REVIEWS

Association Between Depressive Symptoms or Depression and Health Outcomes for Low Back Pain: a Systematic Review and Meta-analysis

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BACKGROUND: Study results vary on whether depressive symptoms are associated with worse prognosis for low back pain (LBP). We assessed the association between depressive symptoms or depression and health outcomes in persons with LBP.

METHODS: We searched MEDLINE, Embase, CINAHL, and PsycINFO from inception to June 2020. Eligible studies were cohort and case-control studies assessing the association between depressive symptoms (questionnaires) or depression (diagnoses) and health outcomes in persons aged ≥16 years with LBP in the absence of major pathology. Reviewers independently screened articles, extracted data, and assessed risk of bias using the Quality in Prognosis Studies tool. We classified exploratory versus confirmatory studies based on phases of prognostic factor investigation. We conducted random-effects meta-analyses and descriptive synthesis where appropriate.

RESULTS: Of 13,221 citations screened, we included 62 studies (63,326 participants; 61 exploratory studies, 1 confirmatory study). For acute LBP, depressive symptoms were associated with self-reported disability (descriptive synthesis: 6 studies), worse recovery (descriptive synthesis: 5 studies), and slower traffic injury–related claim closure (1 study), but not pain or work-related outcomes. Depressive symptoms were associated with greater primary healthcare utilization for acute LBP (1 confirmatory study). For chronic LBP, depressive symptoms were associated with higher pain intensity (descriptive synthesis: 9 studies; meta-analysis: 3 studies, 2902 participants, β=0.11, 95% confidence interval (CI) 0.05–0.17), disability (descriptive synthesis: 6 studies; meta-analysis: 5 studies, 3549 participants, β=0.16, 95% CI 0.04–0.29), and worse recovery (descriptive synthesis: 2 studies; meta-analysis: 2 studies, 13,263 participants, relative risk (RR)=0.91, 95% CI 0.88–0.95), but not incident chronic widespread pain (1 study).

DISCUSSION: Depressive symptoms may be associated with self-reported disability and worse recovery in persons with acute and chronic LBP, and greater primary healthcare utilization for acute LBP. Our review provides high-quality prognostic factor information for LBP. Healthcare delivery that addresses depressive symptoms may improve disability and recovery in persons with LBP. Confirmatory studies are needed to assess the association between depressive symptoms and health outcomes in persons with LBP.

PROTOCOL REGISTRATION: PROSPERO database (CRD42019130047)

KEY WORDS: low back pain; depressive symptoms; prognosis; systematic review; meta-analysis.

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BACKGROUND

Low back pain (LBP) is the leading cause of disability globally, with years lived with disability related to LBP increasing 54% from 1990 to 2015[1–3]. The prevalence of LBP was 7.8% worldwide in 2017[4], and although most LBP episodes resolve, recurrences are common[5]. LBP is also a driver of high healthcare utilization and costs[6–9].

As leading causes of disability, depressive symptoms are common comorbidities among individuals with LBP and may negatively impact outcomes[10–15]. Prior systematic reviews examining depressive symptoms as prognostic factors for LBP have yielded inconsistent results[16–21]. The estimated magnitude of associations between depressive symptoms (or depression) and outcomes varied greatly across

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reviews[17,18,20,21], with some reviews reporting weak or no association with work-related outcomes[16,19]. Inconsistent results may be due to differences in methodological quality, as some reviews were limited by using scoring with cutoffs to determine study quality[17,21], excluding potentially relevant studies based on study design (e.g., secondary analyses of randomized trials)[18], or synthesizing results across different study designs[20]. Importantly, these systematic reviews require updating[16–22]; reviews with most recent literature searches were conducted by Alhowimel et al. (up to 2016)[20] and Pinheiro et al. (up to 2014)[18]. Alhowimel et al. restricted to adults with chronic LBP receiving physiotherapy and excluded spinal stenosis[20], whereas Pinheiro et al. focused on adults with acute/subacute LBP, excluding sciatica and spinal stenosis[18]. Relevant studies have been published since 2016[23–32], particularly on disability and healthcare utilization. To our knowledge, existing reviews have not assessed the impact of depressive symptoms on healthcare utilization for LBP.

It is critically important to identify prognostic factors for LBP to guide management, facilitate recovery, and inform future research. Prognostic research is particularly informative, as individual-based treatments for LBP tend to provide small or short-term benefits[33,34]. In healthcare, high-quality evidence on prognostic factors can guide healthcare providers and patients with education and patient-centered care[35]. At the health system level, identifying factors associated with healthcare utilization for LBP can inform healthcare planning and resource allocation tailored to priority groups.

Our objective was to conduct a systematic review to assess the association between depressive symptoms or depression and health outcomes (i.e., pain, disability, overall health status, satisfaction with care, healthcare utilization) in persons with LBP.

METHODS

Our protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO CRD42019130047)[36] and was previously published[37]. Guidance from the Cochrane Prognosis Methods Group informed our conduct of the review[35,38]. Our review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and Meta-analyses Of Observational Studies in Epidemiology Checklist[39,40](Appendix I).

Eligibility Criteria

Population. We included inception cohorts of individuals aged ≥16 years with LBP with or without radiculopathy (Appendix IIIa). LBP is defined as pain localized between the costal margin and inferior gluteal folds with or without leg pain in the absence of major pathology[41]. Radiculopathy is defined as inflammation, injury an inflammation, injury, or compression of spinal nerve roots with pain, weakness, or numbness in a myotomal or dermatomal distribution, and may be attributed to spinal stenosis or lumbar disc herniation[42,43]. We focused on non-specific LBP, which is LBP not attributed to recognizable and specific major pathology such as fractures, infections, ankylosing spondylitis, inflammatory process, and tumours[41]. Therefore, we excluded LBP due to major pathology (e.g., fractures, spinal cord injury, inflammatory arthritis, tumors, malignancies) and surgical populations.

Exposure. Depressive symptoms are self-reported characteristic attitudes and symptoms of depression, such as little interest or pleasure in doing things or feeling down, depressed, or hopeless. We included depressive symptoms measured on standardized questionnaires (e.g., Center for Epidemiologic Studies Depression Scale). We included diagnosed depression, including diagnoses using standardized codes in administrative data and self-report of diagnosed depression on standardized questionnaires, such as major depressive disorder/episode and dysthymia[44]. Higher severity of depressive symptoms compared to lower severity were also examined based on scoring of standardized questionnaires (e.g., severe versus mild depressive symptoms using standardized thresholds on the Beck Depression Index).

Outcomes. We targeted the following outcomes: (1) pain (e.g., pain intensity); (2) disability (e.g., activity limitations, participation restriction); (3) overall health status (e.g., health-related quality of life); (4) satisfaction with care; and (5) healthcare utilization (e.g., physician visits). These were informed by outcomes considered important for LBP research among international expert panels[45–47]. Based on previous literature in LBP populations, we included time-to-claim closure for traffic injury and workers' compensation claims as common proxies for recovery[48–52]. Only standardized outcome measures (e.g., standardized questionnaires or administrative data) were included. We evaluated the validity and reliability of standardized questionnaires during the risk of bias assessment.

In addition to the above criteria, eligible studies were published in English to increase feasibility, and cohort studies, case-control studies, or secondary analyses of randomized trials. We excluded guidelines, letters, editorials, commentaries, books, conference proceedings, abstracts, consensus statements, case reports, case series, cross-sectional studies, qualitative studies, reviews, laboratory studies, studies not reporting methodology, and cadaveric and animal studies.

Information Sources

We searched MEDLINE, Embase, CINAHL, and PsycINFO from inception to June 25, 2020. The search strategy was developed in consultation with an experienced librarian

(Appendix II) and peer-reviewed by a second librarian using the Peer Review of Electronic Search Strategies Checklist[13,53]. Search terms included subject headings and free-text words for the concepts of LBP, psychological factors, and depressive symptoms/depression. We used EndNote to de-duplicate references electronically. Supplemental searches were conducted using reference lists of included studies and related systematic reviews[16–22].

Study Selection

We used a two-level screening process (titles/abstracts, full-text screening) to select eligible studies. We conducted training with screening a random sample of citations (50 titles/abstracts, 25 full-texts) to achieve agreement ≥80% between reviewers before starting screening. Pairs of reviewers independently screened citations to determine eligibility of studies (JJW, CYL, JAL). Reviewers met to discuss disagreements and reach consensus, and a third reviewer was involved if consensus could not be reached.

Data Collection

The data extraction form was pilot-tested on a random sample of five citations. Two reviewers independently extracted study results (effect estimates, 95% confidence interval (CI)) from included studies and discussed to reconcile differences. For all other data items, the lead author extracted data from studies. A second reviewer verified all other data extraction items by checking extracted data to minimize error. From each study, we extracted data on author, year, study design, setting and participant characteristics, duration of follow-up, definition of exposure and outcomes, and effect estimates.

Methodological Quality Appraisal

Paired reviewers independently appraised a random set of five studies as training using the Quality in Prognosis Studies (QUIPS) tool[54] (Appendix XIIa). We originally indicated the Risk of Bias in Non-randomized Studies of Exposures tool in our protocol[37]. We decided to use the QUIPS tool as it is recommended by the Cochrane Prognosis Methods Group, is designed for prognostic factor review questions, and has adequate inter-rater reliability[38,54]. Trained reviewers assessed study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting (Appendix XIIb). Reviewers summarized judgments to assess overall risk of bias as low, moderate, or high for all studies. Any discrepancies between reviewers were resolved through discussion or by involving a third reviewer.

Synthesis

We assessed inter-rater agreement for screening and risk of bias assessments using percent agreement and kappa coefficients. Clinical, methodological, and statistical heterogeneities among studies were assessed. Clinical heterogeneity may result from differences in populations, exposures, comparators, or outcomes across studies. Results were stratified by LBP type (LBP versus LBP with radiculopathy), duration (acute/subacute: <3 months' duration versus chronic: ≥3 months' duration), exposure (depressive symptoms versus depression), and health outcome (Appendix IIIb). We stratified results for LBP without radiculopathy versus LBP with radiculopathy due to differences in the course, prognosis, and management of the conditions[34,55,56]. Methodological and statistical heterogeneity may result from differences in risk of bias and outcomes across studies beyond what could be expected by chance alone. We assessed methodological heterogeneity across studies as low-to-moderate versus high risk of bias based on overall judgment from the QUIPS tool. We assessed statistical heterogeneity using the I^2 statistic, whereby I^2>75% was deemed considerable heterogeneity as recommended in the Cochrane Handbook[57].

Random-effects meta-analyses were conducted to assess associations between depressive symptoms (or depression) and health outcomes when ≥2 studies reported sufficiently similar data and were clinically homogeneous (Appendix IIIb). Effect measures included odds ratios, risk differences, risk ratios, rate differences, rate ratios, mean differences, and hazard ratios. If not reported, we computed these effect measures when applicable based on available data[37]. As recommended for prognostic factor systematic reviews, we conducted separate meta-analyses for different effect measures and study designs[35]. To explore potential impact of methodological quality on results, the following meta-analyses were conducted: (1) including all studies (low, moderate, high risk of bias studies); and (2) excluding high risk of bias studies. Summary statements in evidence syntheses were based on results from low/moderate risk of bias studies. We used random-effects meta-analyses, which assume heterogeneity of treatment effect sizes across the studies. For meta-analyses with considerable statistical heterogeneity, we conducted subgroup analyses to explore sources of heterogeneity. All meta-analyses were conducted in R v3.6.3 using the

Table 1 Levels of Evidence for Prognostic Factor Studies

Study Phase	Description
Phase I Exploratory	Associations between potential prognostic factors and health outcomes explored in a descriptive way. Only crude (univariable) associations are reported.
Phase II Exploratory	Includes use of well-formulated comparison groups, stratified analyses, or multivariable analyses to identify sets of predictors.
Phase III Confirmatory	The goal is to test a specific hypothesis to confirm or disconfirm an independent relationship between an identified prognostic factor and a health outcome, while explicitly identifying and controlling for confounding.

metafor package[58]. We descriptively synthesized results of studies that were clinically heterogeneous.

When interpreting results, we classified studies into exploratory (phase I, phase II) and confirmatory studies (phase III) based on levels of evidence for prognostic factor studies[59] (Table 1). Finally, for meta-analyses involving ≥10 studies, we visually inspected funnel plots for asymmetry suggestive of publication bias[60,61].

RESULTS

Study Selection

We screened 13,221 citations for inclusion (Fig. 1). We identified 62 studies reported in 66 articles (63,326 participants) as relevant, of which 14 studies (18,843 participants) were included in meta-analyses. We descriptively synthesized results of 48 studies deemed clinically heterogeneous. Inter-rater agreement for screening was kappa=0.79 (95% CI 0.76–0.81). Pilot screening achieved 82% (titles/abstracts) and 80% (full-texts) agreement based on independent results.

Independent critical appraisal before discussion to reach consensus had 85% agreement (312/366 items across the QUIPS tool) (Fig. 2; Appendix XIIb). After risk of bias assessment, 55 studies had low-to-moderate and 7 studies had high risk of bias. We identified 61 exploratory studies (23 phase I, 38 phase II) and one confirmatory study. We identified <10 studies per outcome in meta-analyses, which precluded us from assessing publication bias.

Study Characteristics

Of the 62 included studies, 89% were cohort studies, 10% were secondary analyses of randomized trials, and one study was a combined cohort study and secondary analysis of a randomized trial (Table 2). Sample size ranged 28 to 16,567 participants with LBP, with a median of 339 (interquartile range (IQR) 161–675). The proportions of women in study populations ranged from 0% to 100% (median 51.5%, IQR 41–58%) and mean age ranged 30 to 67 years. Study populations were 34% acute LBP, 42% chronic LBP, 6% mixed duration, and 18% other (e.g., LBP with an index healthcare visit). Fifty-nine studies targeted depressive symptoms and three targeted diagnosed depression[62–64].

ACUTE LBP

Pain

Eight studies (2069 participants; 3 phase I, 5 phase II) assessed pain outcomes[63,65–76]; three provided similar data for meta-analysis[66–68] (Table 3; Appendices V and VI). Unadjusted results suggest that depressive symptoms were associated with pain intensity[68–70], but not pain trajectory (i.e., trajectory of back pain severity at different time points identified using latent class growth analysis)[71]. Pooled results from three phase II studies found depressive symptoms to be associated with slightly higher odds of pain (3 studies, 487 participants, odds ratio (OR)=1.15, 95% CI 0.97–1.36, I^2=78.67%)[66–68]. When excluding one high risk of bias phase II study from the meta-analysis, we observed no association between depressive symptoms and pain[67,68] (2 studies, 314 participants, OR=1.05, 95% CI 0.97–1.15, I^2=35.09%). Two phase II studies found no association between depressive symptoms and pain intensity[65,72]. Overall, exploratory evidence suggests that depressive symptoms are not associated with pain intensity in persons with acute LBP.

One phase I study reported that diagnosed major depression was associated with higher pain intensity[63] (OR ranged 2.42–12.71). Overall, exploratory evidence suggests that major depression is associated with higher pain intensity in persons with acute LBP, but further investigation is needed.

Self-reported Disability

Seven studies (1484 participants; 2 phase I, 5 phase II) assessed self-reported disability[65,66,68–70,72–77] (Table 3; Appendix V). Five studies reported a positive association between depressive symptoms and self-reported disability based on one phase I and four phase II studies[65,66,68–70,77], with β=0.20, 95% CI 0.04–0.36[77]. Overall, exploratory evidence suggests that depressive symptoms are associated with self-reported disability in persons with acute LBP.

Recovery

Five studies (2227 participants; 4 phase I, 1 phase II) assessed LBP recovery, which included composite measures of pain and disability[25,78–81] (Table 3; Appendix V). Results from four phase I studies varied on whether depressive symptoms were associated with worse recovery[25,78,80,81]. Based on one phase II study, depressive symptoms were associated with slower time to recovery[79] (hazard ratio (HR)=0.94, 95% CI 0.91–0.97). Overall, exploratory evidence suggests that depressive symptoms are associated with worse recovery in persons with acute LBP.

Work-related Outcomes

Nine studies (2892 participants; 7 phase I, 2 phase II) assessed work-related outcomes; four provided similar data for meta-analysis[68,73–76,82–84] (Table 3; Appendices V and VII). Pooled results from four phase I studies found no association between depressive symptoms and work non-participation (4 studies, 1356 participants, OR=0.92, 95% CI 0.84–1.01, I^2=93.46%)[68,82–84]. When excluding one high risk of bias study from the meta-analysis, pooled results remained as no association (3 studies, 1035 participants, OR=0.96, 95% CI 0.92–1.00, I^2=75.70%)[68,82,83]. Five phase I studies reported

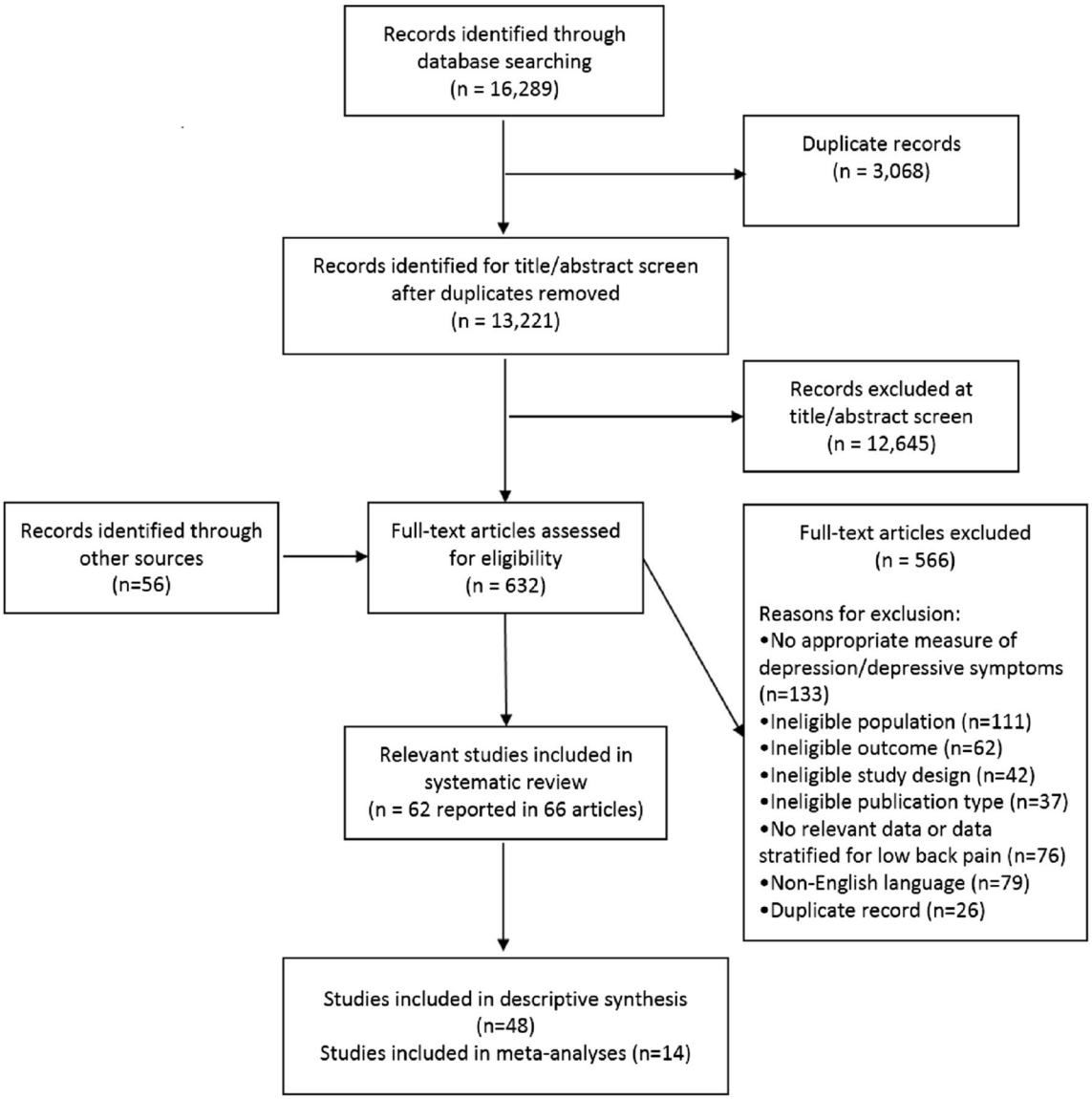

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram showing identification and selection of included studies.

varied results, of which two reported that depressive symptoms were associated with work status[83,85], while three reported no association[82,86,87]. One phase II study found depressive symptoms to be associated with compensation payments based on age/sex-adjusted results[88]. One phase II study reported depressive symptoms as not associated with time-on-benefits during workers' compensation claim[89]. The body of exploratory evidence suggests that depressive symptoms are not associated with work-related outcomes in persons with acute LBP.

Traffic Injury–related Outcomes

Exploratory evidence from one phase II study suggests that depressive symptoms are associated with slower time-to-claim closure from traffic injuries in persons with acute LBP (3232 participants; HR ranged 0.62–0.70)[90] (Table 3; Appendix V).

Healthcare Utilization

Two studies (19,458 participants; 1 phase II, 1 phase III) assessed healthcare utilization[64,91]. One phase III study found depressive symptoms to be associated with rate of LBP-specific primary care visits over 1 year (rate ratio=1.04, 95% CI 1.02–1.07)[91](Table 3; Appendix V). Overall, confirmatory evidence suggests that depressive symptoms are associated with greater LBP-specific primary care utilization in persons with acute LBP.

Diagnosis of depression was associated with all-cause inpatient admissions (OR=1.27, 95% CI 1.13–1.46), but not musculoskeletal-related inpatient admissions based on one phase II study[64]. Overall, exploratory evidence suggests that depression is associated with all-cause, but not musculoskeletal-related inpatient admissions in persons with acute LBP.

CHRONIC LBP

Pain

Twelve studies (8433 participants; 2 phase I, 10 phase II) assessed pain outcomes; three had similar data for meta-analysis[30,77,92] (Table 3; Appendices V and VIII). Three studies reported no association between depressive symptoms and pain intensity based on unadjusted results[32,93,94]. Pooled results from three phase II studies found depressive symptoms to be associated with higher pain intensity (3 studies, 2902 participants, β=0.11, 95% CI 0.05–0.17, I^2=1.04%)[30,77,92]. Of five phase II studies[31,95–98], three studies found depressive symptoms to be associated with higher pain intensity[31] (relative risk (RR)=1.47, 95% CI 1.13–1.94), lower odds of pain reduction[95] (OR=0.47, 95% CI 0.25–0.89), and shorter duration of pain reduction[97] (HR=2.97, 95% CI 1.32–6.65). Overall, exploratory evidence suggests that depressive symptoms are associated with higher pain intensity in persons with chronic LBP.

One phase II study found no association between depressive symptoms and the incidence of chronic widespread pain[99] (OR=1.01, 95% CI not reported, $p>0.05$). Overall, exploratory evidence suggests that depressive symptoms are not associated with incident chronic widespread pain in persons with chronic LBP.

Self-reported Disability

Ten studies (4732 participants; 2 phase I, 8 phase II) assessed self-reported disability; five had similar data for meta-analysis[27,30,77,92,100] (Table 3; Appendices V and IX). Three studies reported unadjusted results[26,98,101], of which two found depressive symptoms to be associated with self-reported disability[26,101]. Pooled results from five phase II studies found depressive symptoms to be associated with self-reported disability (5 studies, 3549 participants, β=0.16, 95% CI 0.04–0.29, I^2=74.69%)[27,30,77,92,100]. We observed similar results when excluding one phase II study with high risk of bias (4 studies, 3065 participants, β=0.15, 95% CI 0.02–0.27, I^2=78.70%)[30,77,92,100]. Three phase II studies found depressive symptoms to be associated with self-reported disability (RR=1.34, 95% CI 1.04–1.72) and family/social disability (β=1.94, 95% CI 1.27–2.60)[30,31,102]. Overall, exploratory evidence suggests that depressive symptoms are associated with self-reported disability in persons with chronic LBP.

Health-related Quality of Life (HRQOL)

Six studies (5837 participants; 1 phase I, 5 phase II) assessed HRQOL[32,94,98,100,103]; two provided similar data for meta-analysis[100,103] (Table 3; Appendices V and X). Pooled results from two phase II studies found no association between depressive symptoms and mental HRQOL (2 studies, 637 participants, β=1.09, 95% CI −1.83 to 4.02, I^2=96.22%). One phase II study found no association between depressive symptoms and mental HRQOL[94]. In contrast, one phase II study found depressive symptoms to be associated with lower odds of improvement in mental HRQOL[32]. Results varied for overall or physical HRQOL based on one phase I (reported no association)[28] and four phase II studies (three studies reported an association[32,98,100], one study reported no association[94]). Overall, the evidence is inconclusive on the association between depressive symptoms and HRQOL in persons with chronic LBP due to inconsistent results across studies.

Recovery

Four studies (13,747 participants; 1 phase I, 3 phase II) assessed LBP recovery, including combined measures of pain and disability[25,29,104,105]; two provided similar data for meta-analysis[29,105] (Table 3; Appendices V and XI). Pooled results from two phase II studies found

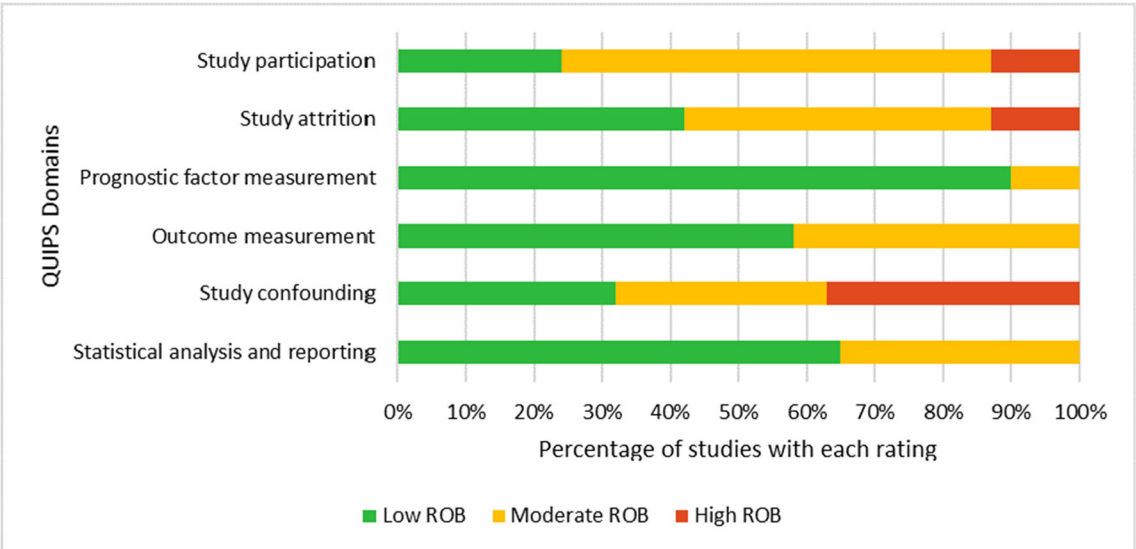

Fig. 2 Risk of bias graph showing assessment of each risk of bias (ROB) domain using the Quality in Prognosis Studies (QUIPS) tool presented as percentages across all included studies (n=62).

Table 2 Characteristics of Included Studies on the Association Between Depressive Symptoms or Depression and Health Outcomes in Individuals with Low Back Pain, Organized by Type of Low Back Pain

Study	Study design	Region	Study period	Setting	Sample size	Type of LBP*	Mean age (years)†	Sex (% female)	Length of follow-up
Acute LBP*									
Lehmann, 1993[87]	Cohort study	USA	Not reported	Occupational	70	Acute	37.2	33	6 months
Gatchel, 1995[86]	Cohort study	USA	Not reported	Health care	421	Acute	35	38	12 months
Epping-Jordan, 1998[65]	Cohort study	USA	Not reported	Health care	78	Acute	31.9	0	12 months
Fritz, 2001[85]	Cohort study	USA	Not reported	Occupational	78	Acute	37.4	38	1 month
Cassidy, 2003[90]	Cohort study	Canada	1994–1995	MVC claims	3232	Acute	Subgroups: ranged 33.9 to 35.8	Subgroups: ranged 57 to 65	Up to claim closure
Sieben, 2005[81]	Cohort study	The Netherlands	2001–2003	Health care	222	Acute	≥18	44	12 months
Truchon, 2005[84]	Cohort study	Canada	Not reported	Occupational	321	Acute	39	44	6 months
Ritzwoller, 2006[64]	Cohort study	USA	1997–1998	Health care	16,567	Acute	51.1	54	24 months
Patel, 2006[69]	Cohort study	USA	1991–1996	Occupational	107	Acute	29.8	0	6 months
Henschke, 2008[79]	Cohort study	Australia	2003–2005	Health care	973	Acute	43.3	45	12 months
Gurcay, 2009[78]	Cohort study	Turkey	2007	Health care	91	Acute	37.9	36	3 months
Reme, 2009[83]	Cohort study	USA	2000–2004	Occupational	496	Acute	37	42	3 months
Smeets, 2009[70]	Secondary analysis of RCT	Australia, New Zealand	2001–2003	Health care	259	Acute	18–80	Subgroups: ranged 44 to 54	12 months
Shaw, 2010[63]	Cohort study	USA	1992–1994	Health care	140	Acute	30	0	6 months
Hiebert, 2012[82]	Cohort study	USA	2009	Occupational	253	Acute	32.3	26	3 months
Melloh, 2013[68,73–76]	Cohort study	New Zealand	2008–2010	Health care	286	Acute	Subgroups: ranged 33.5 to 36.1	Subgroups: ranged 60 to 71	6 months
Enthoven, 2016[71]	Cohort study	The Netherlands	Not reported	Health care	675	Acute	66.4	59	3 years
Steenstra, 2016[89]	Cohort study	Canada	2005	Occupational	113	Acute	44	53	12 months
Traeger, 2016[91]	Cohort study	Australia	2003–2005, 2009–2013	Health care	2891	Acute	Subgroups: ranged 43.9 to 44.8	47	Study 1: 3 months; Study 2: 12 months
Friedman, 2017[72]	Secondary analysis of RCT	USA	2012–2014	Health care	323	Acute	39	51	3 months
Klyne, 2020[67]	Cohort study	Australia	Not reported	Health care	28	Acute	29.5	46	6 months
Chronic LBP*									
Rainville, 1993[104]	Cohort study	USA	1991	Health care	72	Chronic	37	16	Post-treatment
Harkapaa, 1996[107]	Cohort study	Finland	Not reported	Health care	175	Chronic	42.1	48	12 months
Dionne, 1997[102]	Cohort study	USA	1989–1990	Health care	1213	Chronic	46.7	52	24 months
Vendrig, 1999[108]	Cohort study	The Netherlands	Not reported	Health care	143	Chronic	Subgroups: ranged 41.2 to 42.1	Subgroups: ranged 29 to 41	6 months
Michaelson, 2004[93]	Cohort study	Sweden	1997–1999	Health care	167	Chronic	43	62	12 months
Weidenhammer, 2007[94]	Cohort study	Switzerland	Not reported	Health care	4032	Chronic	57.7	79	6 months
Van Der Hulst, 2008[100]	Secondary analysis of RCT	The Netherlands	1998–2000	Health care	163	Chronic	Subgroups: ranged 38 to 40	Subgroups: ranged 38 to 40	6 months
Streitberger, 2011[97]	Cohort study	Switzerland	2006–2008	Health care	41	Chronic	59	41	12 months
Hicks, 2012[95]	Cohort study	Italy	2007–2008	Health care	392	Chronic	66.8	84	12 months
van Hooff, 2014[101]	Cohort study	The Netherlands	Not reported	Health care	524	Chronic	45.4	58	12 months
Cougot, 2015[106]	Cohort study	France	2009	Occupational	217	Chronic	41.3	55	24 months
Scherrer, 2015[109]	Cohort study	USA	2008–2009	Health care	355	Chronic	≥18	72	24 months
Viniol, 2015[99]	Cohort study	Germany	Not reported	Health care	484	Chronic	56.6	58	12 months
Yarlas, 2016[98]	Secondary analysis of RCT	USA	Not reported	Health care	541	Chronic	Subgroups: ranged 49.0 to 49.6	Subgroups: ranged 52 to 64	3 months
Jegan, 2017[27]	Cohort study	Germany	Not reported	Health care	484	Chronic	56.6	58	12 months
Nordeman, 2017[26]	Cohort study	Sweden	2004–2005	Health care	130	Chronic	45	100	24 months
Nordstoga, 2017[105]	Cohort study	Norway	1995–1997, 2006–2008	General population	7523	Chronic		60	11 years

(continued on next page)

Table 2. (continued)

Study	Study design	Region	Study period	Setting	Sample size	Type of LBP*	Mean age (years)†	Sex (% female)	Length of follow-up
							Subgroups: ranged 47.9 to 51.8		
Dengler, 2018[23]	Secondary analysis of RCT	Europe	2013–2015	Health care	101	Chronic	Subgroups: ranged 47.8 to 48.2	Subgroups: ranged 73 to 74	6 months
Glattacker, 2018[28]	Cohort study	Germany	2012–2013	Health care	214	Chronic	50.7	53	6 months
Demarchi, 2019[92]	Cohort study	Brazil	2015–2017	Health care	92	Chronic	40.4	64	6 months
Halonen, 2019[29]	Cohort study	Sweden	2010–2016	Occupational	5740	Chronic	54.1	61	6 years
Oliveira, 2019[30]	Cohort study	Portugal	Not reported	Health care	284	Chronic	60.4	75	24 months
Page, 2019[96]	Cohort study	Canada	2008–2011	Health care	686	Chronic	56.5	56	12 months
Imagama, 2020[103]	Cohort study	Japan	2014–2016	Health care	474	Chronic	73 (median)	58	6 months
Ranger, 2020[31]	Cohort study	Denmark	2013–2014	Health care	633	Chronic	44.5	54	12 months
Zackova, 2020[32]	Cohort study	Italy	2017–2018	Health care	413	Chronic	Subgroups: ranged 62.7 to 65.5	Subgroups: ranged 54 to 59	6 months
Mixed duration*									
Grotle, 2006[66]	Cohort study	Norway	Not reported	Health care	173	Mixed duration	Subgroups: ranged 38.0 to 40.4	Subgroups: ranged 54 to 62	12 months
Newell, 2007[80]	Cohort study	UK	2006	Health care	788	Mixed duration	Not reported	52	3 months
Grotle, 2010[77]	Cohort study	UK	2001–2002, 2004–2006	Health care	926	Mixed duration	46	Subgroups: ranged 58 to 59	12 months
Adnan, 2017[25]	Cohort study	Belgium	2007-2010	Health care	565	Mixed duration	41.5	58	Post-treatment
Other									
Cherkin, 1996[114]	Secondary analysis of RCT	USA	1992–1993	Health care	219	Other (index healthcare visit for LBP)	43.1	47	12 months
Fransen, 2002[88]	Cohort study	New Zealand	1994–1995	Occupational	854	Other (new claimants)	≥15	26	3 months
Tubach, 2004[113]	Cohort study	France	1991–1992	Occupational	622	Other (LBP with radiculopathy ≥1 day in past year)	≥35	16	24 months
Campello, 2006[117]	Cohort study	USA	1996–2000	Occupational	67	Other (off/ restricted duty >8 weeks)	40	27	24 months
Scheele, 2013[116]	Cohort study	The Netherlands	Not reported	Health care	675	Other (new healthcare visit for LBP)	66.4	59	3 months
Fischer, 2014[118]	Cohort study	Germany	Not reported	Health care	395	Other (work absenteeism)	44.3	57	6 months
Kerr, 2015[62]	Secondary analysis of RCT, cohort study	USA	2000–2004	Health care	392	Other (LBP with radiculopathy of ≥6 weeks' duration)	43.8	41	8 years
Kim, 2017[111]	Cohort study	USA	2012–2014	Health care	161	Other (LBP with radiculopathy with non-response to care)	61.3	50	12 months
Lubelski, 2015[112]	Cohort study	USA	2010–2013	Health care	1346	Chronic with radiculopathy	66.3	49	12 months
Hartvigsen, 2018[115]	Cohort study	Denmark	2010–2012	Health care	928	Other (index healthcare visit for LBP)	44	47	12 months
Bahar-Ozmedir, 2020[110]	Cohort study	Turkey	2013–2015	Health care	161	Acute with radiculopathy	48.9	53	3 months

LBP, low back pain; MVC, motor vehicle collision; RCT, randomized clinical trial
**Acute refers to <3 months' duration; chronic refers to ≥3 months' duration; studies with mixed duration report results stratified by duration*
†Mean age of study sample unless otherwise specified

depressive symptoms to be associated with worse recovery[29,105] (2 studies, 13,263 participants, RR=0.91, 95% CI 0.88–0.95, I^2=0%). Similarly, depressive symptoms were associated with worse recovery based on results from one phase I and one phase II study[25,104]. Overall, exploratory evidence suggests that depressive symptoms are associated with worse recovery in persons with chronic LBP.

Table 3 Summary Table of Associations Between Depressive Symptoms or Depression and Health Outcomes in Persons with Low Back Pain Based on Levels of Evidence in Prognostic Factor Studies

Population	Prognostic factor	Outcome	Association	Level of evidence
Acute low back pain (<3 months' duration)	Depressive symptoms	Pain intensity	No	Exploratory (phases I and II)[63,65–76]
	Depression	Pain intensity	Yes (Phase I)	Exploratory (phase I)[63]
	Depressive symptoms	Self-reported disability	Yes	Exploratory (phases I and II)[65,66,68–70,72–77]
	Depressive symptoms	Worse recovery	Yes	Exploratory (phases I and II)[25,78–81]
	Depressive symptoms	Work-related outcome	No	Exploratory (phases I and II)[68,73–76,82–84]
	Depressive symptoms	Slower traffic injury claim closure	Yes	Exploratory (phase II)[90]
	Depressive symptoms	Healthcare utilization (primary care visits)	Yes	Confirmatory (phase III)[91]
	Depression	Healthcare utilization (inpatient admissions)	Inconclusive	Exploratory (phase II)[64]
Chronic low back pain (≥3 months' duration)	Depressive symptoms	Pain intensity	Yes	Exploratory (phases I and II)[30,77,92]
	Depressive symptoms	Chronic widespread pain	No	Exploratory (phase II)[99]
	Depressive symptoms	Self-reported disability	Yes	Exploratory (phases I and II)[27,30,77,92,100]
	Depressive symptoms	Worse health-related quality of life	Inconclusive	Exploratory (phases I and II)[32,94,98,100,103]
	Depressive symptoms	Worse recovery	Yes	Exploratory (phases I and II)[25,29,104,105]
	Depressive symptoms	Work-related outcome	Inconclusive	Exploratory (phase I)[106–108]
	Depressive symptoms	Healthcare utilization (opioid use)	Inconclusive	Exploratory (phase II)[23,109]
Low back pain with an index healthcare visit	Depressive symptoms	Pain intensity	Yes (Phase I)	Exploratory (phase I)[115]
	Depressive symptoms	Self-reported disability	Yes (Phase I)	Exploratory (phase I)[115]
	Depressive symptoms	Worse recovery	Yes (Phase I)	Exploratory (phase I)[116]
	Depressive symptoms	Poor tolerability of symptom severity	Yes	Exploratory (phase II)[114]
Lumbar radiculopathy ≥6 weeks' duration	Depression	Self-reported disability	Yes (Phase I)	Exploratory (phase I)[62]

Work-related Outcomes

Three phase I studies (535 participants) assessed work-related outcomes[106–108] (Table 3; Appendix V). Depressive symptoms were not associated with work status based on three phase I studies[106–108]. Overall, exploratory evidence suggests that depressive symptoms are not associated with work status in persons with chronic LBP, but further investigation is needed.

Healthcare Utilization

Two phase II studies (456 participants) assessed opioid use[23,109] (Table 3; Appendix V). One phase II study found no association between depressive symptoms and continued opioid use[23], while one phase II study reported higher odds of having high-dose (>50 mg/day) opioid use[109] (OR=1.65, 95% CI 0.97–2.81). Overall, the evidence is inconclusive on the association between depressive symptoms and opioid use in persons with chronic LBP due to inconsistent results across studies when comparing continued versus high-dose opioid use.

Lumbar Radiculopathy

Five studies (2682 participants; 2 phase I, 3 phase II) targeted individuals with lumbar radiculopathy[62,110–113] (Table 3; Appendix V). One phase I study found that diagnosed depression was associated with disability for lumbar radiculopathy ≥6 weeks' duration[62]. One phase I and three phase II studies targeted various durations of lumbar radiculopathy but were moderate-to-high risk of bias[110–113].

LBP with Index Healthcare Visit

Three studies (1822 participants; 2 phase I, 1 phase II) assessed outcomes in persons with an index healthcare visit for LBP[114–116] (Table 3; Appendix V). Depressive symptoms were associated with poor tolerability of symptom severity reported by the patient based on one phase II study[114] (OR=2.3, 95% CI 1.4–3.6), and higher pain intensity, disability, and worse recovery based on two phase I studies[115,116] (OR ranged 1.1–2.3). Overall, exploratory evidence suggests that depressive symptoms are associated with self-reported poor tolerability of symptom severity in individuals with

an index healthcare visit for LBP. Other outcomes of pain, disability, and recovery need further investigation.

Other LBP Populations

Two studies (462 participants; 1 phase I, 1 phase II) reported on different populations with LBP in occupational settings[117,118] (Table 3; Appendix V). One phase I study reported no association between depressive symptoms and work retention in individuals with off/restricted duty >8 weeks[117]. In individuals on sick leave for LBP, depressive symptoms were associated with reduced HRQOL, but not return-to-work or pain based on one phase II study[118]. Overall, evidence is limited on the association between depressive symptoms and work-related outcomes in these LBP populations.

DISCUSSION

Exploratory evidence suggests that depressive symptoms are associated with self-reported disability, worse recovery, and slower traffic injury–related claim closure, but not pain or work-related outcomes in persons with acute LBP. Depressive symptoms are associated with greater healthcare utilization in persons with acute LBP based on one confirmatory study. In persons with chronic LBP, exploratory evidence suggests that depressive symptoms are associated with higher pain intensity, disability, and worse recovery, but not incident chronic widespread pain.

Our systematic review provides more comprehensive prognostic factor evidence for depressive symptoms than previous reviews[16–21]. Alhowimel et al. reported an association between depression and disability, and that depression was predictive of poor quality of life and failure to return to work for chronic LBP based on two studies[20]. This review was limited by synthesizing results from one cross-sectional and one cohort study, and a narrow scope that restricted to patients with chronic LBP treated by physiotherapists[20]. In contrast, our systematic review found that depressive symptoms were associated with self-reported disability but not work-related outcomes, and inconclusive evidence for HRQOL due to inconsistent results across studies. Pinheiro et al. reported that depressive symptoms were associated with worse outcomes for acute LBP, including disability and non-recovery[18]. Pinheiro et al. may have missed studies by excluding secondary analyses of randomized trials[18]. We identified seven studies as secondary analyses of randomized trials, of which five were phase II targeting pain, disability, recovery, HRQOL, symptom tolerability, and healthcare utilization. Similar to the findings of Pinheiro et al.[18], we found that depressive symptoms were associated with disability and worse recovery for acute LBP. Our review extends these findings by synthesizing new information on healthcare utilization for acute LBP and prognosis for chronic LBP.

Our findings have implications for clinical management, healthcare delivery, and research for LBP. Understanding the potential impact of depressive symptoms on disability and recovery can guide expectations and management of LBP among patients and healthcare providers. Healthcare providers may assess for depressive symptoms early to identify patients potentially at risk of disability and worse recovery and guide patient-centered care. From a health system perspective, health programs considering depressive symptoms may improve outcomes for LBP. Further investigation of new interventions may be warranted to help manage comorbid depressive symptoms in patients with LBP. Confirmatory studies are needed to assess the association between depressive symptoms and health outcomes with adequate control for confounding. In addition, studies are needed to assess the role of diagnosed depression as a prognostic factor for LBP, as we identified only three studies. For acute LBP, we found that depressive symptoms were not associated with pain intensity based on phase I and II studies. In contrast, diagnosed depression may be associated with higher pain intensity based on one phase I study. It is unclear whether findings differ due to differences in the exposure (e.g., diagnosed depression may present with greater severity compared to self-reported depressive symptoms) or the need for phase II and III studies to account for important covariates in the analysis.

Strengths and Limitations

Our systematic review provides comprehensive prognostic evidence for depressive symptoms and, to our knowledge, is the first to assess outcomes of healthcare utilization for LBP. Our review was planned a priori with a published protocol[37] based on guidance of the Cochrane Prognosis Methods Group[35,38]. We followed guidelines on the conduct and reporting of prognostic factor systematic reviews, including the PRISMA statement, QUIPS tool, and phases of prognostic factor investigation[38,39,59]. Finally, we used meta-analyses and descriptive syntheses to synthesize evidence using carefully outlined criteria to assess for heterogeneity.

Our review has limitations. First, only English studies were included to increase feasibility. However, a previous study found no evidence of systematic bias when using language restrictions in systematic reviews with meta-analyses in conventional medicine[119]. We identified only six possibly relevant non-English articles (1256 participants; Appendix XIII). Second, studies for one outcome (HRQOL for chronic LBP) had considerable heterogeneity, which we could not adequately explore due to a limited number of studies. However, we used descriptive syntheses and meta-analyses to synthesize evidence when appropriate. Third, we could not conduct planned analyses to assess publication bias due to insufficient data. Research is needed to investigate potential publication bias and explore approaches such as protocol registration and reporting checklists for prognostic factor studies[120].

CONCLUSION

Depressive symptoms serve as prognostic factors for consideration in healthcare delivery and resource planning that may improve disability and recovery in persons with LBP. Our systematic review provides high-quality prognostic factor information to guide management among patients and healthcare providers for LBP. Confirmatory studies are needed to assess the association between depressive symptoms and health outcomes in persons with LBP.

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