

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 MSK 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 non-specific 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; six longitudinal and 23 cross-sectional studies were included. Moderate quality evidence from five longitudinal studies (n=42131) showed that children with family history of MSK pain had 58% increased odds of experiencing MSK pain themselves (OR 1.58, 95% CI 1.20 to 2.09). Moderate quality evidence from 18 cross-sectional studies (n=17274) supported this finding (OR 2.02, 95% 1.69 to 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 to 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.

INTRODUCTION

Musculoskeletal (MSK) pain is a leading cause of years lived with disability among children and adolescents [23]. The prevalence of MSK pain during adolescence is high [36; 39; 41] and can result in disability, school absenteeism, and interference to social and sporting activities [15; 29; 39; 59]. Importantly, adolescents who experience persistent MSK pain are at greater risk of poor health later in life [36]. MSK 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 [24; 35]. Given the individual and societal impact, identifying risk factors for MSK pain in children and adolescents is a priority as it could inform strategies to reduce the costs and consequences of MSK pain [39].

Previous studies have investigated a range of potential risk factors for the onset and persistence of MSK pain in children and adolescents [1; 29; 34; 36; 39; 67]. These include physical (e.g. weight, posture), psychological (e.g. distress, anxiety) and social (e.g. socioeconomic status) factors [29; 34; 36; 39]. However, findings are inconsistent and links between risk factors and MSK pain are poorly understood [34; 39]. 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 emphasise the influence of parent and family factors pain in children and adolescents [12; 62]. Aggregation of pain in families may occur due to genetic and/or environmental influences [14; 52; 56; 63]. For example, a variety of genes involved in central nervous system and skeletal tissue development are more common in people with MSK pain [21; 40]. Environmental factors shared by family members such as lifestyle, including physical activity and diet, have also been associated with MSK pain [10; 16; 17; 19; 65]. Further, parental behavior such as maternal catastrophizing seems to influence children's pain and disability [28; 53].

Two reviews have examined the relationship between parental pain and the health of their offspring, at any age [32; 69]. These reviews found that offspring of parents with chronic pain are more likely to have health issues, including poorer psychological and 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 (e.g. 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. Further, we aimed to explore whether family pain factors (e.g. which family member report pain, and the type of pain they report) influence the strength of the association.

METHOD

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).

Search strategy: The search strategy was designed with the assistance of a research librarian and conducted in four electronic databases: EMBASE, Medline, CINAHL, and Web of Science. We combined four set of descriptors to capture: 1. pain (e.g. musculoskeletal pain), 2. children and adolescents (e.g. pediatrics, child), 3. family (e.g. mother, father, sibling) and 4. study design (cross-sectional, cohort) (Appendix table 1). 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.

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 were report of MSK pain in any location (including multi-site pain) without or with consequences (disability and care seeking due to MSK pain). For simplicity, we refer to children and adolescents as children.

Exclusion criteria: We excluded studies that included children with pain caused by a serious or specific underlying disease such as inflammatory rheumatic conditions (e.g. juvenile idiopathic arthritis), cancer, visceral pain (i.e. 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.

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

Data extraction: Data were extracted by one reviewer and cross-checked by another reviewer, including: country, design, sample characteristics, pain definition, sample size, magnitude of

association [odds ratio (OR) and 95% confidence intervals (CI) 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 (e.g. 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 [13]. If required, authors were contacted to provide additional data.

Quality assessment of individual studies: We assessed the methodological quality of observational studies using the Quality in Prognosis Studies (QUIPS) tool [27], 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; 6) analysis and reporting. Each domain was categorised low or high risk of bias based on explicit criteria (Appendix table 2). Overall risk of bias was considered ‘low’ if four 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.

Data synthesis and analysis: We pooled findings when two or more studies were considered sufficiently homogenous. When studies provided more than one estimate for different family members (e.g. mother and father) or pain locations (e.g. 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, 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 [31] 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 random effects model to estimate ORs and 95% CIs.

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 [33]. 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 (e.g. inclusion of different populations and interventions); and 6.publication bias [funnel plot and Egger's 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 (e.g. based on the number of family members reporting pain or number of pain sites) [33].

RESULTS

From 7281 unique citations, we identified 72 full-text articles after screening titles and abstracts, and include 28 [2-5; 9; 11; 18; 20; 25; 26; 30; 38; 42; 43; 48; 49; 51; 54; 55; 57; 58; 60; 67; 68; 71; 72; 74; 75] (Figure 1). Studies reported data from 14 countries. Twenty-six were in English and one in Spanish [51]. The age of children ranged from two to 19 years old at baseline, and only two studies investigated children younger than six years [20; 38].

We included six longitudinal ($n = 42226$ participants, table 1) [2; 26; 38; 43; 58; 68] and 23 cross-sectional studies ($n = 48119$, Table 2) [2-5; 9; 11; 18; 20; 25; 30; 42; 48; 49; 51; 54; 55; 57; 60; 67; 71; 72; 74; 75]. Five longitudinal studies had low risk of bias (Appendix Table 3). 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; 9; 25; 38; 42; 43; 49; 51; 54; 55; 57; 58; 60; 68; 71; 72; 74], either parent or sibling pain [2; 5; 18; 20; 26; 67; 75], or sibling pain [4; 11; 30; 48; 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; 9; 18; 26; 38; 42; 43; 49; 51; 55; 60; 68; 71; 72; 74; 75]. Most studies matched type (e.g. any, disabling) and location of pain in children to their family members (e.g. parents back pain and child back pain) (Table 1; Table 2).

Assessment of the overall quality of the evidence for each analysis can be found in Appendix Table 4. 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 to 2.09, 5 studies, $n = 42131$ participants) (Figure 2). The pooled effect estimate for adjusted results ($OR 1.53$, 95% CI 1.13 to 2.06, 4 studies, $n = 41844$) 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 to 2.42, 18 studies,

n=17274) (Figure 3). The pooled-effect estimate for adjusted results (OR 2.04, 95% CI 1.64 to 2.54, 12 studies, n=13998) was similar to the overall estimate.

We performed subgroup analyses based on family member with pain (Figure 3; Appendix Table 5). We found very low quality evidence that children with maternal history of MSK pain had 61% greater odds of reporting MSK pain (OR 1.61, 95% CI 1.33 to 1.93, 5 studies, n=7515); very low quality evidence that children with paternal history of MSK pain had 59% greater odds (OR 1.59, 95% CI 1.26 to 2.00, 4 studies, n=5059), moderate quality evidence that children with parental history of MSK pain had 84% greater odds of reporting MSK pain (OR 1.84, 95% CI 1.53 to 2.20, 14 studies, n=13622); very low quality evidence that children with two parents who reported pain had 95% greater odds of reporting MSK pain (OR 1.95, 95% CI 1.56 to 2.44, 2 studies, n=4450); very low quality evidence that children with a sibling with history of MSK pain had 99% greater odds of reporting MSK pain (OR 1.99, 95% CI 1.48 to 2.66, 2 studies, n=1449), 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 to 3.88, 5 studies, n=3652).

In subgroup analyses based on type of pain reported by family member (Figure 3; Appendix Table 5), 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 to 2.80, 5 studies, n=3748).

In subgroup analyses based on location of pain reported by a family member (Figure 3; Appendix Table 5), 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 to 2.40, 16 studies, n=14432).

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 1995 (Denmark)	Age: 14y n=640 Female: 52%	FU: 25y Age: 38y n=481 (75%) Female: 54%	LBP	Parent or sibling back disease (e.g. disc degeneration)	p<0.001	2.8 (1.8 to 4.4)	Low
Szpalski 2002 (Belgium)	Age: 9-11 y n=287 Female: 51%	FU: 2y Age: 11-13 y n=287 (100%) Female: 51%	Persistent LBP (baseline & FU)	Parental LBP	2.1 (1.1 to 4.0)	p>0.05	Low
Balague 2010 (Switzerland)	Age: 13-14y n=95 Female: 0%	FU: 2y Age: 15-16y n=85 (90%) Female: 0%	Consequential LBP (baseline & FU)	Treated LBP in parent or sibling	p<0.05	NR	High
Shraim 2014 [#] (United Kingdom)	Age: NA n=NA Female: NR	Age 2–16 y n=12662 Female: NR	Careseeking MSK pain	Maternal Care seeking MSK symptoms	1.5 (1.2 to 1.9)	1.4 (1.2 to 1.8)	High
			Extremities pain	Extremities pain	2.3 (1.2 to 4.5)	2.1 (1.1 to 4.2)	
			Back pain	Back pain	1.7 (0.8 to 3.5)	1.4 (0.7 to 3.1)	
Kroner-Herwig 2017 (Germany)	Age: 7-14y n=5542 Female: NR	FU: 12y Age: 19-27y n=1488 (?) Female: 56.5%	LBP (last 6m)	Parental back pain	1.3 (1.1 to 1.7)	1.3 (1.1 to 1.7)	Low
Kamper 2017 (Denmark)	Age: 6 to 18m n=NR Female: NR	FU: 10y Age: 11y n=23000 Female: 51%	LBP	Maternal MSK symptoms	NR	1.3 (1.1 to 1.5)	Low
			Multisite spinal pain		NR	1.0 (0.8 to 1.2)	

[#]Lifetime prevalence of pain unless indicated; *Results presented as odds ratio and 95% confidence interval unless described otherwise; [#]Case-control study. LBP = low back pain; y = years; m = months; n = number of participants; FU = follow up; NR = not reported; Significant results presented in bold; NA: not applicable.

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 2005 (Tunisia)	Age: 11–19 y n=622 Female: 55%	LBP Chronic LBP	LBP ¹	3.0 (2.1 to 4.3) ^c p<0.01	3.8 (2.9 to 5.9) p>0.05	Low
Evans 2006 (Australia)	Age: 4–6y n=743 Female: 53%	Growing pains	Growing pains ¹	70% of children with growing pain had a family Hx of growing pain	NR	High
Balague 2010 (Switzerland)	Age: 13–14y n=95 Female: 0%	Consequential LBP ¹	Treated LBP ¹	3.4 (1.4 to 8.3) ^c	3.6 (1.3 to 10.2)	High
Dianat 2017 (Iran)	Age: 11–14y n=1611 Female: 53%	LBP (1m prevalence)	LBP (point prevalence) ¹²	1.8 (1.5 to 2.3)	1.8 (1.4 to 2.4)	Low
Szita 2018 (Hungary)	Age: 7–16y n=952 Female: 47%	Spinal pain for days	Spinal pain ¹²	2.1 (1.4 to 3.1)	1.9 (1.3 to 2.8)	Low
Noormohammadpour 2019 (Iran)	Age: 13–19y n=372 Female: 100%	LBP Chronic LBP LBP (1m prevalence)	LBP ¹	NR NR NR	3.5 (1.68 to 7.52) 2.5 (1.24 to 4.99) 2.8 (1.52 to 5.23)	Low
Parents						
Salminen 1984 (Finland)	Age: 11–17y n=370 Female: 52%	Disabling non- specific LBP	Maternal disabling LBP Paternal disabling LBP	2.9 (1.6 to 5.2) ^c 2.4 (1.3 to 4.5) ^c	NR NR	High
Balague 1994 (Switzerland)	Age: 8–16 y n = 1716 Female: 51%	LBP	Parental treated LBP	1.9 (1.4 to 2.5)	2.1 (1.6 to 2.8)	Low
Balague 1995 (Switzerland)	Age: 12–17y n = 615 Female: 53%	LBP	Parental treated LBP	1.1 (0.8 to 1.6) ^c	p>0.05	Low
Gunzburg 1999 (Belgium)	Age: 9y n = 392 Female: 52%	LBP	Parental LBP	2.0 (1.3 to 3.0) ^c	NR	High

Borge 2000 (Norway)	Age: 13–15y n = 229 Female: NR	MSK pain(last 2m)	Maternal LBP, neck & shoulder pain, and arm & leg pain	1.5 (0.7 to 3.3) 2.8 (1.0 to 8.0) 0.9 (0.4 to 1.0)	NR	High
		LBP				
		Neck&shoulder pain	Paternal LBP, neck & shoulder pain, and arm & leg pain	1.9 (0.7 to 4.9) 3.1 (1.2 to 8.3) 0.9 (0.4 to 1.0)	NR	
		Arm&Leg pain				
Sjölöe 2002 (Norway)	Age: 14-16 y n = 88 Female: 43%	LBP	Parental treated	NR	1.4 (0.5 to 4.1)	Low
		LBP (> 1m last y)	LBP	NR	NR	
Kovacs 2003 (Spain)	Age: 13–15y N = 7361 Female: 53%	Back pain	Parental back pain	p>0.05	NR	High
Saunders 2007 (United States)	Age: 11–17 y N = 2466 Female: 51.3%	Persistent LBP (in the last 6m)	Persistent maternal pain (Last 6m)	p < 0.001	1.5 (1.0 to 2.1)	Low
O’Sullivan et al. 2008 (Australia)	Mean age: 14y n = 1608 Female: 51%	LBP	Maternal LBP	1.4 (1.1 to 1.7)	1.4 (1.1 to 1.7)	High
		Chronic LBP		1.6 (1.1 to 2.4)	1.6 (1.1 to 2.4)	
		LBP	Paternal LBP	1.3 (1.0 to 1.7)	NR	
		Chronic LBP		1.6 (1.0 to 2.5)	NR	
Pires 2011 (Spain)	Age: 10–11y n = 834 Girls: 49%	LBP	Both Parents LBP	1.6 (1.1 to 2.5)	NR	High
			LBP	2.9 (2.0 to 4.2)	NR	
Yao 2012 (China)	Age: 10–18y n = 1214 Female: 60.3%	LBP (last 3 m)	Parental LBP	p < 0.001	2.6 (1.9 to 3.6)	Low
Shan 2014 (China)	Age: 15-19y n = 2842 Female: 52%	Neck & shoulder pain	Neck & shoulder pain			High
			Maternal	1.7 (1.4 to 2.0)	1.7 (1.4 to 2.1)	
			Paternal	1.9 (1.3 to 2.1)	1.7 (1.3 to 2.1)	
			Both Parents	2.4 (1.9 to 3.0)	2.1 (1.7 to 2.6)	
Wirth 2013 (Switzerland)	Age: 6–16y n = 836 Female: 53%	Spinal pain	Parental spinal pain	2.4 (1.2 to 4.7)	NR	Low
		LBP	LBP	3.0 (0.9 to 9.6)	NR	
		Thoracic spine pain	Thoracic spine pain	2.5 (0.7 to 9.2)	NR	
		Neck pain	Neck pain	3.3 (0.9 to 11.8)	NR	

Wirth 2015 (Switzerland)	Age: 10–16y n = 412 Female: 51.9%	Spinal pain	LBP	1.46 (NR)	1.46 (0.4 to 4.9)	Low
Sibling						
Salminen 1984 (Finland)	Age: 11–17y n = 370 Female : 52%	Disabling non-specific LBP	LBP	p>0.05	NR	High
Balague 1995 (Switzerland)	Age: 12–17y n = 615 Female : 53%	LBP	LBP	1.7 (1.2 to 2.5)^c	p>0.05	Low
Pires 2011 (Spain)	Age: 10–11y n = 834 Female : 49%	LBP	LBP	2. (2.0 to 2.02)	NR	High
Twin						
Mikkelsen 2001 (Finland)	Age: 11y n = 3578 MZ pairs: 583 DZ pairs: 1789	Widespread MSK pain	Co-twin Widespread MSK pain	Casewise concordance Male MZ: 0.27 Male DZ: 0.26 Female MZ: 0.39 Female DZ: 0.35 OSDZ: 0.25	NR	Low
Champion 2012 (Australia)	Age: 3–16y n = 196 MZ pairs: 34 DZ pairs: 54	Growing pains	Co-twin growing pains	Casewise concordance: MZ: 0.85 DZ: 0.36	NR	Low
Hestbaek 2012 (Denmark)	Age 12–18y n = 16574 MZ pairs: 3818 DZ pairs: 4469	LBP	Co-twin LBP	3.35 (3.06 to 3.67) MZ versus DZ 2.76 (2.30 to 3.32)	NR NR	Low

[#]Lifetime prevalence unless indicated; ^{*}Results presented as odds ratio and 95% confidence interval unless described. LBP = low back pain; m = months; y = years; n = number of participants; OR = odds ratio; CI = confidence interval; NR = not reported; MZ = Monozygotic; DZ = Dizygotic; OSDZ = Opposite sex dizygotic;

^cCalculated from data presented in original paper; ¹Family pain history from parent and/or sibling; ²Family pain history from second degree relative (grandparent, aunt);

³Medical treatment or interference in daily activities; Significant results in bold.

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 children MSK pain with children had maternal (53%), paternal (59%) or sibling (99%) history of pain. There appears 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 $OR=2.0$]. Further, higher odds were also found in children when parent or sibling had a history of consequential MSK pain (treated, disabling or care seeking) ($OR=1.94$). 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; 8; 10; 32; 44-46; 69; 76]. 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 [32]. 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 [44-46], with stronger associations observed when both parents have MSK pain [45; 76]. Furthermore, adults with a sibling with MSK pain have greater odds of experience MSK pain [76].

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 sub-group 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 five 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) [22; 47]. The evidence quality from subgroup analyses (e.g. 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 (i.e.

different types of pain across different family members) and outcome measurements (i.e. 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 represent MSK pain with consequence. Moreover, detailed information about the type of MSK pain was often unclear in longitudinal studies (e.g. first onset or persistent). Confounders included in the adjusted models varied substantially across studies (Appendix table 6). 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]. Further, we do not know whether associations of different strength would be found in samples collected from clinical settings (e.g. pediatrician or physiotherapy visits). The mechanisms by which family pain history affects childhood pain is 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 non-modifiable (e.g. genetic predisposition) or unlikely to change rapidly (i.e. family income), while others are possibly modifiable (e.g. 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 [44].

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 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 marks this area as worthy of further research. This is particularly the case in the current context of poor understanding of childhood MSK pain [37], and the significant global burden of the condition [35].

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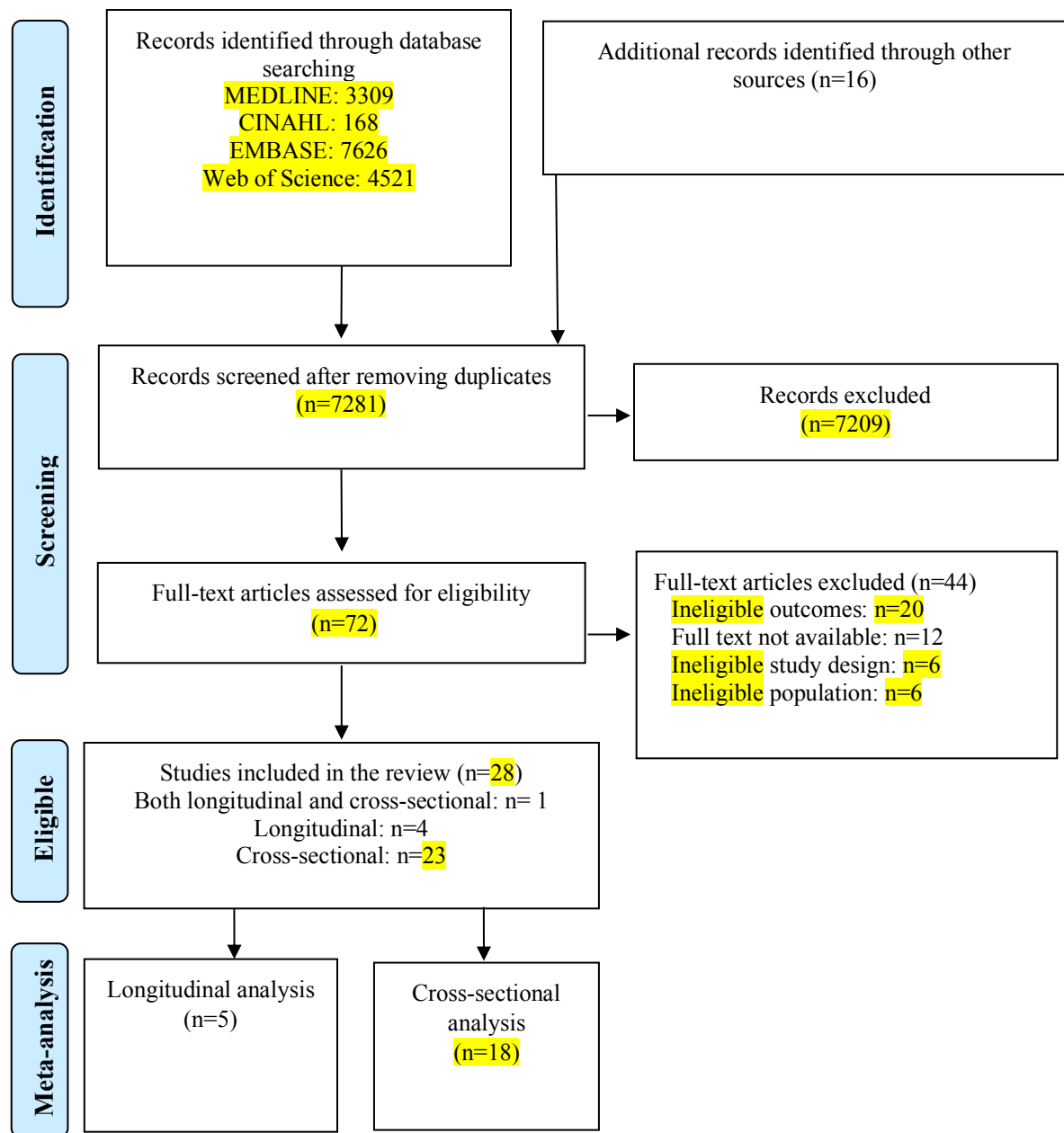
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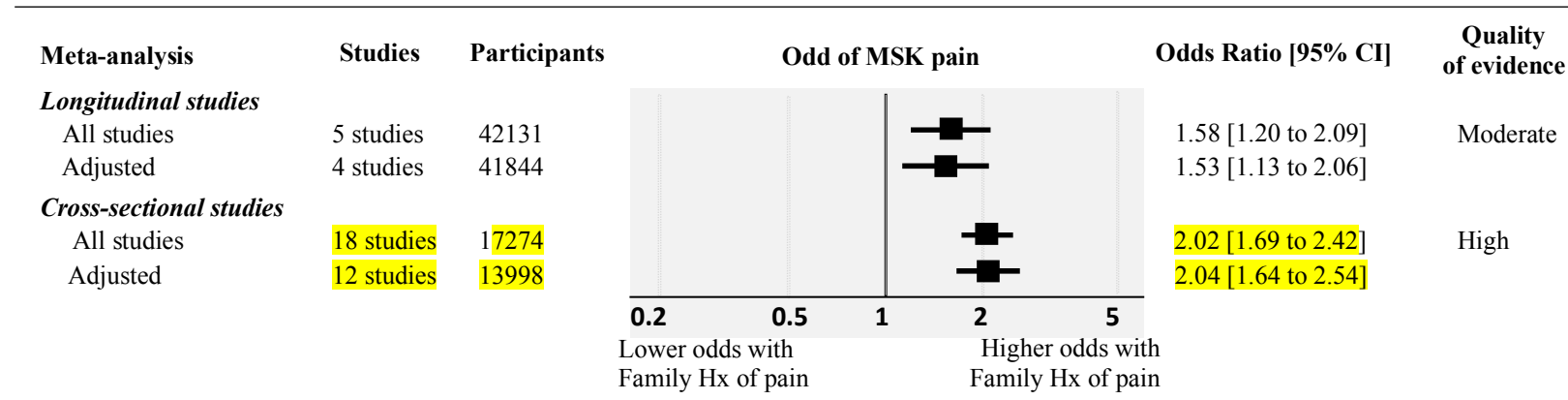
Figure Legend

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

Figure 2. Meta-analysis investigating a family history of MSK pain as a risk factor for children and adolescents developing MSK pain

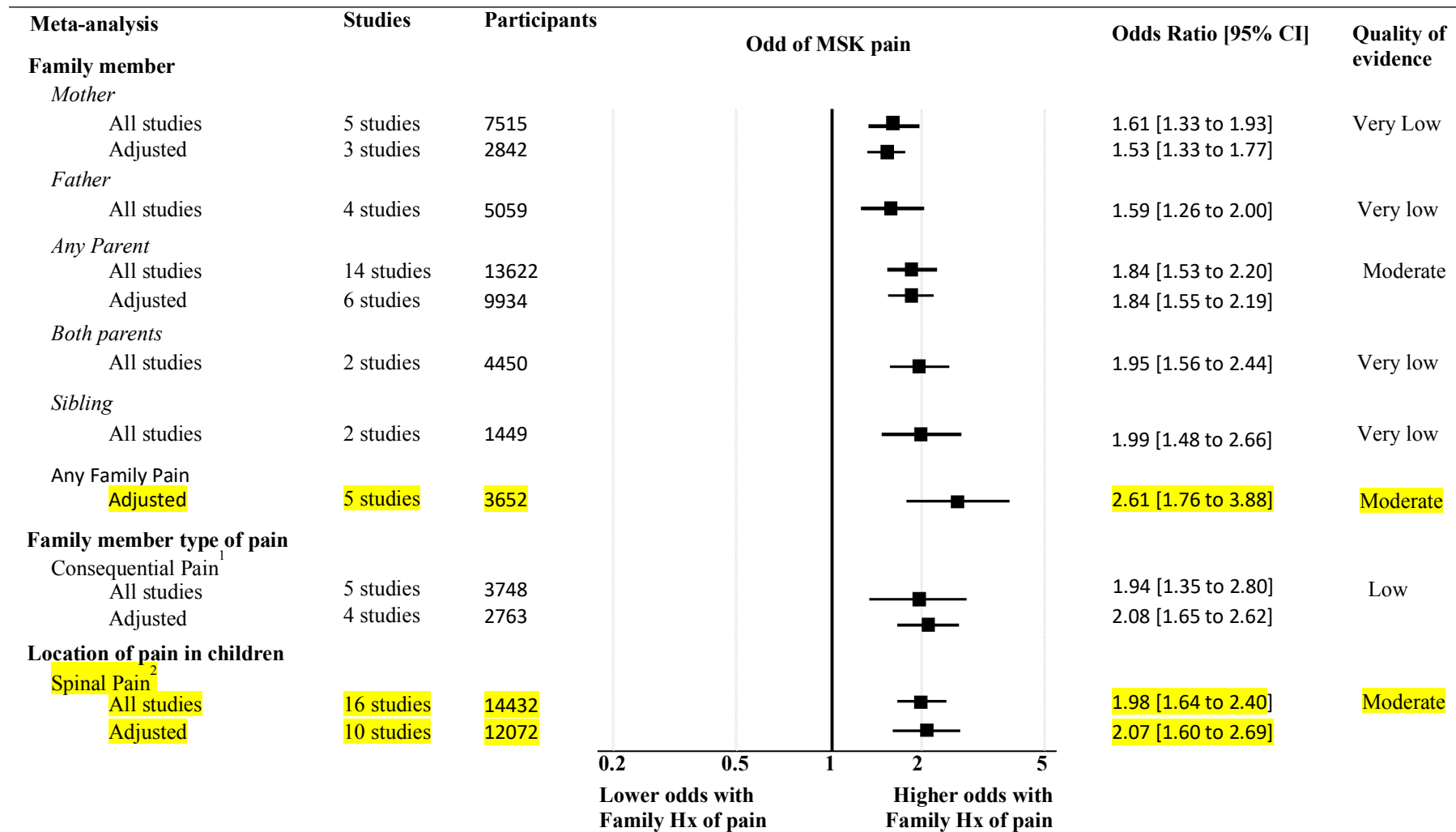
Figure 3. Meta-analysis for subgroup analysis investigating a family history of MSK pain as a risk factor for children and adolescents developing MSK pain





MSK: Musculoskeletal pain; The squares indicate the odds ratios and 95% confidence intervals of random-effects meta-analysis; The vertical line shows the line of no effect (OR = 1); CI: Confidence interval

1



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3

4 The squares indicate the odds ratios and 95% confidence intervals of random-effects meta-analysis; The vertical line shows the line of no effect (OR = 1); ¹ Consequential
 5 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.

Appendix

Table 1. Search Strategy for Medline, EMBASE, CINAHL and Web of Science databases

MEDLINE (Ovid): From 1946 to 26 February 2018	
Term Set #1: Musculoskeletal Pain	
1. pain.tw.	
2. exp Musculoskeletal Pain/	
3. 1 or 2	
Term Set #2: Children and adolescents	
1. exp pediatrics/	
2. exp child/	
3. exp adolescent/	
4. Youth*.tw.	
5. (paediatr* or pediater* or infant* or child* or teenage* or adolescen* or preschooler* or pre-schooler* or schoolchild* or girl* or boy* or teen*).tw.	
6. 4 or 5 or 6 or 7 or 8	
Term Set #3: Family	
1. exp Parents	
2. Famil* history*.tw.	
3. Mother*.tw.	
4. Maternal.tw.	
5. Father*.tw.	
6. Paternal.tw.	
7. Siblings/	
8. family/ or Family.mp. or family characteristics/	
9. family adj3 pain adj3 history.mp.	
10. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18	
Term Set #4: Study design	
1. exp cross-sectional study/	
2. exp prospective study/	
3. exp risk factor/	
4. cohort study.mp. or Cohort Studies/	
5. follow up/ or exp longitudinal study/	
6. predictor.tw.	
7. exp prevalence/	
8. risk.tw.	
9. association.tw.	
10. influenc*.tw.	
11. correlat*.tw.	
12. 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30	
3 and 9 and 19 and 31 = 3040 Citations	
EMBASE (OvidSP): From 1947 to 26 February 2018	
Term Set #1: Musculoskeletal Pain	
1. pain.tw.	
2. exp Musculoskeletal Pain/	
3. 1 or 2	
Term Set #2: Children and adolescents	
7. exp pediatrics/	
8. exp child/	
9. exp adolescent/	
10. Youth*.tw.	
11. (paediatr* or pediater* or infant* or child* or teenage* or adolescen* or preschooler* or pre-schooler* or schoolchild* or girl* or boy* or teen*).tw.	
12. 4 or 5 or 6 or 7 or 8	
Term Set #3: Family	
11. exp Parents	
12. Famil* history*.tw.	
13. Mother*.tw.	
14. Maternal.tw.	
15. Father*.tw.	
16. Paternal.tw.	
17. Siblings/	
18. family/ or Family.mp. or family characteristics/	
19. family adj3 pain adj3 history.mp.	
20. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18	
Term Set #4: Study design	
4. exp cross-sectional study/	
5. exp prospective study/	
6. exp risk factor/	
7. cohort study.mp. or Cohort Studies/	
8. follow up/ or exp longitudinal study/	
9. predictor.tw.	
10. exp prevalence/	

11.	risk.tw.
12.	association.tw.
13.	influen*.tw.
14.	correlat*.tw.
15.	20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
3 and 9 and 19 and 30 = 6929 citations	
CINAHL (EBSCO): From 1982 to 26 February 2018	
Term Set #1: Musculoskeletal Pain	
1.	(TI pain) OR (AU pain)
2.	"Musculoskeletal Pain"
3.	1 or 2
Term Set #2: Children and adolescents	
4.	(MH "Pediatrics+")
5.	(MH "Child+")
6.	(MH "Adolescence+")
7.	(TI Youth*) OR (AU Youth*)
8.	(TI paediatr*) OR (AU paediatr*)
9.	(TI pediater*) OR (AU pediater*)
10.	(TI child*) OR (AU child*)
11.	(TI adolescen*) OR (AU adolescen*)
12.	(TI preschooler*) OR (AU preschooler*)
13.	(TI pre-schooler*) OR (AU pre-schooler*)
14.	(TI schoolchild*) OR (AU schoolchild*)
15.	(TI girl*) OR (AU girl*)
16.	(TI boy*) OR (AU boy*)
17.	(TI teen*) OR (AU teen*)
18.	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
Term Set #3: Family	
21.	(MH "Parents+")
22.	(MH "Mothers+")
23.	(TI Maternal*) OR (AU Maternal*)
24.	(TI Paternal*) OR (AU Paternal*)
25.	Siblings/
26.	(MH "Family+")
27.	19 or 20 or 21 or 22 or 23 or 24
Term Set #4: Study design	
19.	(MH "Cross Sectional Studies")
20.	(MH "Risk Factors+")
21.	(MH "Prospective Studies+")
22.	(TI cohort) OR (AU cohort)
23.	(TI longitudinal study) OR (AU longitudinal study)
24.	(TI predictor) OR (AU predictor)
25.	(MH "Prevalence")
26.	27 or 28 or 29 or 30 or 31 or 32 or 33
3 and 18 and 25 and 33 = 113 citations	
Web of Science: from 1956 to 23 February 2018	
Term Set #1: Musculoskeletal Pain	
1.	ts=(pain)
Term Set #2: Children and adolescents	
2.	ts=(pediatrics)
3.	ts=(adolescence)
4.	ts=(child* or adolescen* or teen* or youth* or young)
5.	ts=(paediatr* or pediater* or preschooler* or pre-schooler* or schoolchild*)
6.	ts=(girl* or boy* or teen*)
7.	#6 or #5 or #4 or #3 or #2
Term Set #3: Family	
28.	ts=(parent*)
29.	ts=(mothers* or maternal*)
30.	ts=(father* or paternal*)
31.	ts=(sibling*)
32.	ts=(famil*)
33.	#12 or #11 or #10 or #9 or #8
Term Set #4: Study design	
8.	ts=(cross sectional stud*)
9.	ts=(risk* or cohort*)
10.	ts=(prospective stud*)
11.	ts=(longitudinal stud*)
12.	ts=(predictor*)
13.	ts=(prevalence)
14.	#19 or #18 or #17 or #16 or #15 or #14
#20 AND #13 AND #7 AND #1 = 4,381 citations	

Table 2. Modified version of the Quality in Prognosis Studies (QUIPS) tool used to assess risk of bias of the observational studies included in this review.

Domain and Prompting items for Consideration	Ratings
Study Participation a. Adequate participation in the study by eligible persons b. Description of the source population or population of interest c. Description of the baseline study sample d. Adequate description of the sampling frame and recruitment e. Adequate description of the period and place of recruitment f. Adequate description of inclusion and exclusion criteria	High bias: > 2 items poorly rated Moderate bias: 1 or 2 items poorly rated Low bias: no item poorly rated
Study Attrition* a. Adequate response rate for study participants b. Description of attempts to collect information on participants who dropped out c. Reasons for loss to follow-up are provided d. Adequate description of participants lost to follow-up e. There are no important differences between participants who completed the study and those who did not	High bias: > 2 items poorly rated Moderate bias: 1 or 2 items poorly rated Low bias: no item poorly rated
Exposure Measurement: Measuring family pain history involves gathering health information about one or more family members. To obtain a valid assessment of family history, it is important to investigate which family member will be able to provide accurate information. Previous evidence emphasize the necessity of an interview of the relatives in family studies (84). a. A clear definition or description of the family pain history is provided b. Method of family pain history measurement is adequately valid and reliable c. The method and setting of measurement of family pain history is the same for all study participants d. Adequate proportion of the study sample has complete data for the family pain history e. Appropriate methods of imputation are used	High bias: Family pain history was reported by children aged 13 or less. Moderate bias: Information provided by adolescents at ages 14 or above is about as reliable as that given by their parents. Low bias: Parental or sibling direct report of pain history instead of indirect report by children and adolescents.
Outcome Measurement: Pain assessment in children and adolescent can be difficult because it is a complex phenomenon (85). Amongst the several types of paediatric pain measures, self-report, when available, is regarded as the primary source of information (85, 86). Good validity and reliability of the children and adolescent pain self-report of musculoskeletal pain has been demonstrated when body pain drawing is used (87, 88). a. A clear definition of the outcome is provided b. Method of outcome measurement used is adequately valid and reliable c. The method and setting of outcome measurement is the same for all study participants	High bias: Data were reported by parents as parents tend to under report their children pain (89); Pain was self-report by young children (i.e. aged seven years or less) as validity of the data has been questioned (90). Moderate bias: Information on musculoskeletal pain were obtained by children (aged seven or more) and adolescents without body pain drawing. Low bias: Information on musculoskeletal pain were obtained by children (aged seven or more) and adolescents with body pain drawing.
Study Confounding: Plausible confounders were based on a conceptual model for the intergenerational transmission of chronic pain from parents to offspring (18) and included: a) Families' characteristics: 1) Parental stress and parental health behaviours; 2) Physical activity and general health habits in parents and their children (i.e. body mass index, diet, health care utilization), 3) Stressful environment (i.e. family functioning, poor family cohesion, high levels of marital conflict, chronic sources of stress), 4) Timing, course, and location of parental chronic pain; b) Children and adolescents' characteristics: 1) Sex; 2) Race or ethnicity, 3) Age. a. Important confounders are measured b. Measurement of important confounders is adequately valid and reliable c. The method and setting of confounding measurement are the same for all study participants d. Appropriate methods are used if imputation is used for missing confounder data e. Important potential confounders are accounted for in the study design	High bias: No relevant confounder was included in the adjusted models. Moderate bias: 1 or 2 relevant confounders were included in the adjusted models. Low bias: ≥ 3 relevant confounders were included in the adjusted models.

f. Important potential confounders are accounted for in the analysis

Statistical Analysis and Reporting

- a. Sufficient presentation of data to assess the adequacy of the analysis
- b. Strategy for model building is appropriate and is based on a conceptual framework or model
- c. The selected statistical model is adequate for the design of the study
- d. There is no selective reporting of results

High bias: > 2 items poorly rated

Moderate bias: 1 or 2 items poorly rated

Low bias: no item poorly rated

Overall Rating

Low Risk of Bias: Low risk of bias on at least four of the seven domains including study confounding.

Supplemental Table 3. Risk of bias scores for the observational studies based on the modified QUIPS tool

Adapted QUIPS	Study participation	Study attrition	Exposure measurement	Outcomes measurement	Confounding	Analysis and reporting	Overall Risk of Bias
Longitudinal studies							
Hareby 1995	✓	✓	✓	✓	✓	!	Low
Szpalki 2002	✓	!	!	✓	✓	✓	Low
Balague 2010	✓	✓	✗	✓	✗	✗	High
Kemper 2017	✓	✓	✓	✓	✓	✓	Low
Kroner-Herwig 2017	✓	✗	✓	!	✓	✓	Low
Cross-sectional studies							
Salminen 1984	✓	NA	!	✓	✗	✗	High
Balague 1994	✓	NA	✓	!	✓	✓	Low
Balague 1995	✓	NA	✓	!	✓	✓	Low
Gunzburg 1999	✓	NA	✗	✓	✗	!	High
Borge 2000	✓	NA	✓	!	!	✓	High
Mikkelsen 2001	✓	NA	✓	✓	✓	✓	Low
Sjölie 2002	✓	NA	✓	!	✓	✓	Low
Kovacs 2003	✓	NA	✓	✓	✗	✓	High
Beija 2005	✓	NA	✓	✓	✓	✓	Low
Saunders 2007	!	NA	✓	!	✓	✓	Low
Evans 2006	✓	NA	✓	✓	✗	✗	High
O'Sullivan 2008	✓	NA	✓	✓	✓	✓	Low
Balague 2010	✓	NA	!	✓	✓	✓	Low
Pires 2011	✓	NA	✓	✗	✗	✗	High
Champion 2012	✓	NA	✓	✓	✓	✓	Low
Hestbaek 2012	✓	NA	✓	✓	✓	✓	Low
Yao 2012	✓	NA	!	✓	✓	✓	Low
Wirth 2013	✓	NA	✓	✓	✗	✓	High
Shan 2014	✓	NA	!	✓	!	✓	High
Shraim 2014	✓	NA	✓	✓	✓	✓	Low
Wirth 2015	✓	NA	✓	✓	✓	!	Low
Dianat 2017	✓	NA	!	✓	✓	✓	Low
Szita 2018	✓	NA	✓	✓	✓	✓	Low
Noormohammadpour 2019	✓	NA	✓	✓	!	✓	Low

NA: Not applicable.

Supplemental table 4. Summary of the quality of evidence and strength of recommendation.

Quality Assessment									
Main Meta-analysis	Downgraded						Upgraded		Overall
	Phase of investigation ¹	Study limitations ²	Inconsistency ³	Indirectness ⁴	Imprecision ⁵	Publication bias ⁶	Effect size ⁷	Exposure-response gradient	
Longitudinal						↓ [#]			Moderate
Cross-sectional	↓								Moderate
Subgroup analysis									
<i>Family member</i>									
Mother	↓	↓				↓ [#]			Very Low
Father	↓	↓				↓ [#]			Very Low
Any Parent	↓								Moderate
Both Parents	↓	↓				↓ [#]			Very Low
Sibling	↓	↓				↓ [#]			Very Low
Any family pain	↓					↓ [#]	↑		Moderate
<i>Type of pain in the family member</i>									
Consequential pain	↓					↓ [#]			Low
<i>Location of pain in the family member</i>									
Spinal pain	↓								Moderate

¹ Cross-sectional studies

² > 25% of the participants from studies with high risk of bias

³ Heterogeneity was based on similarity of point estimates, extent of overlap of confidence intervals, and I² test (> 50%).

⁴ Indirectness: > 25% of results from that failure to apply appropriate eligibility criteria and had poor measurement of both exposure and outcome.

⁵ Fewer than 400 participants in the pooling

⁶ Funnel plot and Egger's test

⁷ Odds ratio > 2.5

↑ Upgraded

↓ Downgraded

[#] Unclear: unable to assess publication bias (< 10 studies)

Supplemental Table 5. All estimates from meta-analyses for longitudinal and cross-sectional studies investigating the association between family history of pain and musculoskeletal pain in children and adolescents.

Analysis	N of participants (N of studies)	OR [95% CI]	I ² Statistics
Longitudinal			
All studies*	42131 (5 studies)	1.58 [1.20 to 2.09]	16%
Unadjusted analysis	18491 (3 studies)	1.41 [1.16 to 1.72]	0%
Adjusted analysis	41844 (4 studies)	1.53 [1.13 to 2.06]	28%
Cross-sectional			
All studies *	17274 (18 studies)	2.02 [1.69 to 2.42]	0%
Unadjusted	12725 (13 studies)	2.07 [1.75 to 2.44]	2%
Adjusted	13998 (12 studies)	2.04 [1.64 to 2.54]	0%
Subgroup Analysis			
Family member			
<i>Mother</i>			
All studies*	7515 (5 studies)	1.61 [1.33 to 1.93]	11%
Unadjusted analysis	5049 (4 studies)	1.65 [1.30 to 2.08]	19%
Adjusted analysis	2842 (3 studies)	1.53 [1.33 to 1.77]	0%
<i>Father</i>			
All studies*	5049 (4 studies)	1.59 [1.26 to 2.00]	0%
Unadjusted analysis	5049 (4 studies)	1.55 [1.32 to 1.83]	0%
<i>Parents (Both parents, either parent, mother or father)</i>			
All studies*	13622 (14 studies)	1.84 [1.53 to 2.20]	0%
Unadjusted analysis	9442 (10 studies)	1.98 [1.59 to 2.46]	0%
Adjusted analysis	9934 (6 studies)	1.84 [1.55 to 2.19]	0%
<i>Both parents</i>			
All studies*	4450 (2 studies)	1.95 [1.56 to 2.44]	0%
Unadjusted analysis	4450 (2 studies)	2.05 [1.40 to 3.02]	
<i>Sibling</i>			
Unadjusted analysis	1449 (2 studies)	1.99 [1.48 to 2.66]	0%
<i>Any Family member</i>			
Unadjusted analysis	3280 (4 studies)	2.27 [1.72 to 3.00]	0%
Adjusted analysis	3652 (5 studies)	2.61 [1.76 to 3.88]	0%
Family member type of pain			
<i>Consequential pain¹</i>			
All studies*	3748 (5 studies)	1.94 [1.35 to 2.80]	4%
Unadjusted analysis	3748 (5 studies)	1.93 [1.36 to 2.74]	9%
Adjusted analysis	2763 (4 studies)	2.08 [1.65 to 2.62]	0%
Location of pain in children and adolescents			
<i>Spinal pain²</i>			
All studies*	14432 (17 studies)	1.98 [1.64 to 2.40]	0%
Unadjusted analysis	11211 (15 studies)	1.82 [1.56 to 2.14]	0%
Adjusted analysis	12,072 (9 studies)	2.07 [1.60 to 2.69]	0%

* Pooling including all available estimates (using adjusted estimates where possible); N = number; OR: odds ratio; CI: confidence interval; ¹ Consequential pain in a family member including treated and disabling pain, or care seeking due to musculoskeletal pain; ² Spinal pain includes lower back, thoracic, and /or neck areas.

1 0

2 **Supplemental Table 6. Confounders included in the adjusted models for longitudinal and cross-sectional**
3 **studies investigating the association between family history of pain and musculoskeletal pain in children**
4 **and adolescents.**

Study	Confounders investigated
Longitudinal studies	
Harreby 1995	Sex, height, radiological changes in the lumbar and thoracic spine, recent back pain, living in apartment, living alone, rejected by draft board, mental distress
Szpalski 2002	Height, daily duration of computer games playing, competition sport, quality of sleep, quality of falling asleep, being tired without any reason, health perception, general happiness, staying at home because of LBP, skipping gym lessons because of LBP, skipping sports because LBP, taking medication for LBP, heavy school satchel, posture, painful palpation of lumbar spine
Balague 2010	Not included
Shraim 2014	Child age, child sex, mother age, child birth order, household members' count, maternal mental health, and GP practice
Kamper, 2017	Sex, birth weight, attention, cognitive development, child health problem, maternal smoking in pregnancy, maternal alcohol in pregnancy, maternal education, family income
Kroner-Herwig 2017	Sex, previous LBP episode, internalizing, anxiety, somatosensory amplification, dysfunction stress copying, catastrophizing
Any Family Member	
Bejia 2005	Sex, age, height, weight, body mass index, school failure (held back for a year), school chair, the home-to-school journey, the satchel (carriage by hand or on the shoulders, relative weight of the satchel by the weight of the child), TV watching, right/left-handed, smoking, history of injury and exercise.
Evans 2008	Not included
Balague 2010	Age, body, mass, height, body mass index, sport participation, trunk mobility, ROM tests, strength tests
Dianat 2017	Sex, difficulty in viewing the (black)board, too much homework, carrying a schoolbag for more than 30 min/d, high emotional symptoms
Szita 2018	Age, afternoon learning (> 2h/d), watching TV (> 2h/d), no sport participation, asymmetric school bag, carrying school bag is tiring, uncomfortable school chair, sleep problems, general discomfort, frequent missing from school
Noormohammadpour 2019	Age, body mass index
Parents	
Salminen 1984	Not included
Balague 1994	older (> 12y); sex, competitive sport participation, TV time a day
Balague 1995	Sex, Time spent participating in sport, Time spent watching TV, negative and positive affect scores
Balague 2010	Body mass, BMI, sport participation, schober value, fingertip floor test, range of motion, maximum isometric torque, peak angular velocity
Gunzburg 1999	Not included
Borge 2000	Parents' distress by pain, parents self-reported health, and chronic illness in the parents
Sjölie 2002	Age, frequency of physical activity, time spent on television or computer, BMI
Szpalski 2002	Feeling schoolbag uncomfortable, basketball playing, rest position between classes, duration of schoolbag carrying
Kovacs 2003	NR
Saunders 2007	Maternal and child age, child sex, and mother's education, marital status and number of pain sites
O'Sullivan 2008	Adolescent and carer sex, carer smoking, household income, family functioning, and number of life stress events
Yao 2012	Age, weight, BMI, weekly frequency of sports, regularly sport game, method of commute to school, gymnastics practicing, swimming, weight of schoolbag, feeling schoolbag heavy, discomfort with school furniture, smoking, drinking, and study or life stresses
Wirth 2013	Not included
Shan 2014	Sex
Wirth 2015	Age, gender, BMI, finger floor distance, Adams sign, single leg stance with closed eyes, tv/computer activities, parental smoking, sleep disorders, headache, abdominal pain, headache and abdominal pain
Sibling/ Twin	
Salminen 1984	Not included
Balague 1995	Sex, Time spent participating in sport, Time spent watching TV, negative and positive affect scores
Mikkelsen 2001	Twins: sex, age, genetics and early shared family environment
Pires 2011	Not included
Champion 2012	Twins: sex, age, genetics and early shared family environment
Hestbaek 2012	Twins: sex, age, genetics and early shared family environment

LBP = Low back pain;; *n* = number; *OR* = odds ratio; *CI* = confidence interval; *SE* = standard error; *NR* = not reported;
MZ= Monozygotic; DZ = Dizygotic; SS = Same sex; OS = opposite sex; WSP = Widespread pain; ° Calculated with data
from original paper

4

5

