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Pain characteristics and impact of pain in individuals with spina Bifida: Systematic review and meta-analysis

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ABSTRACT

Background: Pain is prevalent in spina bifida (SB), yet, it has received limited attention in research and healthcare.

Objective: To investigate pain severity, common pain sites, and pain interference with daily activities and sleep in individuals with SB.

Methods: Literature was last searched in Scopus, Web of Science, Embase, PubMed, CINAHL, and Academic Search Complete in July 2024. Inclusion criteria included observational studies on open or closed SB and published articles in English from January 2000 to January 2024. Other spinal dysraphism conditions were excluded. Meta-analyses were conducted using random effects models. Narrative reviews were provided for studies excluded from the meta-analyses. The methodological quality of included articles was assessed using the risk of bias tool for prevalence studies.

Results: Fifteen studies (1301 participants) were included, with 80 % rated as moderate quality. Meta-analyses showed that adults with SB had moderate to severe pain on average (mean numeric rating score: 5.4, 95 % CI: 3.2, 7.6), with the most prevalent pain sites being the back 59.1 % (95 % CI: 39.8 %, 77.1 %) and hips 35.0 % (95 % CI: 10.0 %, 66.0 %). Literature on pain in newborns is limited. For children/adolescents, pain was observed from head to lower extremities with varying intensity, and pain in the head and back were most consistently reported. Impact of pain on daily activity and sleep was inconclusive.

Conclusions: As individuals with SB can experience pain at any site with varying intensity, pain should be regularly assessed in this population. Findings cannot be generalized to those with communication or cognitive problems.

1. Introduction

Spina bifida (SB) is a congenital birth defect that can cause lifelong disability.[1] The incidence of SB ranges from 1.7 to 19 per 10 000 fetuses worldwide.[2] SB occurs due to a defect in neural tube closure during fetal brain development.[1] Based on the type of neural tube defects, SB can be classified into open SB or SB cystica, including myelomeningocele (MMC) and meningocele, SB aperta (myeloschisis), and closed SB or SB occulta (lipomatous malformation).[3] MMC is the most common and clinically significant type of SB.[4]

Clinical presentations of SB typically include motor and sensory impairments below the lesion level[1] and bladder and bowel incontinence.[4] Hydrocephalus, an accumulation of fluid in and around the brain, is also common in individuals with SB and generally requires cerebral shunting.[1,5] SB can result in a spectrum of physical and intellectual disabilities and behavior dysfunctions.[4,6] Additionally, individuals with SB commonly have multi-comorbidities and secondary complications[7] such as hip dislocations, scoliosis, shunt infection, recurrent urinary tract infections, and pressure injuries.[1,5,8] Overall, health-related quality of life (HRQoL) is compromised in people with SB.[8,9]

Pain is a common problem for individuals with SB. Nearly 70 % of young children with SB in the United States (US) aged three to six years experienced pain that ranged from daily to at least once a month (N = 101).[10] In a study carried out in Canada, 56 % of older children and adolescents with SB aged 8–19 years reported pain at least once a week (N = 68).[11] A meta-analysis on adults with SB indicated a 44 % pain prevalence (95 % confidence interval (CI): 27.4 %, 61.5 %).[7]

There is a growing need to address pain in individuals with SB. Albeit individuals with SB have a lower survival rate compared to those without SB,[12] life expectancy in the SB population has increased in the

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Abbreviations

DL estimator	DerSimonian-Laird estimator
GRADE	The Grading of Recommendations Assessment, Development, and Evaluation
HRQoL	Health-related quality of life
IQR	Interquartile range
LFK	Luis-Furuya-Kanamori index
MMC	Myelomeningocele
NRS	Numeric Rating Scale
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RMLE	Restricted maximum-likelihood estimator
SB	Spina bifida
VAS	Visual Analogue Scale
WUSPI	Wheelchair User's Shoulder Pain Index

last few decades.[13] With increased survival comes an increased demand for healthcare to manage secondary complications, including pain, across the lifespan. Unmanaged or inadequate management of pain can further deteriorate HRQoL.[9]

There are research gaps regarding pain in SB. While individuals with SB often experience reduced or absent sensation in the lower limbs due to sensory deficits,[1] whether they have a lower likelihood of pain in the lower limbs requires clarification. Although evidence exist on the prevalence of pain in SB, knowledge on the extent of pain severity and the pain burden experienced by those with SB throughout their life course is limited. Such information is crucial to enhance the assessment, prevention, and management of pain in individuals with SB.

To the best of our knowledge, there is no systematic review exploring the pain severity, pain sites, and pain interference in individuals with SB. Recently after 2020, more published data have become available on pain in SB. Thus, synthesizing data from existing studies can provide an evidence-based overview of pain profiles and implications of pain on individuals' daily lives. The aim of this systematic review and meta-analysis was to determine pain severity levels, commonly affected pain sites, and the interference of pain on daily activities and sleep in individuals with SB across different age groups.

2. Methods

This systematic review and meta-analysis was conducted and reported in accordance with the 27-items Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Reporting checklist.[14] The entire process of systematic review including duplicates removal, article screening, data extraction, and risk of bias assessment was conducted in the Covidence software, which is an online tool for streamlining systematic reviews.[15]

2.1. Eligibility criteria

Studies were included using the following inclusion criteria: (1) observational studies including cross-sectional, cohort, and case-control, (2) participants with confirmed diagnosis of open or closed SB or with disease specific diagnosis including myelomeningocele, meningocele, myeloschisis, and lipomeningocele or lipomatous malformation of any ages, (3) studies reporting levels of pain severity or count of pain sites (4) studies reporting levels of pain interference on daily activities and/or sleep or count of people who had pain interference with daily activity and/or sleep; and (5) published and in press articles with full text available in English. SB diagnosis was considered confirmed if participants were recruited from SB clinics or centers or identified using the World Health Organization's International Classification of Diseases ICD-10 code (Q05).[16] There were no restrictions on countries, study settings, type of pain (neuropathic or nociceptive pain), pain report (i.e., self or proxy report), and pain assessment tools used. Studies were grouped and analyzed separately by three age categories - newborns, children/adolescents, and adults.

Exclusion criteria included studies on spinal dysraphism conditions other than those specified in the inclusion criteria and traumatic spinal cord injury cases, studies reporting pain prevalence only, animal and *in vitro* studies, unpublished literature, case series, case reports, editorial letters, and conference papers.

2.2. Information sources and search strategy

The review team searched the following six electronic databases: PubMed, Web of Science, Embase, CINAHL, Scopus, and Academic Search Complete. Citation searches of included studies were conducted to identify additional relevant articles. Databases were searched using both medical subheading (MESH Term) such as "spinal dysraphism" and free texts such as "spina bifida" and "myelomeningocele". The search period was from January 1, 2000 to January 31, 2024. Searches in all databases were last re-run on July 4, 2024. A full search strategy is provided in Appendix A.1.

2.3. Study selection

Eligibility criteria were listed in the Covidence, and two reviewers independently screened the articles against the eligibility criteria to identify relevant studies. Excluded articles were tagged with reasons for exclusion. Any disagreements between reviewers were resolved by consensus.

2.4. Data extraction

One reviewer extracted the data using the data extraction template (Appendix B) in the Covidence software. The second reviewer validated the extracted data. No effort was made to contact the study authors for missing data, as the meta-analysis estimates can be calculated from the information provided in the articles.

Outcome data extracted included pain assessment tools, pain severity and pain interference score reported as mean and standard deviation (SD) or median and interquartile range (IQR) and the count and percentage of pain reports by each pain site and pain interference on daily activity or sleep. Pain sites categories were extracted as reported in the individual studies. Pain in the thighs, knees, or legs was combined into one category because studies used varying combinations of these sites. Other data extracted were publication year, authors, study design, setting, study period, characteristics of study population (age, sex), sample size, survey response rate, type of SB, presence of hydrocephalus, prevalence of pain, statistical methods, and funding information.

2.5. Risk of bias assessment

Two reviewers independently assessed the risk of bias of included studies in the Covidence software using the adapted risk of bias tool for prevalence studies by Hoy et al.[17] The tool was designed and validated to assess the prevalence studies on low back pain and neck pain, thus, appropriate to use for this study which focused on pain outcomes. The tool comprised 10 domains and covered four types of bias - selection bias, nonresponse bias, measurement bias, and bias from analysis. The first four domains of the tool assessed the study's external validity while the latter six assessed the study's internal validity. Based on the responses to the 10 domains, a subjective rating on the overall risk of bias was given as low, moderate, or high risk. Articles with incomplete information for rating were marked as high risk of bias. Any discrepancies in ratings were resolved by consensus. The risk of bias assessment template is provided in Appendix C.

2.6. Data synthesis

Study primary outcomes included the mean pain severity level and the prevalence of pain by bodily sites. The secondary outcomes were the mean pain interference level on daily activities and/or sleep, the prevalence of pain interference with daily activities, and the prevalence of pain interference with sleep. If the prevalence was not calculated in the studies, it was calculated using the number of individuals with the outcome of interest as the numerator and the total number of individuals reported pain as the denominator. The results of individual studies and syntheses are presented in Tables (Appendix D).

Extracted data were downloaded from Covidence in Excel format and grouped by age groups, reported outcomes, and pain sites. Only studies reporting the same unit of measurement on pain outcomes and those without significant design-related heterogeneity were included in the meta-analysis. Narrative descriptions of the findings were provided for studies excluded from the meta-analysis.

Meta-analyses were conducted for pain severity and pain sites using the metamean and metaprop functions of the meta package (version 7.0-0) in R software (version 4.4.1), respectively.[18] The random effects model was used as the observed pain levels and sites were assumed to vary across studies due to underlying differences between studies and by chance.[19] The Hartung-Knapp adjustment for the random effects model[19] was used to estimate the CIs of summary estimates. The I2 statistics (using tau^2) and prediction intervals were estimated to assess between-study heterogeneity.[20] For variance estimation, the restricted maximum-likelihood estimator (RMLE)[21] with an untransformed raw mean was used for the meta-analysis of pain severity. Results were compared to the estimates from the conventional DerSimonian-Laird (DL inverse variance) estimator.[22] DL estimators[22] were used for the proportional meta-analyses of pain sites. To account for extreme values, proportions were transformed by the Freeman-Tukey double arcsine transformation.[23] Random-effects weights for each study were calculated based on the variance of the true effect size distribution

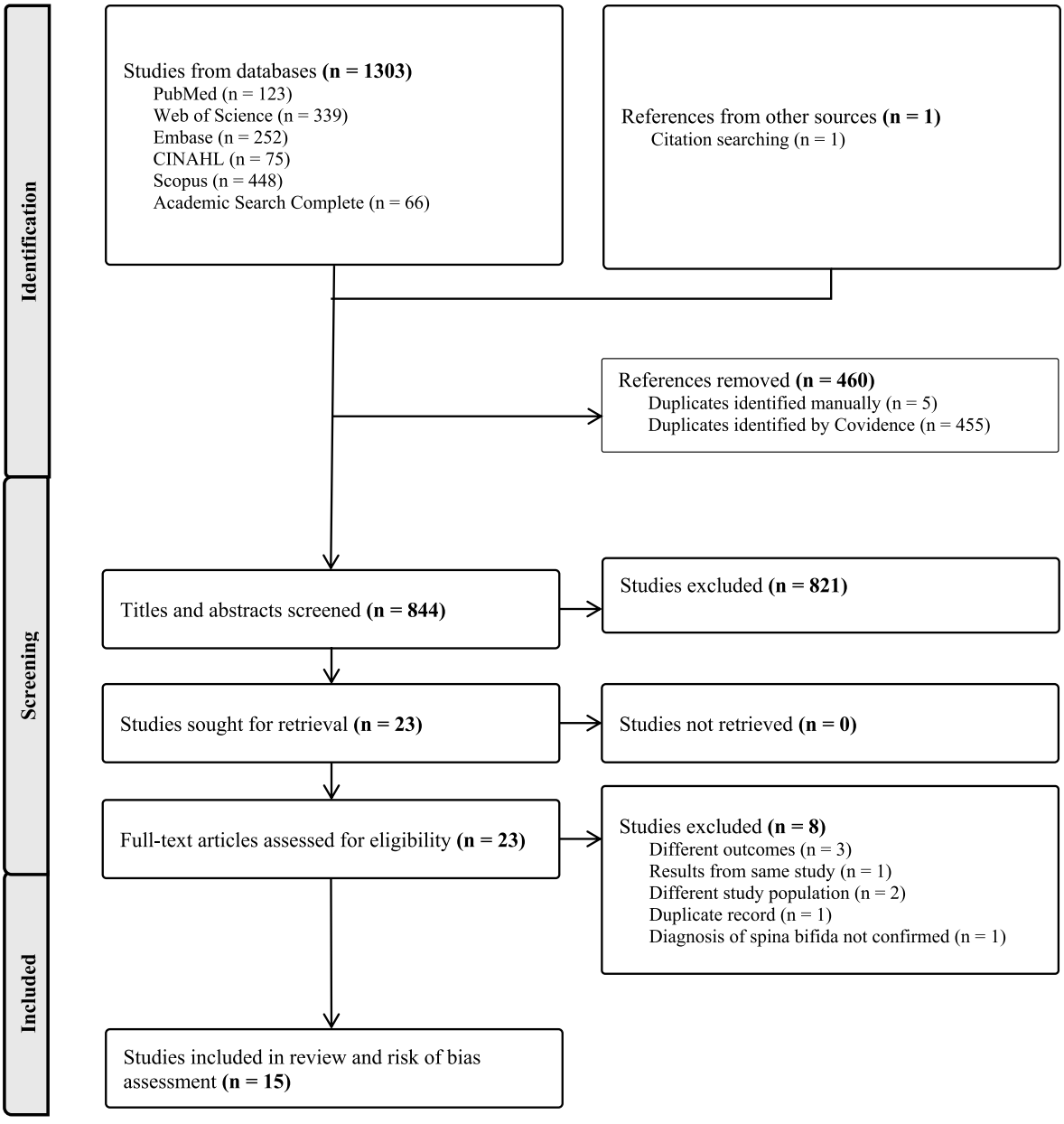

Fig. 1. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram showing screening and selection of articles for present systematic review.

(between-study variance) and the inverse of the variance of each effect size (within-study variance).[21] Studies with lower variance were given more weight.

Meta-analysis results are presented by forest plots generated in R studio. A funnel plot [21] was used to visualize publication and related biases in the meta-analysis of pain severity[21] and Doi plots with the Luis-Furuya-Kanamori (LFK) indices[24] were used for the proportional meta-analyses of pain sites. Subgroup analyses or meta-regression were not performed due to the small number of studies included in the meta-analysis. For the sensitivity analysis, studies with a high risk of bias rating were excluded from the meta-analysis to evaluate its impact on the results.

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach was used to assess the certainty of the evidence generated by this review, rating it across five domains: overall risk of bias, inconsistency, indirectness, imprecision (95 % CI), and publication bias.[25] Since all included studies were observational studies, the evidence rating started from a low grade. Evidence grading can be upgraded to moderate for results with low risk of bias and inconsistency or downgraded to very low for those with significant limitations.

3. Results

3.1. Study selection

A total of 1303 records were identified through the database search, along with one additional record from further citation search. The results of the article search, and screening are outlined in the PRISMA Flow Diagram (Fig. 1). Twenty-three articles were included for full-text screening. Eight articles were excluded due to different outcomes,[9,26,27]

Table 1
Main characteristics of the included articles in the systematic review on pain characteristics and impact of pain in individuals with spina bifida (15 studies, N = 1301).

Study ID	Study design, setting & Country	Type of SB, Hydrocephalus (n, %)	Outcomes, Assessment tools & Type of pain report	Participants (Sample size, Age ± SD/range, Sex)	Pain prevalence (count n, %[a])	Risk of bias rating
Adults						
Smith et al., 2023[32]	Cross sectional, Hospital outpatient adult SB clinic, United Kingdom	SB	NRS scale for pain severity and interference, Pain questionnaires for pain sites, Self-report	N = 51, 41.8 ± 13.1 years, 65.0 % female	n = 30, 58.8 %	Moderate
Bartonek et al., 2023[33]	Cross sectional, Prosthetic and orthotic clinic, Sweden	Open SB, 53 (90.0 %)	EQ (5D) VAS 0 to 100 scale for pain severity, Pain-drawing diagram for pain sites, Self-report	N = 59, 25.8 ± 3.7 years, 42.0 % female	n = 35, 59.3 %	High
Cacioppo et al., 2023[34]	Cross sectional, Multidisciplinary referral center for SB, France	Open and closed SB	NRS for pain severity, Pain questionnaires for pain sites, Self-report	N = 331, 41.2 ± 12.9 years, 57.0 % female Only 201 participants completed the questionnaires.	n = 139, 69.2 %	Moderate
Lidal et al., 2021[35]	Cross sectional, National resource center for rare congenital disorders, Norway	Open and closed SB	NRS for pain severity, Pain-drawing diagram for pain sites, Self-report	N = 30, 57.5 ± 5.6 years, 60.0 % female	n = 29, 96.7 %	Moderate
Alriksson-Schmidt et al., 2018[36]	Cross sectional, Pediatric or adult habilitation service centers, Sweden	Open SB, 41 (80.0 %)	Pain questionnaires for sites, EQ-5D-5L for pain interference, Self-report	N = 51, 30.0 ± 9.0 years, 47.0 % female	n = 37, 72.5 %	Low
Wagner et al., 2015[37]	Cross sectional, Outpatient clinic, United States	SB	Pain questionnaires for pain sites, Self-report	N = 72, 33.0 years (range: 18.0–68.0), 65.0 % female	n = 65, 90.3 %	High
Werhagen et al., 2010[38]	Cohort, Spinalis outpatient clinic, Sweden	SB, 57 (52.0 %)	Pain questionnaires for pain interference on daily activity, Self-report	N = 110, 28.7 years (range: 18.0–64.0), 53.0 % female	n = 11, 10.0 %	Moderate
Verhoef et al., 2004[39]	Cross sectional, Rehabilitation centers, housing facilities, special schools, and SB teams, Netherlands	Open and closed SB, 119 (66.0 %)	Interviews for pain sites, Self-report	N = 179, 20.8 ± 2.9 years, 59.0 % female	n = 86, 48.0 %	Moderate
Newborns, Children, and/or Adolescents						
Ottenhoff et al., 2012[40]	Cohort, Sophia Children's Hospital, Netherlands	Open SB, 26 (93.0 %)	VAS for pain severity, Proxy report	N = 28, 39.1 ± 31.1 weeks, 50.0 % female	n = 28, 100.0 %	Moderate
Spoor et al., 2023[41]	Cross sectional, Sophia Children's Hospital, Netherlands	Open SB	NRS for pain severity, Pediatric Evaluation of Disability Inventory (PEDI-CAT) for daily functioning, Self-report	N = 22, 11 ± 1.4 years, 55.0 % female	n = 16, 72.7 %	Moderate
Alriksson-Schmidt et al., 2021[10]	Cross sectional, Community and clinic setting, part of the multi-site study, Arizona and Utah, United States	Open and closed SB, 68 (67.0 %)	Pain questionnaires, Proxy report	N = 101, 4.5 years (range: 3.0–6.0), 48.0 % female	n = 69, 68.3 %	Moderate
Hemmingsson et al., 2009[42]	Cross sectional, Habilitation centers, Sweden	SB	Pain questionnaires for pain interference, Proxy report	N = 59, 9.2 ± 4.2 years, 43.0 % female	n = 7, 11.9 %	Moderate
Roehrig et al., 2008[43]	Cross sectional, Included SB registered through the Arkansas Spinal Cord Commission, United States	SB	Wheelchair User's Shoulder Pain Index for pain severity and pain interference, Self-report	N = 41, 21.0 years (range: 10.0–31.0), 56.0 % female	n = 12, 29.3 %	Moderate
Clancy et al., 2005[11]	Cross sectional, SB/spinal cord clinic at a regional treatment tertiary center, Canada	Open and closed SB, 49 (72.0 %)	Color-coded rating scales and verbal descriptors for pain sites, Self and proxy reports	N = 68, 12.6 years (range: 8.0–19.0), 55.0 % female	n = 38, 55.9 %	Moderate
Ohanian et al., 2020[44]	Cross sectional, Four hospitals and a statewide SB association in the Midwest, United States	Open and closed SB, 109 (78.0 %)	Pain-drawing diagram for pain sites, Self-report	N = 140, 11.4 ± 2.5 years, 54.0 % female	n = 34, 24.3 %	Moderate

SB: spina bifida, NRS: Numeric Rating Scale 0 to 10, VAS: Visual Analogue Scale 0 to 100.
SD: standard deviation, N = total sample size, n = number of individuals who reported pain.
[a] Calculated based on data provided in the original articles.

different study population,[28,29] duplicate results,[30] duplicate record,[26] and unascertained diagnosis of SB[31] (See Appendix A.2 for lists of excluded articles and Appendix D-Table D.3 for their key findings). Fifteen articles[10,11,32–44] met the eligibility criteria and were selected for this systematic review. No new articles were found during the updated search in July 2024.

3.2. Study characteristics

Eight studies reported pain intensity,[11,32–35,41,43,44] ten studies reported the prevalence of pain by bodily sites[10,11,33–37,39,43,44] and five studies reported on pain interference.[11,32,36,38,42,43] All studies had cross-sectional designs except for two cohort studies.[38,40] The studies included different types of SB - some exclusively MMC (open SB), others included both open and closed SB, or just mentioned SB without differentiating the type of SB. The studies included individuals with different ambulation status from non-ambulators and wheelchairs users to independent ambulators. The pain prevalence reported by individual studies ranged from 10.0 % to 100.0 %. The main characteristics of individual studies included in this systematic review are provided in Table 1 and their results in Appendix D.

3.3. Risk of bias in studies

Of 15 studies, one study (7 %) was considered to have a low risk of bias, 11 (73 %) studies had a moderate risk, and three studies (20 %) were rated as having a high risk of bias (See Table 1 and Appendix E.1). All studies exhibited a high risk of sampling bias. Sixty percent of the studies were rated as low generalizability to the target population (See Appendix E.2).

3.4. Findings

3.4.1. Adults with SB

Eight studies investigated pain in adults with SB with sample sizes ranging from 30 to 331. The settings where participants were recruited varied from multidisciplinary referral centers to outpatient clinics. The mean age of the study participants ranged from 20.3 years (SD: 2.9) to 57.5 years (SD: 5.6) and 42 %–65 % of the total participants were female. All studies investigated self-reported pain. Single-dimensional scales, such as the 11-point Numeric Rating Scale (NRS) and the Visual Analogue Scale (VAS) from EQ (5D) tool or pain survey questionnaires, were used to measure pain intensity. Bodily pain sites were reported using pain questionnaires or pain drawing diagrams. The NRS, EQ-5D-5L questionnaire or selective pain items from the health survey questionnaires were used to explore pain interference.

3.4.1.1. Pain severity. Of four studies reporting pain severity in adults with SB,[32–35] three[32,34,35] were rated as having a moderate risk of bias, while one[33] was rated as having a high risk of bias. Two studies used the same pain measurement scale, i.e., NRS[34,35] to assess pain severity levels, thus were included for the meta-analysis of pain severity. Narrative synthesis is provided for the remaining two studies.[32,33]

3.4.1.2. Meta-analysis results for pain severity. The RMLE and DL estimators gave similar estimates. Results from RMLE are presented below (Fig. 2). In adults with SB with a mean age above 40 years, the pooled average pain level measured by the NRS scale was 5.4 (95 % CI: 3.2, 7.6), denoting moderate to severe pain (Fig. 2). The prediction interval could not be calculated due to the small number of studies (n = 2) included in the meta-analyses. The I^2 statistic was 0.0 %, meaning that the variance in the pooled estimate was only due to chance. However, we could not totally exclude the variance from between-study heterogeneity as meta-analyses with few studies often get a low I^2 value.[20]

3.4.1.3. Narrative reports of pain severity[32,33] (n = 2). In a study by Smith et al.,[32] adults with SB who had pain in the past week had NRS pain scores ranging from 3.5 to 7 (n = 30, median NRS score = 4.0). This number is consistent with our meta-analysis result. Another study[33] (N = 35) showed a greater variability of pain levels among participants, ranging from a minimum score of seven to a maximum score of 98 on EQ (5D) VAS, 0 to 100 scale. The study consisted of much younger adults with MMC (mean age: 25.8 years, SD: 3.7)[33] and had a longer recall period for pain assessment, and thereby, an increased risk of reporting bias, which could explain the greater variability in reported pain levels.

3.4.1.4. Pain sites. Of seven studies reporting pain sites, three studies were excluded from the meta-analyses due to differing study settings,[34,39] data collection methods,[34,39] and categorization of pain sites.[32] Meta-analyses were conducted for the four studies[33,35–37] across seven bodily sites: head and neck, shoulders, upper extremities excluding shoulders, back, hips, thighs/knees/legs, and other sites. Two studies[33,37] were rated as having a high risk of bias, four[32,34,35,39] as moderate, and one as low risk.[36]

3.4.1.5. Meta-analysis results for pain sites. The pooled mean prevalence, 95 % CIs, and prediction intervals for pain at seven bodily sites are presented in Fig. 3. Forest plots showing the prevalence of pain by bodily sites reported by individual studies, meta-analysis estimates, and I^2 values are provided in Appendix F. High I^2 values (>50.0 %), wide CIs, and wider prediction intervals suggested substantial between-study heterogeneity among included studies. As the meta-analyses included fewer than ten studies, subgroup and meta-regression analyses could not be conducted to evaluate the factors causing heterogeneity.[45]

When two studies rated as high risk of bias[33,37] were excluded one at a time, the pooled proportion estimates for different pain sites were minimally reduced, with differences of less than or equal to 0.1 (10.0 %). Thus, the inclusion of those studies in the meta-analyses did not significantly affect the findings.

3.4.1.6. Narrative reports of pain sites[32,34,39] (n = 3). One study[39] investigated the progression of pain in the head, neck and back in adults with open or closed SB (N = 179). The study included younger adults (mean age: 20.7 years, SD: 2.9 years), where 66.0 % had open SB with hydrocephalus, and 41.0 % had high level lesions,[39] thus representing individuals with more health problems. Forty-nine individuals (27.4 %) reported increased pain in the past year from the assessment date[39] and

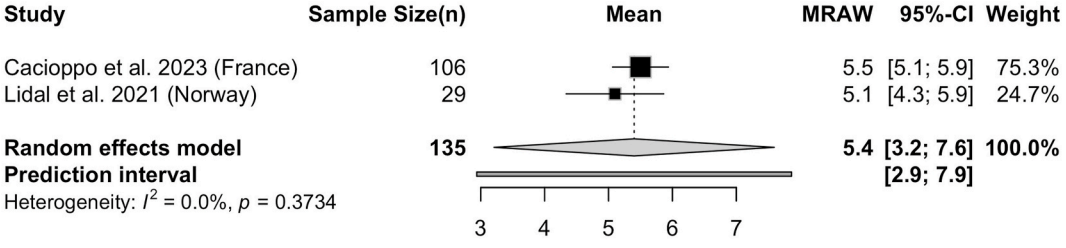

Fig. 2. Forest plot of the pooled average estimate of pain severity in adults with spina bifida with an average age over 40 years (Total studies = 2)
CI: confidence interval, Sample size (n) = individuals who reported pain, MRAW = raw (untransformed) mean pain score reported from individual studies.

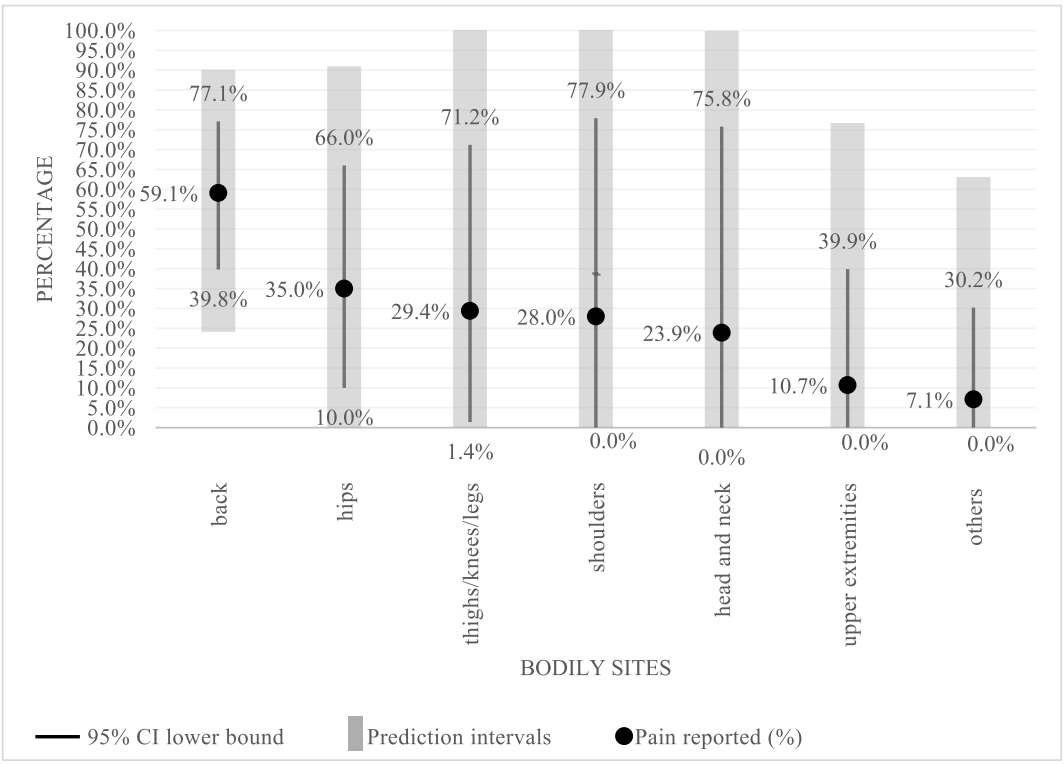

Fig. 3. Meta-analysis results on the prevalence of pain by bodily sites in adults with spina bifida (Total studies = 4, n = 166)
CI: confidence interval, n = individuals who reported pain.

the prevalence of head, neck, and back pain was 29.1 %, 22.1 %, and 33.7 %, respectively.[39] The findings may be prone to measurement bias as there was no information on the reliability and validity testing of the pain questionnaire used.

In another study of older adults (mean age: 41.8 years, SD: 13.1 years, n = 30), a higher prevalence of back pain (80.0 %) was reported, followed by shoulder pain (47.0 %) and hip pain (43.0 %).[32] The prevalence of back pain was higher than that in a study of individuals with scoliosis in the same age range (69.2 %, 139 of 201 participants).[34] This higher prevalence may be due to the study's low survey response rate (28.0 %), which could have resulted in selection bias.[32]

3.4.1.7. Pain interference[32,36,38] *(n = 3).* Only narrative synthesis is provided for pain interference outcomes as the studies[32,36,38] were few and reported heterogenous types of pain i.e., neuropathic or general pain. One study[36] had a low risk of bias and two[32,38] had moderate risk of bias.

A study[38] that primarily investigated pain interference of neuropathic pain (n = 11) reported that five in ten adults with neuropathic pain had pain interference with daily activities. Similarly, a study on general pain with a low risk of bias showed that half of the study participants had pain interference with daily activities (20 of 41 participants) and 32.4 % had pain interference with sleep (12 of 37 participants).[36] Pain interference scores varied among study participants. In one study with 30 participants, the median pain interference score on general daily activities was 4.7 out of 10.0 (IQR: 2.9) and the median pain interference score on sleep was 4.8 out of 10.0 (IQR: 3.5)[32].

3.4.2. Newborns and children, and/or adolescents with SB

For newborns, children and/or adolescents, only narrative descriptions of the findings were provided as studies used different pain measurement tools, recall periods for pain, categorization of pain sites, and units of outcome measure.[10,11,40–44]

3.4.2.1. Pain in newborns[40] *(n = 1).* Limited evidence from one study with moderate risk of bias (N = 28) showed low levels of nurses-reported pain in newborns who received routine analgesics per a validated treatment algorithm.[40]

3.4.2.2. Pain in children and/or adolescents[10,11,41–44] *(n = 6).* All except one study used cross-sectional designs with sample sizes ranging from 28 to 140. The participants were recruited from SB clinics, outpatient clinics of pediatric hospitals, or habilitation centers. The age of the study participants ranged from 3 to 19 years old and 48 %–56 % of the included participants were female. Detailed information on the study population is provided in Table 1.

Studies used self-reports or proxy-reports by parents or caretakers to assess pain in children and adolescents with SB. Various pain measurement tools were used across studies, including the VAS 0 to 10 scale of the Pediatric Pain Questionnaire, the 11-point NRS scale, pain survey questionnaires, and the Wheelchair User's Shoulder Pain Index (WUSPI) for shoulder pain. All studies had moderate risk of bias.

3.4.2.3. Pain severity[11,41,43,44] *(n = 4).* In a Dutch study on children with open SB[41] (N = 22, mean age: 11 years), a high pain prevalence of 72.7 % (n = 16) was found. The average NRS score was 3.5 (range 1.0–6.0)[41], indicating mild to moderate pain. In a study in Canada[11] in children and adolescents with SB (N = 68; age: 8–19 years), the reported pain prevalence in the past week was 55.9 % (n = 38).[11] The reported pain intensity among the participants varied widely, from no pain '0′ to worst possible pain '10′ on a VAS 0 to 10 scale.

In a study on adolescents and young adults using manual wheelchairs (N = 41, age: 10–31 years),[43] the average pain level of participants during daily functional activities, as measured by the WUSPI, was 9.2 (SD: 24.8) out of 150, representing mild intensity.[46] In a cohort study,[44] where the reported pain was mostly chronic, adolescents experienced moderate (VAS score range: 4.0 to 6.9) to severe pain (VAS score range: 7.0 to 10.0) (n = 65).

3.4.2.4. Pain sites[10,11,43,44] (n = 4). Clancy et al.[11] highlighted the discrepancies in reported pain sites between parents and children/adolescents, especially among those with mild pain levels.[11] Parents indicated that children and adolescents with mild pain primarily experienced pain in the head, back, lower extremities (ankles, feet), or abdomen.[11] In contrast, children mostly reported mild pain in the lower body (knees), shoulders, back, and head.[11] For children and adolescents with moderate or severe pain, parents frequently identified the back and abdomen as the main pain sites whereas pain in the back and knees were more frequent in self-reports.[11]

In a study[10] on children with SB, mostly MMC, aged three to six years old in the US (N = 101), the caretaker reported prevalence of pain in the head, abdomen, and lower body were 43.0 %, 40.0 % and 40.0 %, respectively.[10] Pain also affected the back (17.0 %), upper body (17.0 %), upper extremities (16.0 %), and other sites (20.0 %) in the study population.[10] As in Clancy and colleagues' study, pain in more than one body site per individual was noted.[10,11]

In another study on older children and adolescents with SB aged 8–15 years (N = 140),[44] pain in the back, upper and lower extremities (hands, arms, and legs), abdomen, and head were commonly reported. In adolescents who were manual wheelchair users (N = 41),[43] three in ten had mild shoulder pain at the time of assessment and five in ten also reported experiencing pain in the upper limbs (hands, wrists, elbows).

3.4.2.5. Pain interference[42,43] (n = 2). According to the parents' report, four out of seven children (57.1 %) with SB who reported pain (mean age: 9.2 years, SD: 4.2) had pain-induced sleep problems which often were long-lasting.[42] One in three adolescents (33.3 %) with SB who used manual wheelchairs and experienced pain also reported pain interference with usual activities.[43]

3.4.2.6. Evidence grading. The gradings on the evidence synthesized by

Table 2
GRADE[25] evidence rating on present systematic review findings on pain characteristics and impact of pain in adults with spina bifida.

Outcomes	Mean (95 % CI) Meta-analysis (n = 166)	Narrative reports	Number of studies included (sample size)	Certainty of the evidence (GRADE)	
Pain severity	5.4 (3.2, 7.6) Moderate to severe pain at past one week measured by the NRS scale	Median pain intensity level 4.0 (range: 3.5,7.0) on the NRS scale[32] Range of pain intensity level: seven to 98 on EQ (5D) VAS, 0 to 100 scale[33]	4[32–35] (N = 471)	Low (1)	Worst pain severity in the past week at two time points, 15 moths apart, measured by the VAS 0 to 10 scale. Mean pain intensity level at time point-1: 5.17 (SD: 3.19; range: 1, 10) Mean pain intensity level at time point-2: 4.06 (SD: 3.02; range: 1, 10)
Back pain	59.1 % (39.8 %, 77.1 %)	Back (33.7 %)[39] Back pain in people with scoliosis (69.0 %)[34] Back (80.0 %)[32]	7[32–37,39,32] (N = 773)	Low (2)	
Hip pain	35.0 % (10.0 %, 66.0 %)	Hips (43 %)[32]	5[32,33,35–37] (N = 442)	Low (3)	
Pain in head/neck	23.9 % (0.0 %, 75.8 %)	Head (29.1 %), Neck (22.1 %)[39] Head (37.0 %), Neck (40.0 %)[32]	6[32,33,35–37,39] (N = 391)	Low (4)	Pain prevalence in individuals with spina bifida occulta of the atlas using questionnaires and pain localization illustration. Headache 6.25 % Frequent/severe headache 6.25 % Neck pain 37.5 %
Shoulder pain	28.0 % (0.0 %, 77.9 %)	Shoulders (47.0 %)[32]	5[32,33,35–37] (N = 263)	Low (5)	
Thighs/knees/legs pain	29 % (1 %, 71 %)	Upper legs/thighs (37.0 %)[32] Lower legs (33.0 %)[32]	5[32,33,35–37] (N = 263)	Low (6)	
Pain in upper extremities	10.7 % (0.0 %, 39.9 %)	Arms (27.0 %)[32] Hands (30.0 %)[32]	5[32,33,35–37] (N = 263)	Low (7)	
Other pain sites	7.1 % (0.0 %, 30.2 %)	Chest (10.0 %)[32] Buttocks (13.0 %)[32] Abdomen (26.7 %)[32] Abdomen (8.1 %)[36] Feet (33.0 %)[32]	5[32,33,35–37] (N = 263)	Low (8)	
Pain interference on daily activity	–	Prevalence: 48.8 %–55.0 %[36,38] Median pain interference score: 4.7/10 (IQR: 2.9)[32]	3[32,36,38] (N = 212)	Inconclusive findings (9)	
Pain interference on sleep	–	Prevalence: 32.0 %[36] Median pain interference score: 4.8/10 (IQR: 3.5)[32]	2[32,36] (N = 101)	Inconclusive findings (9)	

CI: confidence interval, IQR: interquartile range, NRS: Numeric Rating Scale, VAS: Visual Analogue Scale.
N = Total study sample size including those with or without pain, n = Individuals who reported pain.
GRADE rating[25] across five domains: overall risk of bias, inconsistency, indirectness, imprecision, and publication bias.
GRADE Low: Future research is likely to change the results.
(1) Risk of bias: Moderate, Inconsistency: Low, Indirectness: Low, Imprecision: Low, Publication bias: Low.
(2) Risk of bias: Moderate, Inconsistency: Low. Indirectness: Low. Imprecision: Low, Publication bias: Low.
(3) Risk of bias: Moderate, Inconsistency: Low, Indirectness: Low, Imprecision: High, Publication bias: Low.
(4) Risk of bias: Moderate, Inconsistency: Moderate, Indirectness: Low, Imprecision: High, Publication bias: Low.
(5) Risk of bias: Moderate, Inconsistency: Moderate, Indirectness: Low, Imprecision: High, Publication bias: Low.
(6) Risk of bias: Moderate, Inconsistency: Low, Indirectness: Low, Imprecision: High, Publication bias: Low.
(7) Risk of bias: Moderate, Inconsistency: Low, Indirectness: Low, Imprecision: Low, Publication bias: Low.
(8) Risk of bias: Moderate, Inconsistency: Low, Indirectness: Low, Imprecision: Low, Publication bias: Low.
(9) Limited information to draw a conclusion from lack of comparison across studies.

this systematic review for adults and newborns/children/adolescents are provided in Tables 2 and 3, respectively. For all outcomes, the certainty of the evidence was graded as low due to imprecision from wide CIs and/or potential sampling biases.

Funnel and Doi plot analyses showed that, except for the prevalence of head and neck pain, there was minor or no asymmetry in other outcomes, suggesting low risk of publication bias (Appendix E: Figure E.3–E.5). The asymmetry noted in the metanalysis of head and neck pain may be due to high between-study heterogeneity (I^2 94.0 %).

4. Discussion

4.1. Pain in adults with SB

Adults with SB experienced varying degrees of pain intensity but were found to have moderate to severe pain on average (NRS average score 5.4, 95 % CI: 3.2, 7.6). The pain was reported across different body sites including the lower part of the body. Findings from meta-analyses and individual studies in adults with SB showed that back and hip pain were most prevalent, followed by pain in thighs/knees/legs, shoulders, and head and neck. Causes of back and hip pain in adults with SB could possibly be due to degenerative conditions of spine, joint or muscles, tethered cord syndrome, or mechanical problems related to gait and postural abnormalities.

While some studies were excluded to maintain homogeneity within the review, their findings provide valuable insights and complement the synthesized evidence. The moderate to severe pain intensity found in this review aligns with findings from a study by Bellin et al.,[26] that measured worst pain scores over 15 months. Both included[32–37,39] and excluded studies[26] on adults with SB identified back pain as common. However, headache was less prevalent in the study on individuals with SB occulta at atlas (6.25 %)[29] compared to included ones (29.1 %[39] and 37.0 %[32]) while neck pain prevalence was somewhat similar (37.5 %[29] vs. 40.0 %[32] and 22.1 %[39]). Nociceptive pain has been reported as primarily affecting the upper extremities and the lower back.[27]

The present meta-analysis findings should be interpreted with caution as the summary estimates for the prevalent pain sites have wide CIs and prediction intervals. The variations observed can be caused by the non-uniform assessment of pain among individual studies and the different health conditions, such as hydrocephalus and comorbidities, present in the SB population.

Table 3
GRADE[25] evidence rating on present systematic review findings on pain characteristics and impact of pain in newborns and children/adolescents with spina bifida.

Outcomes	Findings Narrative synthesis	Number of studies included (sample size)	Certainty of the evidence (GRADE)
Newborns			
Pain severity	Low levels of nurses-reported pain in newborns who received routine analgesics	1[40] (N = 28)	Inconclusive findings (11)
Children and/or adolescents			
Pain severity	Varying intensity (mild to severe) measured by VAS or NRS	3[11,41,43] (N = 131)	Low (12)
Pain sites	Pain reported at various anatomical body sites. Pain in the head and back were most consistently reported. Multi-sites pain was common.	3[10,11,44] (N = 309)	Low (13)
Pain in shoulders & upper limbs in manual wheelchair users	Shoulder pain: 30.0 % prevalence, Upper limbs (hands, wrists, elbows): 50.0 % prevalence	1[43] (N = 41)	Low (14)
Pain interference on daily activity and sleep	Prevalence of pain interference with usual activities: 33.3 % (n = 3) [43] Prevalence of pain interference on sleep: 57.1 % (n = 7) [42]	2[42,43] (N = 100)	Inconclusive findings (11)

CI: confidence interval, IQR: interquartile range, NRS: Numeric Rating Scale, VAS: Visual Analogue Scale.
N = Total study sample size including those with or without pain, n = Individuals who reported pain.
GRADE rating [25] across five domains: overall risk of bias, inconsistency, indirectness, imprecision, and publication bias.
GRADE Low: Future research is likely to change the results.
(11) Limited information to draw a conclusion from lack of comparison across studies.
(12) Risk of bias: Overall moderate risk of bias but has high internal validity, Inconsistency: Low, Indirectness: Low, Imprecision: Low, Publication bias: Low.
(13) Risk of bias: Overall moderate risk of bias but has high internal validity, Inconsistency: Low, Indirectness: Low, Imprecision: Low, Publication bias: Low.
(14) Only one study but has high internal validity, Indirectness: Low, Publication bias: Low.

4.2. Pain in newborns, children, and/or adolescents with SB

There is a paucity of literature regarding pain in newborns with SB, which might be explained by the fact that pain is difficult to assess in newborns. For children and adolescents with SB, pain reports were observed at various bodily sites from head to lower extremities with varying intensity. Among the reported pain sites, the head and back were most consistently and commonly reported across the studies. Headache in children with SB is oftentimes related to shunt malfunctioning or infection[10,47] and back pain might be a complication of spinal deformities.

The wide variation in pain levels and pain sites among children and adolescents with SB is likely due to their diverse clinical profiles and the use of different types of reports (self or proxy reports). So far, the proxy report has been used to assess pain in those with profound intellectual and developmental disabilities (IDD) or those unable to communicate when self-reporting of pain is impossible.[48] However, conflicting results have been shown on the degree of consensus between self and proxy reports in individuals with IDD.[11,49]

4.3. Pain in wheelchair users

Similar to other studies on individuals with spinal cord injury,[50] shoulder and upper extremities pain is common among those using manual wheelchairs. The primary cause of shoulder pain, wheelchair self-propulsion, has been extensively discussed in the literature.[50] Sawatzky et al.[28] reported greater shoulder pain and pain interference in adult-onset wheelchair users than childhood-onset users, suggesting that pain experience vary with the age at onset of wheelchair use.

4.4. Pain assessment

The comparison across the studies was limited as different pain measurement tools were used to assess pain in the study population. Pain interference was less frequently studied across all age groups; thus, the amount of pain interference with daily activities and sleep in the SB population is inconclusive. Measuring pain intensity alone may not give a full picture of the pain burden. In a clinical setting, making pain treatment decisions using single-dimensional, self-reported, pain scores alone have been shown to result in over-prescription of opioids and over-sedation.[51]

4.5. Pain severity interpretation

For the VAS 0 to 10 scale, the included studies categorized the severity scores as moderate to severe pain in newborns for scores 4 and above and as mild (score 1.0 to 3.9), moderate (score 4.0 to 6.9), and severe (score 7.0 to 10.0)[44] in the older participants.[40] However, no classification was done for NRS scores due to the lack of consensus on the cut-off points for severity classification for NRS. Thus, for this review, the following severity cut-off points for those with non-traumatic spinal cord injury were referenced[52,53] to interpret the pain intensity scores measured by NRS: mild = 1.0 to 3.0, moderate to severe = 4.0 and above.

4.6. Limitations

Care must be taken in generalizing the review findings to the total population of individuals with SB. Studies often excluded individuals with profound cognitive or communication impairments. The results may be influenced by sampling and non-response biases, as all survey studies relied on convenience sampling methods to recruit participants. Future research with a more representative SB population is likely to change the results. The studies included were from Europe, Canada, and the US. As cultural background can influence pain conceptualization and reporting,[54] review findings cannot be generalized to populations from different cultural backgrounds. Since the studies did not define what constitutes other pain, overlap with the thighs/knees/legs category cannot be ruled out. Although 15 articles were included for review, only two to four studies can be included for each meta-analysis. Having more studies would increase the statistical power of the meta-analysis and enable us to do informative subgroup analyses to explore the causes of heterogeneity between included studies. Lastly, only studies published in English were searched, which introduced the potential for language selection bias.

4.7. Clinical implications

Despite the limitations, this systematic review provides a baseline for understanding pain in individuals with SB. The review findings show that the SB population can experience pain in any part of the body. Pain is also prevalent in the lower part of the body in adults with SB. This calls for routine assessment of pain in the SB population. Additionally, the grouping of the analyses by adult and younger populations enables a clearer understanding of the differing pain landscapes across age groups. It is worth noting that participants reported pain in more than one body site across all studies. Multisite pain in SB is often overlooked and it requires attention and care.

4.8. Future studies

Future studies should explore how to reliably assess pain in SB with profound cognitive or communication difficulties and the impact of pain on individuals' daily lives. Furthermore, pain profiles in individuals with SB by different mobility aids should be investigated to provide targeted preventive interventions.

5. Conclusion

In individuals with SB, pain can indeed manifest in any part of the body, including the lower part of the body. Pain can and does present at more than one location with varying intensity. The impact of pain on daily activities and sleep needs further exploration. Pain and its implication on daily activities and sleep should be regularly assessed in all individuals with SB, regardless of their age and clinical profiles. Population-based studies or studies designed to reduce sampling bias are much needed.

CRediT authorship contribution statement

May Phyu Sin: Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Ann I. Alriksson-Schmidt:** Writing – review & editing, Validation, Supervision, Software, Resources, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Review protocol registration

The review protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO registration: CRD42024547361). The registered protocol is available on the PROSPERO website at the following link.
https://www.crd.york.ac.uk/PROSPERO/view/CRD42024547361.

Disclaimer

The authors of this paper are affiliated with Lund University. However, the views expressed in this paper are their own and are not necessarily shared with the organisation the authors are affiliated with.

Disclosure

Neither the manuscript nor any parts of its content are currently under consideration or published in another journal.

Ethics

No ethical approval was required as the analysis only used publicly available secondary data.

Deviations from the original protocol

The search strategy was expanded to include two additional databases: Embase and Academic Search Complete and search terms were refined to maximize the sensitivity of the search. These changes were made after completion of the preliminary searches. We performed the statistical analysis using R language and the meta package instead of using RevMan 5 software because the R Meta package offers more flexibility in handling prevalence data, particularly in applying transformations. For heterogeneity assessment, we estimated prediction intervals in addition to the originally planned I^2 statistic. This is because relying solely on I^2 in meta-analyses of prevalence, especially with a small number of studies, can often lead to incorrect conclusions about heterogeneity. To clearly communicate the certainty of the evidence to decision-makers, we graded the evidence generated by our systematic review using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach. These decisions were made after the formal screening was completed.

Data sharing

Data sharing does not apply to this article, as the systematic review used publicly available data. For access to the data reported in the studies included in this systematic review, please contact the corresponding authors of those studies.

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Declaration of competing interest

The authors have no conflicts of interest to declare.

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Appendix A. Supplementary data

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