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Overview of the economic burden of musculoskeletal pain in children and adolescents: a systematic review with meta-analysis

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Abstract

Studies suggest a high economic burden among children and adolescents with musculoskeletal pain. There is no summary in the literature on the overall economic burden of musculoskeletal pain in children and adolescents. The aim of this systematic review of cost-of-illness studies was to synthesize the economic burden of musculoskeletal pain in children and adolescents. We conducted electronic searches on MEDLINE, EMBASE, CINAHL, EconLit, NHSEED, and HTA databases. We included cost-of-illness studies that estimated healthcare, patient/family, lost productivity, and/or societal costs in children and adolescents with musculoskeletal pain. The risk of bias was assessed with the Consolidated Health Economic Evaluation Reporting Standards checklist. All values were adjusted to the same reference year (2021) and converted to American Dollar. We included 45 cost-of-illness studies (n = 665,623). Twenty-two studies estimated the annual healthcare costs that ranged from $143 to $41,379 per patient. Nine studies estimated the annual patient/family costs that ranged from $287 to $27,972 per patient. Seven studies estimated the annual lost productivity costs that ranged from $124 to $4671 per patient. Nine studies estimated the annual societal costs that ranged from $1095 to $69,351 per patient. Children and adolescents with juvenile idiopathic arthritis and musculoskeletal pain had higher annual incremental healthcare costs than those without these conditions (mean difference: $3800 higher, 95% confidence interval [CI]: 50-7550; mean difference: $740 higher, 95% CI: 470-1,010, respectively). In conclusion, the estimated annual economic burden of children and adolescents with musculoskeletal pain ranged from $124 to $69,351.

Keywords: Children and adolescents, Musculoskeletal pain, Systematic review, Economic burden

1. Introduction

Musculoskeletal pain in children and adolescents is highly prevalent and disabling, and it increases with age.[25,30,51] Headache and back pain are important contributors to global years-lived with disability among children and adolescents.[12] Musculoskeletal pain directly interferes with the daily life activities of children and adolescents because of school absenteeism, impact on recreational or sports activities, and seeking health services.[17,18,45,48] Longitudinal studies also demonstrate that musculoskeletal pain in childhood increases the likelihood of developing chronic pain in adulthood, and the risk of anxiety and depression disorders and suicide.[22,53,70]

Musculoskeletal pain has been shown to generate high socioeconomic costs in children and adolescents. These costs are mainly related to healthcare utilization and lost productivity of parents and caregivers.[17,19,60] Although studies on the economic burden of musculoskeletal pain in children and adolescents have been published, there is no summary in the literature regarding the healthcare, patient/family, lost productivity, and societal costs for this condition. The aim of this study was to synthesize the economic burden of musculoskeletal pain in children and adolescents.

2. Methods

2.1. Study design and registration

This study is a systematic review of cost-of-illness studies. The protocol was previously published on the Open Science Framework (https://osf.io/s9ytz) and registered on the international prospective register of systematic reviews (PROSPERO) https://www.crd.york.ac.uk/prospero/, number CRD42020211431. This systematic review was written according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020)[49] (see

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Supplemental Digital Content 1 for checklist, available at http://links.lww.com/PAIN/B908).

2.2. Eligibility criteria

We included studies that reported data on the economic burden (healthcare, patient/family, lost productivity, and/or societal costs) of musculoskeletal pain in children and adolescents aged up to 24 years. Cohort studies that investigated interventions and randomized controlled trials were only included if these studies presented cost data at baseline. We included specific conditions such as juvenile idiopathic arthritis, adolescent idiopathic scoliosis, headache/migraine, and mixed pain conditions (eg, back and neck pain, headache, and abdominal pain). Studies on mixed pain conditions including abdominal pain were included if patients with abdominal pain represented less than 50% of the total sample. Studies that included children and adults were considered if the cost data for children and adolescents were presented separately.

We excluded studies of pain caused by cancer, fracture, infections, or life-threatening disease, abdominal pain alone, postsurgery pain, and neurological conditions. We also excluded studies that reported surgery costs only, case studies, trial protocols, pilot studies, reviews, overviews, guidelines, commentaries, and conference abstracts. We did not search grey literature or include studies that have not been published in a peer-review journal. There were no restrictions regarding setting, language, or year of publication.

2.3. Search strategy

We conducted searches on MEDLINE, EMBASE, CINAHL, EconLit, National Health Service Economic Evaluation Database (NHSEED), and Health Technology Assessment (HTA) databases. The final search was conducted in July 2022 for all databases. The search strategy was developed by the team of researchers who have expertise in systematic reviews, including Cochrane reviews.[1,39,75] The search strategy was adjusted for each database, including terms for "children and adolescents," "musculoskeletal pain," and "specific pediatric conditions" (eg, juvenile idiopathic arthritis, adolescent idiopathic scoliosis, and headache/migraine), which were designed by a Cochrane information specialist. The term "economic burden" was used based on previous systematic reviews of cost-of-illness studies[7,54] (see Supplemental Digital Content 2, available at http://links.lww.com/PAIN/B908). Reference lists of the included studies and relevant systematic reviews were manually searched for potential studies.

2.4. Selection of studies

Two reviewers independently screened titles and abstracts for potentially eligible studies (C.M.E.S. and V.S.S.) and screened full texts. All disagreements were solved by discussion and a third reviewer (T.P.Y. or G.C.M.) arbitrate when a consensus could not be reached. All the screening process was performed using EndNote software version X9.[6]

2.5. Data collection and extraction

The data extraction was performed by 2 reviewers independently (C.M.E.S. and V.S.S.). Any disagreement between the reviewers was solved by discussion or by the arbitration of a third reviewer (T.P.Y. or G.C.M.). If any important data were not reported in the article, we contacted the authors by email to request the data. We made 3 attempts over 2 weeks. A data extraction form was developed previously by 2 experienced researchers (T.P.Y. and G.C.M.) to define the items of the data extraction. We extracted the following data for each included study: author(s); year of publication; aims/purpose; study population (eg, health condition, context) and sample size; study design (classification: prospective, retrospective, or unclear); source data (eg, national database, questionnaire, cost diary); details of cost data: country, currency, reference year, perspective (health care, patient/family and societal), time horizon, cost categories (healthcare costs, patient/family costs, lost productivity costs, societal costs, total national costs, and incremental costs), discounting, cost analysis methods, and results (for cohort studies that investigated interventions and randomized controlled trials, we only have extracted cost data from baseline or preintervention). On average, incremental costs represent the additional expenses of children and adolescents related to musculoskeletal pain condition compared with children and adolescents without this condition (ie, the cost differences between these populations).[3,19,35]

We categorized countries according to the World Bank Classification (ie, low, lower-middle, upper-middle, and high-income countries).[76] The studies were categorized into 4 groups: (1) primary care: studies that estimated costs considering visits to general practitioners, healthcare professionals, and diagnostic tests; (2) secondary care: studies that estimated costs considering the number of visits to the emergency department, inpatient care, rehabilitation clinic, and other healthcare institutions; (3) tertiary care: studies that estimated costs considering visits to a specialized clinic, pediatrics hospital, or specialized hospital to manage pain conditions, and other specialized inpatient healthcare services were also classified as tertiary care; and (4) community: studies that did not collect data from a healthcare setting (ie, primary, secondary and, tertiary care). These studies recruited samples from schools, national databases, and population-based surveys.[43]

2.6. Risk of bias in individual studies

The risk of bias assessment of each study was conducted by 2 reviewers independently (C.M.E.S. and V.S.S.). Any disagreement between the reviewers was solved by discussion or by arbitration of a third reviewer (T.P.Y. or G.C.M.). We assessed the risk of bias of the included studies using a checklist based on the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement used and recommended by previous systematic reviews of cost-of-illness studies[13,27,64] (see Supplemental Digital Content 3, available at http://links.lww.com/PAIN/B908). This checklist has 2 main domains: the economic component (5 items) and the epidemiological component (2 items), when applicable. Each item could be classified as "yes," "no," or "unclear." The checklist is composed of items related to (1) unit costs clearly presented—we considered as "yes" if the study described the data sources for expenditure, resource use, and unit costs clearly; (2) expenditures data transparently presented—it was considered as "yes" if the study described and presented the cost and/or expenditure data transparently in the results; (3) productivity costs were included—it was considered as "yes" if the study have included productivity costs associated or not with other costs categories (ie, healthcare costs); (4) if productivity costs were presented separately (when applicable)—it was considered as "yes" when the study met the criterion of item 3, and the results were presented disaggregated with other costs categories; (5) analysis to address uncertainty or

heterogeneity—it was considered as "yes" if the study presented a sensitivity analysis or subgroup analysis according with the costs associated; (6) estimates of incidence/prevalence—it was considered "yes" when the study reported the costs and used reliably methods to estimate incidence/prevalence from a sample; and (7) internal validity—we considered "yes" when the study used reliable methods to estimate incidence/prevalence and when authors described the source of the data (ie, a considerable sample national database or insurance records). Item 4 of the checklist was considered as "not applicable" when studies did not include productivity costs (ie, when item 3 was classified as "no"). Also, the item 6 and item 7 of the checklist were considered as "not applicable" when the studies did not to assess the epidemiological component because both items are considered (when applicable).

2.7. Outcomes

The outcome of interest was cost, separated by categories: healthcare, patient/family, lost productivity, and societal costs.[43] We considered healthcare costs as any expenses on medical care services, such as the use of medication, visits to healthcare professionals, emergency department, hospitalizations, surgery, inpatient stays, diagnostic and imaging tests (eg, radiography, computed tomography, magnetic resonance imaging), insurance premiums (eg, the amount of money that parents paid for an insurance policy that covers health care), assistive devices (eg, aids/splint materials, bracing), complementary and alternative medicine, and other procedures for the treatment of health condition. We considered patient/family costs as any out-of-pocket expenses related to transportation, parking, copayments for treatments, medications, assistive devices, nutrition/food supplements, and complementary services (eg, environmental modifications and caregivers). We considered lost productivity costs as any expenditures related to absenteeism from parent's paid and/or unpaid work. Societal costs were considered as the combination of lost productivity costs and one or more cost categories.[43]

2.8. Data synthesis

All costs were inflated to the same reference year (2021) using consumer price indices[74] and were converted to American dollar ($) using purchasing power parity.[77] When an included study did not report the index year, we used the year of publication as the reference. If studies provided a comparison group (eg, musculoskeletal pain vs other conditions or control), means and SDs of each group were used to estimate the incremental costs and 95% confidence intervals (CIs), when the study did not report these data. We calculated the SDs when these data were not available in the study. Furthermore, we have combined means and SDs through meta-analyses using random-effects models for studies in which the comparison, time horizon (eg, 12-month), context (eg, tertiary care), and cost category (eg, healthcare) were similar. For the forest plots, the values (means and SDs) were expressed with a negative sign and divided by 1000 to better visualize the results graphically and to demonstrate the condition with higher costs. All calculations and analyses were performed in Review Manager 5.4 software.

3. Results

3.1. Study selection

Overall, 17,469 records were identified in the electronic search; 14,189 titles and abstracts were screened once duplicates were removed. We screened 575 full texts for eligibility, and thus, 45 studies were included. We also searched the reference lists of included studies; however, no additional studies were found. The details of the study selection and the reasons for exclusion are presented in the PRISMA flow diagram in **Figure 1**.

3.2. Study characteristics

Fifteen studies[10,17,19,24,34,37,47,56–58,60,61,63,69,81] included children and adolescents with mixed pain conditions, 13 studies[2,9,15,20,29,31,32,42,52,59,66,68,80] with juvenile idiopathic arthritis, 10 studies[3–5,14,28,35,40,46,62,71] with headache/migraine, and 7 studies[36,41,44,55,67,72,79] with adolescent idiopathic scoliosis. Nineteen were cross-sectional studies,[3–5,9,19,28,32,35,41,42,44,46,47,59,62,69,71,72,80] 25 were cohort studies[2,10,14,15,17,20,24,29,31,36,37,40,52,55–58,60,61,63,66–68,79,81] of which 11 provided some type of intervention with cost data collected at baseline or before the intervention,[10,17,20,24,37,52,56–58,61,63] and 1 was a randomized controlled trial with cost data collected at baseline.[34] Seventeen studies were conducted in the United States (37.8%),[3,10,14,17,19,24,34,35,41,55,61,62,66,69,71,79,81] 7 in Germany (15.6%),[37,42,46,47,56–58] 5 in Canada (11%),[2,9,15,44,63] 3 in Turkey (6.7%),[28,72,80] 2 in Brazil (4.4%),[4,5] 2 in the United Kingdom (4.4%),[60,68] 2 in the Netherlands (4.4%)[31,52] 1 in Finland (2.2%),[20] 1 in Italy (2.2%),[40] 1 in Singapore (2.2%),[67] 1 in China (2.2%),[36] and 1 in India (2.2%).[29] Two multinational studies (5.5%)[32,59] were conducted: 1 study in the United States, France, Germany, the Netherlands, and the United Kingdom; and the other in Germany, Italy, Spain, France, the United Kingdom, Bulgaria, and Sweden. Thirty-eight studies (84.4%)[2,3,9,10,14,15,17,19,20,23,31,32,34,35,37,40–42,44,46,47,52,55–63,66–69,71,79,81] were conducted in high-income countries, 6 (13.3%)[4,5,28,36,72,80] in upper-middle-income countries, and 1 (2.2%)[29] in a lower-middle-income country. Healthcare and societal costs were the most common data reported.[2–5,9,10,14,15,17,19,20,24,29,31,32,34–37,40–42,44,46,47,52,55–57,59–63,66–69,71,72,79–81] The characteristics of the included studies are presented in **Table 1**.

3.3. Risk of bias assessment

Regarding the economic component, 75.5%[2–5,10,14,15,17,19,20,28,31,32,34–37,40–42,46,47,52,55–57,60–62,68,69,71,79,80] of the studies clearly presented the unit costs, 69%[2–5,9,10,15,17,19,20,29,31,32,34–37,41,42,46,55,56,58,60,61,66,68,71,79–81] presented the expenditure data transparently, 29%[9,10,17,20,29,34,35,40–42,57,60,80] included the lost productivity costs and presented the lost productivity costs separately, and 42%[3,5,9,15,28,29,31,32,35,40,42,47,55,60,67,68,79–81] performed a sensitivity or a subgroup analysis (**Fig. 2**). Studies that did not estimate incidence/prevalence were judged as "not applicable" on items 6 and 7. Eight studies (17.8%) used reliably methods to estimate incidence/prevalence (item 6),[3,14,19,35,44,47,72,81] and 9 studies (20%) met the criterion of internal validity (item 7).[3,4,14,19,35,44,47,72,81]

3.4. Economic burden

3.4.1. Healthcare costs

The total annual healthcare costs reported in 22 studies ranged from $143[28] to $41,379[32] per patient.[2,3,9,19,28,31,32,34,35,37,42,44,46,52,56,57,60,61,66,68,80,81] Nine studies included children with juvenile idiopathic arthritis[2,9,31,32,42,52,66,68,80] (range from $237[9] to $41,379[32]), 8 with mixed pain conditions[19,34,37,56,57,60,61,81] ($3,716[19] to $12,409[34]), 4 with headache/migraine[3,28,35,46] ($143[28] to $2,942[35]), and 1 with adolescent idiopathic scoliosis[44] ($5795) (**Tables 2 and 3**).

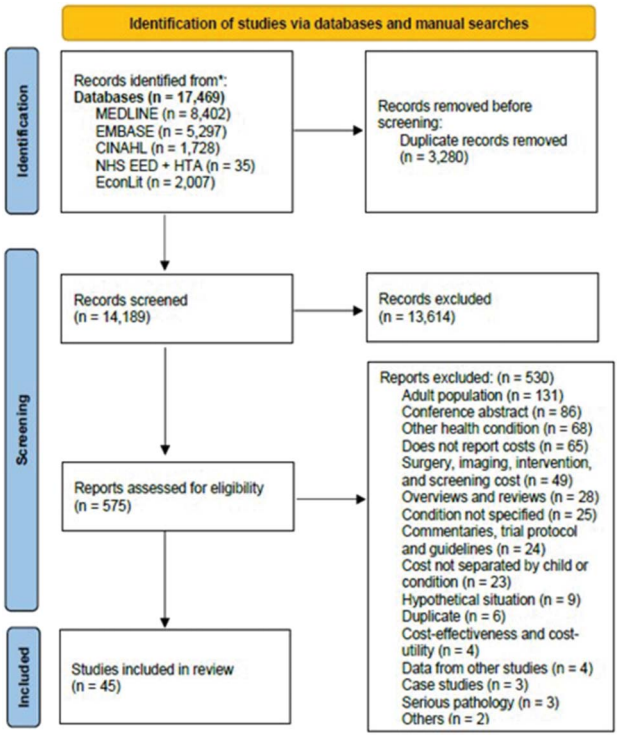

Figure 1. PRISMA 2020 flow diagram for the systematic review which included searches of databases. We reported the number of records identified from each database individually. NHSEED, National Health Service Economic Evaluation Database; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

A meta-analysis was performed to compare the annual healthcare costs in the tertiary care context in children and adolescents with and without juvenile idiopathic arthritis at 12 months. Two studies[2,80] (n = 536) (**Fig. 3**) showed higher annual costs for children and adolescents with juvenile idiopathic arthritis (MD: $3800 higher, 95% CI: 50-7550). The meta-analysis showed heterogeneity of 96%. On average, this represents an incremental annual healthcare cost of $3800 for children and adolescents with juvenile idiopathic arthritis.

Another meta-analysis was conducted to estimate the annual incremental healthcare costs in the community context comparing children and adolescents with and without musculoskeletal pain conditions at 12 months. Three studies[3,19,35] were included, with a total of 40,423 children and adolescents (**Fig. 4**). The results showed higher annual incremental healthcare costs for children and adolescents with musculoskeletal pain conditions (including headache/migraine and mixed pain conditions) (MD: $740 higher, 95% CI: 470-1010). The meta-analysis showed heterogeneity of 70%. On average, this represents an incremental annual healthcare cost of $740 for children and adolescents with musculoskeletal pain conditions.

3.4.2. Patient/family costs

The total annual patient/family costs reported per patient with musculoskeletal pain ranged from $287[80] to $27,972.[32] Overall, 9 studies[3,9,32,34,42,57,59,60,80] estimated annual patient/family costs: 5 in juvenile idiopathic arthritis[9,32,42,59,80] (range from $287[80] to $27,972[32]), 3 in mixed pain conditions[34,57,60] ($1307[34] to $3771[57]), and 1 in headache/migraine[3] ($509.33) (**Tables 2 and 3**).

We could not perform a meta-analysis for patient/family costs because there was only 1 study available estimating annual incremental costs in headache/migraine.[3] However, we estimated annual incremental patient/family costs from this study to graphically illustrate the results. One analysis[3] included a total sample of 4263 children and adolescents with and without headache/migraine (**Fig. 5A**). The results showed that there was no difference in patient/family costs for children and adolescents with or without headache/migraine (MD: $10 lower, 95% CI: −90 to 70).

3.4.3. Lost productivity costs

The total annual lost productivity costs reported per patient with musculoskeletal pain ranged from $124[80] to $4671.[34] Seven studies[9,34,35,42,57,60,80] estimated annual lost productivity costs: 3 in juvenile idiopathic arthritis[9,42,80] (range from $124[80] to $433[42]), 3 in mixed pain conditions[34,57,60] ($1534[60] to $4671[34]), and 1 in headache/migraine[35] ($461) (**Tables 2 and 3**).

We also could not perform a meta-analysis for lost productivity costs because there was only 1 study available estimating annual incremental costs in headache/migraine.[35] However, we estimated annual incremental lost productivity costs from this study to graphically illustrate the results. One analysis[35] included a total sample of 34,633 children and adolescents with and without headache/migraine (**Fig. 5B**). The results showed a slight difference between annual incremental lost productivity costs for children and adolescents with headache/migraine compared with children and

Table 1

Study characteristics.

Author, year of publication	Study population	Context	Sample size	Age	Female n (%)	Study design (classification)	Source data	Details of cost data	Cost categories and analysis
Adolescent idiopathic scoliosis									
Morais et al.,[44] 1985	AIS	Community	1227	Range: 8-15	763 (62.2)	Cross sectional (retrospective)*	Unclear	Country and currency: Canada; Canadian dollar Reference year: 1979 Perspective: healthcare† Time horizon: 12 mo Discounting: NA	Healthcare costs (intermittent traction, braces, radiograph, clinician, and surgery); descriptive analysis
Roubal et al.,[55] 1999	AIS	Community	Unclear	Range: 11-12	Not reported	Cohort (retrospective)*	Questionnaire	Country and currency: United States; American dollar Reference year: Not reported Perspective: healthcare† Time horizon: unclear Discounting: not reported	Healthcare costs (visits doctors, bracing, hospital, surgical); descriptive analysis
Yawn and Yawn,[79] 2000	AIS	Community	21	Range: <19	Not reported	Cohort (retrospective)	Patient medical records	Country and currency: United States; American dollar Reference year: not reported Perspective: healthcare† Time horizon: unclear Discounting: not reported	Healthcare costs (primary care visits, specialty visits, radiographic); descriptive analysis
Thilagaratnam,[67] 2007	AIS	Community	57	Range: 11-12	Not reported	Cohort (retrospective)	Patient medical records	Country and currency: Singapore; Singapore dollar Reference year: not reported Perspective: societal Time horizon: 12 mo Discounting: NA	Societal costs (time cost for parent accompanying their child to clinic, transport, postsurgical follow-up); descriptive analysis
Lee et al.,[36] 2010	AIS	Community	303	Range: 10-19	Not reported	Cohort (retrospective)	Hospital/medical database	Country and currency: China; American dollar Reference year: 2005 Perspective: healthcare† Time horizon: 120 mo Discounting: not reported	Healthcare costs (brace, surgery, brace and surgery); descriptive analysis
Ugras et al.,[72] 2010	AIS	Community	11	Range: 11-14	8 (72.7)	Cross sectional (retrospective)*	Not reported	Country and currency: Turkey; American dollar Reference year: not reported Perspective: healthcare† Time horizon: unclear Discounting: not reported	Healthcare costs (physician, x-rays, treatment); descriptive analysis
Meirick et al.,[41] 2019	AIS	Tertiary care	337	Range: 10-19	248 (74)	Cross sectional (retrospective)	Hospital/medical database and interviews	Country and currency: United States; American dollar Reference year: not reported Perspective: healthcare, patient/family, and societal† Time horizon: unclear Discounting: not reported	Healthcare costs (orthopedic physician, radiography); patient/family costs (transportation); lost productivity costs (paid work); descriptive analysis

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Table 1 (*continued*)

Author, year of publication	Study population	Context	Sample size	Age	Female n (%)	Study design (classification)	Source data	Details of cost data	Cost categories and analysis
Headache/Migraine									
Bigal et al.,[5] 2000	Headache	Tertiary care	148	Range: < 12	Not reported	Cross sectional (retrospective)*	Hospital/medical database	Country and currency: Brazil; American dollar Reference year: 1999 Perspective: healthcare† Time horizon: 3 mo Discounting: NA	Healthcare costs (inpatient care, outpatient care); descriptive analysis
Bigal et al.,[4] 2001	Headache	Primary care	Not reported	Not reported	Not reported	Cross sectional (retrospective)*	Hospital/medical database	Country and currency: Brazil; American dollar Reference year: 1998 Perspective: healthcare† Time horizon: 12 mo Discounting: NA	Healthcare costs (health units, hospital admissions, emergency referral); descriptive analysis
Mazzotta et al.,[40] 2005	Headache	Tertiary care	25	Age mean: 13 Range: 7-18	14 (56)	Cohort (prospective)	Cost diary	Country and currency: Italy; Euro Reference year: not reported Perspective: healthcare, patient/family, and societal† Time horizon: 6 mo Discounting: NA	Healthcare costs (pediatric and specialist visits, diagnostic testing, symptomatic and/or prophylactic pharmacological therapy), lost productivity costs (paid work); descriptive analysis
Bethell et al.,[3] 2013	Headache	Community	434	Age category, n (%): 10-12 y old, 134 (31.4); 13-15 y old, 148 (33.9); 16-17 y old, 152 (34.7) Range: 10-17	232 (53.5)	Cross-sectional (retrospective)*	National database	Country and currency: United States; American Dollar Reference year: 2008 Perspective: Healthcare and patient/family† Time horizon: 12 mo Discounting: NA	Healthcare costs (medical care, emergency department, medications, specialist visit, mental health visits, physical therapist, occupational therapist, hospitalizations); patient/family costs (out-of-pocket expenses related to medications); descriptive analysis
Stang et al.,[62] 2004	Migraine	Community	8891‡	Not reported	Not reported	Cross sectional (retrospective)	National database	Country and currency: United States; American dollar Reference year: not reported Perspective: healthcare† Time horizon: 12 mo Discounting: NA	Healthcare costs (outpatients visits, emergency room use, hospitalization, medications related to migraine); descriptive analysis
Gill et al.,[14] 2021	Headache/migraine	Tertiary care	20,115‡	Median (IQR): 4 (1-12) Range: ≤17	Not reported	Cohort (retrospective)	Hospital/medical database and interviews	Country and currency: United States; American dollar Reference year: 2019 Perspective: healthcare† Time horizon: 48 mo Discounting: NA	Healthcare costs (laboratory tests, imaging, hospital inpatient); descriptive analysis
Karli et al.,[28] 2006	Headache/migraine	Tertiary care	53	Range: < 20	Not reported	Cross sectional (retrospective)	Questionnaire	Country and currency: Turkey; American dollar Reference year: 2004 Perspective: healthcare† Time horizon: 12 mo Discounting: NA	Healthcare costs (physician, specialist outpatient care, diagnostic workup, hospitalization); descriptive analysis
Law et al.,[35] 2019	Headache/migraine	Community	779	Age category, n (%): 3-5 y old, 25 (3.6); 6-	431 (58.8)	Cross sectional (retrospective)	National database	Country and currency: United States; American dollar	Healthcare costs (office visits, hospital outpatient visits, emergency department

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Table 1 (*continued*)

Author, year of publication	Study population	Context	Sample size	Age	Female n (%)	Study design (classification)	Source data	Details of cost data	Cost categories and analysis
				11 y old, 248 (28.3); 12-17 y old, 506 (68.1) Range: 3-17				Reference year: 2016 Perspective: healthcare, patient/family, and societal† Time horizon: 12 mo Discounting: NA	visits, inpatient stays, medications); patient/family costs (out-of-pocket expenses); lost productivity costs (paid work); descriptive analysis
Obermeier et al.,[46] 2021	Headache/ migraine	Community	2597	Age mean: 9.3 (CI 95%: 9.3-9.4) Range: 6-11	1223 (47.1)	Cross sectional (retrospective)	Insurance records	Country and currency: Germany; Euro Reference year: 2017 Perspective: healthcare Time horizon: 12 mo Discounting: NA	Healthcare costs (primary care physicians or specialists, outpatient care, inpatient care, rehabilitation therapy, or aids, drugs); descriptive analysis
Trofimova et al.,[71] 2020	Headache/ migraine	Tertiary care	1159	Age mean: 11.6 Range: 6-21	618 (53.3)	Cross sectional (retrospective)	Hospital/medical database	Country and currency: United States; American dollar Reference year: 2015 Perspective: healthcare† Time horizon: 12 mo Discounting: NA	Healthcare costs (radiography, computed tomography, magnetic resonance imaging); descriptive analysis
Juvenile idiopathic arthritis									
Haapasaari et al.,[20] 2004	JIA	Tertiary care	31	Age mean: 10 Range: 3-15	Not reported	Cohort (retrospective) *§	Patient medical records and interviews	Country and currency: Finland; American dollar Reference year: unclear Perspective: healthcare, patient/family, and societal† Time horizon: 3 mo Discounting: NA	Healthcare costs (inpatient ward therapy, visit at outpatient department, general anesthesia for joint injections, physiotherapy, laboratory visit, visit to a nurse, medications); patient/family costs (transportation); lost productivity costs (paid work); descriptive analysis
Bernatsky et al.,[2] 2007	JIA	Tertiary care	155	JIA sample, age mean: 10 (95% CI: 9.4-10.7) Control sample, age mean: 10.5 (95% CI: 9.9-11.1)	108 (69.7)	Cohort (retrospective)	Questionnaire	Country and currency: Canada; Canadian dollar Reference year: 2005 Perspective: healthcare† Time horizon: 12 mo Discounting: NA	Healthcare costs (medication, health care professionals, laboratory and imaging tests, emergency room visits, outpatient surgery, inpatient stays, assistive devices); descriptive analysis
Grazziotin et al.,[15] 2021	JIA	Tertiary care	389	Age mean (SD): 10.1 (4.6)	232 (56.6)	Cohort (retrospective)	Patient medical records	Country and currency: Canada; Canadian dollar Reference year: 2019 Perspective: healthcare† Time horizon: 72 mo Discounting: NA	Healthcare costs (hospital inpatient, hospital outpatient, emergency, medication, imaging, laboratory tests, joint injections); descriptive analysis
Thornton et al.,[68] 2008	JIA	Tertiary care	297	Age mean (SD): 8.2 (4.3) Range: < 16	191 (64)	Cohort (prospective)	Insurance records and national database	Country and currency: United Kingdom; American Dollar, Euro, Pound Sterling Reference year: 2005 Perspective: healthcare Time horizon: 12 mo Discounting: NA	Healthcare costs (consultant pediatric rheumatologist appointments, referrals to other specialists/care, clinical imaging, laboratory tests, drugs); descriptive analysis
Khatun et al.,[29] 2021	JIA	Tertiary care	60	Age mean (SD): 8.46 (2.24) Range: (4-20)	30 (46.5)	Cohort (prospective)	Unclear	Country and currency: India; Rupia Indiana Reference year: not reported	Healthcare costs (outpatient visits, blood tests, imaging tests, other tests, medications, hospital inpatient); patient/

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Table 1 (*continued*)

Author, year of publication	Study population	Context	Sample size	Age	Female n (%)	Study design (classification)	Source data	Details of cost data	Cost categories and analysis
								Perspective: healthcare, patient/family, lost productivity, and societal Time horizon: 12 mo Discounting: NA	family costs transportation, accommodation); lost productivity costs (loss paid work); descriptive analysis
Kip et al.,[31] 2021	JIA	Tertiary care	691	Median (IQR): 8 (4-12.6) Range: <18	447 (65)	Cohort (retrospective)	Patient medical records	Country and currency: the Netherlands; Euro Reference year: 2019 Perspective: healthcare Time horizon: 12 mo Discounting: NA	Healthcare costs (medication, imaging, laboratory tests, hospital inpatient, surgeries, outpatient care, emergency); descriptive system
Minden et al.,[42] 2009	JIA	Unclear	369	Age mean (SD): 11.9 (4.3) Range: 2-18	263 (71)	Cross-sectional (retrospective)	National database	Country and currency: Germany; Euro Reference year: 2003 Perspective: healthcare, patient/family, and societal Time horizon: 12 mo Discounting: NA	Healthcare costs (pediatric rheumatology service use, ophthalmologist service use, other JIA-related physician service use, nonphysician service use, medication, devices and aids, inpatient services, surgery, rehabilitation); patient/family costs (copayment to treatments, comprehensive alternative medicine, transportation, extra telephone, home alterations, domestic help and care for patients and/or their siblings, remaining); lost productivity costs (paid work); descriptive analysis
Prince et al.,[52] 2011	JIA	Tertiary care	49	Mean (IQR): 11.6 (7.9-14.6) Range: <18	29 (59)	Cohort (retrospective) *§	Patient medical records and questionnaire	Country and currency: the Netherlands; Euro Reference year: 2008 Perspective: healthcare† Time horizon: 12 mo Discounting: NA	Healthcare costs (consultation pediatric rheumatologist, telephonic consultation, consultation other specialists, hospital admissions, physiotherapy, other paramedical care, medication, laboratory, x-ray, imaging tests); descriptive analysis
Yucel et al.,[80] 2012	JIA	Tertiary care	100	Age mean (SD): 10.5 (4.6) Range: 2-18	69 (69)	Cross sectional (retrospective)*	Interviews and questionnaire	Country and currency: Turkey; Euro Reference year: 2009 Perspective: healthcare, patient/family, and societal† Time horizon: 12 mo Discounting: NA	Healthcare costs (outpatient clinic visits, biochemical tests, radiological tests, drugs, devices, physiotherapy, hospitalization, surgeries); patient/family costs (transportation and lodging expenses); lost productivity costs (paid work); descriptive analysis
Ens et al.,[9] 2013	JIA	Tertiary care	54	Median: 14 Range: 5-20	32 (59)	Cross sectional (retrospective)*	Questionnaire	Country and currency: Canada; Canadian dollar Reference year: 2009 Perspective: healthcare, patient/family and societal† Time horizon: 12 mo Discounting: NA	Healthcare (medications, aids/splint materials, physiotherapy); patient/family costs (hospital visits costs, peripheral visit costs, transportation, parking, home adaptations, driving child to school); lost productivity costs (paid work); descriptive analysis
Kuhlmann et al.,[32] 2016	JIA	Unclear	161	Age mean: 14	118 (73.2)	Cross sectional (retrospective)	Questionnaire	Country and currency: Germany, Italy, Spain, France, United Kingdom, Bulgaria, Sweden; Euro	Healthcare costs (medication, tests, healthcare visits, hospitalization, devices, healthcare transportation); patient/family

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Table 1 (*continued*)

Author, year of publication	Study population	Context	Sample size	Age	Female n (%)	Study design (classification)	Source data	Details of cost data	Cost categories and analysis
								Reference year: 2012 Perspective: healthcare, patient/family and societal Time horizon: 12 mo Discounting: NA	costs (main caregivers, secondary caregivers, social service, transportation); lost productivity costs (paid work); descriptive analysis
Thakral et al.,[66] 2020	JIA	Tertiary care	97	Median (IQR): 8.2 (5.6-11.6)	89 (92)	Cohort (retrospective)	Patient medical records	Country and currency: United States; American dollar Reference year: not reported Perspective: healthcare† Time horizon: 12 mo Discounting: NA	Healthcare costs (clinic visits, laboratory testing, radiology, procedures, medications, infusions); descriptive analysis
Shenoi et al.,[59] 2018	JIA	Tertiary care	61	Age mean (SD): 11.3 (4.6) Range: 4-18	29 (48)	Cross sectional (retrospective)	Questionnaire	Country and currency: United States, France, Germany, the Netherlands, and United Kingdom; American dollar Reference year: 2016 Perspective: healthcare and patient/family† Time horizon: 12 mo Discounting: NA	Healthcare costs‖ (insurance premiums, drugs); patient/family costs (petrol/gas, train/bus/ferry tickets, parking fees, co-pay medicine); descriptive analysis
Mixed pain conditions									
Sleed et al.,[60] 2005	Mixed pain conditions	Tertiary care	52	Age mean: 15.3 (1.61) Range: 11-18	38 (73)	Cohort (retrospective) *	Questionnaire	Country and currency: United Kingdom; Pound Sterling Reference year: 2004 Perspective: Healthcare, patient/family, and societal† Time horizon: 12 mo Discounting: NA	Healthcare costs (hospital inpatient, hospital outpatient, accident and emergency, general practitioner, physiotherapist, home tutor); patient/family costs (out-of-pocket expenses); lost productivity costs (paid work); descriptive analysis
Ho et al.,[23] 2008	Mixed pain conditions¶	Secondary care	74	Age mean (SD): 14.5 (2.5) Range: 10-18	51 (69)	Cohort (prospective) *§	Interviews and questionnaire	Country and currency: United States; American dollar Reference year: not reported Perspective: healthcare† Time horizon: 3 mo Discounting: NA	Healthcare costs (physician, specialists, physical therapy and/or other therapy, psychologist/psychiatrist, radiological examinations and emergency department); descriptive analysis
Ochsmann et al.,[47] 2010	Mixed pain conditions	Primary, secondary, tertiary care	644,773	Range: 0-14 and 15-24	176.155 (48.9)	Cross sectional (retrospective)*	Insurance records	Country and currency: Germany; Euro Reference year: 2002 Perspective: healthcare† Time horizon: 12-mo Discounting: NA	Healthcare costs (outpatient and inpatient care); descriptive analysis
Ruhe et al.,[58] 2013	Mixed pain conditions¶	Tertiary care	101	Age mean (SD): 14.3 (2.1) Range: 9-17	78 (77.2)	Cohort (retrospective) *§	Questionnaire	Country and currency: Germany, Euro Reference year: not reported Perspective: patient/family Time horizon: 12 mo Discounting: NA	Patient/family costs (travel, medicines, literature, tutoring, additional payment, nutrition/food supplements, aids); descriptive analysis
Groenewald et al.,[17] 2014	Mixed pain conditions¶	Unclear	149	Age mean: 14.2 (1.7) Range: 10-17	108 (72.5)	Cohort (retrospective)§	Questionnaire	Country and currency: United States; American dollar Reference year: 2012	Healthcare costs (physician, mental health, physical therapy, occupational therapy, complementary and alternative medicine,

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Table 1 (*continued*)

Author, year of publication	Study population	Context	Sample size	Age	Female n (%)	Study design (classification)	Source data	Details of cost data	Cost categories and analysis
								Perspective: healthcare, patient/family, and societal† Time horizon: 12 mo Discounting: NA	other providers, diagnostics tests, community services, medications, emergency department, hospital inpatient); patient/family costs (employing extra help, transport, special equipment, special foods, supplements); lost productivity costs (paid work and leisure time loss of the parents); descriptive analysis
Zhong et al.,[81] 2015	Mixed pain conditions	Secondary care	780	Range: 0-17	452 (57.9)	Cohort (retrospective)	Insurance records	Country and currency: United States; American Dollar Reference year: 2007 Perspective: Healthcare† Time horizon: 12 mo Discounting: not reported	Healthcare costs (pharmacy, outpatient, procedures, radiology, laboratory, emergency department, inpatient); descriptive analysis
Groenewald et al.,[19] 2015	Mixed pain conditions¶	Community	261	Age category, n (%): 6-11 y old, 699 (45.27); 12-17 y old, 845 (54.73) Range: 6-17	Not reported	Cross sectional (retrospective)	National database	Country and currency: United States; American dollar Reference year: 2013 Perspective: healthcare† Time horizon: 12 mo Discounting: NA	Healthcare costs (office visits, hospital outpatient visits, emergency department visits, inpatient stays, medications); descriptive analysis
Evans et al.,[10] 2016	Mixed pain conditions¶	Not reported	127	Age mean (SD): 15.2 (2.60) Range: 8-22	127 (74.6)	Cohort (retrospective) *§	National database	Country and currency: United States, American dollar Reference year: not reported Perspective: healthcare and societal† Time horizon: 12 mo Discounting: NA	Healthcare costs (days hospitalized inpatient, emergency department visits owing to pain, and visits with specialty physicians, primary care/pediatrician, physiotherapy, occupational therapy and psychology); lost productivity costs (paid work); descriptive analysis
Ruhe et al.,[56] 2017	Mixed pain conditions¶	Tertiary care	65	Age mean (SD): 14.3 (2.2) Range: 9-17	48 (73.8)	Cohort (retrospective) *§	Insurance records	Country and currency: Germany; Euro Reference year: 2010 Perspective: healthcare Time horizon: 12 mo Discounting: NA	Healthcare costs (physician, diagnosis, hospitalization, medications, physiotherapy, walking aids); descriptive analysis
Tian et al.,[69] 2018	Mixed pain conditions	Unclear	80	Median (IQR): 15 (13-16)	71 (88.8)	Cross sectional (retrospective)*	National database	Country and currency: United States; American dollar Reference year: not reported Perspective: healthcare† Time horizon: 84 mo Discounting: not reported	Healthcare costs (outpatient, inpatient, emergency department visits); descriptive analysis
Sommers et al.,[61] 2022	Mixed pain conditions	Tertiary care	34	Headache, age mean (SD): 16 (3.62) Musculoskeletal pain, age mean (SD) 16.07 (3.51) Range: 4-22	Headache: 16 (84) and musculoskeletaç pain: 13 (87)	Cohort (retrospective)§	Patient medical records	Country and currency: United States; American dollar Reference year: 2017 Perspective: healthcare† Time horizon: 12 mo Discounting: not reported	Healthcare costs (surgery, inpatient care, outpatient care); descriptive system
Stoopler et al.,[63] 2022	Mixed pain conditions¶	Tertiary care	168	Median (IQR): 15 (13-16)	134 (80)	Cohort (retrospective)§	Patient medical records	Country and currency: Canada; Canadian dollar	Healthcare costs (emergency department visits, administration, housekeeping,

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Table 1 (*continued*)

Author, year of publication	Study population	Context	Sample size	Age	Female n (%)	Study design (classification)	Source data	Details of cost data	Cost categories and analysis
				Range: 2-18				Reference year: not reported Perspective: healthcare† Time horizon: 12 mo Discounting: not reported	laundry, building services, security, laboratory testing, imaging testing, medications, outpatient referrals, hospital admission, specialist consultation); descriptive analysis
Law et al.,[34] 2018	Mixed pain conditions¶	Secondary care	228	Age mean (SD): 14.73 (1.65) Range: 11-17	170 (74.9)	Randomized controlled trial (retrospective)§	Questionnaire	Country and currency: United States, American dollar Reference year: 2014 Perspective: healthcare, patient/family, and societal† Time horizon: 12 mo Discounting: NA	Healthcare costs (primary care, medical specialty, surgical specialty, emergency room, inpatient admission, mental health, physiotherapy and occupation therapy, complementary and alternative medicine, diagnostic tests, community services, medications); patient/family costs (special foods, special medical equipment, transportation); lost productivity costs (paid work); descriptive analysis
Lumbi et al.,[37] 2021	Mixed pain conditions¶	Tertiary care	119	Age mean (SD): 15.3 (2.4) Range: < 21	82 (68.9)	Cohort (retrospective)§	Insurance records	Country and currency: Germany, Euro Reference year: not reported Perspective: healthcare Time horizon: 12 mo Discounting: NA	Healthcare costs (outpatient care, inpatient care, remedies and aids, physiotherapy, orthoses, medications); descriptive analysis
Ruhe et al.,[57] 2020	Mixed pain conditions¶	Tertiary care	56	Age mean (SD): 14.2 (2.2) Range: 9-17	40 (71.4)	Cohort (retrospective) *§	Insurance records	Country and currency: Germany; Euro Reference year: 2010 Perspective: healthcare, patient/family, and societal Time horizon: 12 mo Discounting: NA	Healthcare costs (outpatient medical care, aids, medications, alternative procedures, physiotherapy/massages); patient/family costs (travel expenses, co-payments for medication, travel expenses, literature, tutoring/training, nutrition/food supplements, aids, support staff for the household); lost productivity costs (paid work); descriptive analysis

* When studies did not report the study design, we assumed from characteristic of study.
† When studies did not inform the perspective, we assumed from the data provided by the study.
‡ We considered the number of families [Stang, 2004] and encounters [Gill, 2021] in the sample size.
§ Extracted data costs from baseline or before the intervention deliver.
‖ Out-of-pocket costs of patient/family related to the healthcare service.
¶ Studies that included abdominal pain in their sample.
95% CI, 95% confidence interval; AIS, adolescent idiopathic scoliosis; ANOVA, analysis of variance; IQR, interquartile range; JIA, juvenile idiopathic arthritis; NA, not applicable.

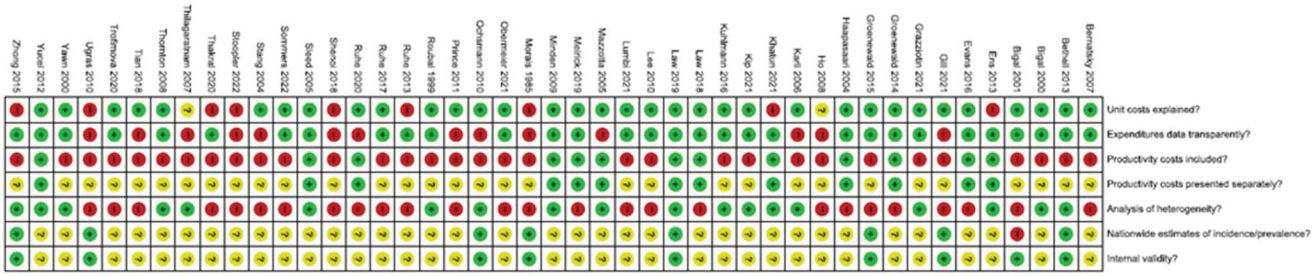

Figure 2. Details of description of the risk of bias assessment of the included studies. Fourth (productivity costs presented separately?) item of the checklist was considered "if applicable" and the studies that did not include productivity costs, then were rated as "not applicable." Sixth (nationwide estimates of incidence/prevalence?) and seventh (internal validity?) items of the checklist were also considered "if applicable," and when the study did not aim to assess the epidemiologic component, then were rated as "not applicable."

adolescents without headache/migraine (MD: $110 higher, 95% CI: 10-220). On average, this represents an annual lost productivity cost of $110 for children and adolescents with headache/migraine.

3.4.4. Societal costs

The total annual societal costs reported per patient with musculoskeletal pain ranged from $1095[9] to $69,351.[32] Overall, 9 studies[9,17,32,34,35,42,57,60,80] estimated annual societal costs: 4 in juvenile idiopathic arthritis[9,32,42,80] (range from $1095[9] to $69,351[32]), 4 in mixed pain conditions[17,34,57,60] ($10,607[57] to $18,388[34]), and one in headache/migraine[35] ($3352) (**Tables 2 and 3**).

We also could not perform a meta-analysis for societal costs because there was only one study available estimating annual incremental costs in headache/migraine.[35] However, we estimated annual incremental societal costs from this study to graphically illustrate the results. One analysis[35] included a total of 34,633 children and adolescents with and without headache/migraine (**Fig. 5C**). The results showed that there was no difference between annual incremental societal costs for children and adolescents with or without headache/migraine (MD: $760 higher, 95% CI: −10 to 1520).

4. Discussion

4.1. Main findings

This systematic review of cost-of-illness studies aimed to synthesize the economic burden of musculoskeletal pain in children and adolescents. The estimates showed that annual cost of children and adolescents with musculoskeletal pain ranged from $124 to $69,351. Children and adolescents with juvenile idiopathic arthritis and musculoskeletal pain conditions had higher annual incremental healthcare costs compared with children and adolescents without these conditions. Most of the included studies (84.4%) were conducted in high-income countries, and only 7 studies (15.6%) were conducted in middle-income countries.

4.2. Comparison with other work

There are only 2 systematic reviews that aimed to assess the economic burden of chronic conditions in children and adolescents: one for pediatric asthma in the United States from 2019[50] (8 studies, n = 3,540,967) and another for inflammatory bowel disease from 2020[8] (9 studies, n = 24,232). Authors reported higher annual incremental healthcare costs for children and adolescents with inflammatory bowel disease with costs ranging from $2099 to $8167.[8] The annual incremental healthcare costs for children and adolescents with inflammatory bowel disease seem higher compared with our findings in the meta-analysis of musculoskeletal pain (**Fig. 4**).

The 2019 systematic review of pediatric asthma[50] presented costs for healthcare resource utilization in different categories such as total costs, emergency department costs, inpatient costs (hospitalizations and long-term care), outpatient care, and intervention costs. However, it is difficult to compare both results because we could not stratify costs by resource used, and we separated all costs by categories (eg, healthcare, patient/family, societal costs). Regarding annual societal costs, the estimated cost per child with asthma ranged from $3197 to $14,146,[50] whereas the estimated cost per child with musculoskeletal pain ranged from $1095 to $69,351 per year. The 2020 systematic review on inflammatory bowel disease[8] showed that the mean annual healthcare costs range from $3246 to $24,411, whereas the mean annual healthcare costs of children and adolescents with musculoskeletal pain ranged from $143 to $41,379. We adjusted all values of these systematic reviews to the same reference year (2021) to facilitate the comparison of their results with our findings.[74]

Those 2 systematic reviews have used 2 different approaches regarding the assessment of risk of bias[8,50]: one review[50] did not assess the risk of bias of the included studies at all, and the other one[8] used an adapted version (13 of the 19 total items) of a specific economic evaluation tool (Consensus on Health Economic Criteria).[11] Despite the scarcity of instruments to assess the risk of bias in cost-of-illness studies, an alternative option would be the CHEC-List tool; however, this tool is also specifically developed to assess the methodological quality of full economic evaluations.[11,33,43] So, in our review, we decided to use a brief checklist based on the items of the CHEERS statement to provide a descriptive overview of the risk of bias of the included studies. In addition, we also provided a graphical representation of the risk of bias results (**Fig. 2**).

Because there is still no clear consensus about whether headaches should be included in the definition of musculoskeletal pain, our rationale for including headaches in the systematic review was that many primary studies included children and adolescents with headaches along with

Table 2

Costs of the studies included separated by cost category.

Author, year of publication	Study population	Healthcare costs	Patient/family costs	Lost productivity costs	Societal costs	Incremental costs
Adolescent idiopathic scoliosis						
Morais et al.,[44] 1985	AIS	Mean: $321.17 per child and $5795.31 per child to immediate treatment	Not reported	Not reported	Not reported	Not reported
Roubal et al.,[55] 1999	AIS	Mean: Boston: $7515.63 and Milwaukee: $7563.40 costs with bracing treatment Mean: $56,535.27 costs per patient (orthotics $1615.98; anesthesia: $1615.98; hospital $38,168.25; surgical $14,111.78) Annual costs to treat scoliosis without screening: $151.9 million	Not reported	Not reported	Not reported	Not reported
Yawn and Yawn,[79] 2000	AIS	Mean: $5247.14 per case identify of scoliosis and $16,792.08 per case with treatment	Not reported	Not reported	Not reported	Not reported
Thilagaratnam et al.,[67] 2007	AIS	Not reported	Not reported	Not reported	Total costs per year: $7834.74 in 1999; $12,751.83 in 2000; $3649.65 in 2001	Not reported
Lee et al.,[36] 2010	AIS	Total costs during 10-y follow-up: $4,565,453.17 (brace treatment: $2,903,841.92; surgery treatment: $377,750.39; brace and surgery: $1,283,860.86) costs per patient treated: $15,067.51	Not reported	Not reported	Not reported	Not reported
Ugras et al.,[72] 2010	AIS	Mean: $285.87 per case of children with scoliosis Total costs for children with scoliosis: $3144.73 Total costs for children with scoliosis to immediate treatment $1572.36	Not reported	Not reported	Not reported	Not reported
Meirick et al.,[41] 2019	AIS	Mean: $572.67 per patient for unnecessary referrals ($123.62 per visit orthopedic healthcare providers; $200.68 per patient for overhead costs; $248.37 per patient for radiography (cohort study)	Mean (SD): $102.20 ($72.95) or range: ($1.39 to $348.77) costs per patient for unnecessary referrals (24 participants from cross-sectional study)	Mean (SD): $137.93 ($62.98) or range ($35.71-$532.40) per patient for unnecessary referrals Mean (SD): $137.93 ($62.98) or range ($35.60 to $532.40) cost wage loss per	Mean: $812.80 per patient for unnecessary referral	Not reported

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Table 2 (*continued*)

Author, year of publication	Study population	Healthcare costs	Patient/family costs	Lost productivity costs	Societal costs	Incremental costs
				family for unnecessary referrals (24 participants from cross-sectional study)		
Headache/ migraine						
Bigal et al.,[5] 2000	Headache	*Outpatient care* Mean: $145.66 costs per 3 mo per patient or $19,082.54 total costs for all participants per 3 mo *Inpatient care* Mean: $200.38 costs per 3 mo per patient or $11,241.00 total costs for all participants per 3 mo	Not reported	Not reported	Not reported	Not reported
Bigal et al.,[4] 2001	Headache	Mean: $37.07 annual cost per visit in basic health units or $8748.10 annual total cost	Not reported	Not reported	Not reported	Not reported
Mazzotta et al.,[40] 2005	Headache	$33,516 total costs per patient	Not reported	Mean: $103 per patient per 6 mo or $2565 total costs per patient per 6 mo	Mean: $1341 per patient per 6 mo or $36,083 total costs for total sample per 6 mo	Not reported
Bethell et al.,[3] 2013	Headache	Mean (SD): $2749.91 (2075.36) annual costs per patient	Mean (SD): $509.33 (775.03) annual costs per patient	Not reported	Not reported	*Healthcare costs* Mean (SD): $2749.91 ($2074.51) for headache and $1862.60 ($2111.69) for nonheadache Mean difference (CI): $887.31 (95% CI $680.91 to $1093.69) annual incremental costs per patient with headache vs nonheadache *Patient/family costs* Mean (SD): $509.33 ($774.53) for headache and $518.01 ($977.77) for nonheadache Mean difference (CI): $-8.67 (95% CI $-87.89 to $70.54) annual incremental costs per patient with headache vs nonheadache
Stang et al.,[62] 2004	Migraine	Mean: $677.97 annual costs per child with migraine or $769.77 annual costs per family with child with migraine	Not reported	Not reported	Not reported	Unclear
Gill et al.,[14] 2021	Headache/ migraine	Mean (95% CI): $9210.53 (9071.28-9348.75) per encounter for headache/migraine in 48-mo	Not reported	Not reported	Not reported	Not reported
Karli et al.,[28] 2006	Headache/ migraine	Mean (SD): $143 ($176) or median (range): $44 ($10 to $800) annual costs per patient	Not reported	Not reported	Not reported	Not reported

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Table 2 (*continued*)

Author, year of publication	Study population	Healthcare costs	Patient/family costs	Lost productivity costs	Societal costs	Incremental costs
Law et al.,[35] 2019	Headache/ migraine	Mean (SD): $2942 (10,436) annual costs per patient	Not reported	Mean (SD): $461 (1422) annual costs per patient	Mean (SD): $3352 (10,393) annual costs per patient	*Healthcare costs* Mean (SD): $2942 ($10,439) for headache and $2255 ($22,077) for nonheadache Mean difference (CI): $687.86 (95% CI $33.12 to $1409) annual incremental costs per patient with headache vs nonheadache *Lost productivity cost* Mean (SD): $461 ($1428) for headache and $349 ($2487) for nonheadache Mean difference (CI): $112.62 (95% CI $12.15 to $212) annual incremental costs per patient with headache vs nonheadache *Societal costs* Mean (SD): $3352 ($10,392) for headache and $2595 ($21,766) for nonheadache Mean difference (CI): $758.53 (95% CI $28.71 to $1487) annual incremental costs per patient with headache vs nonheadache *Total costs in the United States* Mean (SD): $1.2 billion (21.6 trillion) estimated total incremental costs associated with childhood headache
Obermeier et al.,[46] 2021	Headache/ migraine	*Primary care physician or specialist visits* Mean: $518 annual costs for patient with headache *Outpatient hospital care* Mean: $116 annual costs for patient with headache *Inpatient care* Mean: $230 annual costs for patient with headache *Rehabilitation therapy and medical aids* $171 annual costs for patient with headache *Drugs* Mean: $133 annual costs for patient with headache *Total healthcare costs* Mean: $1239 annual total costs for patient with headache	Not reported	Not reported	Not reported	*Primary care physician or specialist visits* Mean difference (CI): $256 (95% CI $228 to $282) annual incremental costs per patient with headache vs nonheadache *Outpatient hospital care* Mean difference (CI): $54 (95% CI $36 to $70) annual incremental costs per patient with headache vs nonheadache *Inpatient care* Mean difference (CI): $125 (95% CI $91 to $37) annual incremental costs per patient with headache vs nonheadache *Rehabilitation therapy and medical aids* Mean difference (CI): $4 (95% CI $-16 to $-25) annual incremental costs per patient with headache vs nonheadache *Drugs* Mean difference (CI): $46 (95% CI $35 to $57) annual incremental costs per patient with headache vs nonheadache *Total healthcare costs*

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Table 2 (*continued*)

Author, year of publication	Study population	Healthcare costs	Patient/family costs	Lost productivity costs	Societal costs	Incremental costs
						Mean (SD): $1289 ($1581) for headache and $751 ($1203) for nonheadache Mean difference (CI): $574 (95% CI $630 to $510) annual incremental costs per patient with headache vs nonheadache
Trofimova et al.,[71] 2020	Headache/ migraine	$360,879.36 total cost of imaging for headache	Not reported	Not reported	Not reported	Not reported
Juvenile idiopathic arthritis						
Haapasaari et al.,[20] 2004	JIA	Mean (SD): $8568.74 (2825.53) costs per 3 mo per patient	Mean (SD): $19.77 (46.10) costs per 3 mo per patient (school transportation)	Mean (SD): $1179.67 (764.75) costs per 3 mo per patient	Mean (SD): $9914 (3199) costs per 3 mo per patient	Not reported
Bernatsky et al.,[2] 2007	JIA	Mean (SD): $3393 (4790) total annual costs per patient	Not reported	Not reported	Not reported	*Healthcare costs* Mean (SD): $3392 ($4786) for JIA and $1485 ($3621), mean for control Mean difference (CI): $1905 (95% CI $989 to $2826) total annual incremental costs per patient with juvenile idiopathic arthritis vs without this condition $1912 total annual incremental costs per patient with juvenile idiopathic arthritis vs asthma
Grazziotin et al.,[15] 2021	JIA	*Year 1* Mean: $9294 overall cost per patient Mean: $4017 JIA-associated costs per patient *Year 2* Mean: $16,534 overall cost per patient Mean: $7988 JIA-associated costs per patient *Year 3* Mean: $24,097 overall cost per patient Mean: $12,019 JIA-associated costs per patient *Year 4* Mean: $30,518 overall cost per patient Mean: $16,004 JIA-associated costs per patient *Year 5* Mean: $36,715 overall cost per patient Mean: $19,860 JIA-associated costs per patient *Year 6* Mean (95% CI): $48,649 ($38,400 to $46,838) overall cumulative cost per patient	Not reported	Not reported	Not reported	Not reported

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Table 2 (*continued*)

Author, year of publication	Study population	Healthcare costs	Patient/family costs	Lost productivity costs	Societal costs	Incremental costs
		Mean (95% CI): $23,495 ($20,598 to $26,392) JIA-associated costs cumulative per patient				
Thornton et al.,[68] 2008	JIA	Mean (SD): $4591 ($3044) or (range): $1116 to $1952 annual costs per patient	Not reported	Not reported	Not reported	Not reported
Khatun et al.,[29] 2021	JIA	*Outpatient visits* Median (IQR): $1.62 (1.48-1.89) annual costs per patient *Blood tests* Median (IQR): $21.03 (18.26-31.65) annual costs per patient *Imaging* Median (IQR): $10.44 (6.22-19.65) annual costs per patient *Other tests* Median (IQR): $4.22 (1.96-8.52) annual costs per patient *Medicines* Mean (SD): $83.67 (40.36) annual costs per patient *Hospitalization* Median (IQR): $42.85 (20.59-70.56) annual costs per patient	*Transport* Median (IQR): $29.15 (17.24-40.58) annual costs per patient *Accommodation* Median (IQR): $0 (0-23.06 annual costs per patient	Median (IQR): $70.28 (39.09-97.79) annual costs per patient for loss productivity	Not reported	Not reported
Kip et al.,[31] 2021	JIA	*Total costs* Mean (range): $5154 (0-227,236) annual total costs per patient *Medications* Mean: $2865 annual costs per patient *Hospital-based services* Mean: $2289 annual costs per patient *Pediatric rheumatologist visits* Mean: $861 annual costs per patient *Hospital stay* Mean: $597 annual costs per patient *Other within-hospital specialist visits* Mean: $441 annual costs per patient *Laboratory tests* Mean: $155 annual costs per patient Imaging Mean: $162 annual costs per patient *Surgeries* Mean: $62 annual costs per patient *Emergency department visits* Mean: $8 annual costs per patient	Not reported	Not reported	Not reported	Not reported
	JIA				Mean (SD): $7485	Not reported

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Table 2 (*continued*)

Author, year of publication	Study population	Healthcare costs	Patient/family costs	Lost productivity costs	Societal costs	Incremental costs
Minden et al.,[42] 2009		Mean (SD): $6697 ($10,665) or median (IQR): $2216 ($913 to $2217) total annual cost per patient	Mean (SD): $358 ($751) annual costs per patient	Mean (SD) $433 (1778) annual cost per patient	($11,121) or 95% CI: $6399 to $8692 or median (IQR): $3247 ($1241 to $8615) annual total cost per patient	
Prince et al.,[52] 2011	JIA	Mean: $5618 annual costs per patient	Not reported	Not reported	Not reported	Not reported
Yucel et al.,[80] 2012	JIA	Mean (SD): $5980 ($6149) annual costs per patient	Mean (SD): $287 ($859) annual costs per patient	Mean (SD): $124 ($393) annual costs per patient	Mean (SD): $6104 ($6267) annual costs per patient	*Healthcare costs* Mean (SD): $5980 ($6150) for JIA and $243 ($116) for FMF Mean difference (CI): $5737 (95% CI $4532 to $6944) annual incremental costs per patient with juvenile idiopathic arthritis compared with familial Mediterranean fever *Patient/family costs* Mean (SD): $287 ($859) for JIA and $32 ($60) for FMF or mean difference (CI): $255 (95% CI $86 to $424) annual incremental costs per patient with juvenile idiopathic arthritis compared with familial Mediterranean fever *Lost productivity costs* Mean (SD): $124 ($392) for JIA and $4 ($21) for FMF or mean difference (CI): $119 (95% CI $42 to $196) annual incremental costs per patient with juvenile idiopathic arthritis compared with familial Mediterranean fever *Societal costs* Mean (SD): $6104 ($6267) for JIA and $246 ($117) for FMF or mean difference (CI): $5856 (95% CI $4628 to $7085) annual incremental costs per patient with juvenile idiopathic arthritis compared with familial Mediterranean fever
Ens et al.,[9] 2013	JIA	Mean (SD): $237 ($354) and median (range): $126 ($0 to $1732) annual costs per patient	Mean (SD): $493 ($535) and median (range): $449 ($0 to $2767) annual costs per patient	Mean (SD): $367 ($734) and median (range): $0 (0 to $2681) annual costs per patient	Mean (SD): $1095 ($1265) and median (range): $639 ($0 to $5707)	Not reported

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Table 2 (*continued*)

Author, year of publication	Study population	Healthcare costs	Patient/family costs	Lost productivity costs	Societal costs	Incremental costs
					annual costs per patient	
Kuhlmann et al.,[32] 2016	JIA	Germany: $22,461 (mean); Italy: $31,907 (mean); France: $16,972 (mean); United Kingdom: $20,748 (mean); Sweden: $41,379 (mean) annual costs per patient	Germany: $21,998 (mean); Italy: $12,017 (mean); France $12,029 (mean); United Kingdom: $16,544 (mean); Sweden: $27,972 (mean) annual costs per patient	Not reported	Germany: $44,459 (mean); Italy: $43,925 (mean); France: $29,001 (mean); United Kingdom: $37,292 (mean); Sweden $69,351 (mean) annual costs per patient	Not reported
Thakral et al.,[66] 2020	JIA	*Clinic visits* Mean (SD): $337 ($316) annual costs per patient *Laboratory testing* Mean (SD): $200 ($220) annual costs per patient *Radiology* Mean (SD): $34 ($125) annual costs per patient *Procedures* Mean (SD): $46 ($124) annual costs per patient *Medications* Mean (SD): $2968 ($4631) annual costs per patient *Infusions* Mean (SD): $399 ($2243) annual costs per patient *Total costs* Mean (SD): $3984 ($7083) annual costs per patient	Not reported	Not reported	Not reported	Not reported
Shenoi et al.,[59] 2018	JIA	*Treatment related* Mean (SD): $1069 ($883) annual costs per patient/family*	*Travel* Mean (SD): $1086 ($1777) annual costs per patient/family*	Not reported	Not reported	Not reported
Mixed pain conditions						
Sleed et al.,[60] 2005	Mixed pain conditions	*Whole sample* Mean (SD): $9091 (14,055) per patient per year *Pain management* Mean (SD): $16,305 (13,844) per patient per year *Rheumatology* Mean (SD): $4936 (4068) per patient per year	*Whole sample* Mean (SD): $1849 (3363) per patient per year *Pain management* Mean (SD): $1710 (3363) per patient per year	*Whole sample* Mean (SD): $1534 (3716) per patient per year *Pain management* Mean (SD): $2915 (3716) per patient per year	*Whole sample* Mean (SD): $16,469 (20,660) per patient per year *Pain management* Mean (SD): $29,052 (19,707) per patient per year	Not reported

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Table 2 (*continued*)

Author, year of publication	Study population	Healthcare costs	Patient/family costs	Lost productivity costs	Societal costs	Incremental costs
			Rheumatology Mean (SD): $1926 (3201) per patient per year	*Rheumatology* Mean (SD): $740 (2843) per patient per year	*Rheumatology* Mean (SD): $9222 (7875) per patient per year *Total costs* $5578 million per year	
Ho et al.,[23] 2008	Mixed pain conditions†	*Outpatient visits* Mean (SD): $2182 ($2856) total costs 3 mo before multidisciplinary assessment and treatment at the pain clinic per patient *Inpatient charges* Mean (SD): $8700 ($51,774) total costs 3 mo before multidisciplinary assessment and treatment at the pain clinic per patient	Not reported	Not reported	Not reported	Not reported
Ochsmann et al.,[47] 2010	Mixed pain conditions	*Outpatient treatment* Children with 0-14 y: $323,463 total annual costs per year; children with 15-24 y: $1,182,260 total annual costs per year *Inpatient treatment* Children with 0-14 y: $338,020 total annual costs per year; children with 15-24 y: $1,158,001 total annual costs per year	Not reported	Not reported	Not reported	Not reported
Ruhe et al.,[58] 2013	Mixed pain conditions†	Not reported	Mean: $2374, 6 mo before intervention per patient	Not reported	Not reported	Not reported
Groenewald et al.,[17] 2014	Mixed pain conditions†	Total costs of $1,378,983.12 for all participants per year	Total costs of $183,589 for all participants per year	Total costs of $464,260 for all participant per year	Annual costs per patient: mean (SD): $13,603 ($18,244) or range: ($279-$144,428) or median (ITQ): $7813 ($3995-$15,231) Total costs of $2,026,831 for all participants per year National costs of $22.5 billion for adolescents with moderate to	Not reported

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Table 2 (*continued*)

Author, year of publication	Study population	Healthcare costs	Patient/family costs	Lost productivity costs	Societal costs	Incremental costs
					severe chronic pain	
Zhong et al.,[81] 2015	Mixed pain conditions	*Back disorders* Mean: $6810.42 annual costs per patient and total annual costs $11,440,683 *Migraine* Mean: $8437.42 annual costs per patient and total annual costs $12,149,360 *Chronic pain* $23,590,000 annual cost	Not reported	Not reported	Not reported	Not reported
Groenewald et al.,[19] 2015	Mixed pain conditions†	Mean (SD): $3716 (10,715) annual costs per patient	Not reported	Not reported	Not reported	*Healthcare costs* Mean (SD): $3715.63 ($10,717.50) for chronic pain and $2194.62 ($6404.37) for without chronic pain Mean difference (CI): $1521.01 (95% CI: 281.71-2779.62) annual incremental costs per patient with chronic pain vs without chronic pain *Total incremental costs in the United States* $13.4 billion (95% CI: 2.47-24.4) incremental costs among children (6-17y) with pain-related conditions compared with children without pain-related condition
Evans et al.,[10] 2016	Mixed pain conditions†	$68,442 total costs per year	Not reported	$13,502 total costs per year	Not reported	Not reported
Ruhe et al.,[56] 2017	Mixed pain conditions†	Mean (SD): $5896 ($6534) or (range) ($476-$43,394) or median (IQR): $4196 ($2029 -$7400) total annual costs per patient	Not reported	Not reported	Not reported	Not reported
Tian et al.,[69] 2018	Mixed pain conditions	Mean (SD): $2017 ($4019) costs per patient between 2008 and 2014 and $161,310 total cost for total sample between 2008 and 2014	Not reported	Not reported	Not reported	Not reported
Sommers et al.,[61] 2022	Mixed pain conditions	Headache: Mean: $2756 annual costs per patient with headache *Total costs* Mean (range): $48,959 ($33,353-$65,391) total annual costs *Emergency department* Mean (range): $20,949 ($15,619-$27,110) annual costs *Hospitalization* Mean (range): $21,573 ($12,583-$30,556) annual costs *Outpatient care with specialist*	Not reported	Not reported	Not reported	Not reported

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Table 2 (*continued*)

Author, year of publication	Study population	Healthcare costs	Patient/family costs	Lost productivity costs	Societal costs	Incremental costs
		Mean (range): $6437 ($5150-$7724) annual costs Musculoskeletal pain: Mean: $5422 annual costs per patient with musculoskeletal pain *Total costs* Mean (range): $80,419 ($62,998-$92,017) total annual costs *Surgery cost* Mean (range): $16,222 ($12,978-$19,467) annual costs *Emergency department* Mean (range): $22,181 ($13,555-$24,030) annual costs *Inpatient care* Mean (range): $32,357 ($26,964-$37,749) annual costs *Outpatient care with specialist* Mean (range): $9658 ($9496-$10,771) annual costs				
Stoopler et al.,[63] 2022	Mixed pain conditions†	*Emergency department visits* Mean (SD): $186 ($136) annual costs per patient with chronic pain *Emergency department visits* $28,250 (total) related to the pain for chronic pain *Total costs* $41,655 ($29,255 for direct costs and $12,400 for indirect costs) total cost of the emergency department consultations for chronic pain	Not reported	Not reported	Not reported	Not reported
Law et al.,[34] 2018	Mixed pain conditions†	Mean (SD): $12,409 ($15,828) annual costs per patient	Mean (SD): $1307 ($4219) annual cost per patient	Mean (SD): $4671 ($14,728) annual cost per patient	Mean (SD): $18,388 ($23,908) annual total costs per patient	Not reported
Lumbi et al.,[37] 2021	Mixed pain conditions†	*Total costs* Mean (min-max): $6091 ($87-$66,260) or median (IQR): $3784 ($2010-$6968) total annual costs per patient *Outpatient care* Mean (min-max): $2230 ($87-$11,560) or median (IQR): $1865 ($1084-$2891) annual costs per patient *Inpatient care* Mean (min-max): $3056 ($0-$57,982) or median (IQR): $435 ($0-3651) annual costs per patient *Remedies and aids*	Not reported	Not reported	Not reported	Not reported

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Table 2 (*continued*)

Author, year of publication	Study population	Healthcare costs	Patient/family costs	Lost productivity costs	Societal costs	Incremental costs
		Mean (min-max): $497 ($0-$4321) or median (IQR): $216 ($9-583) annual costs per patient *Medications* Mean (min-max): $305 ($0-$12,477) or median (IQR): $34 ($0-$88) annual costs per patient				
Ruhe et al.,[57] 2020	Mixed pain conditions†	Mean (SD): $6055 ($6899) or median (IQR range): $2494 ($2011-$7266) annual costs per patient	Mean (SD): $3771 (1662) or median (IQR): $1796 ($665-2513) annual costs per patient	Mean (SD): $1970 ($2424) or median (IQR range): $1152 (0-$2881) annual costs per patient	Mean (SD): $10,607 ($8666) or median (IQR range): $8432 ($5585-$13,765) annual costs total per patient	Not reported

* Out-of-pocket costs of patient/family related to the healthcare services.
† Studies that included abdominal pain in their sample.
95% CI, 95% confidence interval; FMF, familial Mediterranean fever; IQR, interquartile range; JIA, juvenile idiopathic arthritis; not reported, studies did not have costs in these category costs.

musculoskeletal pain.[19,21,45,51,65] We included 15 studies in this systematic review that recruited mixed musculoskeletal pain conditions, of which 11 (73.3%) included children and adolescents with headaches.[10,17,19,24,34,37,56–58,61,63] Because these studies did not separate costs by condition, we felt exclusion of those studies that include participants with headaches would result in an incomplete picture and potentially bias estimates of the economic burden of musculoskeletal pain in children and adolescents.

4.3. Strengths and limitations

The strengths of this review are the inclusion of specific and prevalent conditions in the young population, such as juvenile idiopathic arthritis,[38] scoliosis,[16,44] and headache/migraine.[30] Our searches included specific databases on the health economic area without restrictions for language and year of publication. We provided the estimates of the mean costs organized by condition, cost category, time horizon, and the World Bank Classification (**Table 3**). We defined a priori the variables (such as conditions [eg, mixed pain conditions, juvenile idiopathic arthritis], cost categories [eg, healthcare, patient/family costs], time horizon [eg, 12 months], context [eg, tertiary care], and mean cost by child), and based on that, we combined different studies to provide a range in costs estimates. Also, we conducted 2 meta-analyses for the annual incremental healthcare costs pooling data from studies with the same cost category, context, and time horizon (**Figs. 3 and 4**). The choices about synthesis are commonly contentious in systematic reviews. We acknowledge that there may be heterogeneity in the studies included in the meta-analysis because of variations in the healthcare systems, payer perspectives, and other factors. However, we chose to combine only those data that we could justify being together are transparent about our decisions. We also combined similar studies (regarding the condition, cost category, time horizon, context, and mean cost) into 2 meta-analyses (**Figs. 3 and 4**), allowing a synthesis of the results. Although we believe that our data are sufficiently homogeneous and our meta-analysis provides a valuable summary of the available evidence, we have also presented data from individual studies, so readers can choose to interpret those separately if they believe that it is more appropriate context.

This systematic review has other limitations. First, our search strategy did not include grey literature sources or public documents (eg, websites) of countries that possibly present cost data of musculoskeletal pain in children and adolescents. Second, we adjusted the protocol to include children and adolescents aged up to 24 years instead of 19 year olds. Although the World Health Organization considers adolescence as a transitory phase of life between a child's and an adult's life from age 10 to 19 year old,[78] the definition of these ages can vary according to different countries. According to the United Nations definition, children are considered younger than 14 years, whereas young is considered between 15 and 24 years.[73] Another adjustment from the protocol is related to the included abdominal pain representing less than 50% of the musculoskeletal pain sample. These deviations were registered and updated on PROSPERO, and more details are presented in Supplemental Digital Content 4 (available at http://links.lww.com/PAIN/B908). Third, we did not use a validated tool to assess the risk of bias in cost-of-illness studies because there is no available tool in the literature for

Table 3

Results of costs by cost category, condition, country classification, and cost range at 12 months.

Condition	Country classification	Cost range ($) min-max
Healthcare costs		
Juvenile idiopathic arthritis, n = 9	High-income countries (n = 8)*	$237-$41,379
	Upper-middle-income countries (n = 1)†	$5980
Mixed pain conditions, n = 8	High-income countries (n = 8)‡	$3716-$12,409
Headache/migraine, n = 4	High-income countries (n = 3)§	$1239-$2942
	Upper-middle-income countries (n = 1)†	$143
Adolescent idiopathic scoliosis, n = 1	High-income countries (n = 1)‖	$5795
Patient/family costs		
Juvenile idiopathic arthritis, n = 5	High-income countries (n = 4)¶	$358-27,972
	Upper-middle-income countries (n = 1)†	$287
Mixed pain conditions, n = 3	High-income countries (n = 3)#	$1307-3771
Headache/migraine, n = 1	High-income countries (n = 1)**	$509
Lost productivity costs		
Juvenile idiopathic arthritis, n = 3	High-income countries (n = 2)††	$367-$433
	Upper-middle-income countries (n = 1)†	$124
Mixed pain conditions, n = 3	High-income countries (n = 3)#	$1534-$4671
Headache/migraine, n = 1	High-income countries (n = 1)**	$461
Societal costs		
Juvenile idiopathic arthritis, n = 4	High-income countries (n = 3)‡‡	$1095-69,351
	Upper-middle-income countries (n = 1)†	$6104
Mixed pain conditions, n = 4	High-income countries (n = 4)§§	$10,607-18,388
Headache/migraine, n = 1	High-income countries (n = 1)**	$3352

Costs were inflated to the same reference year (2021) and converted to American dollar ($). Time horizon of all studies were 12 months. Classification by income were defined according to the World Bank.
* Canada (n = 2), Netherlands (n = 2), multinational countries (Germany, Italy, Spain, France, United Kingdom, Bulgaria, Sweden); Germany, United States and, United Kingdom.
† Turkey.
‡ United States (n = 4), Germany (n = 3) and, United Kingdom.
§ United States (n = 2) and Germany.
‖ Canada.
¶ Multinational countries (n = 2 [Germany, Italy, Spain, France, United Kingdom, Bulgaria, Sweden] and [United States, France, Germany, Netherlands, United Kingdom]), Canada and, Germany.
# United States, Germany and, United Kingdom.
** United States
†† Canada and Germany.
‡‡ Canada, multinational countries (Germany, Italy, Spain, France, United Kingdom, Bulgaria, Sweden) and, Germany.
§§ United States (n = 2), Germany and, United Kingdom.
Min, minimum; Max, maximum.

this purpose. As described before, we used a brief checklist of 7 items composed by 2 components (economic [5 items] and epidemiological [2 items]) aiming to provide a descriptive overview of the risk of bias of the included studies in our review. The checklist was based on items of the 2013 CHEERS statement and follows the methods used in previous systematic reviews.[13,27,64] We recognize that the CHEERS statement was designed to improve reporting of full economic evaluations, and its items are not supposed to be used to assess risk of bias. We also recognize that there is a new version of the CHEERS statement (2022), which contains different considerations to the 2013 statement.[26,27] At present, however, there is no brief checklist derived from the updated version. Our decision was based on the desire for consistency and comparability with prior research and using the best available tools transparently. These issues mean that caution is needed when interpreting the findings of our review due to unknown risk of bias.

Interpretation of the costs is challenging for several reasons: (1) there is no accepted cutoff as to what high or low costs in musculoskeletal pain represent for children and adolescents. Furthermore, the definition of high or low cost may differ

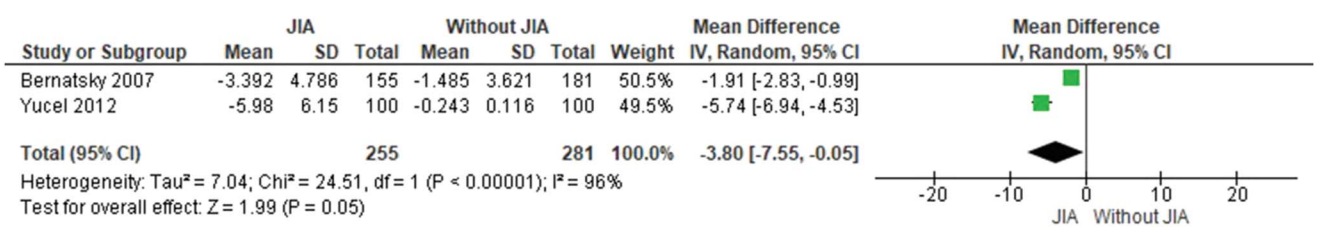

Figure 3. Forest plot of the comparison between healthcare costs ($*1000) of juvenile idiopathic arthritis vs without juvenile idiopathic arthritis from a 12-month time horizon. The studies presented the same cost category, time horizon, and context. The pooled estimate (diamond) is on side of the condition with higher costs. CI, confidence interval; JIA, juvenile idiopathic arthritis.

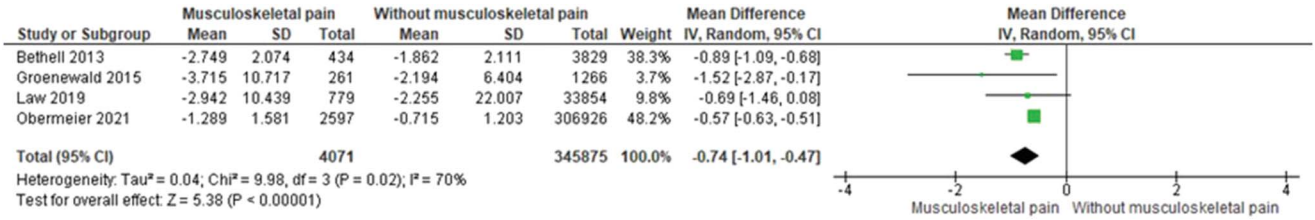

Figure 4. Forest plot of the comparison between healthcare costs ($*1000) of musculoskeletal conditions (eg, headache/migraine and mixed pain conditions) vs without musculoskeletal pain conditions from a 12-month time horizon. The pooled estimate (diamond) is on side of the condition with higher costs. The studies presented the same cost category, time horizon, and context. CI, confidence interval.

between countries; (2) the comparison of the costs between low-, middle-, and high-income countries was not possible to be done because there was only one study from upper-middle-income country in each comparison (according to the condition and cost category) (**Table 3**); and (3) in **Table 3**, we presented the costs range (minimum to maximum) from studies with the same condition, cost category, and time horizon, based on data from middle-income and high-income countries. The studies with the highest costs were conducted in secondary and tertiary care contexts, and most studies did not provide disaggregated cost estimates per context. The wide range of cost estimates in all categories (healthcare, patient/family, lost productivity, and societal costs) and according to the World Bank classifications (upper-middle and high-income countries) made the interpretation challenging. Inconsistencies in cost estimates may be because of the differences in healthcare and social security systems, geographical locations, inclusion of different types/locations of musculoskeletal pain, or variations in how studies measured costs.

4.4. Implications for practice and recommendations

Estimates of the economic burden of children and adolescents with musculoskeletal pain in different cost categories may be useful for policymakers and decision-makers. This review can inform initiatives related to the management of musculoskeletal pain for children and adolescents (eg, reducing costs by avoiding overdiagnosis and overtreatment). However, there is no evidence on the economic burden in low-income countries, and there is a little evidence available on the middle-income countries. Thus, future high-quality cost-of-illness studies on the economic burden in children and adolescents with musculoskeletal pain are needed, especially in low-income and middle-income countries. In addition, efforts in future cost-of-illness studies should be directed for the improvement of the cost assessment and description (eg, including unit costs, disaggregated information by cost categories/perspectives, reporting reference year), as well as for the development of a tool designed and validated to assess the risk of bias of the cost-of-illness studies in systematic reviews.

5. Conclusion

Overall, the results of this systematic review of cost-of-illness studies showed that the annual economic burden of musculoskeletal pain per child and adolescent ranged from $143 to $41,379 for healthcare costs, $287 to $27,972 for patient/family

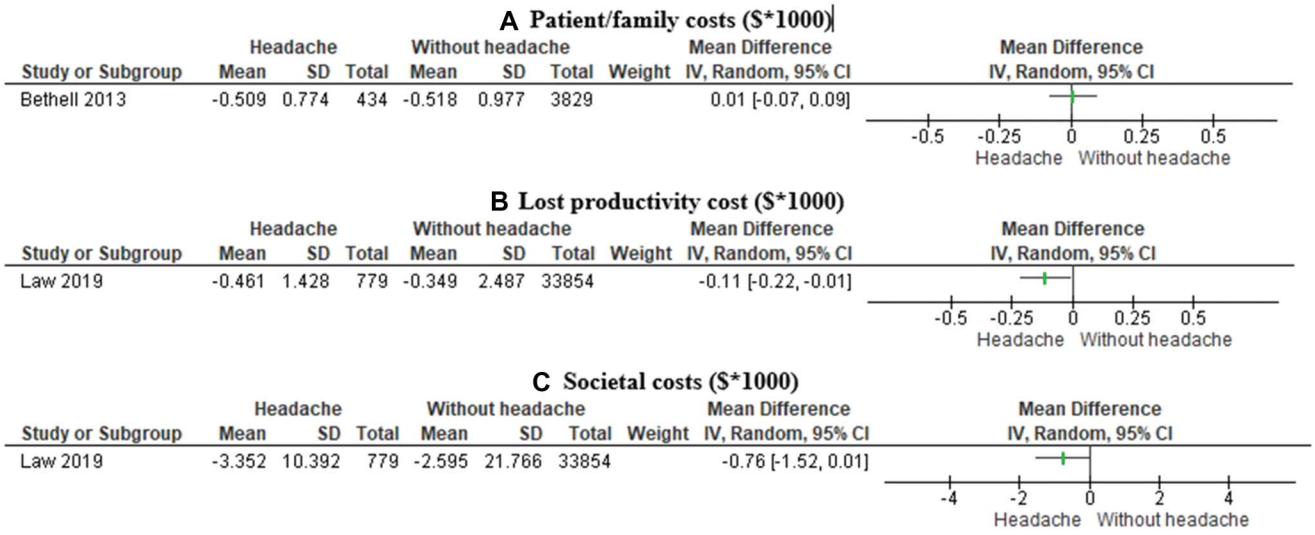

Figure 5. Forest plots of the comparison between (A) patient/family costs, (B) lost productivity costs, and (C) societal costs of headache vs without headache from a 12-month time horizon. The pooled estimate (diamond) is on side of the condition with higher costs. CI, confidence interval.

costs, $124 to $4671 for lost productivity, and $1095 to $69,351 for societal costs.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Data sharing: All data included in this study are freely available upon request to the study authors.

No ethics approval is required for this study.

Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PAIN/B908.

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