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 pediatr* 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 pediatr* 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. influenc*.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): From1982 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 pediatr*) OR (AU pediatr*)
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 23or 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 pediatr* 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	**High bias:** > 2 items poorly rated
a. Sufficient presentation of data to assess the adequacy of the analysis	**Moderate bias**: 1 or 2 items poorly rated
b. Strategy for model building is appropriate and is based on a conceptual framework or model	**Low bias**: no item poorly rated
c. The selected statistical model is adequate for the design of the study	
d. There is no selective reporting of results	

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							
Harreby 1995	✓	✓	✓	✓	✓	!	Low
Szpalki 2002	✓	!	!	✓	✓	✓	Low
Balague 2010	✓	✓	✗	✓	✗	✗	High
Shraim 2014	✓	✓	✓	✓	✓	✓	Low
Kamper 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
Mikkelsson 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
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.

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									
Family member									
Mother	↓	↓				↓#			Very Low
Father	↓	↓				↓#			Very Low
Any Parent	↓								Moderate
Both Parents	↓	↓				↓#			Very Low
Sibling	↓	↓				↓#			Very Low
Any family pain	↓					↓#	↑		Moderate
Type of pain in the family member									
Consequential pain	↓					↓#			Low
Location of pain in the family member									
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 I^2 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]	I² 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			
Mother			
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%
Father			
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%
Parents (Both parents, either parent, mother or father)			
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%
Both parents			
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]**	
Sibling			
Unadjusted analysis	1449 (2 studies)	**1.99 [1.48 to 2.66]**	0%
Any Family member			
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			
Consequential pain[1]			
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			
Spinal pain[2]			
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.

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Supplemental Table 6. Confounders included in the adjusted models for longitudinal and cross-sectional studies investigating the association between family history of pain and musculoskeletal pain in children 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
<mark>Noormohammadpour 2019</mark>	<mark>Age, body mass index</mark>
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
Mikkelsson 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; [c] Calculated with data from original paper