

To avoid data duplication, a hierarchy was constructed to guide decisions about extraction and improve the homogeneity of included studies. In cases where studies reported multiple alcohol variables (e.g. binary, and continuous), binary variables were extracted, as most studies measured alcohol use via the presence/absence of an alcohol use disorder diagnosis. In studies where alcohol use, or a specific suicide outcome, was recorded at multiple time points (e.g. recent and lifetime), summary effects were pooled to generate one combined outcome metric. Furthermore, where identical samples were used across different studies, eligible papers were chosen sequentially based on predetermined criteria: (1) the presence of binary alcohol variables; (2) the number of suicide outcome variables; or (3) sample size.

Effect size computation and statistical analysis

All analyses were performed using the meta-analysis commands of Stata version 14.0 (StataCorp, 2013). The computation of summary effects was performed using a random-effects model with DerSimonian–Laird estimation, as between-study heterogeneity was expected due to variability in study methods, measures, and sample characteristics. Six models were computed to summarize effects across different suicide-related outcomes, including: (1) odds of suicide; (2) risks of suicide; (3) odds of attempted suicide; (4) risks of attempted suicide; (5) odds of suicidal ideation (including suicidal ideation, thoughts, and plans); and (6) risks of suicidal ideation.

Odds ratios (ORs) and hazard ratios (HRs) were chosen as main outcome metrics. When available, unadjusted ORs and HRs were extracted from included studies. When not reported, adjusted HRs were used, or both ORs and 95% confidence intervals were estimated from available descriptive statistics using 2×2 tables following standard computational techniques for dichotomous data (Fleiss & Berlin, 2009). In cases where studies reported correlational analysis or between groups parametric or non-parametric analysis for continuous level data, the correlation statistic and direction, sample size, mean, standard deviation and significance (p-value) were used to convert to ORs using Comprehensive Meta-Analysis (CMA) software (Borenstein, 2022).

In all analyses, heterogeneity analyses were computed using Cochran Q and I^2 statistics to examine and quantify the amount of observed variance accounted for by true heterogeneity (Higgins, Thompson, Deeks, & Altman, 2003). An I^2 value of less than 25% was considered to have low inconsistency, 25% to 75% indicated medium inconsistency, and greater than 75% indicated high inconsistency. Publication and other selection bias were assessed by visual inspection of funnel plots supplemented by Egger's test for funnel plot asymmetry (Egger, Smith, Schneider, & Minder, 1997). Given the potential risks of inflated type-1 error associated with Egger's test, especially for dichotomous outcomes with small numbers, it was only performed on outcomes with ten or more data points (Deeks, Higgins, & Altman, 2019). The 'Trim-and-Fill' method was also utilized to adjust for publication bias or other selection bias on outcomes with ten or more data points (Duval & Tweedie, 2000).

Sensitivity analyses were used to investigate the impact of study omission on overall summary estimates in cases where studies held significant weighting or in the event of outliers. For analyses with significant heterogeneity and with ten or more data points (Deeks et al., 2019), meta-regression analysis was used to determine whether publication year, sample age of cases or PANSS total scores of cases influenced any observed associations between alcohol use and suicide outcome. Subgroup analyses were also computed to evaluate the same effects of gender, study design, quality, or illness course (first episode/chronic schizophrenia samples).

Results

52 550 studies were identified via database search and two were found through examination of reference lists and contact with authors of eligible papers. After title screening, 3652 articles were screened by abstract and 60 were included in the final coding phase. We excluded 12 studies at this stage to minimize heterogeneity associated with composite measures of suicidality, to minimize data duplication associated with overlapping samples, and where available statistics were not suitable for conversion to ORs. This resulted in 50 studies comprising 65 separate samples, which were subject to meta-analysis (see Fig. 1). Of these, 17 samples concerned alcohol and suicide, 36 samples concerned alcohol and attempted suicide, and 12 samples concerned alcohol and suicidal ideation. Table 1 and online Supplementary Appendix B and C provide a summary of eligible study characteristics.

Quality assessment

For the 50 eligible studies, seven were deemed to be of weak quality, 26 were deemed to be of moderate quality and 17 were deemed to be of strong quality. Across studies, most common weaknesses were due to selection bias (representativeness of sample to wider population), presence of confounders and use of unvalidated measures during data collection. Risk of bias assessments are described in online Supplementary Appendix D-I.

Association between alcohol use and suicide

Overall, alcohol use significantly increased the odds of suicide in people with a diagnosis of schizophrenia ($k = 11$, OR 1.38, 95% CI 1.21–1.58) (see Fig. 2). Alcohol use also increased the risks of suicide, albeit non-significantly ($k = 6$, HR = 1.32, 95% CI 1.00–1.74) (see Fig. 3). The Q and I^2 tests indicated that between-sample heterogeneity was low and non-significant in analyses of odds between alcohol use and suicide ($I^2 = 0.0\%$, $p = 0.597$), but high and significant in analyses of risk ($I^2 = 84.2\%$, $p < 0.01$). This remained significant following removal of Hjorthøj et al. (2015) whose outcome metrics lay outside of the 95% CIs of the overall summary effect ($I^2 = 70.8\%$, $p = 0.01$). Despite this, meta-regression and subgroup analyses were not performed as analyses of risks had fewer than ten outcomes (Deeks et al., 2019).

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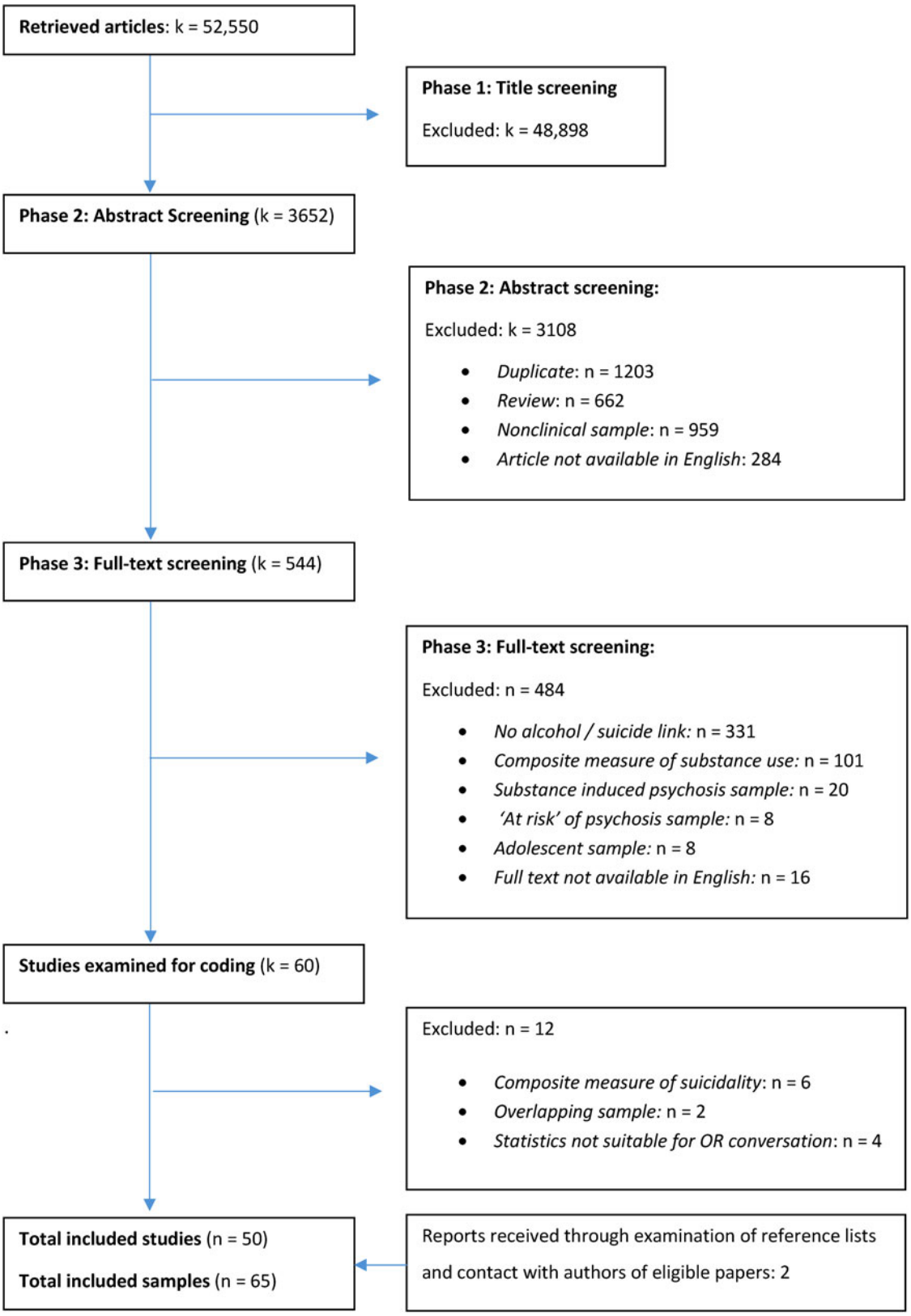

Figure 1. PRISMA diagram.

Funnel plot inspection and results of Egger's test suggested there was a low risk of publication or other selection bias for analyses of odds between alcohol use and suicide ($\beta = 0.35$, S.E. = 0.09, $p = 0.65$) (see online Supplementary Appendix J). Trim and Fill analysis also identified no missing studies (see online Supplementary Appendix M). Analyses of risks had too few

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Table 1. Summary of eligible studies

Source	Study methodology	Sample	Sample size	No. of cases (Suicide outcome)	No. of controls (No suicide outcome)
Suicide					
Allebeck, Varla, Kristjansson, and Wistedt, (1987) (Sweden) – Females	Cross-sectional / Case control	Chronic	50	17	33
Allebeck et al., (1987) (Sweden) – Males	Cross-sectional / Case control	Chronic	46	15	31
Cohen, Leonard, Farberow, and Shneidman, (1964) (USA)	Cross-sectional / Case control	Chronic	80	40	40
Fazel et al., (2014) (Sweden) – Females	Longitudinal	Chronic	9676	264	9412
Hjorthøj et al., (2015) (Denmark)	Longitudinal	Chronic	41 470	1138	-
Kuo, Tsai, Lo, Wang, and Chen, (2005) (Taiwan)	Cross-sectional / Case control	Chronic	156	78	78
Lähteenvuo et al., (2021) (Finland)	Longitudinal	Chronic	30 860	8110	22 750
Lähteenvuo et al., (2021) (Sweden)	Longitudinal	Chronic	14 616	4514	10 102
Limosin, Loze, Philippe, Casadebaig, and Rouillon, (2007) (France)	Longitudinal	Chronic	3434	141	3293
McGirr et al., (2006) (Canada)	Cross-sectional / Case control	Chronic	81	45	36
Olfson et al., (2021) (USA)	Longitudinal	Chronic	668 836	-	-
Østergaard et al., (2017) (Denmark)	Longitudinal	Chronic	35 625	1300	34 325
Reutfors et al., (2009) (Sweden)	Cross-sectional / Case control	Chronic	168	84	84
Shaffer, Perlin, Schmidt, and Stephens, (1974) (USA)	Cross-sectional / Case control	Chronic	89	12	75
Sinclair, Mullee, King, and Baldwin, (2004) (UK)	Cross-sectional / Case control	Chronic	133	51	82
Stephens, Richard, and McHugh, (1999) (USA)	Longitudinal	Chronic	1212	28	1184
Zaheer et al., (2020) (Canada)	Longitudinal	Chronic	75 989	1302	74 687
Attempted Suicide					
Abderemane et al., (2022) (Morocco)	Cross-sectional / Case control	Chronic	34	10	24
Adan et al., (2017) (Spain) – Males	Cross-sectional / Case control	Chronic	50	24	26
Altamura, Bassetti, Bignotti, Pioli, and Mundo, (2003) (Italy)	Cross-sectional / Case control	Chronic	103	22	81
Altamura et al., (2007) (Italy) – EEUR	Cross-Sectional / Case Control	Chronic	199	156	43
Altamura et al., (2007) (Italy) – EUR	Cross-sectional / Case control	Chronic	236	176	60
Altamura et al., (2007) (Italy) – NA	Cross-sectional / Case control	Chronic	414	371	43
Altamura et al., (2007) (Italy) – SA	Cross-Sectional / Case Control	Chronic	93	82	11
Altamura et al., (2007) (Italy) – SAf	Cross-sectional / Case control	Chronic	37	31	6
Ayesa-Arriola et al., (2015) (Spain)	Longitudinal	FEP	397	60	337
Bani-Fatemi, Polsinelli, Kennedy, and De Luca, (2013) (Canada)	Cross-sectional / Case control	Chronic	566	192	374
Barak, Baruch, Achiron, and Aizenberg, (2008) (Israel)	Cross-sectional / Case control	Chronic	2188	1094	1094
Barrett et al., (2010) (Norway)	Cross-sectional / Case control	FEP	104	44	60
Canal-Rivero et al., (2016) (Spain) – EFSA	Longitudinal	FEP	65	14	51
Canal-Rivero et al., (2016) (Spain) – LFSA	Longitudinal	FEP	51	6	45
Cohen, Abdallah, and Diwan, (2010) (USA)	Cross-sectional / Case control	Chronic	196	58	138
Dai et al., (2022) (China) – Males	Cross-sectional / Case control	Chronic	616	194	422
Fedyszyn et al., (2012) (Australia)	Cross-sectional / Case control	FEP	180	72	108
Goldstein, Haas, Pakrashi, Novero, and Luther, (2006) (USA) – Males	Cross-sectional / Case control	Chronic	93	31	62

(*Continued*)

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Table 1. (*Continued.*)

Source	Study methodology	Sample	Sample size	No. of cases (Suicide outcome)	No. of controls (No suicide outcome)
Harkavy-Friedman et al., (1999) (USA)	Cross-sectional / Case control	Chronic	156	52	104
Hu et al., (2014) (Canada)	Cross-sectional / Case control	Chronic	234	51	183
Harkavy-Friedman et al., (1999) (USA)	Cross-sectional / Case control	Chronic	156	52	104
Hu et al., (2014) (Canada)	Cross-sectional / Case control	Chronic	234	51	183
Jovanovic et al., (2019) (UK, Croatia)	Cross-sectional / Case control	Chronic	194	62	132
Leposavić et al., (2015) (Serbia)	Cross-sectional / Case control	Chronic	50	19	31
Lopez-Morinigo et al., (2019) (UK) – AESOP	Cross-sectional / Case control	FEP	162	16	146
Lopez-Morinigo et al., (2019) (UK) – GAP	Cross-sectional / Case control	FEP	112	22	90
Lückhoff, Koen, Jordaan, and Niehaus, (2014) (South Africa) – A	Cross-sectional / Case control	Chronic	243	113	130
Lückhoff et al., (2014) (South Africa) – D	Cross-sectional / Case control	Chronic	71	50	21
Mauri, Paletta, Maffini, Moliterno, and Altamura, (2013) (Italy)	Cross-sectional / Case control	Chronic	106	35	71
McLean, Gladman, and Mowry, (2012) (Australia)	Cross-sectional / Case control	Chronic	812	315	497
Østergaard et al., (2017) (Denmark)	Longitudinal	Chronic	35 625	8763	26 862
Pratt et al., (2010) (UK)	Cross-sectional / Case control	Chronic	84	58	26
Robinson et al., (2010) (Australia)	Longitudinal	FEP	282	61	221
Temmingh, Mall, Howells, Sibeko, and Stein, (2020) (South Africa)	Cross-sectional / Case control	Chronic	248	-	-
Uzun et al., (2009) (Turkey)	Cross-sectional / Case control	Chronic	300	104	196
Waterreus et al., (2018) (Australia) – Females	Cross-sectional / Case control	Chronic	725	88	637
Waterreus et al., (2018) (Australia) – Males	Cross-sectional / Case control	Chronic	1065	80	985
Yan et al., (2013) (China)	Cross-sectional / Case control	Chronic	540	65	475
Yoo et al., (2015) (Korea)	Cross-sectional / Case control	Chronic	87	20	67
Zhang et al., (2013) (China)	Cross-sectional / Case control	Chronic	520	48	472
Suicidal Ideation					
Amir et al., (2019) (Indonesia)	Cross-sectional / Case control	Chronic	1130	-	-
Barrett et al., (2010) (Norway)	Cross-sectional / Case control	FEP	126	66	60
Dai et al., (2022) (China) – Males	Cross-Sectional / Case Control	Chronic	616	194	422
Fialko et al., (2006) (UK) – M	Cross-sectional / Case control	Chronic	290	92	198
Fialko et al., (2006) (UK) – S	Cross-sectional / Case control	Chronic	290	26	264
Freeman et al., (2019) (UK)	Cross-sectional / Case control	Chronic	110	-	-
Goldstein et al., (2006) (USA) – Males	Cross-sectional / Case control	Chronic	93	46	47
Kim et al., (2010) (South Korea)	Cross-sectional / Case control	Chronic	84	43	41
Olfson et al., (2021) (USA)	Longitudinal	Chronic	64 565	-	-
Strauss et al., (2006) (USA) – Males	Cross-sectional / Case control	Chronic	165	82	83
Temmingh et al., (2020) (South Africa)	Cross-sectional / Case control	Chronic	248	-	-
Wang et al., (2022) (Canada) – C	Cross-sectional / Case control	Chronic	85	11	74
Yan et al., (2013) (China)	Cross-sectional / Case control	Chronic	540	114	426

Note: A, Abuse; AESOP, Aetiology and Ethnicity in Schizophrenia and Other Psychoses; C, Current; D, Dependence; E, Emergent; EFSA, Early First Suicide Attempt; EUR, Europe; EEUR, East Europe; GAP, Genetics and Psychosis; LFSA, Late First Suicide Attempt; M, Mild; NA, North America; S, Severe; SA, South America; SAF, South Africa.

studies to estimate or calculate publication or other selection bias. Across all analyses of suicide, one study carried significant weighting and one study was an outlier. Sensitivity analyses revealed the relationship between alcohol use and odds of suicide reduced but remained significant following removal of Zaheer et al. (2020), which contributed 72.2% of the overall summary

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effect ($k = 10$, OR 1.30, 95% CI 1.01–1.69) (see online Supplementary Appendix P). Analysis of risks was significant following the removal of Hjorthøj et al. (2015) whose outcome metrics lay outside of the 95% CIs of the overall summary effect ($k = 5$, HR = 1.47, 95% CI 1.12–1.92) (see online Supplementary Appendix P).

Association between alcohol use and attempted suicide

Overall, alcohol use significantly increased the odds of attempted suicide in people with a diagnosis of schizophrenia ($k = 35$, OR 1.69, 95% CI 1.45–1.98) (See Fig. 2). Furthermore, data from one study found that alcohol use significantly increased the risk of attempted suicide (HR = 2.34, 95% CI 1.34–4.09) (Østergaard et al., 2017). The Q and I^2 tests indicated that between-sample heterogeneity was medium and significant in analyses of odds between alcohol use and attempted suicide ($I^2 = 39.6\%$, $p = 0.01$). Publication or other selection bias was low and non-significant ($\beta = 0.38$, S.E. = 0.17, $p = 0.42$) (see online Supplementary Appendix K). Trim and Fill analysis identified three missing studies with small effects and high precision. However, the imputed pooled summary effect between alcohol use and odds of attempted suicide remained significant ($k = 38$, OR 1.64, 95% CI 1.40–1.92) (see online Supplementary Appendix N). Across all analyses of attempted suicide, one study was an outlier. Sensitivity analyses revealed the relationship between alcohol use and attempted suicide increased following the removal of Jovanovic et al. (2019) whose outcome metrics lay outside of the 95% CIs of the summary effect ($k = 34$, OR 1.75, 95% CI 1.54–2.00) (see online Supplementary Appendix Q).

Subgroup analyses (see online Supplementary Appendix S-W) showed that alcohol use was significantly associated with attempted suicide in cross-sectional / case–control studies ($k = 32$, OR 1.70, 95% CI 1.45–2.01, $I^2 = 40.4\%$, Q = 52.00), but effects were non-significant in longitudinal studies ($k = 3$, OR 1.60, 95% CI 0.86–3.00, $I^2 = 51.1\%$, Q = 4.09). Furthermore, alcohol was significantly associated with attempted suicide in studies using male only ($k = 4$, OR 1.62, 95% CI 1.18–2.23, $I^2 = 0\%$, Q = 2.66) and gender combined samples ($k = 30$, OR 1.66, 95% CI 1.39–1.98, $I^2 = 42.0\%$, Q = 50.01). While only one study reported outcomes using a female only sample, this was also significant (OR 2.55, 95% CI 1.62–4.02) (Waterreus et al., 2018). In addition, summary effects of studies investigating samples with First Episode Psychosis (FEP) ($k = 7$, OR 1.80, 95% CI 1.27–2.56, $I^2 = 27.8\%$, Q = 8.31) and chronic presentations ($k = 28$, OR 1.67, 95% CI 1.40–1.99, $I^2 = 43.2\%$, Q = 47.54) were significant, as were summary effects in studies categorized as strong ($k = 13$, OR 1.54, 95% CI 1.19–1.99, $I^2 = 60.3\%$, Q = 30.24), moderate ($k = 19$, OR 1.79, 95% CI 1.49–2.14, $I^2 = 6.6\%$, Q = 19.27) and weak in quality ($k = 3$, OR 3.08, 95% CI 1.15–8.23, $I^2 = 42.7\%$, Q = 3.49). Meta-regression showed that neither publication year ($k = 35$, $\beta = 0.99$, S.E. = 0.02, $p = 0.50$), cases sample age ($k = 26$, $\beta = 0.99$, S.E. = 0.01, $p = 0.17$), nor cases baseline PANSS total score ($k = 7$, $\beta = 1.01$, S.E. = 0.02, $p = 0.67$) had a significant effect on the overall summary estimate.

Association between alcohol use and suicidal ideation

Overall, alcohol use significantly increased the odds of suicidal ideation in people with a diagnosis of schizophrenia ($k = 11$, OR 1.69, 95% CI 1.22–2.34) (see Fig. 2). Data from one study found a non-significant relationship between alcohol use and risk of suicidal ideation (HR: 1.00, 95% CI 0.79–1.27) (Olfson et al., 2021). The Q and I^2 tests indicated that between-sample heterogeneity was medium and significant in analyses of odds between alcohol use and suicidal ideation ($I^2 = 56.0\%$, $p = 0.01$). However, there was no evidence of publication or other selection bias ($\beta = 0.99$, S.E. = 0.44, $p = 0.35$) (see online Supplementary Appendix L) and Trim and Fill analysis identified no missing studies (see online Supplementary Appendix O). Across all analyses of suicidal ideation, one study was an outlier. Sensitivity analyses revealed the relationship between alcohol use and suicidal ideation reduced but remained significant following the removal of Amir et al. (2019) whose outcome metrics lay outside of the 95% CIs of the summary effect ($k = 10$, OR 1.54, 95% CI 1.24–1.91) (see online Supplementary Appendix R).

There was insufficient data to perform subgroup analyses for the effect of study design, female only samples or studies categorized as strong in quality. However, subgroup analyses (see online Supplementary Appendix X-AA) showed that alcohol use was significantly associated with suicidal ideation in studies using male only samples ($k = 3$, OR 1.82, 95% CI 1.32–2.50, $I^2 = 0\%$, Q = 0.52), but not gender combined samples ($k = 8$, OR 1.63, 95% CI 0.99–2.67, $I^2 = 68.5\%$, Q = 22.19). Alcohol use was also significantly associated with attempted suicide in studies investigating chronic samples ($k = 10$, OR 1.69, 95% CI 1.19–2.41, $I^2 = 60.3\%$, Q = 22.66). While only one study reported outcomes using a FEP sample, this was non-significant (OR 1.59, 95% CI 0.61–4.16) (Barrett et al., 2010). In terms of study quality, the combined summary effect between alcohol use and suicidal ideation was significant in studies categorized as moderate in quality ($k = 10$, OR 1.54, 95% CI 1.24–1.91, $I^2 = 0.0\%$, Q = 6.61). The summary effect was also significant for studies categorized as weak in quality; however, this was based on one finding (OR 3.08, 95% CI 1.15–8.23) (Amir et al., 2019). Meta-regression showed that neither publication year ($k = 11$, $\beta = 1.01$, S.E. = 0.03, $p = 0.73$), nor mean sample age ($k = 5$, $\beta = 1.0$, S.E. = 0.03, $p = 0.97$) influenced the overall summary estimate. There was insufficient data to calculate the effect of baseline PANSS score.

Discussion

This review found that alcohol use significantly increases the odds of suicide-related outcomes in people with a diagnosis of schizophrenia. In particular, the pooled effect estimates were equivalent for suicidal ideation and attempted suicide, which were stronger than and suicide, respectively. We also report comparable, albeit non-significant, estimates between alcohol use and risks of suicide. As all estimates remained or were significant following removal of outliers and studies holding significant weighting, confident conclusions can be made regarding the overall effect of alcohol use on suicide-related outcomes. As presented in subgroup analyses, among studies examining alcohol use and odds of attempted suicide, the pooled OR was significant in cross-sectional studies, involving male-only, female-only or gender combined samples, chronic and FEP samples, and in studies categorized as strong, moderate, or weak in methodological quality. Furthermore, among studies examining alcohol use and odds of suicidal ideation, the pooled OR was significant in studies using male only samples, chronic samples, and in studies of moderate or weak methodological quality. Neither publication year, mean sample age, nor baseline PANSS score significantly influenced any observed associations between alcohol use and suicide-related outcomes.

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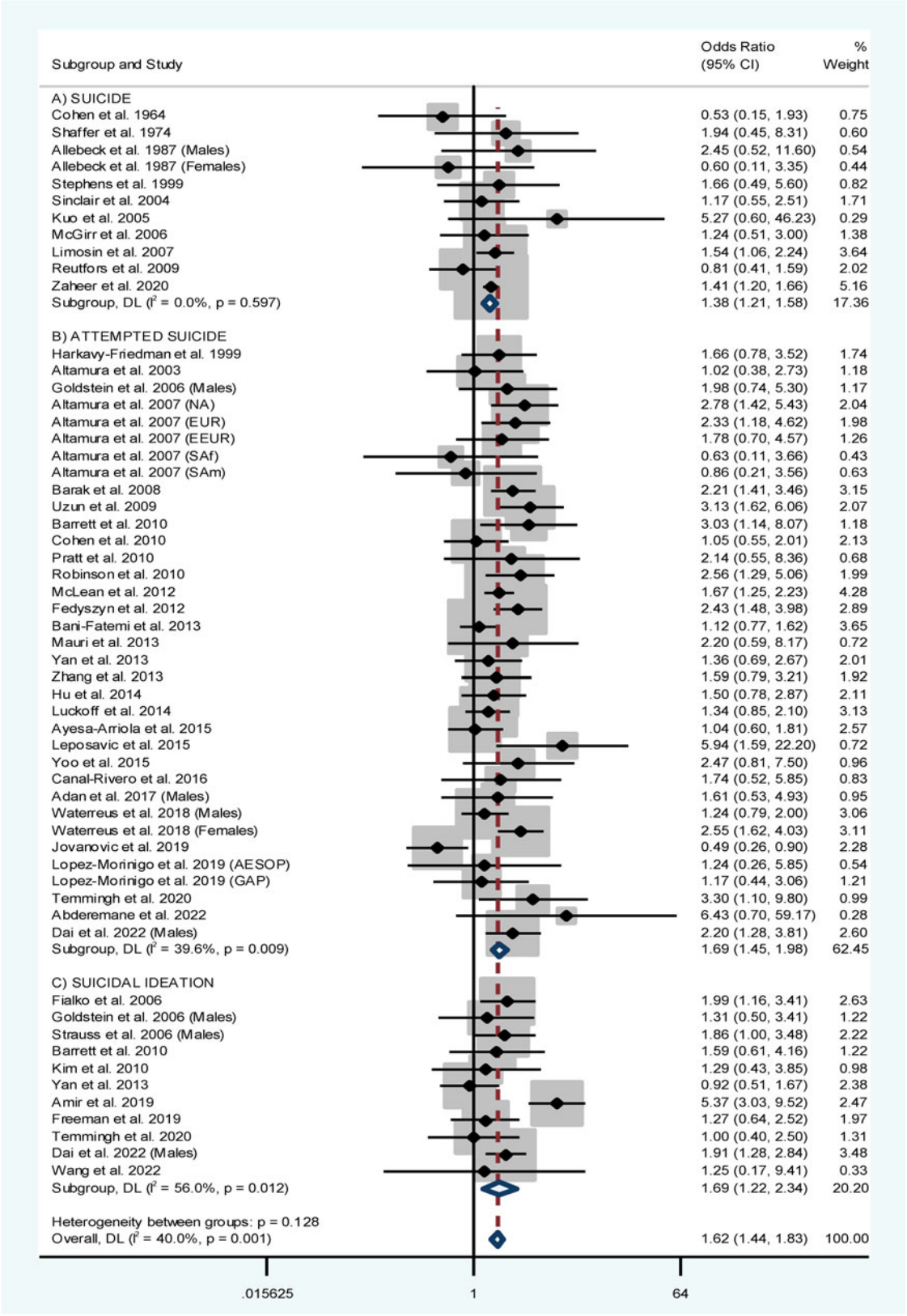

Figure 2. Forest plot for the meta-analysis examining odds ratios between alcohol use, suicide, attempted suicide, and suicidal ideation.

Our findings are novel and extend the outcomes of previous meta-analyses of global risk factors for suicide and attempted suicide in those with a diagnosis of schizophrenia (Cassidy et al., 2018; Hawton et al., 2005). The ORs reported in the current paper are larger than those previously described, possibly due to the inclusion of a greater number of eligible papers, including

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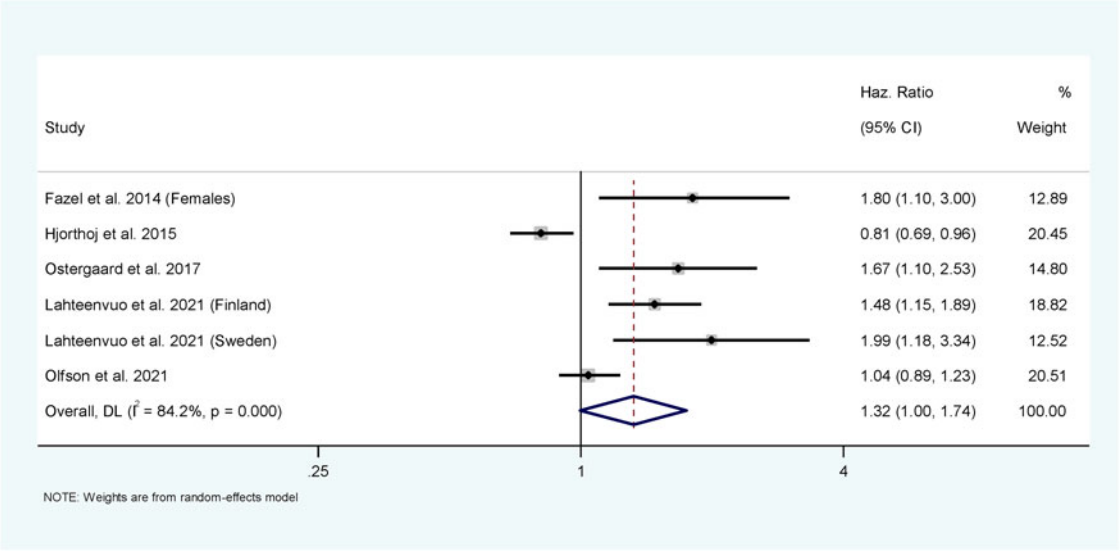

Figure 3. Forest plot for the meta-analysis examining hazard ratios between alcohol use and suicide.

non-published data. The application of statistical conversion (Borenstein, 2022) also permitted the inclusion of studies employing categorical and continuous measures of alcohol use. Our results lend support for individual studies demonstrating positive associations between alcohol use and suicide-related outcomes in this client group (Dai et al., 2022; Fazel et al., 2014; Lähteenvuo et al., 2021; Uzun, Tamam, Özcüler, Doruk, & Ünal, 2009).

Several potential mechanisms could underscore the summary effects observed in this meta-analysis. Firstly, previous studies have demonstrated positive relationships between alcohol use, depression, physical health complications and medication non-compliance in schizophrenia (Margolese, Malchy, Negrete, Tempier, & Gill, 2004), all of which are significant predictors of suicide and attempted suicide (Cassidy et al., 2018). Therefore, the effect of alcohol use on suicide-related outcomes in schizophrenia could be mediated by other factors. Secondly, alcohol use and suicidality share some distal factors, such as impulsivity (Stautz & Cooper, 2013) and childhood trauma (Hughes et al., 2017), which are characteristic of people with a diagnosis of schizophrenia (Pompili et al., 2013; Varese et al., 2012). Therefore, alcohol use and suicidality might represent likelier ways of problem solving or coping with stress reactivity in this group (Gierski et al., 2022; Muddle, Jones, Taylor, & Jacobsen, 2022). Finally, alcohol can induce long-term biological changes, such as neuro-inflammation (Hillemacher, Bachmann, Kahl, & Frieling, 2018), alterations to the hypothalamic-pituitary-adrenal axis (Sudol & Mann, 2017), and reduction to the volume and density of cortices in the frontal and parieto-occipital regions of the brain (Lange et al., 2017), all of which are recognized biological markers for suicidality (Courtet et al., 2016; Currier & Mann, 2008).

To our knowledge, this is the first ever, focused, and comprehensive systematic review and meta-analysis of the relationship between alcohol use and suicidal-related outcomes in those with a diagnosis of schizophrenia. By executing whole article searches and including previously non-published data, we identified a significant number of papers not included in recent meta-analysis of global risk factors (Cassidy et al., 2018). Therefore, our estimates most accurately reflect the evidence to date and provide the first ever pooled estimates on the relationship between alcohol use and suicidal ideation. Rigor was further assured as the identification of papers, study eligibility, data extraction and ratings of methodological quality were conducted by two researchers, independently.

Nevertheless, this study has some limitations. Medium to high levels of between-study heterogeneity were recorded in most analyses. Although subgroup analyses identified some differences in observed effects according to study design, unexplained heterogeneity could be related to the effects of other demographic, behavioral or clinical variables known to correlate with alcohol use and suicide-related outcomes, such as ethnicity, drug comorbidity, or depression (Hawton et al., 2005). Future research exploring relationships between alcohol use and suicidality in those with schizophrenia should include all variables relevant to both outcomes to facilitate greater precision in results. Furthermore, for some variables, the subgroup and meta-regression analyses might have been underpowered to detect true effects as not all studies recorded or reported necessary data. Therefore, our results of the sources of heterogeneity between alcohol and suicide-related outcomes should be considered exploratory. Although the analyses found no significant evidence of publication or other selection bias across all suicide-related outcomes, our search strategy was limited to peer-reviewed, English-language papers and gray literature was excluded. Therefore, it is possible that some relevant studies were overlooked. Nevertheless, as whole articles were screened for search terms, we identified a large pool of studies.

There were also some noteworthy methodological limitations of the primary studies included in this meta-analysis. Most studies assessed alcohol use using binary measures (i.e. presence or absence or alcohol use) without specifying frequency, degree, or impact of use sufficient to classify distinct groups (i.e. misuse, abuse, or dependence). Unknown variance in these factors could have contributed to between-study heterogeneity observed in specific analyses. Furthermore, it is recognized that alcohol use is not always a static risk factor for suicide (Hjorthøj et al., 2015) and its binary measurement is somewhat unreliable. Future research on alcohol use and suicidality in those with schizophrenia should include validated tools, such as the

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Alcohol Use Disorders Identification Test (AUDIT; Saunders, Aasland, Babor, De la Fuente, & Grant, 1993), as this would better conceptualize the nature, duration, function, and impact of use, facilitate comparisons across studies, and inform translation to clinical practice.

Furthermore, most eligible studies employed cross-sectional methodology. While informative, cross-sectional studies are vulnerable to recall bias and are unable to examine relationships on a micro-scale (Althubaiti, 2016). Future studies employing repeated, longitudinal measures of individual psychotic symptoms, alcohol use and suicide risks, including experience sampling methodology (Myin-Germeys et al., 2018), could help to examine temporal relationships between specific variables and allow for more nuanced conclusions regarding underlying triggers, mediators, and moderators of observed effects. Lastly, few studies stratified results by gender and some included male only samples. This is problematic as females with diagnoses on the schizophrenia-spectrum have a higher suicide mortality ratio comparative to their male counterparts (Leung & Chue, 2000). Future studies exploring suicide risk factors, including alcohol use, should report combined and gender-specific analyses as this could inform more precise risk management among subgroups.

Our findings have some important implications for patient care and policy. Firstly, clinicians should routinely inquire about alcohol use to inform comprehensive risk management and care plans when working with individuals with schizophrenia (Hor & Taylor, 2010). This could identify those at greater risk of adverse outcomes and focus preventative treatment efforts. Secondly, psychosocial interventions to reduce alcohol use may also hold promise in reducing suicide-related outcomes in this group. This is important given the high prevalence of suicidality in those with a diagnosis of schizophrenia (Correll et al., 2022; Fialko et al., 2006) and focus of international public health priorities (Lu et al., 2020). However, evidence for the effectiveness of existing interventions for substance use in those with severe and enduring mental health difficulties is lacking (Hunt, Siegfried, Morley, Brooke-Sumner, & Cleary, 2019). The development of new, bespoke, psychosocial interventions, designed in collaboration with experts by experience, targeting specific mechanisms that contribute to substance use in schizophrenia, may hold the greatest value in reducing alcohol use and the associated suicide risk.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291723002738.

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Authors' contributions. LM, FV, KH, and GH designed the study. LM and KH conducted the literature search, assessed studies for eligibility, extracted all data and rated study quality. LM analyzed the data and interpreted them together with FV and GH. LM, FV, KH, and GH critically reviewed the report for important intellectual content and approved the final submitted version. LM had final responsibility for the decision to submit for publication.

Competing interest. None.

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008

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