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Psychiatric Comorbidities and Outcomes in Palliative and End-of-Life Care: A Systematic Review

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Abstract

Background: Although psychiatric comorbidities are common among individuals at end of life, their impact on outcomes is poorly understood.

Methods: We conducted a systematic literature review of six databases following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and aimed at assessing the relationship between psychiatric comorbidities and outcomes in palliative and end-of-life care. Six databases were included in our search. This review is registered on PROSPERO (CRD42022335922).

Results: Our search generated 7,472 unique records. 88 full texts were reviewed for eligibility and 43 studies were included in the review. Clinically, psychiatric comorbidity was associated with poor quality of life, increased physical symptom burden, and low function. The impact of psychiatric comorbidity on health utilization varied, though many studies suggested that psychiatric comorbidity increased utilization of palliative care services. Quality of evidence was limited by lack of consistent approach to confounding variables as well as heterogeneity of the included studies.

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Conclusion: Psychiatric comorbidity is associated with significant differences in care utilization and clinical outcome among patients at end of life. In particular, patients with psychiatric comorbidity and serious illness are at high risk of poor quality of life and high symptom burden. Our finding that psychiatric comorbidity is associated with increased utilization of palliative care likely reflects the complexity and clinical needs of patients with serious illness and mental health needs. These data suggest that greater integration of mental health and palliative care services may enhance quality-of-life among patients at end of life.

Keywords

Psychiatry; mental health; depression; anxiety; end of life; palliative care

Introduction

Mental health comorbidities are common among individuals with serious illness and include both *de novo* conditions and exacerbations of pre-existing comorbidities.[1] The etiology of mental health comorbidities of serious illness is multifactorial and includes the psychosocial stressors and/or neurobiological impact of serious illness. While epidemiologic data vary, about 40% of individuals with life-limiting serious illness experience clinically significant mood and anxiety symptoms.[2–10] These data are reflected in studies across diverse serious illness settings, including oncology clinics,[9,10] palliative care,[2,5] and hospice.[7] While the most well-studied mental health comorbidities among individuals with serious illness are anxiety and depression, there is growing recognition of the burden of other mental health comorbidities. Serious mental illness (psychotic disorders, bipolar affective disorder, severe personality disorders),[11,12] trauma-related disorders,[13,14] and substance use disorders[15–17] may all be prevalent and negatively impact patients with serious illnesses.

Palliative care is recognized as the standard of care for managing symptoms, improving quality of life, aligning care with patients‘ goals and values, and providing psychosocial, spiritual, and existential elements of serious illness care. The prevalence of mental health comorbidities among individuals with serious illness is reflected in palliative care guidelines. Palliative care considers the psychiatric and psychological aspects of serious illness care as one of its core domains.[18] Depression and anxiety may predict or prompt referral to palliative care providers among adults with serious illness and are among the most frequent concerns raised by patients during encounters with palliative care clinicians.[5,19,20] Furthermore, mental health outcomes are frequently included in studies of palliative care interventions.[21] Despite this, formalized mental health services are rarely integrated into palliative care.[22] Further, patients with depression and anxiety receiving palliative care may be underdiagnosed and undertreated.[23–25] Many palliative care clinicians feel unprepared to manage psychiatric comorbidities; in one survey of clinicians, 93% reported difficulties managing anxiety and only 33% felt they received adequate training in this area.[8,26–28] These gaps impact palliative care research as well; in a review of 59 palliative care intervention studies, 70% did not provide any details about the psychological care component and only 25% used formal psychiatric scales.[29]

There are robust data from a range of medical settings and populations that mental health comorbidities negatively impact medical care and outcomes.[6,30] The impact of mental health comorbidity across domains such as symptom burden, care utilization, survival, and quality-of-life has been demonstrated among individuals with diabetes,[31,32] cardiovascular disease,[33,34] cancer,[35–37] and multiple other populations. However, there is a dearth of such data synthesized in palliative care which has inherent heterogeneity because it is transdiagnostic, delivered across settings, and ideally continued over the trajectory of serious illness. Understanding the association between mental health and outcomes in palliative care is important for a couple ofreasons. First, it enables palliative care clinicians to better tailor care to individual patients‘ needs through risk stratification and collaboration with mental health clinicians. Second, it provides a foundation for psychosocial palliative care research aimed at improving serious illness outcomes through interventions focused on the psychiatric and psychological aspects of palliative care.

In this paper, we present the results of a systematic literature review characterizing the associations between mental health comorbidity and clinical as well as health services outcomes among patients receiving palliative and end-of-life care. To the authors‘ knowledge, this is the first review to assess for associations between mental health comorbidity and health outcomes that is inclusive of a trans-diagnostic, trans-setting population of patients with serious illness receiving palliative and/or end-of-life care. Our hypotheses were that mental health comorbidity would be associated with worse clinical outcomes, higher health care utilization at end of life, and decreased access to and utilization of palliative care services relative to control groups.

Methods:

The review protocol was prospectively registered in PROSPERO (CRD42022335922), an international repository of prospective review protocols aimed at improving scientific transparency and reducing reporting bias.[38] Our review was conducted and is reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[39]

Search strategy

We performed comprehensive searches to identify studies that addressed associations between mental health comorbidities and healthcare utilization, as well as patient-reported clinical outcomes in palliative and end-of-life care settings. Searches were run on March 7, 2022 in the six following databases: Ovid MEDLINE (ALL - 1946 to Present); Ovid EMBASE (1974 to present); CINAHL (EBSCO); and The Cochrane Library (Wiley); AgeLine (EBSCO); and PyscINFO (EBSCO). The search strategy, which was developed by a medical librarian (MD) in collaboration with KS and DS, included all appropriate controlled vocabulary and keywords for the concepts of “palliative/end-of-life care” and “mental illness.” The full search strategies for all databases are available in Supplement 1. To limit selection bias, there were no language, publication date, or article type restrictions on the search strategy.

Eligibility:

We used the following eligibility criteria for included studies:

Study design: We included cohort, case-control, and cross-sectional studies, as well as secondary analyses of data from other study types analyzed as one of the above study types (e.g., observational data collected from a control group in an RCT).

Population: We included studies that enrolled adults (as defined by study locations; either age ≥ 16 or 18) receiving palliative and/or end-of-life (defined as the last six months of life based on common definitions in the literature[40]) care.

Exposure: We included as our exposure either diagnosis of mental health comorbidity identified by chart, clinical diagnosis, or validated scale. We also included studies that treated mental health symptoms as a continuous variable by virtue of using numeric scales (e.g., PHQ-9 for depression).

Control: Studies included in this review either compared individuals with mental health disorders against those without mental health disorders or sought associations between mental health symptom severity and a given outcome.

Outcomes: We included studies with clinical palliative care outcomes including symptom burden and quality of life. Health services outcomes including degree of health care utilization at the end of life and place of death were also ascertained. High-intensity end-of-life care was defined based on previously established criteria[41–44], and included service use indicators such as intrahospital chemotherapy in the last 14 days of life, artificial nutrition, gastrostomy, tracheal intubation, cardiopulmonary resuscitation, mechanical ventilation, blood transfusion, surgery, imaging, or endoscopy in the last 31 days of life, at least one emergency department (ED) or intensive care unit (ICU) admission in the last 31 days of life, hospitalization in acute care unit during the 31 days preceding death, length in days of the last hospital stay, and death in ICU or ED. Palliative care was defined as care focused on improving the quality of life, reducing pain and other symptom burden, and providing psychosocial support to patients and their families, with the recognition that it can be provided in a variety of contexts such as ambulatory clinics, home-based programs, inpatient consultation services as well as inpatient palliative care units and dedicated hospice facilities.[45,46]

Setting: We did not restrict inclusion by study setting.

Publication status and language: We included full-text articles available in English and published in peer reviewed journals since 2000. The year 2000 was selected as a cutoff in order to identify studies showing associations in outcomes in contemporary care settings. Prior to 2000, hospital-based palliative care programs were unusual[47] and we were concerned that end-of-life and palliative care experiences might be too different from contemporary care to make meaningful inferences.

Studies were excluded if the study population did not include terminally ill individuals (e.g., advanced cancer patients with prognosis of less than 6 months of life), patients receiving specialized palliative or end-of-life care, or decedents. Studies were also excluded if the comparator was psychological distress rather than a specific symptom or disorder (e.g., anxiety or depression), if the mental health diagnosis was limited to neurocognitive disorders or delirium, or if the study population was exclusively focused on pediatric patients.

Study selection

Retrieved studies were screened for inclusion using Covidence,[48] a web-based literature review platform. Titles and abstracts were reviewed against the protocolized inclusion/exclusion criteria by two independent reviewers. KS voted on each title and abstract, with the second vote coming from DH, ME, SM or TF. Conflicts were resolved by a consensus method including the whole study team and led by DS, the senior investigator and a physician trained in both psychiatry and palliative medicine.

All studies screened in for full-text review were evaluated by both the primary and senior investigators (KS and DS) and any discrepancies were resolved by consensus.

Data Extraction

Data extraction was conducted using a templated tool integrated into the Covidence platform (see supplement 2). Data from each article were extracted by two independent reviewers (KS, ME, DH, SM, and TF) and subsequently both data templates for each article were jointly reviewed by the study team to ensure consistency. Extracted data included: year(s) of data collection; study location; study design; data sources; sample inclusion and exclusion criteria, analytical sample size; sample characteristics; setting(s) of end-of-life care; psychiatric comorbidity studied; measures of psychiatric comorbidity; definitions of clinical or process of care outcomes; measures of outcomes used; main findings, including numerical values for correlation coefficients (r), Cohen‘s d (d), regression coefficients (β), adjusted or unadjusted odds ratios (aOR/OR), adjusted or unadjusted hazard ratios (aHR/HR) and statistical significance of reported results (p-value); and confounding variables accounted for in the analysis. With respect to identifying confounding variables, we included *a priori* confounders for our data extraction team including age, gender, race, ethnicity, disease status (e.g., stage), and comorbidity status. However, in recognition of the diverse study types we included and of the large number of potential confounders, we also gave study team members agency to identify and include other confounders identified in the studies. As all data were extracted by two study team members, we utilized consensus method about confounders. Study team members also used the study text to identify whether confounders were accounted for in statistical analytic strategies (which was treated as a binary yes/no) and this determination also underwent consensus discussion.

Critical appraisal

The quality of the evidence and the risk of bias was assessed for each retained study using The Joanna Briggs Institute Critical Appraisal tools for cross-sectional, case-controlled and cohort studies.[49]

Data Synthesis:

Each outcome of interest reported in included studies was integrated into the review. We distinguished those outcomes that achieved statistical significance ($P<0.05$) from those that did not in the narrative component of the review results. Those outcomes that could be aggregated based on overlap in construct and in statistical tool used for analysis (e.g., correlation scores between depression symptom severity and pain) are represented as a range.

We reported outcomes from across studies in two primary categories: clinical outcomes and health services outcomes. Within those categories, we reported outcomes in subcategories. For clinical outcomes, we reported quality-of-life and functional status (these were grouped together because functional status was a component of commonly used quality-of-life scales), symptom burden, and survival. For health services outcomes, we reported palliative care utilization (in which we included hospice and specialist-level palliative care across settings) and high-intensity care at the end of life (in which we included chemotherapy, acute & intensive care utilization, emergency department utilization, and procedures).

Results

Search results

The literature search generated 7,472 references after de-deduplication. Following title and abstract screening, 88 full texts were reviewed for eligibility and 43 studies were included in the final sample (see Figure 1). At the full text review stage, substantial inter-rated reliability was achieved (Cohen‘s kappa = 0.73 for full text review).

Study characteristics

The 43 included studies were published between 2003 and 2021 and included 20 cohort studies, 15 cross-sectional studies, and eight secondary analyses of experimental data (see Table 1). Twenty-four studies included only clinical outcomes, 16 studies included only health services outcomes, and three studies reported both. In terms of geographic setting, 19 studies were conducted in Europe and 17 studies were conducted in North America, with the remaining studies coming from Australia, Brazil, India, Mexico, China and Taiwan. The size of the analytic samples varied greatly, ranging from 45 to 160,367 subjects. Fourteen of the included papers were retrospective cohort studies relying exclusively on decedent data,[50–63] 12 of which were described as nationwide or population-based and relied on large scale health databases.[52,64,53–55,57–60,65,62,63]

All of the samples included cancer patients. In 33 studies the whole sample consisted of advanced cancer patients,[66–69,64,53,55,70,56,71–74,57,75–77,58,78–81,65,75,82,83,61,84–90,63] and in one study the whole sample consisted of cancer patients, but with heterogeneity in prognosis.[54] Sixteen studies analyzed data exclusively from patients receiving palliative care or hospice care services.[50,67,69,75,76,79–83,85–87,89,91,92]

The most studied psychiatric comorbidities were depression in 31 reports and anxiety in 17 investigations. Twelve studies included both anxiety and depression but conducted subgroup

analyses for each separately. Seven studies looked at schizophrenia. One study looked at post-traumatic stress disorder and one study looked at bipolar disorder in isolation. Three studies looked at more broadly defined categories of psychopathology – one study looked at “severe mental illness” defined as presence of either depression, schizophrenia or bipolar disorder,[55] one study looked at “psychiatric illness” defined as presence of either depression, anxiety or schizophrenia[59] and one study focused on “mental illness” defined as presence of depression, anxiety, schizophrenia, or bipolar disorder, but featured subgroup analyses for each of these distinct mental disorders.[58]

Included studies employed a variety of approaches to either assess or define psychiatric comorbidity. Eighteen studies relied on chart diagnoses and/or diagnostic codes (e.g., International Classification of Diseases codes). Studies that utilized ICD codes used either ICD-9 or -10 codes with older studies relying on ICD-9 codes and newer studies utilizing ICD-10 codes. Studies using data from a broader time perior (e.g., Chochinov‘s 2012 study utilizing records generated from 1995–2008[52]) utilized both ICD-9 and -10 codes. Twenty-four studies utilized validated psychiatric symptom scales, with The Patient Health Questionnaire (PHQ),[70–72,80,81] The Center for Epidemiologic Studies Depression Scale (CES-D),[50,75,84,92] The Hospital Anxiety and Depression Scale,[67–70,73,74,77,86,89,90] The Edmonton Symptom Assessment Scale,[82,87] and The Edinburgh Depression Scale (EDS)[79,80] being the most commonly used scales. One study relied on neuropsychiatric symptom assessment which was obtained through structured medical interviews performed at hospital admission.[91]

EOL clinical outcomes

Quality of life and functional status—Quality of life and functional status were assessed using The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire,[50,67,68,71,73–75,77,79,89] which includes the Functional Scale, Symptom Scale and Global Health Status; The Karnofsky Performance Status Scale,[81,85,88] The Hospice Quality of Life Index,[74,75] The World Health Organization Quality of Life scale,[89] Assessment of Quality of Life at the End of Life scale,[73] and postmortem assessment completed by patients‘ primary caregivers.[88]

Thirteen studies found statistically significant inverse correlations between depressive symptoms and quality of life or functional status, including global quality of life, global health status, Karnofsky performance status, role, emotional, cognitive, social, and physical functioning. Seven studies found statistically significant inverse correlations between symptoms of anxiety and quality of life or functional status. Detailed findings are described in Table 2.

Symptom burden—Symptom burden was assessed by The Edmonton Symptom Assessment Scale,[69,72,78,82,85,87,90] Memorial Symptom Assessment Scale[92] and The Numerical Rating Scale for pain assessment.[81,91] Two studies relied solely on the patients‘ verbal report. [79,93]

Sixteen studies found statistically significant associations between depression and symptom burden, including overall symptom burden or distress, number of symptoms endorsed, worse

overall well-being, pain, lower energy, drowsiness or fatigue, gastrointestinal symptoms, dyspnea, poor appetite, insomnia, and additional symptoms of dizziness, dry mouth, numbness or tingling and sweats. Eight studies found statistically significant associations between anxiety and symptom burden, including overall symptom burden, worse overall well-being, pain, lower energy, drowsiness or fatigue, gastrointestinal symptoms, dyspnea, poor appetite and insomnia. Detailed findings are described in Table 3.

Survival—No studies examined the relationship between anxiety and survival, but four studies found an association between depression and shorter survival among patients with advanced cancer.[79,80,84,85] One study from the United Kingdom found that a one-point increase in the EDS score at baseline increased risk of death over the 12-month follow-up period by 7%.[79] In another study conducted by the same research team, patients with a PHQ < 9 at baseline survived 3 weeks longer than those with a PHQ > 9 (indicating moderate or severe depression), and the adjusted Cox proportional hazards regression model estimated risk of death to be 1.38 times higher among patients with PHQ > 9.[80] A secondary analysis of 2 US-based randomized controlled trials of early palliative care interventions indicated that higher baseline CES-D scores were significantly associated with greater mortality risk (HR= 1.042) [84]. Finally, major depressive disorder was associated with lower probability of 1-year survival in Latin American palliative care patients.[85]

Healthcare utilization at the EOL

Palliative care—Associations between palliative care and mental health comorbidities are described in Table 4.

Four studies investigated the relationship between depression and palliative care use, and all found an association between depression and increased palliative care utilization, with the difference between patients with depression and healthy controls becoming more pronounced closer to death.[53,59,65,76] Patients with depression had greater odds of hospice enrollment and greater odds of using palliative care services, as well as longer period of hospice care and longer palliative care follow-up before death.[65,76]

Three studies investigated the relationship between anxiety and palliative care use.[61,88,91] Anxiety was associated with a higher likelihood of having a palliative care encounter in the last six months of life and with longer duration of palliative care treatment, but was not associated with an increased odds of dying under hospice care.[61,88] A study from Poland found that among patients receiving palliative care, those with anxiety at the time of a hospital admission were five times more likely to have emergency admission to a palliative care unit.[91]

Six studies investigated the relationship between schizophrenia and palliative care use.[52,56,57,62–64] Overall, a diagnosis of schizophrenia was associated with increased utilization of palliative care services. Patients with schizophrenia were more likely to access palliative care in the last two years of life, more likely to be admitted to a palliative care unit in the last month of life, and in the last three days of life, had longer average hospice stays and longer periods of palliative care follow-ups before death. However, a study from Taiwan showed schizophrenia diagnosis was not associated with any significant differences

in the use of palliative care, hospice ward care, or hospice home care in the last month of life, but was associated with lower odds of using palliative care consultation services in the last month of life.[57]

Only one study investigated the relationship between bipolar disorder and palliative care use.[54] Patients with bipolar disorder were more likely to access palliative care services at the end of life and had longer palliative care follow-up before death than controls without bipolar disorder.

Similarly, a study looking at severe mental illness defined as the presence of either depression, schizophrenia or bipolar disorder found that among women who died from breast cancer, women with severe mental illness were more likely to access palliative care in the last month of life and had longer palliative care follow-up period than controls without severe mental illness.[55]

High-intensity care—Associations between high-intensity end-of-life care and mental health comorbidities are described in Table 5.

Six studies investigated the relationship between depression and high intensity care.[53,58,61,65,70,76] Patients with depression had lower odds of receiving blood transfusion, surgery and imaging, but higher odds of undergoing artificial nutrition in the last month of life.[53] No statistically significant differences were found for undergoing mechanical ventilation or cardiopulmonary resuscitation in the last month of life.[53] Data on administration of chemotherapy at the end of life were mixed.[53,61,65,70] Patients with depression had slightly lower odds of repeated admissions to acute care units in the last month of life[53] but once admitted, their average length of stay was longer.[53,76] Patients with depression were less likely to die in the ICU or ED, [53] but no conclusion could be drawn on the likelihood of ED visits or ICU admissions in the last month of life.[53,61]

Four studies investigated the relationship between anxiety and high intensity care.[58,61,70,88] As with depression, data on administration of chemotherapy at the end of life were mixed.[61,70] No associations were found between anxiety and resuscitation, mechanical ventilation, or artificial nutrition.[88] Patients with anxiety had greater odds of iterative ED visits[58] as well as inpatient hospitalizations[61] in the last month of life. No clear pattern has been identified for anxiety and ICU use.[61,88]

Nine studies investigated the relationship between schizophrenia and high intensity end-of-life care.[52,56–58,60,62–65] Individuals with schizophrenia were less likely to initiate and undergo chemotherapy in the last month or 14 days of life,[56,57,63,64] and less likely to undergo surgery[63,64] or imaging[57,63,64] in the last month of life. No clear pattern could be identified for mechanical ventilation,[57,63,64] blood transfusion,[63,64], cardiopulmonary resuscitation,[57,64] and artificial nutrition[63,64] in the last month of life. Data on the likelihood of receiving care in the ICU or ED context were mixed. [57,58,63–65] However, individuals with schizophrenia were less likely to receive other forms of inpatient care at the end of life,[62–65] are hospitalized less frequently,[52,60] and are ultimately less likely to die in ICU, ED or in

the broader hospital setting. [60,63–65] The relationship between schizophrenia and length of inpatient stay remains unclear. [52,60,63]

Two studies investigated the relationship between bipolar disorder and high-intensity end-of-life care.[54,58] Patients with bipolar disorder had lower odds of undergoing surgery, imaging, and chemotherapy, but higher odds of receiving artificial nutrition in the last month of life.[54] No statistically significant differences were found for mechanical ventilation, cardiopulmonary resuscitation, or blood transfusion in the last month of life.[54] Although patients with bipolar disorder were less likely to be admitted to an acute care unit, they stayed longer if admitted.[54] Patients with bipolar disorder were more likely to have recurrent ED visits in the last month of life,[58] but no statistically significant differences were found for the odds of death in ED/ICU setting or the odds of ED and ICU admission in the last month of life.[54]

One study investigated the relationship between post-traumatic stress disorder (PTSD) and high-intensity end-of-life care.[51] In a population of veterans receiving care in the Veterans Administration, PTSD diagnosis was associated with more ER visits and more hospital admissions in the last 12 months of life. No significant differences were found for the mean length of inpatient stay or odds of artificial nutrition at the point of death.

In a study aggregating patients with “preexisting psychiatric illness” defined as presence of either depression, anxiety or schizophrenia, psychiatric illness was associated with lower odds of acute care hospitalizations or ICU care in the last month of life. Patients with preexisting psychiatric illness spent fewer days in the ICU in the last month of life and were less likely to die in the hospital, but were more likely to have an ED visit in the last month of life.[59] Another study looking at “severe mental illness” defined as the presence of either depression, schizophrenia or bipolar disorder found that among women who died from breast cancer, women with severe mental illness were less likely to receive chemotherapy in the last 14 days of life, less likely to undergo surgery and imaging or endoscopy studies in the last month of life, as well as less likely to have an ED visit or be admitted to ICU in the last month of life.[55] No significant association was found between severe mental illness and mechanical ventilation or blood transfusion in the last 31 days of life.[55]

Quality of studies

The quality of studies was variable. Included studies met between 100% and less than 40% of the quality and bias criteria delineated by The Joanna Briggs Institute Critical Appraisal tools (see tables 6–8). Regardless of the type of data analysis used (i.e., cohort, cross-sectional, case-controlled), all studies used appropriate statistical analysis and measured outcomes in a valid and reliable way. Lack of appropriate identification of confounding factors and lack of strategies to deal with confounding factors were the most common gaps in study quality.

Discussion

This systematic review assesses the impact of mental health comorbidity on serious illness outcomes at both the clinical and health services levels, provides descriptive results about

the study populations and methods used to assess mental health disorders, and provides an appraisal of the quality of the existing literature. Even in the setting of heterogeneity in study design, measurement methods for mental health comorbidity, and outcomes, our results demonstrate that mental health comorbidity negatively impacts a broad range of outcomes relevant to palliative care. Individuals with mental health comorbidity experience poorer quality of life, lower levels of function, and greater physical symptom burden. However, these associations are currently limited to depression and anxiety because of a lack of studies reporting on the association between other mental health symptoms and diagnoses (e.g., psychotic disorders, post-traumatic stress disorder, bipolar affective disorder) and clinical outcomes. There is greater diversity of mental health comorbidities in health services-oriented studies; we identified studies examining both common mental health comorbidities (anxiety, depression) and serious mental illness (chronic mental illnesses which have a persistent impact on function such as psychotic disorders).

Studies focused on clinical outcomes (such as symptom burden and quality of life) versus health services outcomes (such as health care utilization) generally differed in several aspects. Most studies examining clinical outcomes were cross-sectional studies that treated mental health comorbidity as a continuous symptom variable (e.g., severity of depressive symptoms), rather than a dichotomous diagnostic variable (e.g., presence or absence of a major depression diagnosis). In contrast, health services studies were predominantly large, population-based cohort studies that relied on national hospital databases or insurance claims data sets and used specific mental disorder diagnostic codes to define the cohorts.

Our review has several notable strengths. To our knowledge, it is the first systematic review to evaluate associations between transdiagnostic mental health comorbidity and a range of serious illness outcomes at both the clinical and health services level. We were able to identify studies of patients receiving palliative or end-of-life care across a range of countries and clinical settings and were expansive in our outcome measures. Even in the setting of this breadth, we maintained a high degree of methodologic rigor including using prospective protocol registration and following PRISMA guidelines.

Weaknesses of our review include the exclusion of grey literature, conference abstracts, and non-English literature, introducing publication and selection bias. Because of heterogeneity in study design, mental health comorbidity measures, and outcome measures, we were unable to conduct aggregate analysis of the data. Included studies were also variable in quality, particularly with respect to their approach to confounding variables. Of note, few studies controlled for the potential confounder of multiple mental health comorbidities and studies did not generally differentiate between pre-existing mental health comorbidity versus new onset comorbidity in the setting of serious illness. Furthermore, our inclusion of data from multiple countries was complicated by differences in care models and nomenclature across countries and by the overrepresentation of high-income countries and by overrepresentation of cancer patients, which is a common challenge in palliative care research because of its longstanding close connection to oncology. Finally, identifying associations between psychiatric symptoms or disorders and other outcomes is contingent on being able to effectively measure mental health status. Accurate psychiatric diagnosis can be challenging among individuals with life-limiting medical illnesses. While many

common screenings such as the PHQ-9 and the Hospital Anxiety and Depression Scale have been validated among patients with serious illness, other screening tools may underperform relative to other forms of assessment.[3,94,95] Furthermore, clinical psychiatric diagnosis may be particularly challenging among patients with serious illness and may be confounded by overlapping symptoms (e.g., anergia, anorexia, and insomnia in depression).[28] These complexities may influence the outcomes of included studies and present an additional potential confounder.

Our *a priori* hypothesis was that mental health comorbidity would be associated with poorer clinical outcomes and increased use of low-value, high-intensity care at the end of life. Interestingly, studies demonstrated that mental health diagnoses were associated with increased utilization of palliative care services. This was contradictory to our hypothesis that mental health diagnosis would confer decreased access to or utilization of palliative care services. One possible reason for this finding is that individuals with serious illness and mental health comorbidity may be perceived as more complex by medical subspecialists and may also experience more significant symptoms and poorer quality of life, all of which may drive palliative care referral. This reformulated hypothesis is consistent with data demonstrating that mental health comorbidity may predict palliative care referral,[19,61] that mental health concerns are among the most frequently reported concerns by patients to palliative care clinicians,[5] and that palliative care itself operationally identifies psychiatric and psychological care in the context of serious illness as one of its core domains.[18]

Our *a priori* hypotheses also did not bear out with respect to high intensity end-of-life care. Our data did not show an association between psychiatric comorbidity and high-intensity end-of-life care. Additional study may help determine whether decreased use of aggressive and/or disease-focused end-of-life care are related to stigma against individuals with mental illness (particularly serious mental illness),[96] differential care choices among patients living with mental illness, or another cause.

Our findings have implications for both research and clinical practice. There is a pressing need for more sophisticated epidemiologic research and for intervention research focused on mental health comorbidity among individuals with serious medical illness. As noted, studies included in our analytic sample were heavily skewed towards depression and anxiety and varied widely in their management of confounders and their methods of diagnosis or screening. There is a particular need for further research on the prevalence and impact of potentially significant but understudied mental health comorbidities in patients with serious medical illness including trauma-related disorders, panic disorder, sleep disorders, and eating disorders. There is also a need for greater consensus about valid psychiatric diagnosis in patients with serious medical illness, including systematized research and clinical methods for differentiating normative and pathological states. Few studies in our analytic sample were able to control for the possibility of multiple mental health comorbidities or for the diagnostic blurring that may occur when a patient with a related disorder screens positive for another disorder (e.g, a patient with PTSD may screen positive on a PHQ-9 due to related symptoms such as affective disturbance and insomnia). As such, while many studies accounted for common general confounders such as age, gender, and medical status, further psychiatric palliative care research will depend on more extensive

and targeted assessment, a broader range of included disorders, and management of unique psychiatric-palliative care confounders such as *de novo* versus pre-existing illness, prior mental healthcare exposure, and attitudes/stigma about mental health. Furthermore, there are only very limited data on the causality between mental health comorbidity and the associated outcomes included in this review. Research focused on downstream effects of mental health interventions on symptom burden, quality of life, functional status, and health care utilization patterns may help establish causality and guide further intervention development. Epidemiologic research must be linked to a greater investment in intervention studies in the psychological and psychiatric aspects of palliative care. Such study should include both development and assessment of interventions themselves, but also a focus on understanding what approaches may minimize stigma and increase acceptability of mental health interventions for patients with serious illness more broadly. Currently, most existing mental health intervention research—both pharmacologic and behavioral—has not been conducted in individuals with serious medical illness. In addition, mental health components of palliative care interventions are poorly described and measured.[29]

Clinically, our findings reinforce that mental health comorbidity is impactful in serious illness. Even without a fully realized understanding of causality between symptom clusters, mental health comorbidity—in addition to conferring its own suffering—is part of a constellation of poor function, low quality of life, and high symptoms. Importantly, patients with serious illness and mental health comorbidity access palliative care at higher rates than controls. Palliative care clinicians are well positioned to become stewards of mental health for individuals with serious mental illness—a role reinforced by the inclusion of a domain on psychological and psychiatric aspects of care in Clinical Practice Guidelines for Quality Palliative Care.[18] However, there are a number of existing barriers to addressing mental health comorbidity effectively. Diagnosis and management of psychiatric comorbidities in the palliative care setting is extremely complex.[28] Clinicians may face uncertainty about the applicability of existing screening tools to patients with serious illness and there may be equipoise between normative and pathological reactions. Furthermore, patients who accept medical interventions such as pain management may reject treatments perceived to be psychological in nature. More robust evidence around the diagnosis and management of psychiatric comorbidities may help clinicians feel empowered to make accurate diagnoses and effective interventions. Furthermore, buttressing the expertise of palliative care social workers with doctoral-level mental health clinicians who have specialized training in serious illness may help expand both the clinical workforce and the evidence base for psychiatric and psychological treatment of palliative care patients.

In summary, we conducted a systematic review of associations between mental health comorbidity and clinical and health services outcomes in palliative and end-of-life care. As we expected, mental health comorbidity was consistently associated with a range of negative clinical outcomes, including increased pain and symptom burden, decreased quality of life, and loss of function. Although mental health comorbidity was associated with differential health care utilization, some of the patterns, including increased utilization of palliative care services, were surprising to us. Our study indicates the need for further research on mental health comorbidity in palliative and end-of-life care given the links between mental health and many of the core aims of palliative care. Furthermore, many of the studies included

in the review were situated in high-income countries, oncologic settings, and specifically focused on depression and anxiety suggesting the need for more globally oriented research inclusive of non-oncologic palliative care patients and of a wider range of mental health comorbidities.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Message:

Palliative care clinicians should be aware that common psychiatric symptoms and/or disorders are impactful across a range of serious illness and end-of-life outcomes.

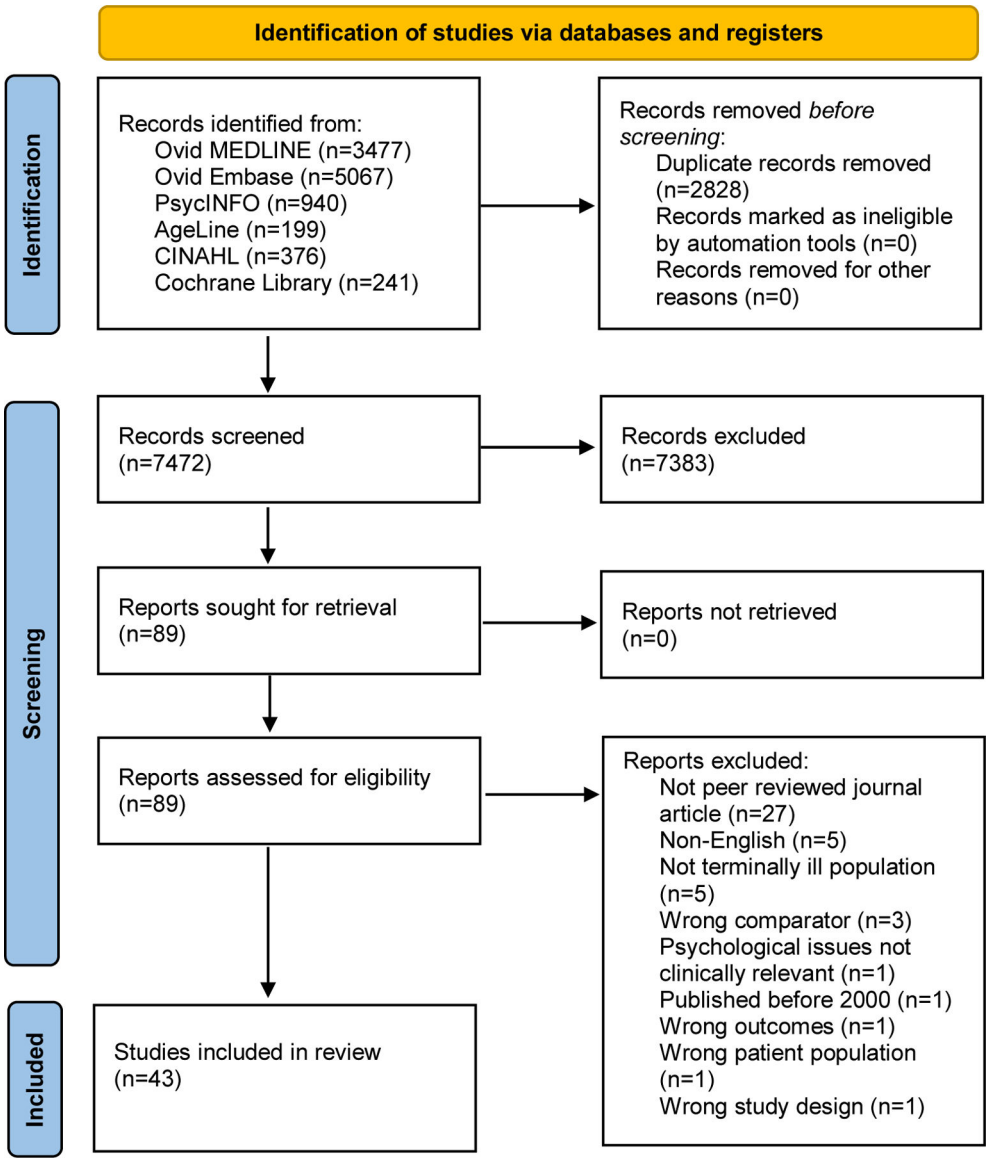

Figure 1:
PRISMA Diagram.

Table 1

Basic characteristics of the included studies

Study ID	Country	Total analytic sample	Study design	Psychiatric comorbidities studied	Measure of psychiatric comorbidity	Data on clinical outcomes	Data on healthcare utilization outcomes
Azevedo 2017	Brazil	115	Cross-sectional study	Depression	Validated psychometric scale	✓	
Bickel 2020	US	5,341	Secondary data analysis	PTSD	Chart diagnosis		✓
Bryniarski 2021	Poland	134	Cross-sectional study	Anxiety	Clinical diagnosis	✓	✓
Buzgova 2014	Czech Republic	93	Cross-sectional study	Depression; anxiety	Validated psychometric scale	✓	
Buzgova 2015	Czech Republic	225	Cross-sectional study	Depression; anxiety	Validated psychometric scale	✓	
Chan 2014	China	312	Secondary data analysis	Depression	Validated psychometric scale	✓	
Chochinov 2012	Canada	15,770	Cohort study	Schizophrenia	Chart diagnosis		✓
Delgado-Guay 2009	US	216	Secondary data analysis	Depression; anxiety	Validated psychometric scale	✓	
Fond 2019	France	12,373	Cohort study	Schizophrenia	Chart diagnosis	✓	✓
Fond 2020 – 1	France	224,492	Cohort study	Bipolar disorder	Chart diagnosis		✓
Fond 2020 – 2	France	20,320	Cohort study	Depression	Chart diagnosis		✓
Fond 2021	France	38,612	Cohort study	Depression, schizophrenia OR bipolar disorder	Chart diagnosis		✓
Fujisawa 2015	US	125	Secondary data analysis	Depression; anxiety	Validated psychometric scale		✓
Ganzini 2010	US	256	Cross-sectional study	Schizophrenia	Chart diagnosis		✓
Grotmol 2017	8 EU countries	563	Cross-sectional study	Depression	Validated psychometric scale	✓	
Grotmol 2019	8 EU countries	935	Cross-sectional study	Depression	Validated psychometric scale	✓	
Henoch 2007	Sweden	105	Cross-sectional study	Depression; anxiety	Validated psychometric scale	✓	
Hermann 2011	US	80	Cohort study	Depression; anxiety	Validated psychometric scale	✓	
Huang 2018	Taiwan	9,555	Cohort study	Schizophrenia	Chart diagnosis		✓
Huang 2019	US	660	Secondary data analysis	Depression	Validated psychometric scale	✓	

Study ID	Country	Total analytic sample	Study design	Psychiatric comorbidities studied	Measure of psychiatric comorbidity	Data on clinical outcomes	Data on healthcare utilization outcomes
Irwin 2008	US	2,716	Cross-sectional study	Anxiety	Chart diagnosis		✓
Janssens 2019	Belgium	125	Cross-sectional study	Depression; anxiety	Validated psychometric scale	✓	
Kashyap 2021	US	160,367	Cohort study	Depression; anxiety; schizophrenia; bipolar disorder	Chart diagnosis		✓
Lavin 2017	US	16,214	Cohort study	Depression, schizophrenia OR anxiety	Chart diagnosis		✓
Liu 2017	China	196	Cohort study	Depression	Validated psychometric scale	✓	
Lloyd-Williams 2009	UK	87	Cohort study	Depression	Validated psychometric scale	✓	
Lloyd-Williams 2014	UK	629	Cohort study	Depression	Validated psychometric scale	✓	
Martens 2013	Canada	15,770	Cohort study	Schizophrenia	Chart diagnosis		✓
Masel 2016	Austria	68	Cross-sectional study	Depression; anxiety	Validated psychometric scale	✓	
McDermott 2018	US	13,827	Cohort study	Depression	Chart diagnosis		✓
McMillan 2009	US	275	Secondary data analysis	Depression	Validated psychometric scale	✓	
Mercadante 2019	Italy	314	Secondary data analysis	Depression; anxiety	Validated psychometric scale	✓	
Meyer 2003	UK	45	Cohort study	Depression	Validated psychometric scale	✓	
Mossman 2021	US	1,333	Cohort study	Depression; anxiety	Chart diagnosis		✓
Prescott 2017	US	529	Secondary data analysis	Depression	Validated psychometric scale	✓	
Rodriguez-Mayoral 2020	Mexico	100	Cohort study	Depression	Chart diagnosis	✓	
Smith 2003	UK	68	Cross-sectional study	Depression; anxiety	Validated psychometric scale	✓	
Smitz 2006	US	109	Cross-sectional study	Depression	Validated psychometric scale	✓	
Spencer 2010	US	635	Cohort study	Anxiety	Chart diagnosis	✓	✓
Spilsbury 2018	Australia	63,508	Cohort study	Schizophrenia	Chart diagnosis		✓

Study ID	Country	Total analytic sample	Study design	Psychiatric comorbidities studied	Measure of psychiatric comorbidity	Data on clinical outcomes	Data on healthcare utilization outcomes
Sudarisan 2019	India	234	Cross-sectional study	Depression	Validated psychometric scale	✓	
Teunissen 2007	The Netherlands	79	Cross-sectional study	Depression; anxiety	Validated psychometric scale	✓	
Viprey 2021	France	67,102	Cohort study	Schizophrenia	Chart diagnosis		✓

Table 2

Summary of findings for quality of life and functional status measures

	Depression	**Anxiety**
Global quality of life	r=−[0.29–0.68] [50,67,68,71,73–75,77,79,89]	r=−[0.23–0.49] [67,68,74,77,88]
Role functioning	r=−0.40; r=−0.54 [67,68] No association [86]	r=−0.31 [67,68] No association [86]
Emotional functioning	r=−[0.35–0.59] [67,68,86]	r=−[0.31–0.79] [67,68,86]
Cognitive functioning	r=−[0.34–0.43] [67,68,86]	r=−[0.28–0.42] [67,68,86]
Social functioning	r=−0.31; r=−0.43 [67,68] No association [86]	r=−[0.34–0.38] [67,68,86]
Physical functioning	r=−[0.45–0.49][67,68] No association [86]	r=−[0.30–0.36] [67,68] No association [86]
Global health status	r=−0.38; β=−2.11[86]	r=−0.37; β=−1.75 [86]
Poor Karnofsky performance status	OR=5.4 [85] No association [81]	Average score: 61.22 vs 68.97 [88] No association [81]

Table 3

Summary of findings for symptom burden measures

	Depression	Anxiety
Overall symptom burden or distress	r=[0.49–0.68]; d=1.08 [72,82,87,92]	d=1.35 [82]
Number of symptoms endorsed	r=0.45 [92]	no data available
Overall well-being	r=−[0.44–0.73] [69,77,82,85,87]	r=−[0.21–0.44] [69,77,82]
Intensity of specific physical symptoms:		
Pain	r=[0.19–0.51] [67,69,77,78,82,85,87,92,93] No association[79,90,92]	r=[0.41–0.46] [67,69,77,82,91] No association[87,90]
Lower energy, drowsiness or fatigue	r=[0.25–0.49] [67,69,77–79,82,85–87,90,92] No association[78,81,82,90,92]	r=[0.25–0.48] [67,69,82,86,90] No association[90]
Gastrointestinal symptoms	r=[0.29–0.32] [67–69,77–79,85,91] No association[86,87,97]	r=[0.35–0.36] [67–69,77,86] No association[90]
Dyspnea	r=[0.24–0.44] [67,69,77,78,85,92] No association[79,87,90,92]	r=0.21 [69,77,82] No association[90]
Poor appetite	r=[0.35–0.46] [67,69,77,82,84,85] No association[87]	r=0.24 [67,82]
Insomnia	r=0.20 [77,85,90] No association[82,97]	r=0.38 [77,82,90]
Other symptoms	r=[0.21–0.34] [92]	no data available

Table 4

Summary of findings for palliative care use outcomes. “Severe mental illness” is defined by the authors of the cited paper as the presence of either depression, schizophrenia or bipolar disorder. NS: No significant difference.

	Depression	Anxiety	Schizophrenia	Bipolar Disorder	Severe mental illness
Odds of palliative care (PC) use	Any PC use in last 6 months of life: OR=1.34[61] -In last month: aOR=1.82[53] -In last 3 days: aOR=2.23[53] Hospice enrollment: SHR=1.19[65]	PC use in the last 6 months of life: OR = 1.95[61] Emergency PC admission: OR=5.129[91] Death at hospice: NS[88]	Any PC in the 2 years prior to death: 6.57% schizophrenia vs 17.40% control [52] Admissions to PC units: -In the last month of life: aOR=1.27, 1.61[63,64] -In the last 3 days of life: aOR=1.44, 2.52[63,64] PC consultation in the last month of life: aOR=0.59[57] Use of community-based specialist PC in the last month of life (limited to decedents with chronic illness): 11.9% schizophrenia vs. 24.7% control[62]	PC use in the last month of life: aOR=1.49[54] -In the last 3 days of life: aOR=2.14[54]	PC use in the last month of life: aOR=1.32[55]
Duration of palliative care (PC) use	Duration of PC follow-up: 28 days depression vs. 19 days control[53] Duration of hospice care:75 days depression vs. 38.97 days control[76] Duration of inpatient hospice care: 19 days depression vs. 9 days control[76] Likelihood of 90+ days of hospice stay: aOR=1.29[65]	Duration of PC follow-up: OR=1.044[91] (duration not provided)	Duration of PC follow-up: 9–36% longer with schizophrenia[63,64] Duration of hospice care: 107 schizophrenia vs 63 days control[56]	Duration of PC follow: 29 days bipolar vs. 19 days control[54]	Duration of PC follow-up: 45% longer[55]

Table 5

Summary of findings for high intensity care utilization outcomes

		Depression	Anxiety	Schizophrenia	Bipolar Disorder	PTSD	Aggregated psychiatric illness
Blood transfusion	↑						
	⇔			no difference[63]	no difference[54]		no difference[55]
	↓	aOR =0.82[53]		aOR=0.72[64]			
Surgery	↑						
	⇔						
	↓	aOR=0.82[53]		aOR=0.71[64];aOR=0.73[63]	aOR=0.86[54]		aOR=0.83[55]
Imagining	↑						
	⇔						
	↓	aOR=0.69[53]		OR=[0.37–0.80][57,63,64]	aOR=0.77[54]		aOR=0.88[55]
Artificial nutrition	↑	aOR=1.37[53]		OR = 1.41[57]	aOR=1.31[54]		
	⇔		no difference[88]	no difference[64]		no difference[51]	
	↓			aOR = 0.62[63]			
Mechanical ventilation	↑			OR = 1.15[57]			
	⇔	no difference[53]	no difference[88]	no difference[63,64]	no difference[54]		no difference[55]
	↓						
Cardiopulmonary resuscitation	↑			OR = 1.34[57]			
	⇔	no difference[53]	no difference[88]	no difference[64]	no difference[54]		
	↓						
Chemotherapy	↑	70	OR= 1.42[61]				
	⇔	no difference[61,65,70]	no difference [70]				
	↓	aOR=0.70[53]		OR=[0.53–0.60][57,63,64]; [56]	aOR=0.78[54]		aOR=0.70[55]
Odds or frequency of ED or ICU use	↑		aOR=1.26[58];OR=1.40[61]	HR=1.20[62]; OR = 1.21[57]	aOR=1.12[58]	RR=1.10[51]	OR=1.64[59]; RR=1.38[59]
	⇔	no difference[53,58]	no difference [88]	no difference [58,63,64]	no difference [54]		
	↓	aOR=0.90[53]		aOR=0.78[65]			OR=[0.41–0.85][55,59]
Odds or frequency of other acute or inpatient care	↑		OR = 1.85[61]	aOR=1.41[63]		RR=1.09[51]	
	⇔	no difference [61]					
	↓	aOR=0.90[53]		HR=0.30[62]; aRR=0.73[52]; aOR=0.73[64]; RR=0.73[60];	aOR=0.79[54]		OR=0.59[59]

		Depression	Anxiety	Schizophrenia	Bipolar Disorder	PTSD	Aggregated psychiatric illness
				aOR=0.74[65]; aRR=0.79[52]			
Length of acute or inpatient care, including ED or ICU	↑	β=1.24[53] ; [76]		22%[63]; 20%[64] longer	22% longer[54]		
	⇔			no difference [57]		no difference[51]	
	↓			aRR=0.80[52]; RR=0.79[60]			RR=0.88[59]
In-hospital death, including death in ED or ICU	↑						
	⇔			no difference [56]	no difference [54]		
	↓	aOR=0.81[53]		OR=[0.65–0.75][63–65]; [60]			OR =0.67[59]

Table 6:

Quality assessment of cohort studies

	COHORT ANALYSIS										
Citation	**1. Were the two groups similar and recruited from the same population?**	**2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?**	**3. Was the exposure measured in a valid and reliable way?**	**4. Were confounding factors identified?**	**5. Were strategies to deal with confounding factors stated?**	**6. Were the groups/ participants free of the outcome at the start of the study (or at the moment of exposure)?**	**7. Were the outcomes measured in a valid and reliable way?**	**8. Was the follow up time reported and sufficient to be long enough for outcomes to occur?**	**9. Was follow up complete, and if Not, were the reasons to loss to follow up described and explored?**	**10. Were strategies to address incomplete follow up utilized?**	**11. Was approp statistic analysi used?**
Bickel 2020	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Unclear	Unclear	Yes
Chochinov 2012	Yes	Yes	Yes	Yes	Yes	Yes	Yes	N/A	N/A	N/A	Yes
Fond 2019	Yes	Yes	Yes	Yes	Yes	Yes	Yes	N/A	N/A	N/A	Yes
Fond 2020 – 1	Yes	Yes	Yes	Yes	Yes	Yes	Yes	N/A	N/A	N/A	Yes
Fond 2020 – 2	Yes	Yes	Yes	Yes	Yes	Yes	Yes	N/A	N/A	N/A	Yes
Fond 2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes	N/A	N/A	N/A	Yes
Hermann 2011	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Unclear	Yes
Huang 2018	Yes	Yes	Yes	Yes	Yes	Yes	Yes	N/A	N/A	N/A	Yes
Kashyap 2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes	N/A	N/A	N/A	Yes
Lavin 2017	Yes	Yes	No	Yes	Yes	Yes	Yes	N/A	N/A	N/A	Yes
Liu 2017	Yes	Yes	Yes	No	No	Unclear	Yes	N/A	N/A	N/A	Yes
Lloyd-Williams 2009	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lloyd-Williams 2014	Yes	es	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Martens 2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes	N/A	N/A	N/A	Yes
McDermott 2018	Yes	Yes	Yes	Yes	Yes	Yes	Yes	N/A	N/A	N/A	Yes
Mercadante 2019	Yes	Yes	Yes	Yes	Yes	No	Yes	Unclear	Unclear	Unclear	Yes
Meyer 2003	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Unclear	Unclear	Yes
Mossman 2021	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	N/A	N/A	N/A	Yes
Prescott 2017	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes

	COHORT ANALYSIS										
Citation	**1. Were the two groups similar and recruited from the same population?**	**2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?**	**3. Was the exposure measured in a valid and reliable way?**	**4. Were confounding factors identified?**	**5. Were strategies to deal with confounding factors stated?**	**6. Were the groups/ participants free of the outcome at the start of the study (or at the moment of exposure)?**	**7. Were the outcomes measured in a valid and reliable way?**	**8. Was the follow up time reported and sufficient to be long enough for outcomes to occur?**	**9. Was follow up complete, and if Not, were the reasons to loss to follow up described and explored?**	**10. Were strategies to address incomplete follow up utilized?**	**11. Was approp statistic analysi used?**
Rodriguez-Mayoral 2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes
Spencer 2010	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear	Unclear	Yes
Spilsbury 2018	Yes	Yes	Yes	Yes	Yes	Yes	Yes	N/A	N/A	N/A	Yes
Viprey 2021	Yes	Yes	Yes	Yes	Yes	N/A	Yes	N/A	N/A	N/A	Yes

Table 7:

Quality assessment of cross-sectional studies

	CROSS-SECTIONAL ANALYSIS							
Citation	**1. Were the criteria for inclusion in the sample clearly defined?**	**2. Were the study subjects and the setting described in detail?**	**3. Was the exposure measured in a valid and reliable way?**	**4. Were objective, standard criteria used for measurement of the condition?**	**5. Were confounding factors identified?**	**6. Were strategies to deal with confounding factors stated?**	**7. Were the outcomes measured in a valid and reliable way?**	**8. Was appropriate statistical analysis used?**
Azevedo 2017	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Bryniarski 2021	No	No	No	No	No	Yes	Yes	Yes
Buzgova 2014	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Buzgova 2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Chan 2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Delgado-Guay 2009	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Ganzini 2010	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Grotmol 2017	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Grotmol 2019	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
HeNoch 2007	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Huang 2019	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Irwin 2008	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Janssens 2019	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Masel 2016	Yes	Yes	Yes	Yes	No	No	Yes	Yes
McMillan 2009	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Smith 2003	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Smitz 2006	Yes	Yes	No	Yes	No	No	Yes	Yes
Sudarisan 2019	No	Yes	Yes	Yes	Yes	No	Yes	Yes
Teunissen 2007	Yes	Yes	Yes	Yes	No	No	Yes	Yes

Table 8:

Quality assessment of case-control studies

	CASE-CONTROL ANALYSIS									
Citation	**1. Were the groups comparable other than the presence of disease in cases or the absence of disease in controls?**	**2. Were cases and controls matched appropriately?**	**3. Were the same criteria used for identification of cases and controls?**	**4. Was exposure measured in a standard, valid and reliable way?**	**5. Was exposure measured in the same way for cases and controls?**	**6. Were confounding factors identified?**	**7. Were strategies to deal with confounding factors stated?**	**8. Were outcomes assessed in a standard, valid and reliable way for cases and controls?**	**9. Was the exposure period of interest long enough to be meaningful?**	**10. Was appropriate statistical analysis used?**
Fujisawa 2015	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes