Alpha Psychiatry

SYSTEMATIC REVIEW
Alpha Psychiatry 2024;25(4):429-439
DOI: 10.5152/alphapsychiatry.2024.231359

Anxiety and Depression after Colorectal Cancer Surgery: A Systematic Review and Meta-Analysis of Short- and Long-Term Outcomes

ABSTRACT

Objective: Anxiety and depression commonly afflict colorectal cancer (CRC) surgery patients, but their impact on survival remains uncertain.

Methods: We systematically reviewed three databases for relevant articles. Data included study and patient characteristics, cancer type, anxiety/depression measures, timing, and prevalence. Meta-analyses, using common- or random-effects models, assessed associations. Subgroup analyses based on follow-up duration and publication bias assessment were performed.

Results: We analyzed seven cohort studies, examining anxiety and depression's impact on mortality in colorectal cancer patients. Samples ranged from 215 to 567 for anxiety and 215 to 46 710 for depression. Using common- or random-effects models based on heterogeneity, anxiety and depression showed increased mortality risk. Pooled odds ratio (OR) for anxiety was 1.07 (95% CI [confidence interval] 1.05–1.10), depression's OR was 2.76 (95% CI 1.25–6.11; random-effects). Pooled hazard ratio (HR) for anxiety was 1.33 (95% CI 1.28–1.37; common-effects) and 1.30 (95% CI 1.19–1.43; random-effects). HRs for depression were 1.45 (95% CI 1.30–1.61; random-effects) and 1.28 (95% CI 1.25–1.32; common-effects). Subgroup analyses revealed stronger effects on mortality in a shorter follow-up (0–5 years) compared to a longer follow-up (5–28 years).

Conclusion: This meta-analysis shows that anxiety and depression are linked to increased mortality in patients with CRC. The findings suggested that screening and treating mental distress improve survival and quality of life in this population.

Keywords: Anxiety, depression, colorectal cancer, mortality, meta-analysis

Introduction

Colorectal cancer (CRC) is one of the most common and deadly cancers worldwide, with an estimated 1.9 million new cases and 935 000 deaths in 2020.[1] According to the estimates of the China National Cancer Center, approximately 406 000 new cases of CRC were diagnosed in China in 2016, accounting for 10% of all cancer cases and causing approximately 167 000 related deaths.[2] Patients with CRC face many physical and mental challenges during and after their diagnosis and treatment, and these challenges may affect their quality of life and survival outcomes. Among the mental challenges, anxiety and depression are the most prevalent and distressing mental health disorders in this population.[3] Anxiety and depression can have negative impacts on adherence to treatment, immune function, pain perception, recovery process, and overall well-being of patients with CRC.[4] Moreover, anxiety and depression may increase the risk of mortality in these patients.[5]

However, evidence of the associations among anxiety, depression, and mortality in patients with CRC is inconclusive. Previous studies have used different methods to measure and define anxiety and depression, particularly self-report questionnaires, clinical interviews, and diagnostic criteria. They vary in terms of timing and frequency of assessments, duration of

Peiwen Yuan[1]
Dong Wang[2]
Dafei Xie[2]

[1]*Department of Hemodialysis Room, Zhejiang Hospital, Zhejiang Province, China*
[2]*Department of General Surgery, Zhejiang Hospital, Zhejiang Province, China*

Corresponding author:
Dafei Xie
✉ lastfengying@163.com

Received: September 27, 2023
Revision Requested: October 18, 2023
Last Revision Received: April 8, 2024
Accepted: April 16, 2024
Publication Date: September 2, 2024

Cite this article as: Yuan P, Wang D, Xie D. Anxiety and depression after colorectal cancer surgery: A systematic review and meta-analysis of short- and long-term outcomes. *Alpha Psychiatry.* 2024;25(4):429-439.

follow-up, adjustment for confounding factors, and statistical models used to estimate effect sizes. These methodological differences may explain the heterogeneity and inconsistency of the results of the studies. Similarly, our research has certain limitations in terms of generalizability. Whereas past studies primarily concentrated on specific subgroups of patients with CRC, such as those with advanced or metastatic disease or those undergoing specific treatments, including chemotherapy or surgery, our study focused on postoperative patients with CRC. Our findings, despite contributing to the broad understanding of the impact of anxiety and depression on the outcomes of patients with CRC, may not encompass all the conditions or stages of CRC.

To address these gaps in the literature, we conducted a systematic review and meta-analysis of cohort studies that evaluated the association of anxiety or depression, or both with mortality in patients with CRC. We aimed to synthesize existing evidence and quantify the effect sizes using standardized measures. We also aimed to explore the potential sources of heterogeneity in the studies by conducting subgroup analyses based on the basis of follow-up duration. We hypothesized that anxiety and depression would be associated with increased mortality risk among patients with CRC, but the effect sizes would vary according to the length of follow-up.

Methods

Literature Search Strategy

To systematically review and meta-analyze the short- and long-term outcomes of anxiety and depression after CRC surgery, we searched PubMed, EMBASE, and Web of Science databases from inception to August 2023 using a combination of relevant keywords and index terms related to CRC, surgery, anxiety, and depression. For example, in the PubMed database, we used the following search strategy: ((((((((((((((Colorectal Neoplasms[Title/Abstract]) OR (Colorectal Neoplasm[Title/Abstract])) OR (Neoplasm, Colorectal[Title/Abstract])) OR (Neoplasms, Colorectal[Title/Abstract])) OR (Colorectal Tumors[Title/Abstract])) OR (Colorectal Tumor[Title/Abstract])) OR (Tumor, Colorectal[Title/Abstract])) OR (Tumors, Colorectal[Title/Abstract])) OR (Colorectal Cancer[Title/Abstract])) OR (Cancer, Colorectal[Title/Abstract])) OR (Cancers, Colorectal[Title/Abstract])) OR (Colorectal Cancers[Title/Abstract])) OR (Colorectal Carcinoma[Title/Abstract])) OR (Carcinoma, Colorectal[Title/Abstract])) OR (Carcinomas, Colorectal[Title/Abstract])) OR (Colorectal Carcinomas[Title/Abstract])) AND ((((surgery[Title/Abstract]) OR (surgical[Title/Abstract])) OR (operation[Title/Abstract])) OR (resection[Title/Abstract]))) AND (((((((((Anxiety[Title/Abstract]) OR (Angst[Title/Abstract])) OR (Social Anxiety[Title/Abstract])) OR (Anxieties, Social[Title/Abstract])) OR (Anxiety, Social[Title/Abstract])) OR (Social Anxieties[Title/Abstract])) OR (Hypervigilance[Title/Abstract])) OR (Nervousness[Title/Abstract])) OR (Anxiousness[Title/Abstract]))) AND ((((((Depression[Title/Abstract]) OR (Depressive Symptoms[Title/Abstract])) OR (Depressive Symptom[Title/Abstract])) OR (Symptom, Depressive[Title/Abstract])) OR (Emotional Depression[Title/Abstract])) OR (Depression, Emotional[Title/Abstract])). The search strategies in the EMBASE and Web of Science databases are shown in Supplementary File 1. We manually screened the reference lists of eligible studies and relevant reviews to identify additional studies. No language or date restrictions were applied.

Study Screening and Eligibility Criteria

Studies were included when they (1) enrolled adult patients undergoing CRC surgery; (2) assessed anxiety or depression, or both by using validated measures; and (3) reported prevalence of anxiety or depression, or both before surgery, within one month, between 1 and 6 months, and beyond six months after surgery. Studies were excluded when they (1) had a sample size of less than 100; (2) were reviews, meta-analyses, case reports, or conference abstracts; and (3) did not report extractable data on anxiety or depression prevalence. Two reviewers independently screened titles, abstracts, and full texts using these criteria. Conflicts were resolved through discussion with a third reviewer.

Data Extraction and Quality Assessment

Two independent reviewers performed data extraction and quality assessment, and discrepancies were resolved through discussion or consultation with a third reviewer for consensus. Data extraction encompassed key details, such as first author, publication year, country of origin, study design, sample size, patient demographics, cancer type, the hospital anxiety and depression scale (HADS) used to assess anxiety and depression, the timing of assessments, and the prevalence of anxiety and depression at each designated time point. Quality assessment was conducted utilizing the Newcastle–Ottawa Scale,[6] which evaluates the quality of studies according to sample-selection methods, comparability of study cohorts, and adequacy of outcome assessments. Any disagreement between the reviewers was resolved through consensus discussions, and the accuracy and reliability of the data extraction and quality assessment were ensured.

Statistical Analysis

We performed meta-analyses to pool the effect size estimates from the individual studies by using the meta package in R software with the RevMan5 (The Nordic Cochrane Centre, Copenhagen, Denmark) layout. We used odds ratios (ORs) for studies that reported binary outcomes (e.g., mortality yes/no) and hazard ratios (HRs) for studies that reported time-to-event outcomes (e.g., survival time). We converted log ORs and log HRs to their natural units for ease of interpretation. We used a common-effects model when no significant heterogeneity was found in the studies or a random-effects model when significant heterogeneity was found. We assessed heterogeneity by using

MAIN POINTS

- *This meta-analysis of seven cohort studies found that anxiety and depression were associated with increased mortality risk in patients with colorectal cancer.*
- *The pooled odds ratio for the association between anxiety and mortality was 1.07, and the 95% confidence interval (CI) was 1.05-1.10. The pooled odds ratio for depression and mortality was 2.76 (95% CI 1.25–6.11).*
- *The pooled hazard ratio for the association between anxiety and mortality was 1.30 (95% CI 1.19–1.43). The pooled hazard ratio for depression and mortality was 1.45 (95% CI 1.30–1.61).*
- *Significant heterogeneity of studies was found for anxiety and depression likely because of differences in follow-up periods and cutoffs used to define severity.*
- *Subgroup analyses showed that anxiety and depression had stronger associations with mortality in the first 5 years after diagnosis than during long-term follow-ups of 5-28 years.*

Cochran's *Q* test and I^2 statistic. We conducted subgroup analyses by follow-up duration (0–5 years vs. 5–28 years) to explore the potential sources of heterogeneity. We assessed publication bias by using Egger's test and contour-enhanced funnel plots. We performed Galbraith radial and Baujat plots to identify outlier studies and their influence on pooled results. We considered *P* values less than .05 statistically significant.

Results

Search Results

A systematic literature search was conducted using PubMed, EMBASE, and Web of Science databases, which identified 1230 records, with 92 from PubMed, 440 from EMBASE, and 698 from Web of Science. After duplicates were removed, 358 records remained. The screening of titles and abstracts led to the exclusion of 290 records, leaving 68 articles for a full-text review. Of these articles, four were reviews and meta-analyses, 10 had sample sizes less than 50, and 47 had insufficient data. Overall, seven studies met the eligibility criteria for inclusion in the meta-analysis (Figure 1).

Study Characteristics

This meta-analysis included seven cohort studies conducted in the US and Spain. The studies examined anxiety, depression, or both after a cancer diagnosis (Table 1). Study sample sizes ranged from 215 to 567 for the anxiety group and from 215 to 46 710 for the depression group. Data sources included the National Health Survey and Health and Retirement Study in the United States, the Utah Population Database in the United States, the Spanish National Health Survey in Spain, and other institution-specific cohorts. Follow-up periods spanned from 6 months to 28 years, and most studies assessed outcomes at multiple time points within the first 5 years after diagnosis. Five studies examined anxiety and depression, whereas 2 studies focused only on depression. The diversity of data sources and the broad range of follow-up assessments enabled the characterization of the trajectory of mental outcomes from diagnosis through long-term survivorship.

Meta-Analysis of Anxiety and Mortality Risk with OR Value

In the meta-analysis including the five datasets from 2 studies, the pooled OR for the association between anxiety and mortality was 1.07 with a 95% confidence interval (CI) of 1.05-1.10 (Figure 2A). Nearly all (99.9%) of the weight came from the study by Orive et al., 2022. After the study by Orive et al., 2022, was excluded, the pooled OR was 1.01 (95% CI 0.52–1.99; Figure 2B). The pooled OR of 1.07 from the full meta-analysis suggests there may be a small but significant association between anxiety and increased mortality risk. However, the CI ranged from 1.05 to 1.10, indicating the precision of this estimate was largely driven by the study by Orive et al., 2022.

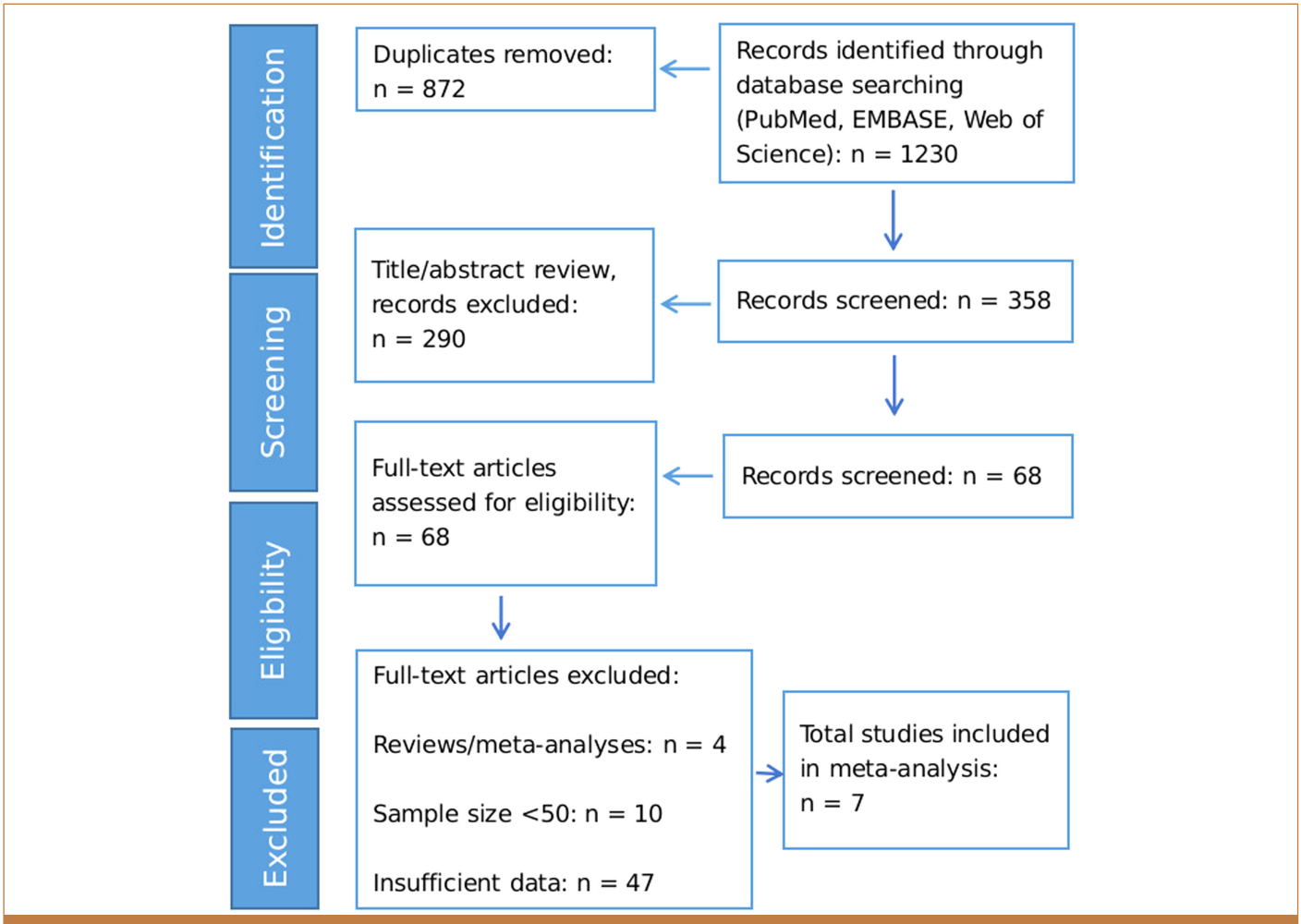

Figure 1. PRISMA of meta-analysis.

Table 1. Characteristics of Included Studies on Mental Health Disorders (Anxiety and Depression) in Patients with CRC

Study	Country	Study Design	Data Source	Follow-Up Timeline	Sample Size		Depression Scale
					Anxiety	Depression	
Trudel-Fitzgerald et al., 2020[7]	USA	Cohort	NHSa and HPFSb	0–28 years	567	1,056	MHI-5 | CES-D | GDS-SF
Lloyd et al., 2019[8]	USA	Cohort	UPDBc	0–2, 2–5, and 5+ years	522/214/321	629/266/289	N/A
Orive et al., 2023[9]	Spain	Cohort	SNHSd	0–5 years	N/A	2,531	HADS-Depression: 8-14 vs ≤ 7 | ≥ 15 vs ≤ 7
Soria-Utrilla et al., 2022[10]	Spain	Cohort	This study	0–6 and 0–12 months	215	215	N/A
Weissman et al., 2021[11]	USA	Cohort	This study	0–1 years	N/A	46,710	N/A
Varela-Moreno et al., 2022[12]	Spain	Cohort	CARESS-CCR	0–5 years	N/A	619	HADS-depression: Normal (< 8) 1983 76 | Probable case (8–11) 291 11 | Positive case (>11) 328 13
Orive et al., 2022[13]	Spain	Cohort	SNHS	0–5 years	N/A	N/A	N/A

CRC, colorectal cancer; HADS, Hospital Anxiety and Depression Scale.
[a]Nurses Health Study (NHS).
[b]Health Professional Follow-Up Study (HPFS).
[c]The Utah Population Database (UPDB).
[d]Spanish National Health Service (SNHS).

It dominated the meta-analysis likely because it had a substantially more precise effect size estimate than the other studies, as evidenced by its narrow CI. Precise studies received large weights in meta-analysis models. After the study by Orive et al., 2022, was excluded, the pooled effect size markedly shifted closer to the null, and the CI widened substantially. This result suggests significant heterogeneity in the findings of Orive et al., 2022, and the other studies. Potential sources of heterogeneity included differences in follow-up times and patient populations. Orive et al., 2022, conducted a 5-year follow-up, whereas the other studies examined outcomes within 1 year. The

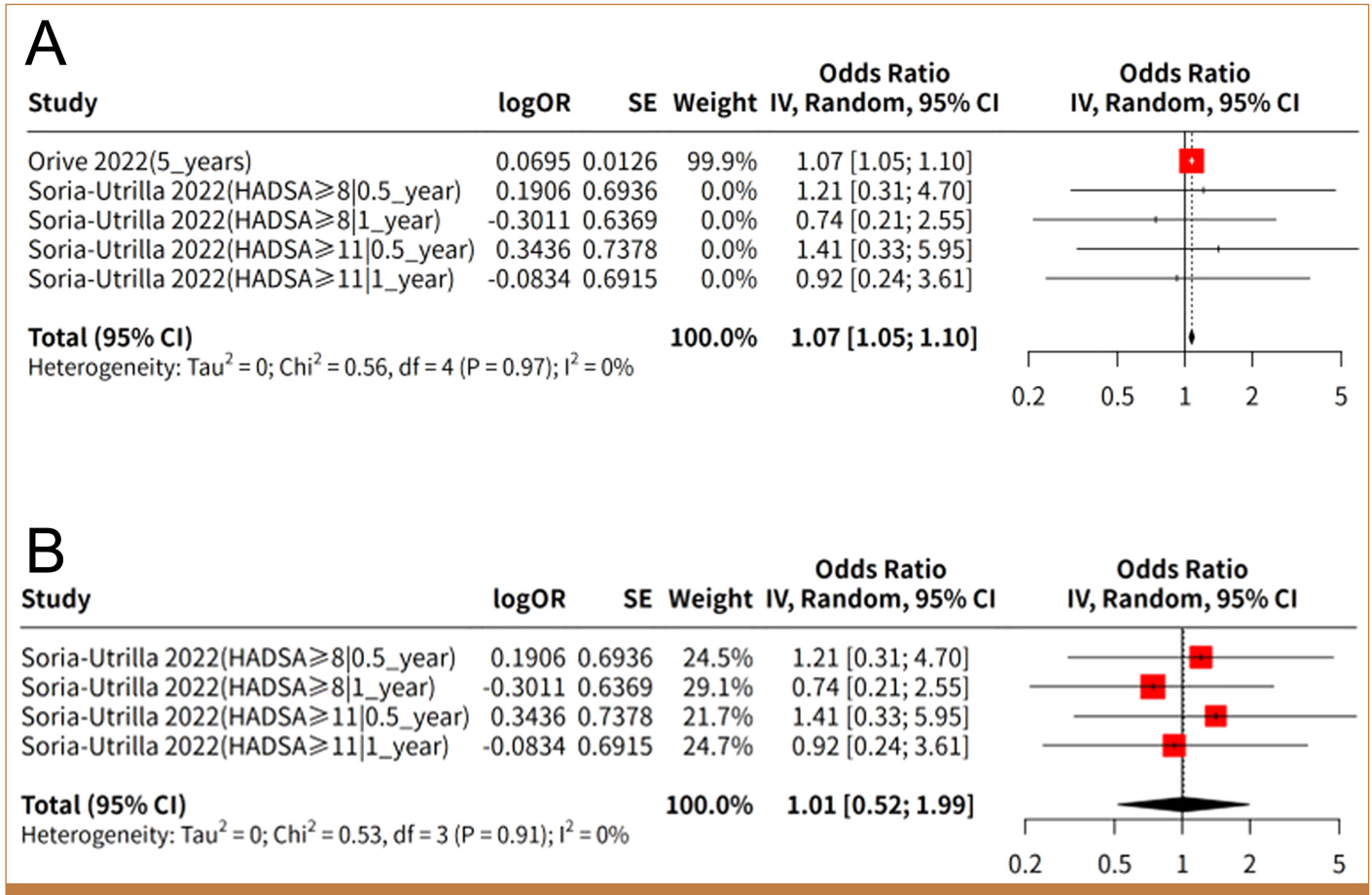

Figure 2. Forest plots of meta-analysis of anxiety and mortality risk with Odds Ratio (OR) value. (A) Pooled ORs for anxiety and mortality including all studies. (B) Pooled ORs after the study by Orive et al., 2022, was excluded.

long follow-up may have resulted in the detection of additional mortality events.

Meta-Analysis of Depression and Mortality Risk with OR Value

The meta-analysis of five datasets from 2 studies found significant heterogeneity ($I^2 = 72\%$, $Tau^2 = 0.4727$, $\chi^2 = 14.51$, df = 4, $P < .01$) in the relationship between depression and mortality risk. The pooled ORs were 2.76 (95% CI 1.25–6.11) when the random-effects model was used and 1.12 (95% CI 1.09–1.15) when the common-effects model was used (Figure 3A).

The random-effects model accounted for variability across studies and yielded a pooled OR of 2.76, suggesting that depression was associated with over 2.5 times the mortality risk in this population. However, the common-effects model produced a modest OR of 1.12 (95% CI 1.09–1.15). This discrepancy may be due to the common-effects model assuming homogeneity across studies and the random-effects model incorporating heterogeneity.

Potential sources of heterogeneity likely include differences in follow-up duration and cutoffs used in defining depression severity. For instance, the included studies had follow-up periods ranging from 6 months to 5 years and used different thresholds on depression scales to categorize patients. We found that studies with short follow-up periods (6 months to 1 year) reported stronger associations between depression and mortality than a 5-year follow-up study. This result suggests that mortality risk associated with depression is pronounced in the short-term postoperative period.

The contour-enhanced funnel plot indicated no evidence of publication bias in the included studies (Figure 3B). All studies fell within the shaded areas representing statistical significance, and no studies fell

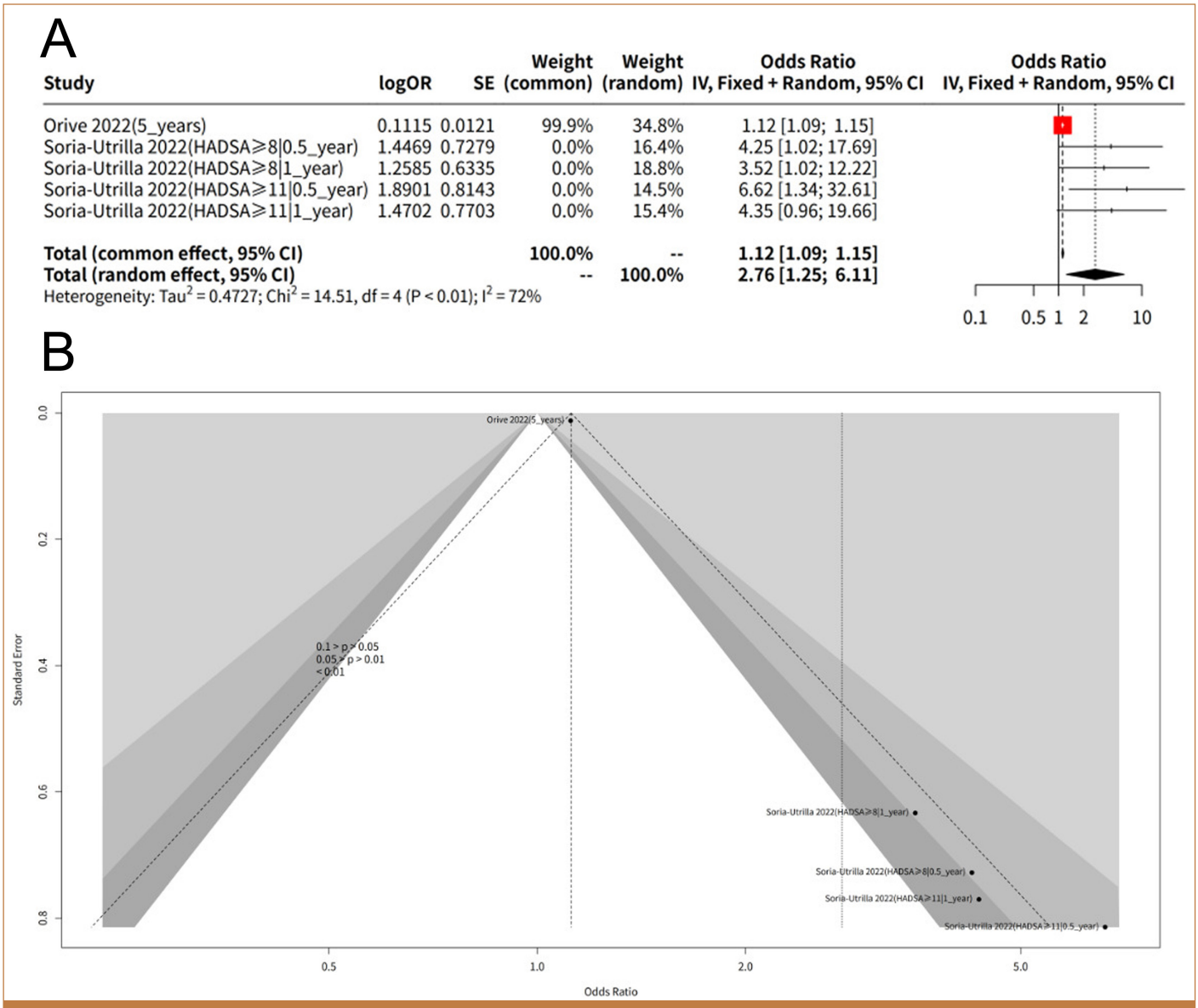

Figure 3. Forest plots of meta-analysis of depression and mortality risk with OR value. (A) Pooled OR for depression and mortality including all studies. (B) Contour-enhanced funnel plot of included studies.

within the white nonsignificant areas. Small studies and those with low precision were symmetrically distributed at the bottom, whereas large and precise studies were clustered near the top. The symmetric funnel shape and absence of studies in the white areas suggested a low risk of publication bias. That is, the meta-analysis likely provided an accurate representation of the available evidence rather than an overestimate of the true effect size due to the selective publishing of positive studies. However, the included studies all had relatively large sample sizes, as evidenced by their distribution clustered at the top half of the plot. The lack of smaller studies in the bottom left and right areas indicated the underrepresentation of small negative trials. The contour shading showed that most studies fell within the .01 significance level, reflecting their adequate statistical power and precision. This finding lent credibility to the pooled results.

Meta-Analysis of Anxiety and Mortality Risk with HR Value

The meta-analysis of 25 datasets from four studies found a significant relationship between anxiety and mortality risk, but substantial heterogeneity was observed ($I^2 = 90\%$, $P < .01$). The pooled HRs were 1.33 (95% CI 1.28–1.37) when the common-effects model was used and 1.30 (95% CI 1.19–1.43) when the random-effects model was used (Figure 4A).

Considerable heterogeneity, evidenced by the I^2 value of 90% and a highly significant Q test ($P < .01$) indicated the presence of variability in effects among studies. The random-effects model yielded a pooled HR of 1.33, suggesting that anxiety is associated with a 33% higher mortality risk. The common-effects model produced a slightly lower estimate (1.30). The difference may be because the common-effects analysis did not account for the heterogeneity. The potential sources of heterogeneity included differences in follow-up periods, which ranged from 2 years to 28 years, and varying cutoffs for defining anxiety severity. The studies adjusted for different sets of confounders and may have thus introduced variability.

Egger'sTest and Funnel Plot for Assessing Publication Bias of Anxiety and Mortality Risk

The Egger's linear regression test showed no evidence of significant publication bias, and a *P*-value of .6813 (>.05) was obtained. The contour-enhanced funnel plot (Figure 4B) showed an asymmetrical distribution, and several studies by Trudel-Fitzgerald et al., 20 2020, fell in the white nonsignificant areas. Smaller and less precise studies were spread across the bottom portion, and larger and more precise studies were concentrated near the top center. The nonsignificant result indicated that the funnel plot was symmetrical and the meta-analysis likely provided an unbiased estimate of the true effect size. The Egger's test indicated no significant publication bias, and the contour-enhanced funnel plot appears asymmetrical. This discrepancy might be attributed to several factors. Firstly, the limited number of studies included in our meta-analysis could reduce the power of Egger's test to detect publication bias. A small sample of studies may not provide enough data points for a robust regression analysis, leading to a non-significant p-value. Secondly, the observed asymmetry in the funnel plot, despite a non-significant Egger's test, could be influenced by the heterogeneity of the study results, or even chance. Variability in study designs, populations, and methodologies can lead to such heterogeneity, which might manifest as asymmetry in the funnel plot. Therefore, while Egger's test suggests an absence of publication bias, the funnel plot advises caution and highlights the need for a nuanced interpretation of these results.

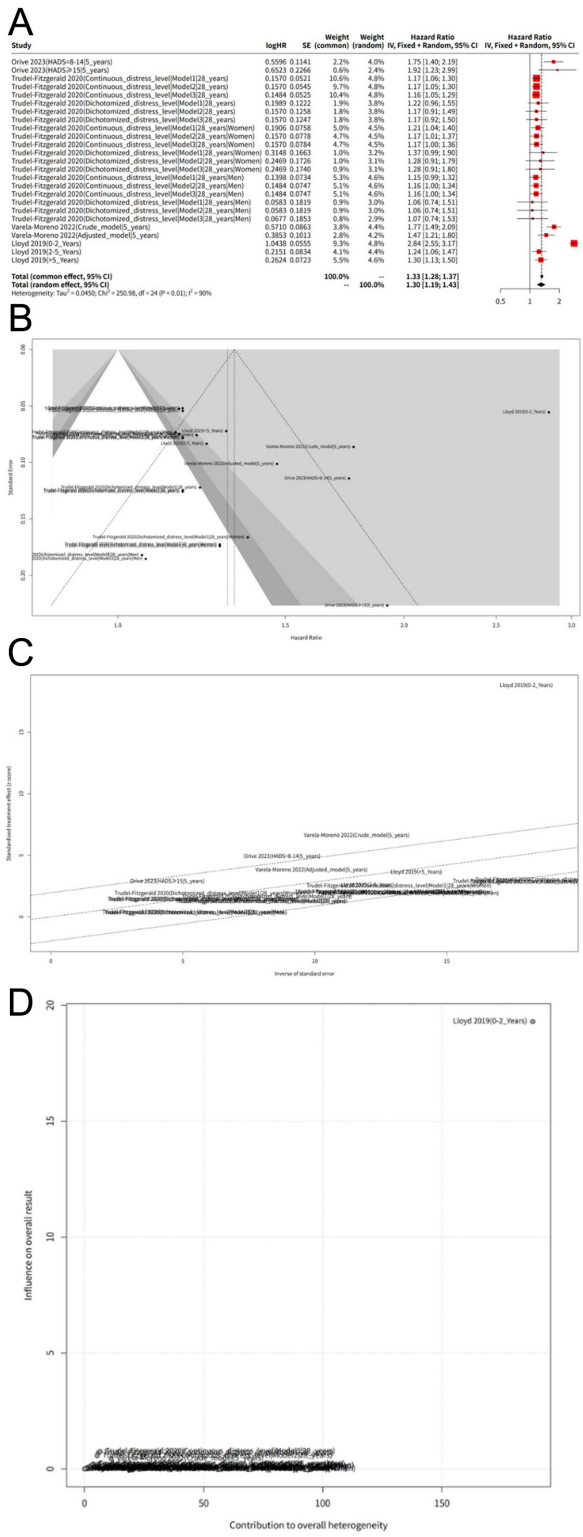

Figure 4. Meta-analysis of anxiety and mortality risk with HR values. (A) Forest plot of meta-analysis examining the association between anxiety and mortality risk. (B) Contour-enhanced funnel plot of studies included in the meta-analysis. (C) Galbraith radial plot showing studies outside the credibility bounds as sources of heterogeneity in the meta-analysis. (D) Baujat plot identifying the study of Lloyd et al., 2019 (follow-up: 0–2 years) as having the highest influence on the pooled results.

Galbraith Radial and Baujat Plots of Anxiety and Mortality Risk

The Galbraith plot (Figure 4C) outliers confirmed that some studies, such as those of Lloyd et al., 2019 (follow-up: 0–2 years) and Varela-Moreno et al., 2022 (crude model, follow-up: 5 years), were the sources of the substantial heterogeneity observed in the meta-analysis. Their large and variable effect sizes skewed the pooled estimate. The study of Lloyd et al., 2019 (follow-up: 0–2 years), impacted the overall results according to the Baujat analysis (Figure 4D). The possible reason was its large sample size and extremely large effect size (HR = 2.84) relative to the effect sizes of other included studies. The heterogeneity introduced by the studies can be due to short follow-up periods capturing acute postoperative mortality, lack of adjustment for confounders, or clinical and methodological differences.

Meta-Analysis of Depression and Mortality Risk with HRValue

The meta-analysis of 25 datasets from four studies found a significant relationship between depression and increased mortality risk, but substantial heterogeneity ($I^2 = 92\%$, $P < .01$). The pooled HRs were 1.45 (95% CI 1.30–1.61) when the random-effects model was used and 1.28 (95% CI 1.25–1.32) when the common-effects model was used (Figure 5A).

Significant heterogeneity in the included studies was shown (high I^2 value of 92% and statistically significant Q test; $P < .01$). This result indicated variability in the strength of association between depression and mortality risk. The random-effects model accounting for heterogeneity yielded a pooled HR of 1.45, suggesting that depression was associated with a 45% increase in mortality risk. The common-effects estimate was low at 1.28, likely because heterogeneity was unaccounted for. The sources of heterogeneity may include differing follow-up periods ranging from 2 years to 28 years, use of varying cutoffs to define depression severity, and inconsistencies in confounder adjustment among different studies.

Egger's Test and Funnel Plot for Assessing Publication Bias of Depression and Mortality Risk

The Egger's linear regression test showed evidence of possible publication bias, and a statistically significant *P*-value of .0138 (<.05) was obtained. The test evaluated funnel plot asymmetry by determining whether the intercept significantly deviated from zero in a regression of the standardized effect estimates against their precision. Here, the intercept was 0.0425, the standard error was 0.0882, and a *t*-value of 2.67 was considered significant. The contour-enhanced funnel plot showed a symmetrical distribution; all the studies fell within the shaded areas representing statistical significance, and none fell in the white nonsignificant areas (Figure 5B). Small studies and those with low precision were clustered symmetrically at the bottom, whereas large and precise studies were concentrated in the top-center portion. The statistically significant Egger's test suggested the presence of publication bias. However, the contour-enhanced funnel plot demonstrated a symmetrical distribution, and studies clustered by precision. There were no missing studies in nonsignificant areas. Overall, the findings provided preliminary but inconclusive evidence regarding publication bias in the meta-analysis, warranting further investigation through quantitative techniques and influence analyses.

Galbraith Radial and Baujat Plots of Depression and Mortality Risk

The Galbraith radial plot (Figure 5C) identified several outlier studies falling outside the credibility bounds, including the studies of Lloyd

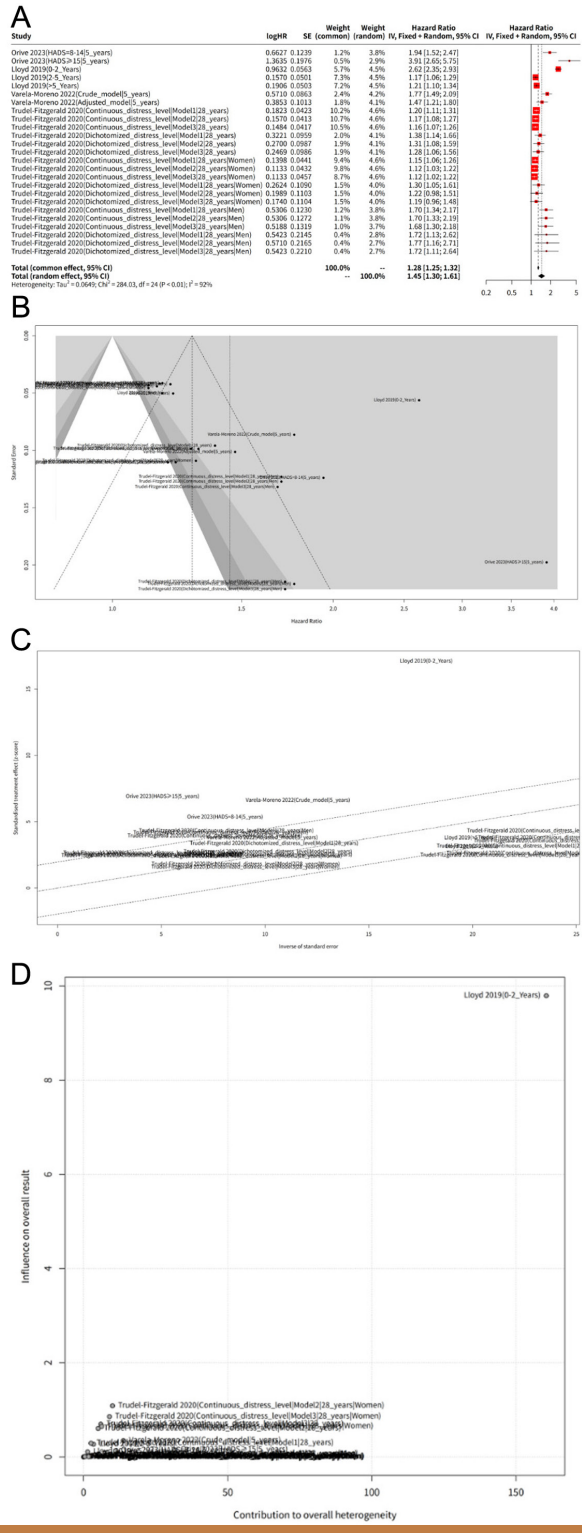

Figure 5. Meta-analysis of depression and mortality risk with an HR values. (A) Forest plot of meta-analysis examining the association between depression and mortality risk. (B) Contour-enhanced funnel plot of studies included in the meta-analysis. (C) Galbraith radial plot showing studies outside the credibility bounds as sources of heterogeneity in the meta-analysis. (D) Baujat plot identifying the study of Lloyd et al., 2019 (follow-up: 0-2 Years) as having the highest influence on the pooled results.

et al., 2019 (follow-up: 0-2 years), Varela-Moreno et al., 2022 (crude mode, follow-up: 5 years), and Orive et al., 2023 (HADS ≥ 15, follow-up: 5 years). These studies had large standardized effect sizes; that is, they were major contributors to heterogeneity. The Baujat plot (Figure 5D) showed that the study of Lloyd et al., 2019 (follow-up: 0–2 years) had the highest influence on the overall meta-analysis results.

Subgroup Meta-Analysis of Anxiety and Mortality Risk with HR Value

For the subgroup with a follow-up period of 5 to 28 years, moderate heterogeneity was found in the studies ($Tau^2 = 0.0087$, $\chi^2 = 43.53$, df = 22, $P < .01$, $I^2 = 49\%$). The common-effects model showed that anxiety was associated with a 23% increase in the risk of mortality (HR = 1.23, 95% CI = 1.18–1.27). The random-effects model showed a similar result (HR = 1.25, 95% CI = 1.18–1.32). For the subgroup with a follow-up of 0 to 5 years, high heterogeneity was found in the studies ($Tau^2 = 0.3383$, $\chi^2 = 68.39$, df = 1, $P < .01$, $I^2 = 99\%$). The common-effects model showed that anxiety was associated with a 120% increase in the risk of mortality (HR = 2.20, 95% CI = 2.01–2.41). The random-effects model showed a low but still significant result (HR = 1.88, 95% CI = 0.84-4.24). The results suggested that anxiety is a significant predictor of mortality in both subgroups, but the effect was stronger in the subgroup with a short follow-up period. This result indicated that anxiety had a more immediate impact on health outcomes or that other factors may have mediated or moderated the relationship between anxiety and mortality over time (Figure 6).

Subgroup Meta-Analysis of Depression and Mortality Risk with HR Value

For the subgroup with a follow-up of 5 to 28 years, high heterogeneity was found in the studies ($Tau^2 = 0.0440$, $\chi^2 = 112.63$, df = 22, $P < .01$, $I^2 = 80\%$). The common-effects model showed that depression was associated with a 23% increase in the risk of mortality (HR = 1.23, 95% CI = 1.20–1.27). The random-effects model showed a higher result (HR = 1.41, 95% CI = 1.28–1.55). For the subgroup with a follow-up of 0 to 5 years, extremely high heterogeneity was found in the studies ($Tau^2 = 0.3221$, $\chi^2 = 114.5$, df = 1, $P < .01$, $I^2 = 99\%$). The common-effects model showed that depression was associated with a 67% increase in the risk of mortality (HR = 1.67, 95% CI = 1.55–1.80). The random-effects model showed a similar result (HR = 1.75, 95% CI = 0.79–3.86). The results suggested that depression is a significant predictor of mortality in both subgroups, but the effect was stronger in the subgroup with short follow-up periods. This result indicated that depression exerted an immediate impact on health outcomes or

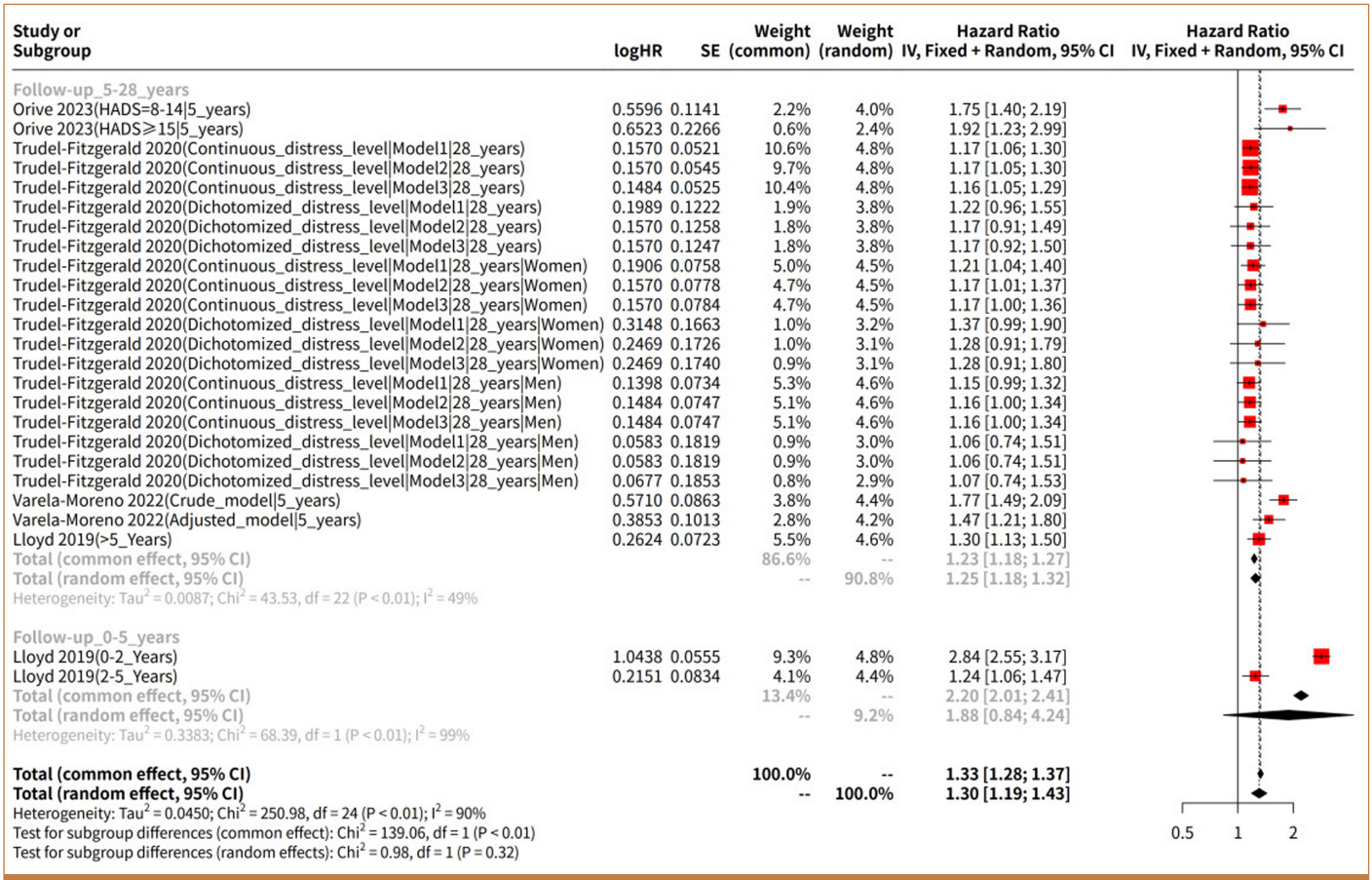

Figure 6. Forest plots of the subgroup meta-analysis of anxiety and mortality risk with HR values. The horizontal lines represent the 95% confidence intervals of the HR estimates for each study. The diamonds represent the pooled HR estimates for each subgroup. The size of the squares reflects the weight of each study in the meta-analysis. The vertical dashed line indicates the null value of HR = 1, which indicated that no association was found between anxiety and mortality. The forest plots showed that most studies and subgroups had HR estimates above 1, indicating a positive association between anxiety and mortality. The forest plots also showed that the subgroup with a follow-up of 0-5 years had wider confidence intervals and more heterogeneity than the other subgroup, suggesting uncertainty and variability in the results.

other factors that may have mediated or moderated the relationship between depression and mortality over time (Figure 7).

Discussion

The results of this meta-analysis suggested that anxiety and depression are associated with increased mortality risk in patients with CRC but showed substantial heterogeneity in the studies. The effect sizes varied according to follow-up duration, the definition and measurement of anxiety and depression, and adjustment for confounding factors. The findings were consistent with previous reviews that reported the negative impact of mental distress on survival outcomes in patients with cancer.[14] However, this meta-analysis focused specifically on patients with CRC and included the most recent and comprehensive evidence available.

The substantial heterogeneity observed in our meta-analyses of the relationship among anxiety, depression, and mortality risk in patients with CRC can be attributed to several factors. First, the heterogeneity may have stemmed from differences in study design and methodology. The included studies varied in assessment methods for anxiety and depression, using self-reported questionnaires or clinical diagnoses, and this difference may have led to variable measured effects. Second, patient characteristics across the studies were not uniform, and variations in demographics, cancer stage, treatment type, and comorbidity contributed to differences in the observed associations between mental health conditions and mortality risk. Third, the follow-up durations of the studies considerably varied. Studies with short follow-up periods may have captured the immediate effects of anxiety and depression on mortality, whereas those with long follow-up periods might have reflected the cumulative impact of psychological factors over time. Finally, differences in how studies adjusted for potential confounders may have also contributed to heterogeneity. Some studies might have controlled for a wide range of variables, whereas others may not, and this difference may have led to variations in the estimated effects of anxiety and depression on mortality.

The potential mechanisms underlying the association among anxiety, depression, and mortality are not fully understood, but several biological and behavioral pathways have been proposed. Anxiety and depression may impair immune function, increase inflammation, alter hormonal levels, and interfere with DNA repair, which may

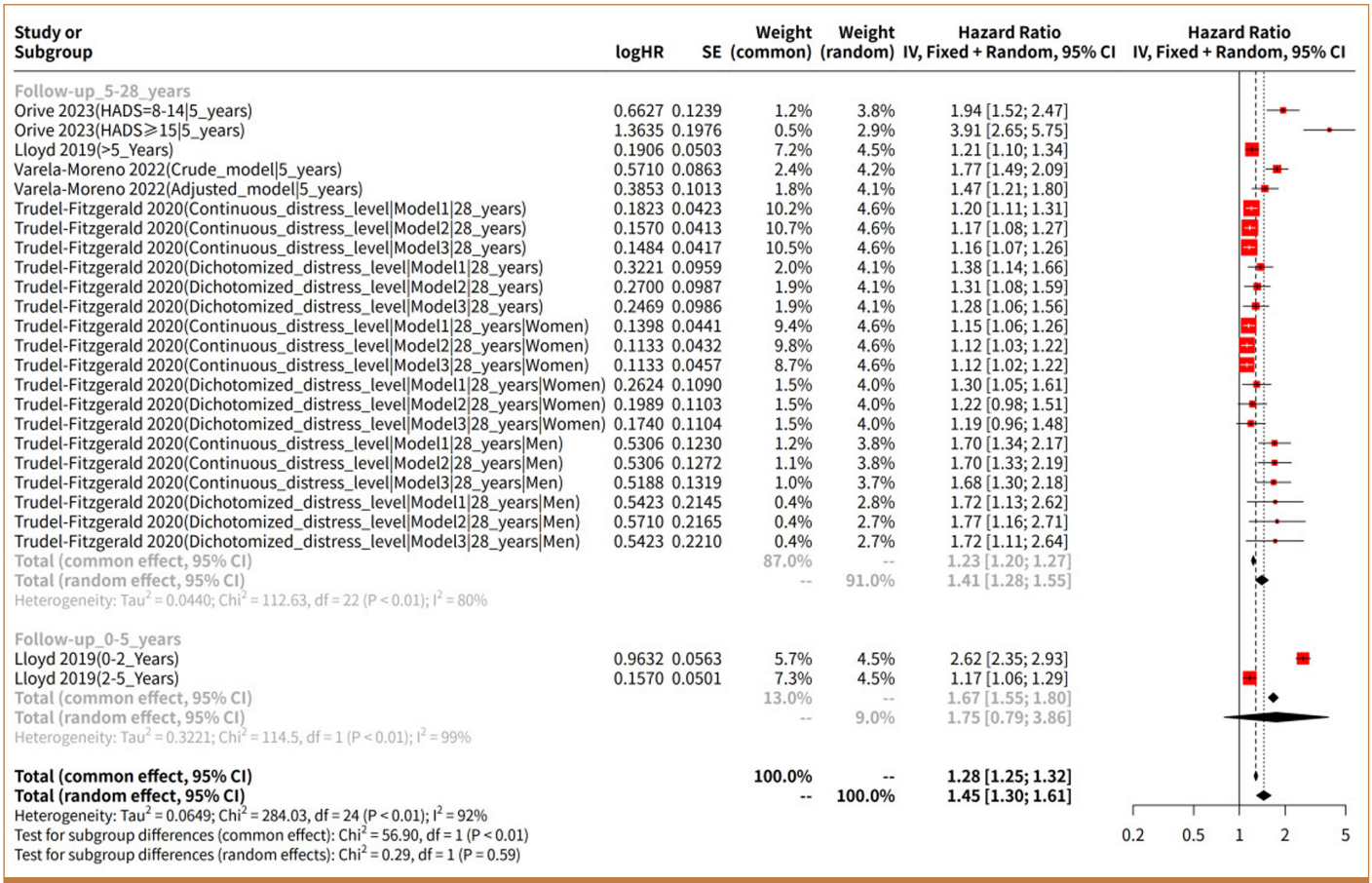

Figure 7. Forest plots of the subgroup meta-analysis of depression and mortality risk with an HR values. The horizontal lines represent the 95% confidence intervals of the HR estimates for each study. The diamonds represent the pooled HR estimates for each subgroup. The size of a square reflects the weight of each study in the meta-analysis. The vertical dashed line indicates the null value (HR = 1), which indicates the absence of association between depression and mortality. The forest plots show that most studies and subgroups have HR estimates above 1, indicating a positive association between depression and mortality. The forest plots also show that the subgroup with a follow-up of 0 to 5 years has wider confidence intervals and more heterogeneity than the subgroup with a follow-up of 5 to 28 years, suggesting uncertainty and variability in the results.

promote tumor growth and metastasis.[15-17] Anxiety and depression may also affect different types of health behavior, such as adherence to treatment, physical activity, smoking, alcohol consumption, and dietary habits, and may influence survival outcomes.[18,19] Moreover, anxiety and depression may reduce quality of life, social support, coping skills, and self-efficacy, thereby affect mental well-being and resilience.[20,21]

The results of this meta-analysis have several implications for clinical practice and research. First, they highlight the importance of screening for anxiety and depression in patients with CRC, especially in the early postoperative period when mental distress may be prevalent and detrimental. Second, they suggest the need for developing and implementing effective psychosocial interventions to prevent and treat anxiety and depression in this population. Such interventions may include cognitive-behavioral therapy, mindfulness-based stress reduction, relaxation training, psychoeducation, and supportive care.[22-24] Third, they indicate the necessity of conducting rigorous and homogeneous studies to examine the causal relationships among anxiety, depression, and mortality in patients with CRC. Moreover, factors such as comorbidities, socioeconomic status, treatment modalities, and social support networks may intricately intertwine with psychological well-being, resulting in a multifaceted impact on patient outcomes. In-depth research is essential to explore the complex interplay of these variables and their specific contributions to the mental health and survival of patients with CRC. This intricate relationship necessitates comprehensive investigation not only to deepen our understanding of underlying mechanisms but also to guide the development of targeted interventions aimed at improving the overall quality of life and survival prospects for patients with CRC.

However, the limitations of this meta-analysis should be recognized, including the heterogeneity of the included studies; potential publication bias; absence of data on the specific subtypes of anxiety and depression; potential confounding variables such as comorbidities and treatment modalities; and the inability to establish causality because of the observational nature of the studies. Besides, only 2 studies reported the mean and standard deviation of age, while the others reported the age distribution in categories or percentages. Hence, we could not calculate the weighted mean age for each study or compare the effect sizes across different age groups. As for the severity degree of depression's effect on mortality, the effect of the severity degree of depression on mortality could not be assessed, as the data provided by the studies are insufficient. Only three studies reported the subgroup data based on different cut-off scores of depression scales, while the others did not. Moreover, the studies used different types of depression scales, such as HADS, MHI-5, CES-D, and GDS-SF, which could not be standardized or compared. Thus, the pooled effect size could not be calculated. Therefore, despite our findings providing valuable insights, they should be interpreted with caution. Besides, this meta-analysis was not registered on a publicly available website, such as PROSPERO, but the steps of conducting a meta-analysis were strictly followed to avoid duplication and effectively avoid selection bias. For duplication avoidance, before conducting this meta-analysis, we conducted a comprehensive search of relevant literature and found that evidence of the associations among anxiety, depression, and mortality in patients with CRC is inconclusive, and prior studies primarily paid attention to specific subgroups of patients with CRC, such as those with advanced or metastatic disease or those undergoing specific treatments, including chemotherapy or surgery. The current meta-analysis focused on postoperative patients with CRC. For the avoidance of selection bias, this meta-analysis established clear and strictly unified literature eligibility criteria. In addition, 2 reviewers independently screened titles, abstracts, and full texts using the criteria, and conflicts were resolved through discussion with a third reviewer. Further research is needed to validate and elucidate the associations among anxiety, depression, and mortality in patients with CRC.

Conclusion

This meta-analysis provided evidence that anxiety and depression are associated with increased mortality risk in patients with CRC but observed the substantial heterogeneity in the studies. The effect sizes varied according to follow-up duration, the definition and measurement of anxiety and depression, and the adjustment for confounding factors. The results suggested that anxiety and depression have biological and behavioral impacts on health outcomes and that psychosocial interventions improve survival and quality of life in this population. However, rigorous and homogeneous studies are needed to confirm and elucidate the causal relationships among anxiety, depression, and mortality in patients with CRC. The findings of this meta-analysis have implications for clinical practice and research because they highlight the importance of screening for and treating mental distress in these patients.

Availability of Data and Materials: *The data and materials utilized in this meta-analysis were sourced from publicly available databases and are described in the Methods section. Extracted data, study characteristics, and quality assessments are summarized in a standardized spreadsheet, which is accessible upon request from the corresponding author. We are committed to promoting data transparency and reproducibility, and researchers interested in the complete dataset may contact the corresponding author for further details on data availability.*

Acknowledgments: *The authors gratefully acknowledge the authors of the primary studies included in this meta-analysis, the editorial and peer review teams of the journals, and colleagues and collaborators for their valuable input. This research was self-funded with no conflicts of interest. The authors also extend their appreciation to the patients with CRC, whose participation and data sharing are instrumental in advancing our understanding of the relationships among anxiety, depression, and mortality. Their contributions, along with the support and insights of various contributors, are indispensable to the completion of this study.*

Ethics Committee Approval: *Not applicable.*

Informed Consent: *Not applicable.*

Peer-review: *Externally peer-reviewed.*

Author Contributions: *Conception – P.Y., D.W., D.X.; Design – P.Y., D.W., D.X.; Supervision – P.Y., D.W., D.X.; Materials – D.W., D.X.; Data Collection and/or Processing – P.Y., D.X.; Analysis and/or Interpretation – P.Y.; Literature Review – D.W., D.X.; Writing – P.Y., D.W., D.X.; Critical Review – P.Y., D.W., D.X.*

Declaration of Interests: *The authors have no conflicts of interest to declare.*

Funding: *The authors declared that this study has received no financial support.*

References

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71(3):209-249. [CrossRef]
2. Research and Markets. *Colorectal Cancer: Epidemiology Analysis and Market Forecast to 2030 (Report No. 5642605)*; 2021.
3. Peng YN, Huang ML, Kao CH. Prevalence of depression and anxiety in colorectal cancer patients: A literature review. *Int J Environ Res Public Health*. 2019;16(3):411. [CrossRef]
4. Alacacioglu A, Binicier O, Gungor O, Oztop I, Dirioz M, Yilmaz U. Quality of life, anxiety, and depression in Turkish colorectal cancer patients. *Support Care Cancer*. 2010;18(4):417-421. [CrossRef]
5. Mosher CE, Winger JG, Given BA, Shahda S, Helft PR. A systematic review of psychosocial interventions for colorectal cancer patients. *Support Care Cancer*. 2017;25(7):2349-2362. [CrossRef]
6. Lo CK, Mertz D, Loeb M. Newcastle-Ottawa Scale: comparing reviewers' to authors' assessments. *BMC Med Res Methodol*. 2014;14:45. [CrossRef]
7. Trudel-Fitzgerald C, Tworoger SS, Zhang X, Giovannucci EL, Meyerhardt JA, Kubzansky LD. Anxiety, depression, and colorectal cancer survival: results from two prospective cohorts. *J Clin Med*. 2020;9(10):3174. [CrossRef]
8. Lloyd S, Baraghoshi D, Tao R, et al. Mental health disorders are more common in colorectal cancer survivors and associated with decreased overall survival. *Am J Clin Oncol*. 2019;42(4):355-362. [CrossRef]
9. Orive M, Barrio I, Lázaro S, et al. REDISSEC-CARESS/CCR group. Five-year follow-up mortality prognostic index for colorectal patients. *Int J Colorectal Dis*. 2023;38(1):64. [CrossRef]
10. Soria-Utrilla V, Sánchez-Torralvo FJ, González-Poveda I, et al. Prevalence of anxiety and depression symptoms and their relationship with nutritional status and mortality in patients with colorectal cancer. *Int J Environ Res Public Health*. 2022;19(20):13548. [CrossRef]
11. Weissman S, Ghoneim S, Sanayei A, et al. New-onset depression after colorectal cancer diagnosis: a population-based longitudinal study. *Int J Colorectal Dis*. 2021;36(12):2599-2602. [CrossRef]
12. Varela-Moreno E, Rivas-Ruiz F, Padilla-Ruiz M, et al. Influence of depression on survival of colorectal cancer patients drawn from a large prospective cohort. *Psychooncology*. 2022;31(10):1762-1773.
13. Orive M, Anton-Ladislao A, Lázaro S, et al. Anxiety, depression, health-related quality of life, and mortality among colorectal patients: 5-year follow-up. *Support Care Cancer*. 2022;30(10):7943-7954. [CrossRef]
14. Walker ZJ, Xue S, Jones MP, Ravindran AV. Depression, anxiety, and other mental disorders in patients with cancer in low- and lower-middle-income countries: A systematic review and meta-analysis. *JCO Glob Oncol*. 2021;7:1233-1250. [CrossRef]
15. Currier MB, Nemeroff CB. Depression as a risk factor for cancer: from pathophysiological advances to treatment implications. *Annu Rev Med*. 2014;65:203-221. [CrossRef]
16. Aminisani N, Nikbakht H, Asghari Jafarabadi M, Shamshirgaran SM. Depression, anxiety, and health related quality of life among colorectal cancer survivors. *J Gastrointest Oncol*. 2017;8(1):81-88. [CrossRef]
17. Cheng V, Oveisi N, McTaggart-Cowan H, Loree JM, Murphy RA, De Vera MA. Colorectal cancer and onset of anxiety and depression: A systematic review and meta-analysis. *Curr Oncol*. 2022;29(11):8751-8766. [CrossRef]
18. Niedzwiedz CL, Knifton L, Robb KA, Katikireddi SV, Smith DJ. Depression and anxiety among people living with and beyond cancer: a growing clinical and research priority. *BMC Cancer*. 2019;19(1):943. [CrossRef]
19. Li M, Fitzgerald P, Rodin G. Evidence-based treatment of depression in patients with cancer. *J Clin Oncol*. 2012;30(11):1187-1196. [CrossRef] Epub 2012 Mar 12. Erratum in: *J Clin Oncol*. 2013;31(28):3612
20. Roohafza HR, Afshar H, Keshteli AH, et al. What's the role of perceived social support and coping styles in depression and anxiety? *J Res Med Sci*. 2014;19(10):944-949.
21. Karataş T, Ayaz-Alkaya S, Özdemir N. Fear, Anxiety, and coping self-efficacy of individuals with cancer during COVID-19 and predictive risk factors: A descriptive and correlational study. *Semin Oncol Nurs*. 2023;39(4):151420. [CrossRef]
22. Jacobsen PB, Jim HS. Psychosocial interventions for anxiety and depression in adult cancer patients: achievements and challenges. *CA Cancer J Clin*. 2008;58(4):214-230. [CrossRef]
23. Andersen BL. Psychological interventions for cancer patients to enhance the quality of life. *J Consult Clin Psychol*. 1992;60(4):552-568. [CrossRef]
24. Singh B, Olds T, Curtis R, et al. Effectiveness of physical activity interventions for improving depression, anxiety and distress: an overview of systematic reviews. *Br J Sports Med*. 2023;57(18):1203-1209. [CrossRef]

Section and Topic	Item #	Checklist item	Page No.
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Pages 1-2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 2
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Pages 2-3
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Pages 3-4
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 3
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 3
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 3
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 4
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 3
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Pages 3-4
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 4
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 4
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	N/A
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	N/A
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	N/A
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 4
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 4
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 4
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	N/A
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Pages 4-5
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Pages 5-6
Study characteristics	17	Cite each included study and present its characteristics.	Page 5
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 5
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	N/A
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Pages 6-17
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Pages 6-17
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Pages 6-17
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Pages 6-17
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	N/A
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Pages 17-18
	23b	Discuss any limitations of the evidence included in the review.	Pages 18-19
	23c	Discuss any limitations of the review processes used.	N/A
	23d	Discuss implications of the results for practice, policy, and future research.	Pages 17-18
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	N/A
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	N/A
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	N/A
Competing interests	26	Declare any competing interests of review authors.	N/A
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	N/A

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Supplementary Figure 1. PRISMA 2020 Checklist.