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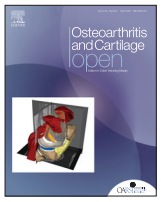

Depression predicts decreased lumbar bone mineral density: A scoping review of chronic psychological stress and spinal tissue pathology

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ABSTRACT

Objective: Chronic low back pain (cLBP) is a complex disease with biological, psychological, and social components and the complex interactions of these components are poorly understood. Chronic psychological stress (CPS) (anxiety, depression, etc.) and pathological changes in spinal tissue (osteoporosis, disc degeneration, etc.) are frequently and independently associated with cLBP, yet their explicit relationship has not been collectively reviewed. The objective of this scoping review is to investigate the current state of research on how CPS may impact spinal tissue pathology.

Design: Five steps were utilized to conduct this scoping review: 1) identify a research objective and establish a search strategy, 2) identify research articles, 3) select research articles that meet search criteria, 4) extract data, 5) summarize and report results.

Results: We identified N = 56 articles relating CPS to spinal pathology. Of those that identified a relationship between CPS and spine pathology (N = 39), most (N = 24) described decreased lumbar vertebral bone mineral density (BMD) between depression and control groups. Animal studies (N = 8) were limited to mice and confirmed a causal relationship between CPS and lower vertebral BMD. Only a few additional human studies (N = 9) documented relationships between other various forms of CPS and spinal tissue pathologies.

Conclusion: This scoping review documents evidence of a relationship between CPS and decreased spine health in humans as well as a causal relationship between the initiation of CPS and decreased BMD in animals. As few studies evaluated disease in other spinal anatomy in relationship to CPS, future work in this area is warranted. Further exploration of CPS beyond depression is warranted as well.

1. Introduction

Chronic low back pain (cLBP) is a heterogeneous disease with biological, psychological, and social components [1]. While cLBP care is primarily biomedical (e.g., analgesics, physical therapy, surgery), the importance of addressing psychological components is becoming more widespread [2]. For example, The American College of Physicians recommends the use of multidisciplinary approaches for treatment of cLBP including physical health and mental health interventions [3]. Still, 90% of patients seeking care for LBP are labeled with "non-specific" LBP as no underlying cause can be identified [4]. Our global hypothesis is that understanding the complex interactions between biopsychosocial components may improve cLBP patient care.

One psychological factor frequently cited in cLBP is chronic psychological stress (CPS) [5]. CPS is defined as a state of pressure or overwhelm for an extended period [6]. While CPS can arise from a variety of conditions, the overall impact of all CPS on the body is consistent and regulated by the autonomic nervous system. At the onset of acute stress, a cascade of events occurs involving the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic-adrenal-medullary systems [7]. Multiple biological systems are impacted downstream, including increases in stress hormones like cortisol and inflammatory mechanisms [8]. In the short term, this helps the body respond to a stressful environment, regulating cardiovascular and metabolic function [9]. However, when stress is overwhelming or cannot be resolved, an acute stress response can become chronic stress [10]. The impact of CPS on many diseases and

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areas of health have been well-defined, such as in coronary artery disease [11], stroke [12], cognitive function [13], mental health [14], diabetes [15], cancer [6], and autoimmune diseases [16]. Furthermore, there is a clear link between inflammation in response to CPS and the development of these chronic diseases [17].

Another factor frequently cited in the development of cLBP, is spinal tissue pathology. These changes include disc degeneration [18], spondylolisthesis [19], osteoporosis [20], and spondylo-arthritis [21] and are often attributed to age- or disease-related inflammation [22]. For example, degradation of spinal disc tissue is signaled through pro-inflammatory cytokines [23], and surgical samples of discs from patients with cLBP, have higher levels of pro-inflammatory cytokines when compared to patients with asymptomatic discs [24]. Pro-inflammatory cytokines are also measured systemically as a biomarker of disc degeneration [25]. Second, sensory nerves are known to penetrate into degenerating discs [26] and inflammation is thought to irritate these sensory nerves and directly cause pain [27]. While inflammation plays an important role in both spinal tissue pathology and CPS, there is limited knowledge on how CPS impacts spinal musculoskeletal tissue pathology [28].

Both CPS and spinal tissue pathology are strong predictors of cLBP, yet their explicit relationship has not been collectively reviewed [5,18]. The objective of this scoping review is to investigate the current state of research on how CPS may impact spinal tissue pathology. This is an important step towards understanding the complex interactions between biological and psychological aspects of cLBP and developing personalized approaches to cLBP treatment. While cLBP is an important motivating factor for this review, the relationships betwen pain and spinal tissue pathology has been reviewed extensively. Thus, this review focuses the relationships between spinal tissue pathology and on other prevalent psychological stressors (e.g., depression, anxiety).

2. Methods

2.1. Study design

We conducted a scoping review using the recommended frameworks by Arksey and O'Malley and Levac et al. [29,30] Additionally, we followed best practices for scoping reviews and PRISM-ScR guidelines [31–33]. Five steps were utilized: 1) identify a concise research objective and establish search strategies, 2) identify all relevant research articles, 3) select research articles that meet search criteria, 4) extract data, 5) summarize and report results. Project pre-registration was published on Open Science Framework (https://osf.io/z9v2t/) on April 6th, 2023.

2.2. Review question

How do spinal tissues adapt to chronic psychological stress?

2.3. Literature search strategies

A comprehensive literature search was designed by the authors and performed by an experienced medical librarian (JW) on April 6th, 2023 in the following databases: PubMed/MEDLINE, Scopus, CINAHL, PsycINFO, Cochrane Database of Controlled Trials, the Cochrane Database of Systematic Reviews, and Google Scholar. Both controlled vocabularies (e.g. MeSH terms) and keywords were searched for in the title and abstract fields. There were no restrictions on geography, age of participants or language of publication. Additionally, a manual search was conducted of the reference lists of selected articles. A reproducible search strategy is attached – see Appendix.

2.4. Eligibility criteria: inclusion criteria

The population included any human or animal research. Eligible interventions included any testing condition or experimental design evaluating circumstances expected to induce chronic psychological stress. We defined chronic as more than one application of a stressful stimulus at one time or more than one evaluation of stress across time. We define conditions that induce psychological stress as conditions that induce anxiety or depression, physical pain, discomfort, or physical distress, deprivation of basic needs such as food or maternal nurture at birth, witnessing or experiencing war, abuse, or violence, experiencing discrimination of any kind, or any psychological reaction to an event or experience that initiates a trauma response (fight/flight/freeze/fawn). The paper was also required to include a non-stressed control group. Finally, the outcome was required to include spinal tissue adaptations in: bone, muscle, tendon, ligament, cartilage, or disc quality, shape, or size, muscle tension; as assessed by tools such as electromyography, histological appearance, inflammatory markers, imaging features of tissue structure such as Dual X-ray Absorptiometry, Micro-Computed Tomography, Densitometer, Magnetic Resonance Imaging, Computed Tomography, or Dissecting Microscopy, or cellular level changes such as gene expression, protein expression, glucose metabolism, or cell viability.

2.5. Eligibility criteria: Exclusion criteria

Articles that were not peer reviewed, not written in English, or had the incorrect study design, intervention, or outcomes were excluded. Study designs that did not include psychological stress as defined within our scope were excluded. Studies with interventions that did include a control group or included some type of treatment were excluded. Studies that did not include tissue-level measurements of spinal tissue pathology were excluded.

2.6. Identification and selection of studies

All studies that met inclusion criteria were included in this scoping review. A total of 5133 studies were imported for screening. There were 1257 duplicates removed. The remaining 3876 articles were screened by two independent reviewers (M.A.B and E.G.). These same reviewers screened 99 full text articles to confirm that they met inclusion criteria. When there was a disagreement, a third researcher (J.T.M) was consulted for a final decision. Fig. 1 describes this process in additional detail.

2.7. Data extraction

Data was extracted by two independent reviewers (M.A.B and E.G). Discrepancies in data extraction were reviewed and then confirmed by the reviewers. The data extracted from each article were: article title, first author, year published, study design, control group, intervention, age of participants, number of participants, test group inclusion criteria, control group inclusion criteria, tissue evaluated, measure of tissue change, human/animal, description of CPS, relationship between CPS and tissue, and explanation about relationship.

2.8. Collection and evaluation of results

First, study characteristics were summarized including the number of studies, the range of years that the studies were published, location where the studies took place, the type of study designs, difference between number of human and animal papers, as well as total number of participants were evaluated. Next, quantitative and descriptive analyses of the study designs were conducted. Studies were evaluated based on what type of spinal anatomy was analyzed and the type of CPS evaluated. Finally, quantitative and descriptive analyses of the results were conducted. This included separating papers into human versus animal research. Within these categories, papers were summarized based on overlapping study design and results.

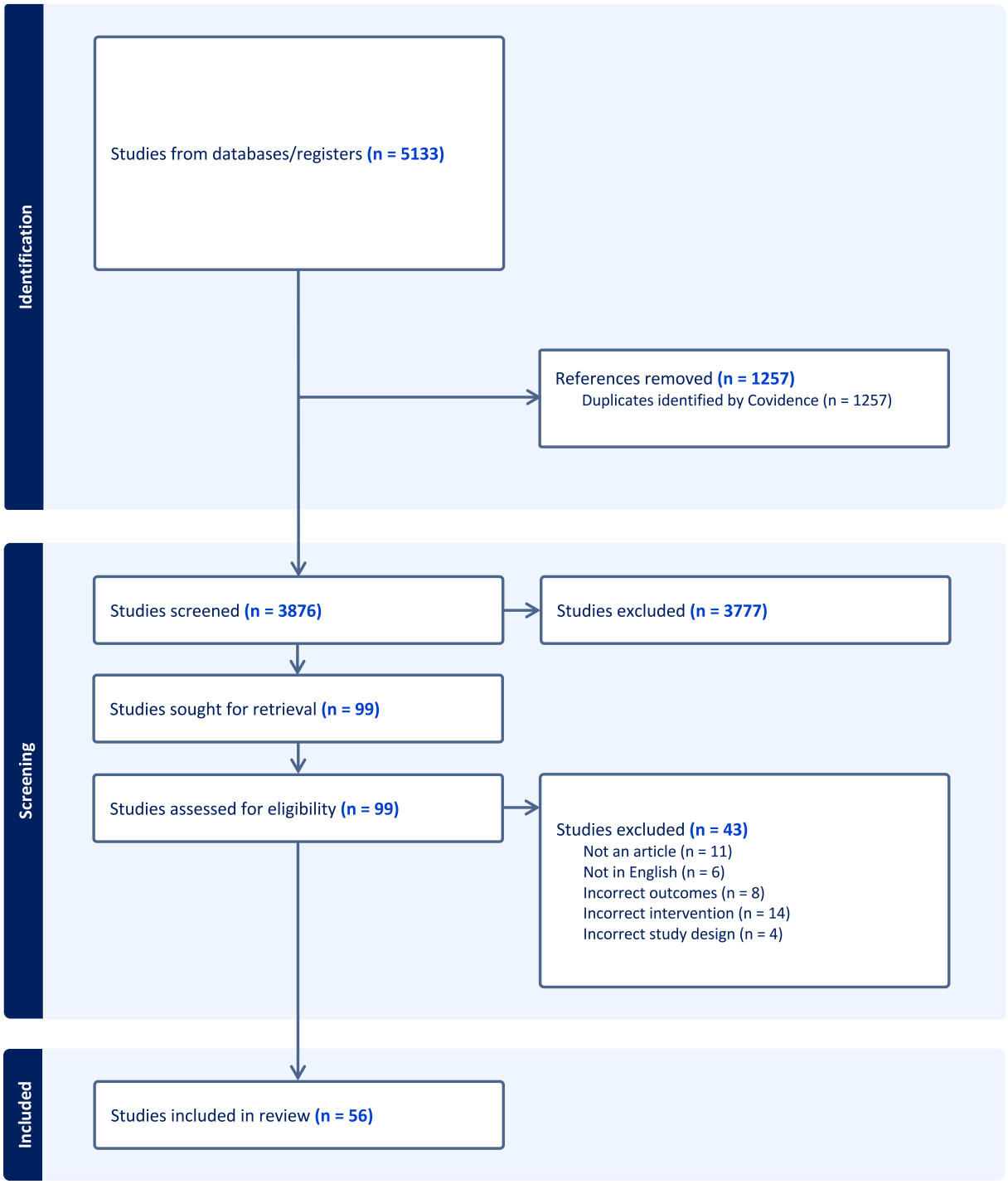

Fig. 1. Describes the process of selecting articles for this review, including identification, screening, and which articles are included in the study. Two authors (M.A.B and E.G.) conducted this analysis.

3. Results

3.1. Study characteristics

Table 1 and Table 2 present characteristics of the 56 included studies. The years that the studies were published ranged from 1995 to 2023. Studies took place across the globe including in Australia [34–36], Brazil [37], Canada [38,39], England [40–47], France [48], Germany [49–51], Greece [52], India [53], Ireland [54,55], Italy [56,57], Netherlands [58], Turkey [59], and the United States [60–87]. There were various study designs including 35 cross-sectional [38–41,45–48,52–57,59–61,64–69,71–75,78–81,88,89], seven prospective cohort [43,51,62,63,83–85], eight interventional [34–37,44,70,86,87], two retrospective cohort [49,50], one case-control [58], one case-cohort [77], one experimental [76], and one longitudinal study [82]. Most studies (n = 48) were conducted with human participants [38–41,43,45–69,71–76,78–85,88,89], while eight studies were conducted on mice [34–37,44,70,86,87] (Fig. 2A). The total number of participants in the studies were 131,504 humans and 685 mice.

Table 1
Human experiments. Abbreviations: Bone mineral density (BMD), Dual X-ray Absorptiometry (DEXA), L (lumbar), Magnetic Resonance imaging (MRI), electromyography (EMG), major depressive disorder (MDD), borderline personality disorder (BPD), Standard Deviation (SD), Standard Error (SE).

Author, year	Study Design	Number of Participants	Age of Participants	Tissue Evaluated	Measure of Tissue Change	Measure of Chronic Stress	Results
[53]Altindag, 2007	Cross-sectional	36-Test, 41-control	39.8 ± 8.8 test 42.8 ± 5.3 control	Lumbar	DEXA	Depression	Lower BMD in depression group
[40]Amsterdam, 1998	Cross-sectional	6-Test, 5-control	41 ± 13 test 38 ± 4 control	L1-L4	DEXA	Depression	No differences
[56]Atteritano, 2013	Cross-sectional	50-Test, 50-control	53.63 ± 1.93 test 53.36 ± 2.47 control	L2-L4	DEXA	Depression	Lower BMD in depression group
[88]Bedford, 2010	Cross-sectional	132	22.3 ± 3.6	L1-L4	DEXA	Perceived stress	Lower BMD in perceived stress group
[60]Calarge, 2014	Cross-sectional	127-Current MMD, 23-past MDD, 72-control	18.9 ± 1.6 current MDD 19.3 ± 1.2 past MDD 19.1 ± 1.4 no MDD	L1-L4	DEXA	Depression and anxiety	Lower BMD in depression group. No differences in anxiety group
[61]Catalano, 2018	Cross-sectional	192	67.5 ± 9.5	L1-L4	DEXA	Anxiety	Lower BMD in anxiety group
[38]Charles, 2012	Cross-sectional	97	43.9 ± 7.6	L1-L4	DEXA	Depression	Lower BMD in depression group (female) No differences (male)
[62]Cizza, 2012	Prospective cohort	92-Test, 44-control	36 ± 6.9 test 35.3 ± 6.9 control	Lumbar	DEXA	Depression	Lower BMD in depression group
[63]Dorn, 2013	Prospective cohort	262	14.35 ± 2.16	Lumbar	DEXA	Depression and anxiety	Lower BMD in depression and anxiety group
[64]Dorn, 2011	Cross-sectional	261	14.9 ± 2.2	Lumbar	DEXA	Depression and anxiety	No differences
[65]Dorn, 2008	Cross-sectional	207	14 ± 2.2	Lumbar	DEXA	Depression and anxiety	No differences
[89]Erdal, 2007	Cross-sectional	20-Test, 20-control	33.65 ± 7.7 test 34.45 ± 7.03 control	Lumbar	DEXA	Depression	Lower BMD in depression group
[41]Erez, 2012	Cross-sectional	33-Osteoporosis, 61-osteopenia, 34-control	64.12 ± 8.44 osteoporosis 62.79 ± 8.39 osteopenia 61.35 ± 6.44 control	L2-L4	DEXA	Depression and anxiety	Lower BMD in depression and anxiety group
[42]Eskandari, 2007	Cross-sectional	44-Test, 44-control	35 ± 6.9 MDD 35 ± 6.8 control 35 ± 6.8 test-matched	L1-L4	DEXA	Depression	Lower BMD in depression group
[43]Follis, 2019	Prospective cohort	11,020	63 ± 7 low strain group 61 ± 7 high strain group	Lumbar	DEXA	Social environment	Lower BMD in higher social stress group
[66]Furlan, 2005	Cross-sectional	9-Test, 10 control	65.9, SD 10.7 test 62.5, SD 8.8 control	L1-L4	DEXA	Depression	Lower BMD in depression group
[67]Hafizi, 2022	Cross-sectional	45,716	64.1 ± 10.4	L1-L4	Trabecular bone score	Schizophrenia, depression, anxiety	No differences
[68]Hahn, 2017	Cross-sectional	4010-Postmenopausal female 4836-Premenopausal females 7016-Males	62.8(0.2 SE) postmenopausal 35.3(0.2 SE) premenopausal 43.7(0.3. SE) male	Lumbar	DEXA	Depression, stress, suicidal ideation	Lower BMD in depression group Lower BMD in stress group (male) Lower BMD in suicidal ideation group (male)
[69]Halbreich, 1995	Cross-sectional	68	39.4 ± 11.8	L2-L4	DEXA	Depression, schizophrenia, schizoaffective disorder, mania, adjustment disorder	Lower BMD in depression group Lower BMD in schizophrenia group
[71]Hlis, 2018	Cross-sectional	2285	49.8 ± 10.9	L1-L4	DEXA	Depression	No differences
[72]Jacka, 2007	Cross-sectional	155-Test, 1124 control	51.8 (41.8–66.6) test 56.6 (39.8–73.3) control	L2-L4	DEXA	Depression	Lower BMD in depression group
[73]Jacka, 2005	Cross-sectional	14-Test, 64 control	50.5 (47.8–55.4) test 53.4 (49.9–57.1) control	L2-L4	DEXA	Depression	No differences
[74]Kahl, 2006	Cross-sectional	73	28.6 ± 7.2 MDD + BPD 30 ± 4.6 MDD young 42.9 ± 5.2 MDD older 25.9 ± 5 BPD	Lumbar	DEXA	Depression, borderline personality	Lower BMD in depression and borderline personality group

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Table 1 (*continued*)

Author, year	Study Design	Number of Participants	Age of Participants	Tissue Evaluated	Measure of Tissue Change	Measure of Chronic Stress	Results
[75]Kahl, 2005	Cross-sectional	38	26.1 ± 5.1 healthy 25.9 ± 5 BPD alone 31.8 ± 6.5 BPD + lifetime major depressive disorder 24.2 ± 5.9 BPD +current MDD	Lumbar	DEXA	Depression, borderline personality	Lower BMD in depression and borderline personality group
[49]Lambrechts, 2023	Retrospective cohort	605	58.2 ± 13.4 test 48.1 ± 15 control	T12-S1	MRI	Depression	Increased disc degeneration severity but not cumulative score in depression group
[76]Luijcks, 2016	Experimental	115	38.6 ± 17.1	Trapezius muscle	EMG	Adverse childhood experiences	Higher EMG in higher adverse childhood experience score
[50]Lu, 2017	Retrospective cohort	1258-Test, 12,580-control	9.1 ± 3.1 test 9.2 ± 3.3control	Spine	Fracture	Tourette syndrome	Increased risk of fracture in Tourette syndrome group
[45]Ma, 2022	Cross-sectional	9766	59.747 ± 10.876 mild depression 59.744 ± 10.820 moderate depression 60.133 ± 11.019 moderate/severe depression 60.027 ± 9.078 severe depression 60.909 ± 11.116 control	Spine	DEXA	Depression	Lower BMD in depression group
[77]Mezuk, 2008	Case-cohort	98	71.5 ± 6.6	L2-L4	DEXA	Depression	Lower BMD in depression group
[78]Michelson, 1996	Cross-sectional	24-Test, 24-control	41 ± 8 test 41 ± 7 control	L1-L4	DEXA	Depression	Lower BMD in depression group
[79]Milliken, 2006	Cross-sectional	264	55.6 ± 4.8	Lumbar	DEXA	Depression	No differences
[80]Mori, 2014	Cross-sectional	703	56 ± 8	L1-L4	DEXA	Allostatic load	Lower BMD with higher load
[57]Niolu, 2016	Cross-sectional	101	60.02 ± 6.51 test 58.04 ± 6.65 control	L1-L4	DEXA	Depression	Lower BMD in depression group
[81]Petronijevic, 2008	Cross-sectional	73-Test, 47-control	40.7 ± 4.6 test 40.5 ± 5.7 control	Lumbar	DEXA	Depression	Lower BMD in depression group
[52]Rauma, 2015	Cross-sectional	928	60.0 (46.3–73.2)	L2-L4	DEXA	Depression	No differences
[54]Reginster, 1999	Cross-sectional	121	63.4 ± 0.6	Spine	DEXA	Depression	No differences
[82]Schweiger, 2000	Longitudinal	39	61 ± 12 test female 57 ± 10 test male 63 ± 13 control female 65 ± 7 control male	L1-L3	CT	Depression	Lower BMD in depression group
[39]Silverman, 2007	Cross-sectional	3798	69 test 65.6 control	T4-L4	Radiographs	Depression	Increased vertebral fractures in depression group
[46]Sommerhage, 2013	Cross-sectional	80	50 ± 12 test 46 ± 11 control	Lumbar	DEXA	Depression	Lower BMD in depression group
[83]Spangler, 2008	Prospective cohort	6441	62 ± 8 test 64 ± 7 control	L2-L4	DEXA	Depression	No differences
[59]Tander, 2010	Cross-sectional	90	42.04 ± 1 0.22 test 37.44 ± 1.16 control	L2-L4	DEXA	Depression	No differences
[51]Whitson, 2008	Prospective cohort	5827	65.5 ± 10.2 male with depression 66.2 ± 9.3 male without depression 65.8 ± 9.3 females with depression 66.8 ± 9.2 females without depression	L1-L4	DEXA	Depression	No differences
[84]Whooley, 2004	Prospective cohort	515	64.6 ± 8.6 test 66.7 ± 7.5 control	Lumbar	DEXA	Depression	No differences
[85]Whooley, 1999	Prospective cohort	7414	74.5 ± 5.3 test 73.3 ± 5.1 control	Lumbar	DEXA	Depression	No differences
[58]Williams, 2022	Case-control	117-Test, 909-control	48.1 (39.1–57.2) test 47.8 (32.4–61.0) control	L2-L4	DEXA	Bipolar disorder	Lower BMD in bipolar disorder
[47]Wong, 2005	Cross-sectional	169-Test, 1830-control	72.34 ± 4.96	L1-L4	DEXA	Depression	Lower BMD in depression group
[48]Yazici, 2005	Cross-sectional	30-Test, 35-control	44.8 ± 5.4 test 46.2 ± 4.2 control	L2-L4	DEXA	Depression	No differences
[55]Yazici, 2003	Cross-sectional	40	30.8 ± 8.4 test 31.2 ± 7.9 control	L1-L4	DEXA	Depression	Lower BMD in depression group

Table 2
Animal experiments. Abbreviations: Standard Deviation (SD), Standard Error (SE), Computed Tomography (CT), bone mineral density (BMD).

Author, year	Study Design	Number of Participants	Age of Participants	Tissue Evaluated	Measure of Tissue Change	Measure of Chronic Stress	Results
[34]Azuma, 2015	Interventional	10-Test, 10-control	12 months	L4	Micro-CT	Restraint	Lower BMD in restraint group
[35]Azuma, 2017	Interventional	15-Control, 15-stress, 15-stress with chewing	5 months	L4	Micro-CT	Restraint	Lower BMD in restraint group
[44]Furuzawa, 2014	Interventional	15-Stress, 15-stress chew, 15-control	5 months	L4	Micro-CT	Restraint	Lower BMD in restraint group
[70]Henneicke, 2017	Interventional	11/Group for males and 8/group for females	8 week	L3	Micro-CT	Unpredictable environment	Lower BMD in unpredictable environment group (male)
[36]Minagi, 2009	Interventional	239-Test, 255-control	18 day old fetus	Lumbar	Dissecting microscope	Restraint	Less bone in restraint group
[37]Valente, 2016	Interventional	20	5 months	L4	Densitometer	Unpredictable environment	Lower BMD in unpredictable environment group
[86]Yirmiya, 2006	Interventional	24	12 weeks	L3	Micro-CT	Unpredictable environment	Lower bone volume in unpredictable environment group
[87]Yu, 2012	Interventional	48	3 weeks old	Lumbar	Densitometer	Electric shocks	Lower BMD in electric shock group

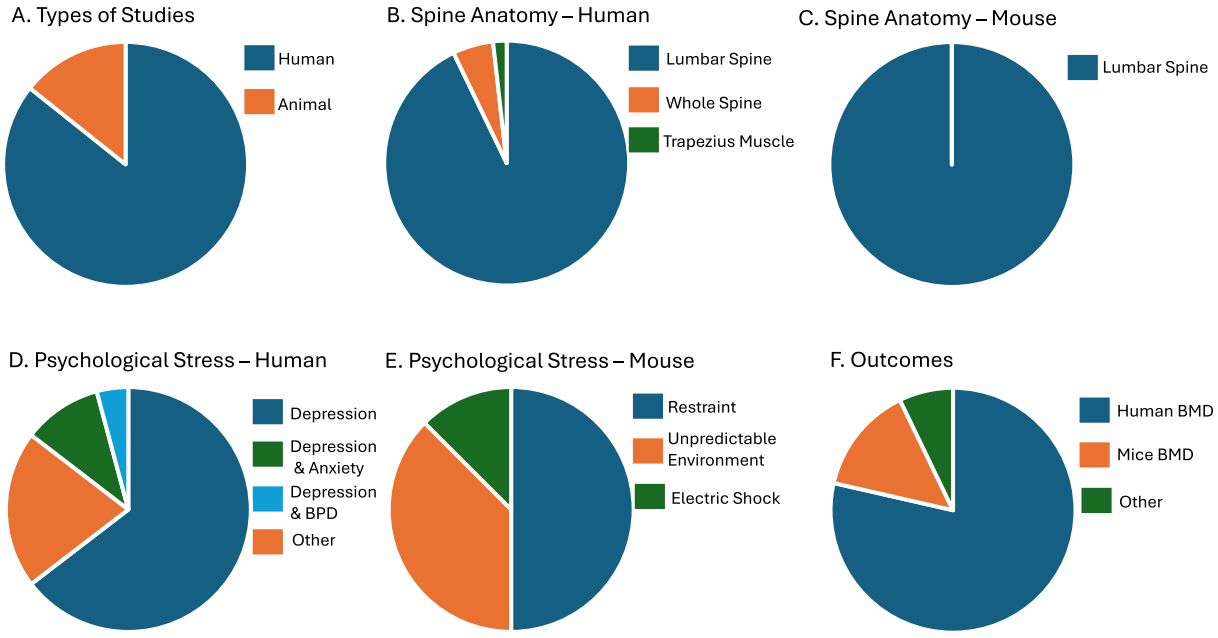

Fig. 2. Summary of results. A. types of studies, B. spine anatomy in humans, C. spine anatomy in mice, D. psychological stress in humans, (BPD = borderline personality disorder) E. psychological stress in mice, F. outcomes.

3.2. Study design: evaluating spine anatomy

Of the 56 studies, 52 studies evaluated the lumbar spine [34–41,43,44,46–49,51–53,55–75,78–89], three studies evaluated the whole spine [45,50,54], and one study evaluated the trapezius muscle [76] which interfaces with the thoracic spine (Fig. 2B & C). The most common method of evaluating the spine tissue was Dual X-ray Absorptiometry (DEXA) with 43 studies using this method [38,40,41,43,45–48,51–66,68,69,71–75,78–81,83–85,88,89]. Additionally, there were five studies that used Micro-Computed Tomography [34,35,44,70,86], two that used a Densitometry [37,87], one that used Radiographs [39], one that used Electromyography (EMG) [76], one that used MRI [49], one that used CT [82], one that used a Dissecting Microscope [36], and one that counted number of self-reported fractures [50].

3.3. Study design: evaluating chronic psychological stress

For humans, the most common method of evaluating CPS was to assess depression, which was done in 31 of the studies (Fig. 2D) [38–40,45–49,51–57,59,62,65,66,71–73,78,79,81–85,89]. Additionally, there were five studies that assessed depression and anxiety [41,60,63–65]; two that assessed borderline personality disorder and depression [74,75]; one that assessed social environmental stress [43]; one that assessed perceived stress [88]; one that assessed anxiety [61]; one that assessed schizophrenia, depression, and anxiety [67]; one that assessed depression, stress, and suicidal ideation [68]; one that assessed depression, schizophrenia, schizoaffective disorder, mania, adjustment disorder [69]; one that assessed Tourette syndrome [50]; one that assessed adverse childhood experiences [76]; one that assessed allostatic load [80]; and one that assessed bipolar disorder [58]. CPS in humans was quantified by medical evaluation and diagnosis, along with questionnaires. For experiments on mice, four of the studies used restraint stress [34–36,44], three used an unpredictable environment [37,70,86], and one used electric shock [87] (Fig. 2E).

3.4. Vertebral bone mineral density in humans

Of the 39 studies that evaluated bone mineral density (BMD) and depression in humans, 24 of the studies found significant differences between depression and control groups [38,41,42,45–47,53,55–57,60,

62,63,66,68,69,72,74,75,78,81,82,89,90], with 17 of the studies only evaluating depression [38,42,45–47,53,55–57,62,66,72,78,81,82,89,90], and seven of the studies evaluating depression in addition to other psychological outcomes [41,60,63,68,69,74,75]. These studies found that there was lower vertebral BMD in the depression groups compared to control. In contrast, 15 studies found no significant differences in vertebral BMD between depression and control groups [40,48,51,52,54,59,64,65,71,73,79,83–85], with 13 of these studies evaluating depression [40,48,51,52,54,59,71,73,79,83–85] and two studies evaluating depression as well as other psychological outcomes (Fig. 2F) [64,65].

Of the studies that evaluated vertebral BMD and anxiety, three studies found lower BMD in the group with anxiety compared to controls [41,61,63], while three studies found no difference [60,64,65].

Of the studies that evaluated other psychological states of CPS, all studies found significant results, except for one study evaluating schizophrenia [67]. These studies found that participants with CPS had lower BMD compared to a control group. Of the studies that found a significant difference in vertebral BMD between the CPS group and control group, two studies evaluated borderline personality disorder [74,75], one study evaluated perceived stress [88], one study evaluated social stress [43], one evaluated allostatic load [80], one study evaluated suicidal ideation [68], one study evaluated schizophrenia [69], and one evaluated bipolar disorder [58].

3.5. Vertebral bone mineral density in mice

All articles reporting experiments on mice identified significant difference in vertebral BMD, suggesting that there is lower BMD in mice subjected to CPS (Fig. 2F) [34–37,44,70,86,87]. Four of the studies stressed the mice with restraint stress [34–36,44], three with unpredictable environments [37,70,86], and one with electric shock [87].

3.6. Other studies in humans

There were a few additional studies that evaluated CPS in humans (Fig. 2F). One study included an evaluation of depression and disc degeneration [49], which identified that depression increases disc degeneration. Another study looked at muscle tension in the trapezius muscle and adverse childhood experiences and found that a greater number of adverse childhood experiences resulted in greater muscle tension [76]. Finally, two studies evaluated fractures, and both found significant differences, suggesting that depression [39] and Tourette syndrome [50] both resulted in an increase in fracture risk.

4. Discussion

This scoping review documents a relationship between increased CPS and decreased spine health. While previous literature has reviewed and documented a relationship between depression and BMD, this is the first study to evaluate broadly the impact of CPS on the spine [77,91]. With the focus of cLBP management shifting towards holistic practices that include both physical health and mental health interventions, it is critical to understand the complex interactions of these biological and psychological components [3]. We identified N = 56 articles relating CPS to spinal pathology and found that most of the work evaluated the relationship between depression and vertebral bone mineral density (BMD) (N = 39). Of the studies that evaluated BMD and depression in humans, 24 found significant differences between depression and control groups. The remainder of human studies (N = 9) documented relationships between various forms of CPS (anxiety, post-traumatic stress disorder, etc.) and spinal tissue pathologies (BMD, muscle atrophy, etc.). Animal studies in this area (N = 8) were limited to mice and confirmed a causal relationship between CPS and lower vertebral BMD.

Evaluation of BMD using DEXA scans in humans with depression was the most prominent evaluation found in this scoping review. This specific method was also one of the only sources with opposing results, with 38% of the studies finding no significant difference in spine health between depressed and control groups and 62% finding a significant difference. All studies that found a significant difference observed that an increase in CPS is associated with a decrease BMD in the spine. The study with the most participants, a cross-sectional study with 15,862 participants [68], suggested that there was a significant relationship between CPS and BMD. Furthermore, there have been two meta-analysis that evaluate BMD (in the spine and other sites) and depression, and these studies found a significant relationship as well [92,93].

In addition to the evaluation of BMD in humans with depression, other manifestations of CPS were evaluated in the context of BMD, including anxiety, borderline personality disorder, perceived stress, social stress, allostatic load, suicidal ideation, schizophrenia, and bipolar disorder. Most of these studies found decreased BMD with CPS. Again the HPA axis is implicated, as bipolar disorder [94], suicidal ideation [95], borderline personality disorder [96], and schizophrenia [97] are all associated with increased HPA axis activity and cortisol levels. Thus, there is an emergent relationship between psychological stress and decreased BMD in humans that extends beyond depression.

Mice were also evaluated for changes in BMD in response to CPS. The CPS that mice underwent included restraint, unpredictable environments, and electric shock. Consistent with humans, all eight studies found that there was lower BMD in mice subjected to CPS. Furthermore, two studies observed that providing mice with something to chew on, known as active mastication, reversed the effects of loss of BMD induced by the CPS [34,35]. The proposed mechanism underlying this is increased noradrenaline turnover and oxygen in the brain [98,99]. Thus, there is a developing relationship between induced CPS and a decrease in BMD, which appears to be ameliorated in mice by coping with active mastication.

In papers covered by this scoping review, both molecular and behavioral mechanisms were suggested to drive the relationship between CPS and spinal tissue pathology. The most consistent hypothesis was that hyperactivity of the HPA axis drives decreased BMD. This theory was supported as Altindag et al. who demonstrated that cortisol was higher in individuals with depression compared to healthy controls and was related to lower BMD [53]. Furthermore, the HPA axis is associated with systemic inflammation, and Kahl et al. demonstrated that the pro-inflammatory cytokine TNF-α was related to lower BMD [75]. In animal studies, molecular mechanisms describing the relationship between CPS and BMD also further support a role of the HPA axis as well as the sympathetic nervous system. For example Henneicke et al. demonstrated that CPS increased circulating cortisol, increased osteoclast activity, and reduced bone mass, and that these processes were mitigated by disrupting cortisol signaling in osteoblasts [70]. Yirmiya et al. demonstrated that CPS increased bone norepinephrine, reduced osteoblasts, and reduced bone mass, and that bone loss was prevented by blocking epinephrine/norepinephrine signaling via propanolol [86]. Propanolol similarly improved disrupted fracture healing in a murine model of CPS, suggesting a broad musculoskeletal role for epinephrine/norepinephrine signaling [100]. Personal habits and behaviors were also proposed to impact BMD in the context of depression, including exposure to sun [71], decreased physical activity [71], and antidepressant use [41]. Future work dissecting the behavioral and molecular mechanisms impacting CPS and musculoskeletal metabolism is warranted.

Outside of vertebral BMD, the impact of CPS on the spine is unclear. As few studies evaluated pathological changes with CPS beyond bone (disc degeneration, muscle tension, fracture), it appears there is a limited understanding the relationship between CPS and the musculoskeletal system. Furthermore, other manifestations/sources/outcomes of CPS beyond depression are limited in the literature as well, representing an area of future work. Finally, because most work covered in this scoping review did not evaluate pain, we cannot make broad conclusions about the relative contribution of musculoskeletal health and mental illness on pain. Future work should include measurements of pain when evaluating biopsychosocial components and musculoskeletal health.

5. Conclusion

In conclusion, this scoping review documents a relationship between increased CPS and decreased spine health. Many studies have evaluated bone mineral density (BMD) and depression in humans, and a majority identify significant differences between depression and control groups. Other human studies document relationships between other forms of CPS and other spinal tissue pathologies, though the scope is limited. Articles reporting experiments on mice demonstrate a causal relationship between CPS and decreased vertebral BMD. The body of literature suggests a direct mechanistic connection between the HPA axis and musculoskeletal metabolism that should be further explored. Based on these results, we propose that research on CPS and spine health is still emerging and will likely provide insight into the complex biopsychosocial relationships in cLBP.

Contributions

Conception and design (MB, EG, JW, MG, JM); Analysis (MB, EG); Interpretation of data (MB, EG, JW, MG, JM); Drafting of the article (MB, EG, JM); Critical revision of article (JW, MG); Obtaining of funding (MB, JM).

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Declaration of competing interest

None to disclose.

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