Systematic Review and Meta-Analysis

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Family history of pain and risk of musculoskeletal pain in children and adolescents: a systematic review and meta-analysis

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Abstract

Emerging evidence suggests that musculoskeletal (MSK) pain should be viewed from a biopsychosocial perspective and consider the influence of family factors. We conducted a review with meta-analysis to provide summary estimates of effect of family history of pain on childhood MSK pain and explore whether specific family pain factors influence the strength of the association (PROSPERO CRD42018090130). Included studies reported associations between family history of pain and nonspecific MSK pain in children (age <19 years). The outcome of interest was MSK pain in children. We assessed the methodological quality using a modified version of the Quality in Prognosis Studies instrument and quality of evidence for the main analyses using the GRADE criteria. After screening of 7281 titles, 6 longitudinal and 23 cross-sectional studies were included. Moderate quality evidence from 5 longitudinal studies (n = 42,131) showed that children with a family history of MSK pain had 58% increased odds of experiencing MSK pain themselves (odds ratio [OR] 1.58, 95% confidence interval 1.20-2.09). Moderate quality evidence from 18 cross-sectional studies (n = 17,274) supported this finding (OR 2.02, 95% 1.69-2.42). Subgroup analyses showed that the relationship was robust regardless of whether a child's mother, father, or sibling experienced pain. Odds were higher when both parents reported pain compared with one ([mother OR = 1.61; father OR = 1.59]; both parents OR = 2.0). Our findings show moderate quality evidence that children with a family history of pain are at higher risk of experiencing MSK pain. Understanding the mechanism by which this occurs would inform prevention and treatment efforts.

Keywords: Musculoskeletal pain, Family history, Child, Adolescent

1. Introduction

Musculoskeletal (MSK) pain is a leading cause of years lived with disability among children and adolescents.[22] The prevalence of MSK pain during adolescence is high[35,38,40] and can result in disability, school absenteeism, and interference to social and sporting activities.[14,28,38,59] Importantly, adolescents who experience persistent MSK pain are at greater risk of poor health later in life.[35] Musculoskeletal pain in adolescents is also responsible for health care utilization and parental productivity loss, placing a significant burden on families and the health care system.[23,34] Given the individual and societal impact, identifying risk factors for MSK pain in children and adolescents is a priority because it could inform strategies to reduce the costs and consequences of MSK pain.[38]

Previous studies have investigated a range of potential risk factors for the onset and persistence of MSK pain in children and adolescents.[1,28,33,35,38,67] These include physical (eg, weight and posture), psychological (eg, distress and anxiety), and social (eg, socioeconomic status) factors.[28,33,35,38] However, findings are inconsistent and links between risk factors and MSK pain are poorly understood.[33,38] Even generally accepted risk factors such as the use of backpacks and pubertal growth have failed to demonstrate strong and consistent associations with MSK pain.[66,73]

Emerging evidence suggests that MSK pain has multiple contributors and should be viewed from a biopsychosocial perspective.[6,62] Current biopsychosocial models emphasize the influence of parent and family pain factors in children and adolescents.[11,62] Aggregation of pain in families may occur because of genetic and/or environmental influences.[13,52,56,63] For example, a variety of genes involved in the central nervous system and skeletal tissue development are more common in people with MSK pain.[20,39] Environmental factors shared by family members such as lifestyle, including physical activity and diet, have also been associated with MSK pain.[9,15,16,18,65] Furthermore, parental behavior such as maternal catastrophizing seems to influence children's pain and disability.[27,53]

Two reviews have examined the relationship between parental pain and the health of their offspring, at any age.[31,69] These reviews found that offspring of parents with chronic pain are more likely to have health issues, including poorer psychological and

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pain outcomes. Neither of the reviews quantitatively evaluated the association between family history of pain and MSK pain in offspring, which means the strength of the observed associations is unclear. The importance of family pain factors (eg, family member with pain and type of pain) in MSK pain was also not explored in these reviews. Understanding the influence of family history of pain could guide strategies to prevent MSK pain in children and inform targets for interventions. The aim of this review was to evaluate whether children and adolescents with a family history of pain are more likely to experience MSK pain, without or with consequences (disability and care seeking), than those without. Furthermore, we aimed to explore whether family pain factors (eg, which family member report pain and the type of pain they report) influence the strength of the association.

2. Method

2.1. Design

We conducted a systematic review in accordance with the Meta-analysis Of Observational Studies in Epidemiology checklist[64] and registered the protocol a priori on the International Prospective Register for Systematic Reviews (PROSPERO) (CRD42018090130).

2.2. Search strategy

The search strategy was designed with the assistance of a research librarian and conducted in 4 electronic databases: EMBASE, MEDLINE, CINAHL, and Web of Science. We combined 4 set of descriptors to capture: (1) pain (eg, musculoskeletal pain), (2) children and adolescents (eg, pediatrics and child), (3) family (eg, mother, father, and sibling), and (4) study design (cross-sectional and cohort) (Appendix table 1, available at http://links.lww.com/PAIN/A836). We considered all records from the inception to April 2019; searches were not restricted by language. Hand-searching reference lists of eligible studies supplemented database searches.

2.3. Inclusion criteria

We included longitudinal and cross-sectional observational studies that reported associations between a family history of pain [defined as pain experienced by an individual's parent(s) or sibling(s)] and MSK pain in children and/or adolescents (mean age <19 years at baseline). For longitudinal studies, follow-up was not restricted to the period of childhood. The outcome of interest was report of MSK pain in any location (including multisite pain) without or with consequences (disability and care seeking due to MSK pain). For simplicity, we refer to children and adolescents as children.

2.4. Exclusion criteria

We excluded studies that included children with pain caused by a serious or specific underlying disease such as inflammatory rheumatic conditions (eg, juvenile idiopathic arthritis), cancer, visceral pain (ie, abdominal pain), or neurological pain. We also excluded studies that investigated acute pain following medical procedures, such as vaccinations or surgery, and studies where the full text was not available.

2.5. Study selection

After removal of duplicates, identified records were screened independently by 2 reviewers using Covidence (Cochrane, 2018) in 2 stages; titles and abstracts followed by full-text articles. Disagreement was resolved by discussion or consultation with a third reviewer.

2.6. Data extraction

Data were extracted by one reviewer and cross-checked by another reviewer, including country, design, sample characteristics, pain definition, sample size, and magnitude of association (odds ratio [OR], 95% confidence intervals [CIs], and *P* values). For twin studies, when the OR was not reported, we extracted a measure that reflected the concordance for pain in twin pair (eg, case-wise concordance). We extracted data from unadjusted and adjusted analyses, and listed confounders included in the adjusted models. When measures of associations or CIs were unavailable, we calculated them using methods recommended in the Cochrane Handbook.[12] If required, the authors were contacted to provide additional data.

2.7. Quality assessment of individual studies

We assessed the methodological quality of observational studies using the Quality in Prognosis Studies (QUIPS) tool,[26] modified for risk factors instead of prognostic factors.[73] The tool included the following domains: (1) study participation; (2) study attrition; (3) measurement of exposure; (4) measurement of and controlling for confounders; (5) measurement of outcomes; and (6) analysis and reporting. Each domain was categorised low or high risk of bias based on explicit criteria (Appendix table 2, available at http://links.lww.com/PAIN/A836). Overall risk of bias was considered "low" if 4 or more domains (including study confounding) were rated as low risk of bias; otherwise, the overall risk of bias was considered "high." Two reviewers assessed the risk of bias independently; discrepancies were resolved by discussion.

2.8. Data synthesis and analysis

We pooled findings when 2 or more studies were considered sufficiently homogenous. When studies provided more than one estimate for different family members (eg, mother and father) or pain locations (eg, shoulder and spine), we included the most commonly reported estimate in the main meta-analysis. Adjusted estimates were preferred for the main analysis. We planned subgroup analyses to explore the influence of family member (mother only, father only, both parents, or sibling), parental or sibling pain type (consequential pain including treated, disabling, or care seeking), parental pain location, and child pain location. The I^2 statistic[30] was used to assess heterogeneity, and it was incorporated into assessment of evidence quality. We assessed and pooled longitudinal and cross-sectional studies separately. Because of the methodological advantages of longitudinal studies over cross-sectional studies, we based our conclusions primarily on longitudinal data. Meta-analyses were conducted with Comprehensive Meta-analysis software (Version 3) using the random-effect model to estimate ORs and 95% CIs.

2.9. Quality of evidence

Two reviewers independently used a modified version of the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) criteria to assess the quality of evidence for the main analyses.[32] Modifications made the criteria relevant to observational studies examining risk factors. Evidence was downgraded from high by one level based on: (1) phase of investigation (if cross-sectional); (2) study limitations (>25% of

participants from studies with high risk of bias); (3) inconsistency of results ($I^2 > 50\%$); (4) imprecision (sample size < 400 participants for each outcome); (5) indirectness (eg, inclusion of different populations and interventions); and (6) publication bias (funnel plot and the Egger test if ≥10 studies[61]). The quality of evidence could be upgraded if there was moderate or larger (OR > 2.5) effect size, or evidence of exposure–response gradient (eg, based on the number of family members reporting pain or number of pain sites).[32]

3. Results

From 7281 unique citations, we identified 72 full-text articles after screening titles and abstracts, and include 28[2–5,8,10,17,19,24,25,29,37,41,42,47–49,51,54,55,57,58,60,67,68,71,72,74] (**Fig. 1**). Studies reported data from 14 countries. Twenty-six were in English and 1 in Spanish.[51] The age of children ranged from 2 to 19 years at baseline, and only 2 studies investigated children younger than 6 years.[19,37]

We included 6 longitudinal (n = 42,226 participants, **Table 1**)[2,25,37,42,58,68] and 23 cross-sectional studies (n = 48,119, **Table 2**).[2–5,8,10,17,19,24,29,41,47–49,51,54,55,57,60,67,71,72,74] Five longitudinal studies had low risk of bias (Appendix Table 3, available at http://links.lww.com/PAIN/A836). The most common sources of bias related to study attrition (2 studies), exposure measurement (2 studies), and statistical analysis and reporting (2 studies). Most cross-sectional studies (16/23 studies) were rated low risk of bias. The most common sources of bias in cross-sectional studies were lack of control for confounders (9 studies), followed by poor definition of exposure (6 studies) and outcome (6 studies) measurements.

Individual studies reported family history of pain based on parental pain,[3,4,8,24,37,41,42,49,51,54,55,57,58,60,68,71,72,74] either parent or sibling pain,[2,5,17,19,25,48,67] or sibling pain.[4,10,29,47,51,54] Back pain was the type of pain most frequently reported by family members, and pain was only sometimes linked to disability,[54] care seeking,[58] or treatment.[2–4,67] The most common type of pain investigated in children was lifetime experience of back pain.[5,8,17,25,37,41,42,48,49,51,55,60,68,71,72,74] Most studies matched type (eg, any, disabling) and location of pain in children to their family members (eg, parents' back pain and child back pain) (**Tables 1 and 2**).

Assessment of the overall quality of the evidence for each analysis can be found in Appendix Table 4 (available at http://links.lww.com/PAIN/A836). We found moderate quality evidence from longitudinal studies that children with a parent or sibling reporting a history of MSK pain had 58% greater odds of reporting MSK pain (OR 1.58, 95% CI 1.20-2.09, 5 studies, n = 42,131

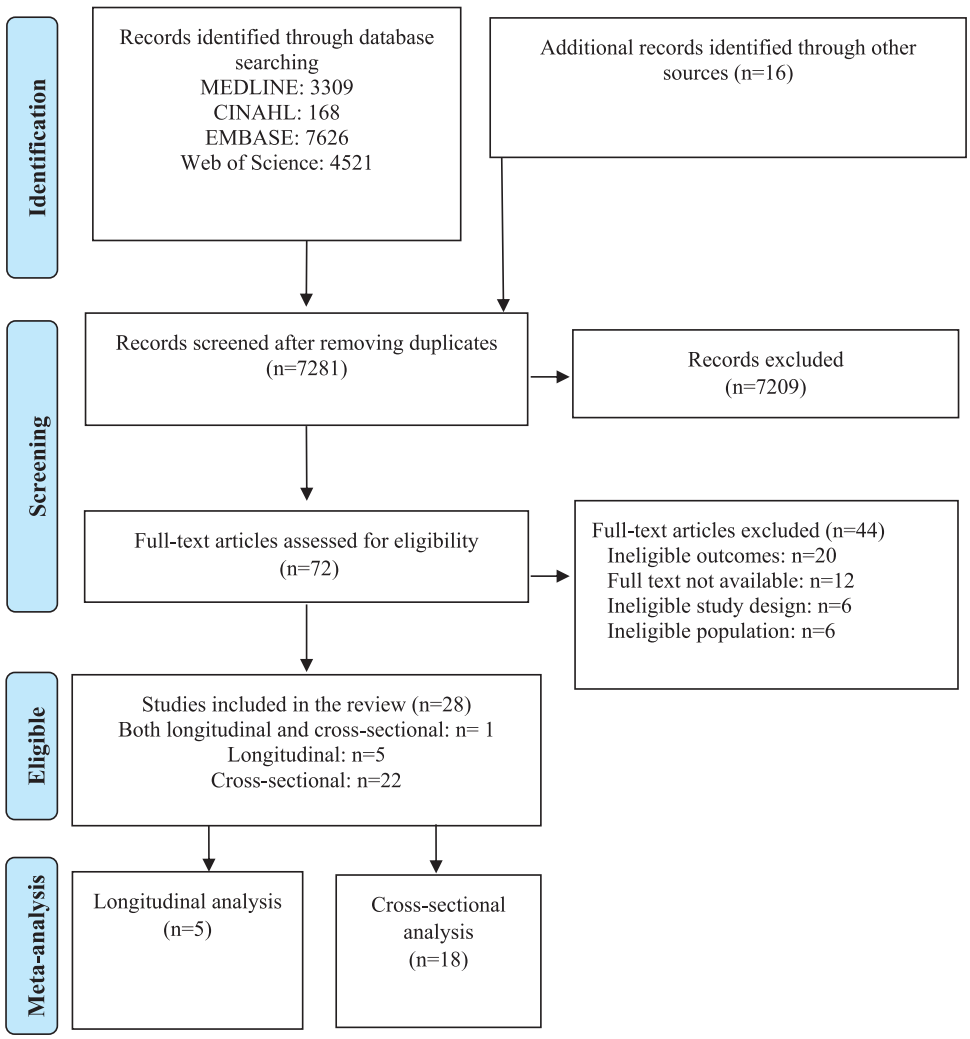

Figure 1. Flow chart of the included studies in this review.

Table 1

Characteristics of longitudinal studies.

Study (country)	Study population		Pain type in children*	Family history*	Unadjusted associations†	Adjusted associations†	Risk of bias
	Baseline	Follow-up					
Harreby et al.[25] (Denmark)	Age: 14 y n = 640 Female: 52%	FU: 25 y Age: 38 y n = 481 (75%) Female: 54%	LBP	Parent or sibling back disease (eg, disk degeneration)	**$P < 0.001$**	**2.8 (1.8-4.4)**	Low
Szpalski et al.[68] (Belgium)	Age: 9-11 y n = 287 Female: 51%	FU: 2 y Age: 11-13 y n = 287 (100%) Female: 51%	Persistent LBP (baseline and FU)	Parental LBP	**2.1 (1.1-4.0)**	$P > 0.05$	Low
Balague et al.[2] (Switzerland)	Age: 13-14 y n = 95 Female: 0%	FU: 2 y Age: 15-16 y n = 85 (90%) Female: 0%	Consequential LBP (baseline and FU)	Treated LBP in parent or sibling	**$P < 0.05$**	NR	High
Shraim et al.[58] (United Kingdom)‡	Age: NA n = NA Female: NR	Age 2-16 y n = 12,662 Female: NR	Care seeking: MSK pain Extremities' pain Back pain	Maternal: Care-seeking MSK symptoms Extremities' pain Back pain	**1.5 (1.2-1.9)** **2.3 (1.2-4.5)** 1.7 (0.8-3.5)	**1.4 (1.2-1.8)** **2.1 (1.1-4.2)** 1.4 (0.7-3.1)	Low
Kroner-Herwig et al.[42] (Germany)	Age: 7-14 y n = 5542 Female: NR	FU: 12 y Age: 19-27 y n = 1488 (?) Female: 56.5%	LBP (past 6 mo)	Parental back pain	**1.3 (1.1-1.7)**	**1.3 (1.1-1.7)**	Low
Kamper 2017 (Denmark)	Age: 6-18 mo n = NR Female: NR	FU: 10 y Age: 11 y n = 23,000 Female: 51%	LBP Multisite spinal pain	Maternal MSK symptoms	NR NR	**1.3 (1.1-1.5)** 1.0 (0.8-1.2)	Low

* Lifetime prevalence of pain unless indicated.

† Results presented as odds ratio and 95% confidence interval, unless described otherwise.

‡ Case–control study.

FU, follow-up; LBP, low back pain; MSK, musculoskeletal; n, number of participants; NR, not reported.

Significant results presented in bold.

participants) (**Fig. 2**). The pooled-effect estimate for adjusted results (OR 1.53, 95% CI 1.13-2.06, 4 studies, n = 41,844) was similar to the overall estimate.

We found moderate quality evidence from cross-sectional studies that children with a family history of MSK pain had greater odds of reporting MSK pain (OR 2.02, 95% 1.69-2.42, 18 studies, n = 17,274) (**Fig. 3**). The pooled-effect estimate for adjusted results (OR 2.04, 95% CI 1.64-2.54, 12 studies, n = 13,998) was similar to the overall estimate.

We performed subgroup analyses based on family member with pain (**Fig. 3**; Appendix Table 5, available at http://links.lww.com/PAIN/A836). We found very low quality evidence that children with a maternal history of MSK pain had 61% greater odds of reporting MSK pain (OR 1.61, 95% CI 1.33-1.93, 5 studies, n = 7515); very low quality evidence that children with a paternal history of MSK pain had 59% greater odds of reporting MSK pain (OR 1.59, 95% CI 1.26-2.00, 4 studies, n = 5059); moderate quality evidence that children with a parental history of MSK pain had 84% greater odds of reporting MSK pain (OR 1.84, 95% CI 1.53-2.20, 14 studies, n = 13,622); very low quality evidence that children with 2 parents who reported pain had 95% greater odds of reporting MSK pain (OR 1.95, 95% CI 1.56-2.44, 2 studies, n = 4450); very low quality evidence that children with a sibling with a history of MSK pain had 99% greater odds of reporting MSK pain (OR 1.99, 95% CI 1.48-2.66, 2 studies, n = 1449); and moderate quality evidence that children with any family history of MSK pain (parent and/or sibling) had 2.61 times the odds of reporting MSK pain (OR 2.61, 95% CI 1.76-3.88, 5 studies, n = 3652).

In subgroup analyses based on type of pain reported by a family member (**Fig. 3**; Appendix Table 5, available at http://links.lww.com/PAIN/A836), we found low quality evidence that when a parent or sibling had a history of consequential MSK pain (treated, disabling, or care seeking), children had 94% greater odds of MSK pain (OR 1.94, 95% CI 1.35-2.80, 5 studies, n = 3748).

In subgroup analyses based on location of pain reported by a family member (**Fig. 3**; Appendix Table 5, available at http://links.lww.com/PAIN/A836), we found moderate quality evidence that children whose parent or sibling had a history of spinal pain had 98% greater odds of spinal pain themselves (OR 1.98, 95% CI 1.64-2.40, 16 studies, n = 14,432).

4. Discussion

There is moderate quality evidence from longitudinal studies that children and adolescents with a family history of MSK pain have 58% higher odds of experiencing MSK pain themselves than children from families without history of pain. Cross-sectional analyses show somewhat stronger associations but are consistent with longitudinal studies. Subgroup analyses showed greater odds of MSK pain in children, with children had maternal (53%), paternal (59%), or sibling (99%) history of pain. There seems to be increase in odds of a child having pain when both parents reported pain [one parent (mother or father) OR = 1.6; both parents OR = 2.0]. Furthermore, higher odds were also found in children when parent or sibling had a history of consequential MSK pain (treated, disabling, or care seeking) (OR = 1.94).

Table 2

Characteristics of cross-sectional studies.

Study (country)	Study population	Pain type in children*	Family history*	Unadjusted associations†	Adjusted associations†	Risk of bias
Any family member						
Bejia et al.[5] (Tunisia)	Age: 11-19 y n = 622 Female: 55%	LBP Chronic LBP	LBP§	**3.0 (2.1-4.3)‡** ***P* < 0.01**	**3.8 (2.9-5.9)** *P* > 0.05	Low
Evans et al.[19] (Australia)	Age: 4-6 y n = 743 Female: 53%	Growing pains	Growing pains§	70% of children with growing pain had a family Hx of growing pain	NR	High
Balague et al.[2] (Switzerland)	Age: 13-14 y n = 95 Female: 0%	Consequential LBP§	Treated LBP§	**3.4 (1.4-8.3)‡**	**3.6 (1.3-10.2)**	High
Dianat et al.[17] (Iran)	Age: 11-14 y n = 1611 Female: 53%	LBP (1-month prevalence)	LBP (point prevalence)§‖	**1.8 (1.5-2.3)**	**1.8 (1.4-2.4)**	Low
Szita et al.[67] (Hungary)	Age: 7-16 y n = 952 Female: 47%	Spinal pain for days	Spinal pain§‖	**2.1 (1.4-3.1)**	**1.9 (1.3-2.8)**	Low
Noormohammadpour et al.[48] (Iran)	Age: 13-19 y n = 372 Female: 100%	LBP Chronic LBP LBP (1-month prevalence)	LBP§	NR NR NR	**3.5 (1.68-7.52)** **2.5 (1.24-4.99)** **2.8 (1.52-5.23)**	Low
Parents						
Salminen[54] (Finland)	Age: 11-17 y n = 370 Female: 52%	Disabling nonspecific LBP	Maternal disabling LBP Paternal disabling LBP	**2.9 (1.6-5.2)‡** **2.4 (1.3-4.5)‡**	NR NR	High
Balague et al.[3] (Switzerland)	Age: 8-16 y n = 1716 Female: 51%	LBP	Parental treated LBP	**1.9 (1.4-2.5)**	**2.1 (1.6-2.8)**	Low
Balague et al.[4] (Switzerland)	Age: 12-17 y n = 615 Female: 53%	LBP	Parental treated LBP	1.1 (0.8-1.6)‡	*P* > 0.05	Low
Gunzburg et al.[24] (Belgium)	Age: 9 y n = 392 Female: 52%	LBP	Parental LBP	**2.0 (1.3-3.0)‡**	NR	High
Borge et al.[8] (Norway)	Age: 13-15 y n = 229 Female: NR	MSK pain (past 2 mo) LBP Neck and shoulder pain Arm and leg pain	Maternal LBP, neck and shoulder pain, and arm & leg pain Paternal LBP, neck and shoulder pain, and arm & leg pain	1.5 (0.7-3.3) **2.8 (1.0-8.0)** 0.9 (0.4-1.0) 1.9 (0.7-4.9) **3.1 (1.2-8.3)** 0.9 (0.4-1.0)	NR NR	High
Sjölie[60] (Norway)	Age: 14-16 y n = 88 Female: 43%	LBP LBP (>1 month last year)	Parental treated LBP	NR NR	1.4 (0.5-4.1) NR	Low
Kovacs et al.[41] (Spain)	Age: 13-15 y N = 7361 Female: 53%	Back pain	Parental back pain	*P* > 0.05	NR	High
Saunders et al.[55] (United States)	Age: 11-17 y N = 2466 Female: 51.3%	Persistent LBP (in the past 6 mo)	Persistent maternal pain (past 6 mo)	***P* < 0.001**	**1.5 (1.0-2.1)**	Low
O'Sullivan et al.[49] (Australia)	Mean age: 14 y n = 1608 Female: 51%	LBP Chronic LBP LBP Chronic LBP LBP	Maternal LBP Paternal LBP Both parents LBP	**1.4 (1.1-1.7)** **1.6 (1.1-2.4)** **1.3 (1.0-1.7)** 1.6 (1.0-2.5) **1.6 (1.1-2.5)**	**1.4 (1.1-1.7)** **1.6 (1.1-2.4)** NR NR NR	High
Pires et al.[51] (Spain)	Age: 10-11 y n = 834 Girls: 49%	LBP	LBP	**2.9 (2.0-4.2)**	NR	High
Yao et al.[74] (China)	Age: 10-18 y n = 1214 Female: 60.3%	LBP (past 3 mo)	Parental LBP	***P* < 0.001**	**2.6 (1.9-3.6)**	Low
Shan et al.[57] (China)	Age: 15-19 y n = 2842 Female: 52%	Neck and shoulder pain	Neck and shoulder pain: Maternal Paternal Both parents	 **1.7 (1.4-2.0)** **1.9 (1.3-2.1)** **2.4 (1.9-3.0)**	 **1.7 (1.4-2.1)** **1.7 (1.3-2.1)** **2.1 (1.7-2.6)**	High

(*continued on next page*)

Table 2 (*continued*)

Study (country)	Study population	Pain type in children*	Family history*	Unadjusted associations†	Adjusted associations†	Risk of bias
Wirth et al.[72] (Switzerland)	Age: 6-16 y n = 836 Female: 53%	Spinal pain LBP Thoracic spine pain Neck pain	Parental spinal pain LBP Thoracic spine pain Neck pain	**2.4 (1.2-4.7)** 3.0 (0.9-9.6) 2.5 (0.7-9.2) 3.3 (0.9-11.8)	NR NR NR NR	Low
Wirth and Humphreys[71] (Switzerland)	Age: 10-16 y n = 412 Female: 51.9%	Spinal pain	LBP	1.46 (NR)	**1.46 (0.4-4.9)**	Low
Sibling						
Salminen[54] (Finland)	Age: 11-17 y n = 370 Female: 52%	Disabling nonspecific LBP	LBP	$P > 0.05$	NR	High
Balague et al.[4] (Switzerland)	Age: 12-17 y n = 615 Female: 53%	LBP	LBP	**1.7 (1.2-2.5)**‡	$P > 0.05$	Low
Pires et al.[51] (Spain)	Age: 10-11 y n = 834 Female: 49%	LBP	LBP	**2. (2.0-2.02)**	NR	High
Twin						
Mikkelsson et al.[47] (Finland)	Age: 11 y n = 3578 MZ pairs: 583 DZ pairs: 1789	Widespread MSK pain	Co-twin widespread MSK pain	Case-wise concordance Male MZ: 0.27 Male DZ: 0.26 Female MZ: 0.39 Female DZ: 0.35 OSDZ: 0.25	NR	Low
Champion et al.[10] (Australia)	Age: 3-16 y n = 196 MZ pairs: 34 DZ pairs: 54	Growing pains	Co-twin growing pains	Case-wise concordance: MZ: 0.85 DZ: 0.36	NR	Low
Hestbaek et al.[29] (Denmark)	Age 12-18 y n = 16,574 MZ pairs: 3818 DZ pairs: 4469	LBP	Co-twin LBP	**3.35 (3.06-3.67)** MZ vs DZ **2.76 (2.30-3.32)**	NR NR	Low

* Lifetime prevalence unless indicated.
† Results presented as odds ratio and 95% confidence interval, unless described.
‡ Calculated from data presented in the original article.
§ Family pain history from parent and/or sibling.
‖ Family pain history from second-degree relative (grandparent and aunt).
Significant results in bold.
CI, confidence interval; DZ, dizygotic; LBP, low back pain; MSK, musculoskeletal; MZ, monozygotic; n, number of participants; NR, not reported; OR, odds ratio; OSDZ, opposite sex dizygotic.

Current evidence suggests that MSK pain clusters in families, and considering MSK pain in the context family influences may help to understand and address MSK pain in children and adolescents.

Although this is the first meta-analysis examining associations of family history of pain and MSK pain in children, our findings are consistent with other studies in the field.[7,9,31,43–45,69,75] We found that maternal (OR 1.6) and paternal (OR 1.6) pain were associated with greater odds of childhood MSK pain. These associations are comparable to another study, which found that offspring (at any age) whose mother (OR 1.6) or father (OR 1.3) had chronic pain were more likely to report pain.[31] Similar associations have also been reported in adult offspring with MSK pain, indicating that family history of pain is associated with experience of MSK pain across the lifespan. For example, parental chronic MSK pain is associated with increased occurrence of chronic MSK pain in adult offspring,[43–45] with stronger associations observed when both parents have MSK pain.[44,75] Furthermore, adults with a sibling with MSK pain have greater odds of experiencing MSK pain.[75]

Our review represents a significant advance on the understanding of risk factors for childhood pain by providing quantitative estimates specific to MSK pain from a total of over 40,000 children and adolescents. We used a broad search strategy and focused on population-based studies that are more representative of the general population, including 27 studies from 14 countries. We assessed the overall quality of the evidence to help readers interpret our findings. We conducted subgroup analyses to investigate whether the risk of MSK pain in children is influenced by the member or number of family members with pain, and the type and location of pain reported by family members.

This review has limitations. As only 5 studies reported longitudinal estimates, we could not accurately assess publication bias. For cross-sectional studies, we cannot exclude the possibility of a child's pain influencing pain in parents or siblings (reverse causation).[21,46] The evidence quality from subgroup analyses (eg, mother, father, and sibling) is mostly low or very low, suggesting that further research may change these estimates. There was variability in definitions of the exposure (ie, different types of pain across different family members) and outcome measurements (ie, location and consequences of pain). For example, although we did not mention MSK pain associated with care seeking as an outcome in our original protocol, we included one study[58] that investigated MSK pain associated with care seeking in children because we believe it represents MSK pain with consequence. Moreover, detailed information about the type

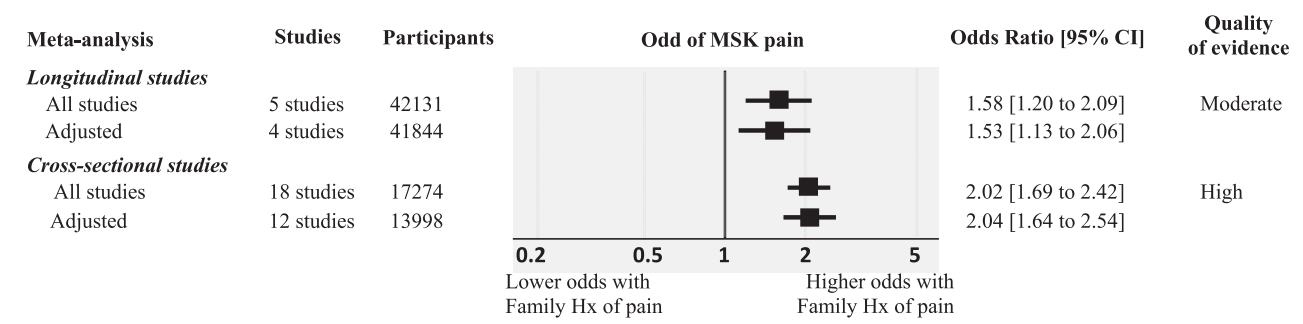

Figure 2. Meta-analysis investigating a family history of MSK pain as a risk factor for children and adolescents developing MSK pain. The squares indicate the odds ratios and 95% confidence intervals of random-effect meta-analysis; the vertical line shows the line of no effect (OR = 1). CI, confidence interval; MSK, musculoskeletal.

of MSK pain was often unclear in longitudinal studies (eg, first onset or persistent). Confounders included in the adjusted models varied substantially across studies (Appendix Table 6, available at http://links.lww.com/PAIN/A836). This is likely due to poorly developed theories linking the exposure and outcome.

Several questions could not be answered by our review. First, despite adjustment, estimates from multivariable analyses in observational studies may still be biased by residual confounding. This uncertainty could be reduced in future studies by implementing sensitivity analyses that estimate the strength of residual confounding that would invalidate the observed associations.[70] Furthermore, we do not know whether associations of different strength would be found in samples collected from clinical settings (eg, pediatrician or physiotherapy visits). The mechanisms by which family pain history affects childhood pain are also unclear. These mechanisms likely involve complex biological, social, and behavioural interactions.[50,63] Understanding these mechanisms could identify targets for prevention. Determining which family pain characteristics are most relevant and how these factors can be best measured remains a challenge. Some family factors are nonmodifiable (eg, genetic predisposition) or unlikely to change rapidly (ie, family income), whereas others are possibly modifiable (eg, family function, parental behaviour, and lifestyle). Nevertheless, targeting modifiable family factors or discovering modifiable mechanisms could be a useful approach to reduce the risk of MSK pain among children.[43]

Obtaining information on family history of MSK pain may be a simple approach to identifying children at risk of MSK pain. At this point, we do not know whether intervening at the family level will prevent MSK pain in children. Similarly, based on this review,

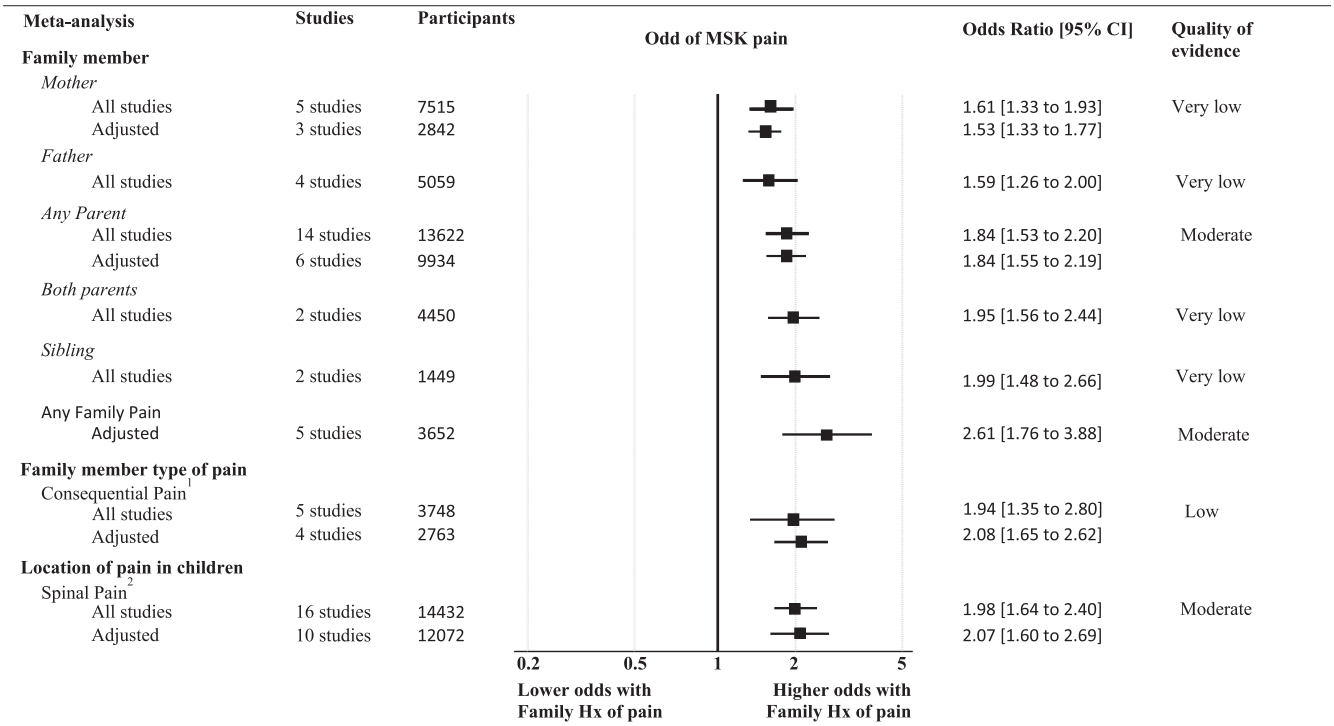

Figure 3. Meta-analysis for subgroup analysis investigating a family history of MSK pain as a risk factor for children and adolescents developing MSK pain. The squares indicate the odds ratios and 95% confidence intervals of random-effect meta-analysis; the vertical line shows the line of no effect (OR = 1). [1]Consequential pain in a family member including treated and disabling pain, or care seeking due to MSK pain; [2]spinal pain includes lower back, thoracic, and/or neck areas. CI, confidence interval; MSK, musculoskeletal.

we cannot confidently recommend that treatment of children with pain should involve parents and siblings. However, our results confirm the relationship between child and adolescent MSK pain experience and family pain history and mark this area as worthy of further research. This is particularly the case in the current context of poor understanding of childhood MSK pain[36] and the significant global burden of the condition.[34]

Conflict of interest statement

The authors have no conflicts of interest to declare.

Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PAIN/A836.

Supplemental video content

A video abstract associated with this article can be found at http://links.lww.com/PAIN/A837.

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