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Systematic Review

Are perinatal factors associated with musculoskeletal pain across the lifespan? A systematic review with meta-analysis

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ABSTRACT

Background: Musculoskeletal conditions are common health issues with great impact on individuals. Although many factors have been associated with the development of musculoskeletal pain, such as perinatal factors, its aetiology is still poorly understood.
Objective: To systematically investigate whether perinatal factors can increase the risk of having musculoskeletal pain across the lifespan.
Methods: MEDLINE, CINAHL, Scopus, Web of Science and EMBASE databases were searched from their inception to December 2017. Descriptors used in our search strategy were related to "perinatal factors" and "musculoskeletal pain". There were no language, age, sex or date restrictions. Meta-analysis was used to pool the estimates of association between perinatal factors and musculoskeletal pain.
Results: Among the six articles included in this systematic review, three were extracted for the meta-analysis. The pooled of three and two studies showed no association between chronic musculoskeletal pain and low birth weight (OR 1.8, 95% CI 0.9–3.8, $I^2 = 0$; n = 157) or pre-term birth (OR 0.5, 95% CI 0.0–4.5; $I^2 = 78\%$; n = 374) in adults, respectively. Overall, the quality of evidence after applying the GRADE approach was very low across all the studies.
Conclusion: In adults, our meta-analysis showed no association between birth weight or pre-term birth and musculoskeletal pain, and the quality of the evidence was very low. Thus, the very low quality of evidence and limited number of studies do not suggest a direct clear association. Further high-quality longitudinal studies accounting for more relevant confounders are needed to better understand the complex mechanism that may operate between perinatal factors and musculoskeletal pain.

1. Introduction

Musculoskeletal conditions, such as back and neck pain, are common health issues with great impact on individuals and society. In accordance with the latest Global Burden of Disease results, musculoskeletal conditions were the second highest cause of global disability, and low back pain was the top contributor to disability (Vos et al., 2016). All age groups seem to be affected by musculoskeletal conditions. Although many factors have been associated with the development of musculoskeletal pain, its aetiology is still poorly understood (Clark and Horton, 2018). Current evidence suggests complex interactions involving social, biophysical, psychological and genetic factors (Hartvigsen et al., 2018). Studies have also suggested that the development of musculoskeletal pain may be influenced by early life stress factors (Hestbaek et al., 2003; Iversen et al., 2015, 2017).

Birth weight is one early life factor that has been associated with development of musculoskeletal pain, however the evidence is conflicting. While some studies found an association between low birth weight and increased risk of musculoskeletal pain in adults (Iversen et al., 2017; Littlejohn et al., 2012), other studies did not find any association (Mallen et al., 2006). Other perinatal factors, such as post-term birth, lower Apgar score and higher birth weight, have also been investigated as a risk factor of musculoskeletal pain and the results are inconclusive (Hestbaek et al., 2003; Iversen et al., 2015).

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To best of our knowledge, no study has summarised the evidence of perinatal factors influence on musculoskeletal pain later in life. Thus, in an attempt to address this gap, we conducted a systematic review to investigate whether perinatal factors are associated with musculoskeletal pain across the lifespan.

2. Methods

The protocol for this systematic review was registered in PROSPERO (CRD42017083693) and is available at: http://www.crd.york.ac.uk/PROSPERO. We used the Meta-analysis of Observational Studies in Epidemiology guidelines to structure this systematic review (Stroup et al., 2000).

2.1. Identification of the studies

The search was conducted using MEDLINE, CINAHL, Scopus, Web of Science, and EMBASE databases from their inception to December 2017.

2.2. Inclusion and exclusion criteria

We included cross-sectional and longitudinal studies that investigated the association between perinatal factors and musculoskeletal pain. Descriptors used in our search strategy were related to "perinatal factors" and "musculoskeletal pain". There were no language, age, sex or date restrictions. Studies were included if they investigated the association between any perinatal factor related to the newborn health and nonspecific musculoskeletal pain across life span. Studies were excluded if they investigated musculoskeletal pain related to specific conditions (fracture, cancer, systemic diseases, osteoarthritis and sports injuries) or were pregnancy-related. Screening of titles, abstracts and full text identified in the search were undertaken by two independent reviewers (FSM and HRL). Any disagreement was resolved by a third reviewer (VCO).

2.3. Exposure factors

The perinatal exposure factors of interest were: delivery characteristics, such as gestational age (premature [< 37 weeks] or post-term birth [> 42 weeks]) (Liu et al., 2016), birth weight (very low [< 1500 g], low [< 2500 g], full [≥ 2500 g] and high [> 4500 g]) (Organization, 2014), Apgar scores (1–5 min), delivery types (vaginal or caesarean), neonatal intensive care unit admission, artificial ventilation and factors related to acute fetal distress inducing threatened spontaneous abortion conditions, such as amniotic fluid loss, bleeding during gestation, and suboptimal intrauterine conditions (Hadjkacem et al., 2016).

2.4. Outcome factors

The outcomes of interest were prevalence of musculoskeletal pain (e.g., back pain, neck pain, low back pain, widespread pain and limb pain) in cross-sectional studies (i.e., using perinatal factor as exposure); and future occurrence (incidence) of musculoskeletal pain in longitudinal studies. We accepted all studies' definitions of musculoskeletal pain, as they tended to vary significantly among studies in terms of location and duration of symptoms.

2.5. Data extraction

Data were extracted from each paper with customized data extraction forms. Attempts were made to retrieve missing data by contacting the corresponding author of the particular study. Data from included studies (design, study population, outcomes, exposures and results) and potential confounders (e.g., income, parent's education, maternal health and parent's age) were extracted by two independent reviewers (FSM and HRL); with a third reviewer (VCO) available to resolve any discrepancies. For those studies with different degrees of control for confounders, we extracted the model that adjusted for the greatest number of variables and had highest sample size. For those studies where the adjusted data were not available, the authors were contacted by e-mail. For those studies for which we received no reply from the authors, the unadjusted value was used. We extracted raw data, percentages, p-value, association estimates (Odds Ratio, OR; and Relative Risk, RR) and confidence intervals (CI) for the associations between perinatal factors and musculoskeletal pain.

2.6. Risk of bias assessment

The Newcastle-Ottawa Scale (NOS) was used to assess the quality of non-randomized studies, including cohort studies (Wells et al., 2009). The risk of bias score, modified from the NOS (Modesti et al., 2016) (adapted for cross-sectional studies), was used to assess appropriateness of research selection (representative sample, sample size, non-respondents and ascertainment of the exposure), outcome (assessment of the outcome, such as independent blind assessment, record linkage and self-report; and statistical test) and comparability (statistical adjustment). Two independent reviewers (FSM and HRL) performed the quality appraisal. Disagreements were resolved by a third reviewer (VCO).

2.7. Data analysis and data synthesis

Extracted estimates of association (OR and RR) and CIs were synthesized in a meta-analysis when two or more studies reported sufficiently homogeneous data. The non-homogeneous data (e.g., RR) was transformed to OR from the original raw data available in the paper. Study heterogeneity was analyzed using visual inspection of graphs and the *I*-square (I (Clark and Horton, 2018)) statistic. True homogeneity was considered to be $I^2 = 0\%$, low heterogeneity lower than 30%, moderate 30%–49%, substantial 50%–74%, and considerable heterogeneity greater than 75% (Higgins, 2011). In the case of heterogeneity equal to or higher than substantial, a random effects model was used to calculate the pooled OR estimates and their variances. Comprehensive Meta-analysis 2.2.04 software (Biostat, Englewood, NJ) was used for all analyses.

2.8. Strength of evidence

The strength of the evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) classification (Atkins et al., 2004). The GRADE has four levels, ranging from high to very-low quality. In the current study, assessment of the strength of the evidence started from low quality because all included studies were cross-sectional. From low quality, the evidence was downgraded in one point for each of the following criteria: (i) inconsistency among studies, I (Clark and Horton, 2018) > 50%, heterogeneity or absence of pooling; (ii) indirectness when participants were selected by no reliable methods or when their inclusion criteria in any of the analyzed trials was not clear; (iii) imprecision for samples < 300 participants for each outcome; (iv) risk of bias, < 5 points on the 0–10 scale; and (v) publication bias (Atkins et al., 2004). Disagreements were resolved by a third reviewer (VCO).

3. Results

The systematic search identified 1493 publications, of which 964 were removed after screening for duplicates and ineligible titles and abstracts (Fig. 1). Ten studies were identified as potentially eligible and, after full-text screening, six publications met our inclusion criteria and were included in the review (Hestbaek et al., 2003; Iversen et al., 2015,

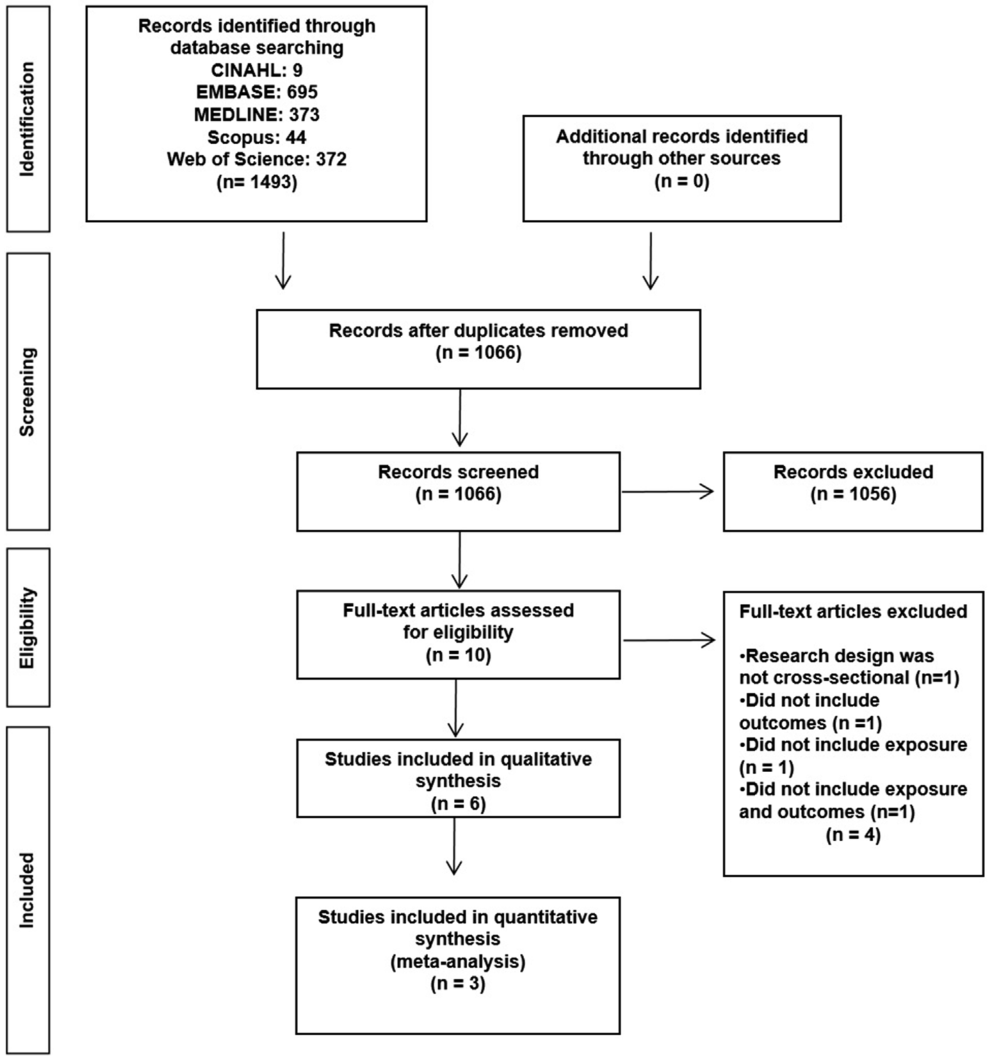

Fig. 1. Selection of the included studies.

2017; Littlejohn et al., 2012; Mallen et al., 2006; Spiegler et al., 2017). The participants' ages ranged between five (Spiegler et al., 2017) to 45 (Littlejohn et al., 2012) years old. One study included children at five years (Spiegler et al., 2017) and two studies included adolescents and young adults ranging from 12 to 22 years (Hestbaek et al., 2003; Iversen et al., 2015). Only two studies (Hestbaek et al., 2003; Iversen et al., 2015) provided disaggregated data for males and females (adolescents and young adults). The included studies were published between 2003 and 2017. The total number of participants from studies that assessed musculoskeletal pain was 25,628. Included studies recruited participants from registries and surveys in Denmark Hestbaek et al., 2003, Norway (Iversen et al., 2015, 2017), Germany (Spiegler et al., 2017) and the United Kingdom (Mallen et al., 2006; Littlejohn et al., 2012). Comprehensive descriptions are provided in Table 1.

3.1. Risk of bias

A summary of the risk of bias of included studies is shown in Table 2. Regarding selection criteria, four studies (Hestbaek et al., 2003; Iversen et al., 2015, 2017; Littlejohn et al., 2012) (66%) had a representative sample and three studies (Hestbaek et al., 2003; Iversen et al., 2015; Littlejohn et al., 2012) (50%) had a justified and satisfactory sample size. Four (Hestbaek et al., 2003; Iversen et al., 2015, 2017; Littlejohn et al., 2012) (57%) studies had established comparability between respondents and non-respondents characteristics, and the response rate was satisfactory. Overall, for outcome criteria, all included studies (Hestbaek et al., 2003; Iversen et al., 2015, 2017; Littlejohn et al., 2012; Mallen et al., 2006; Spiegler et al., 2017) used a validated tool for assessing predictors. Five studies (Hestbaek et al., 2003; Iversen et al., 2015, 2017; Littlejohn et al., 2012; Mallen et al., 2006) (83%) reported at least one assessment of the outcome (independent blind assessment, record linkage and/or self-report) and three studies (Hestbaek et al., 2003; Iversen et al., 2017; Littlejohn et al., 2012) (50%) described clear and appropriate statistical tests to analyze the data. For comparability (control for the most important factor, and/or control for any additional factor) five studies (Hestbaek et al., 2003; Iversen et al., 2015, 2017; Littlejohn et al., 2012; Mallen et al., 2006) (83%) adjusted analyses for potentially confounding factors. Overall the risk of bias of the studies was moderate (63%).

3.2. Assessment and definition of perinatal measures

Perinatal factors were extracted from National Medical Birth Register (Hestbaek et al., 2003; Iversen et al., 2015), study's database (Iversen et al., 2017; Littlejohn et al., 2012; Spiegler et al., 2017) or medical records (Mallen et al., 2006). The most common measure of perinatal factors in the included studies was low birth weight (< 2500 g) (Hestbaek et al., 2003; Iversen et al., 2015, 2017; Littlejohn et al., 2012; Mallen et al., 2006; Spiegler et al., 2017). The second most common measure was gestational age (Hestbaek et al., 2003; Iversen

Table 1
Summary of included studies (n = 6).

Study	Design	Study population	Perinatal factors	Musculoskeletal pain	Results	Results after adjusting for confounders
Hestbaek et al. (2003)	Cross-sectional	Survey including Danish Twins aged at 12 to 22 y N = 8278 twins Sex: 56% female	Birth weight (≤2000, 2001–2500, 2501–3000, > 3000 g) 1- or 5-min Apgar scores (total score) Gestational age (≤35, 36–37, 38–39, > 40 wk)	LBP (one-year incidence or LBP ever) LBP was defined as pain in the last year in the area between the lower ribs and the lower gluteal folds)	One-year incidence of LBP and LPB ever, was associated with highest values of birth weight (> 3500), in males OR 1.85 (95% CI 1.26–2.71, $p < 0.05$) and females OR 1.97 (95% CI 1.35–2.88), respectively (data adjusted for age) 1- or 5-min Apgar and gestational age was not associated with low birth weight in male and females (data adjusted for age). There was no difference between males and females.	The only factor that was found to be consistently associated with LBP was birth weight after adjustment for BMI, weight or height (data did not change after adjusting). Perinatal factors were not associated after adjustment for genetics (within-twin pair analysis)
Iversen et al. (2015)	Cross-sectional	Third Nord-Trondelag Health Study (HUNT3) aged 13–18 y N = 7120 Sex: 49% female	Birth weight (< 2500, 2500–3249, 3250–3749, 3750–4999 and ≥ 4500 g) Preterm birth (< 34, 34–36, 37–41 and ≥42 wk) Apgar score (< 7, 7 and > 7)	Chronic nonspecific pain (defined as pain at least once a week for the last three months regardless of the number of localizations) Chronic multisite pain (defined as chronic nonspecific pain from three or more localizations) Chronic daily pain (chronic nonspecific pain almost every day regardless of the number of localizations)	There were no consistent associations between preterm birth OR 0.9 (95% CI 0.5–1.7) and OR 0.8 (95% CI 0.4–1.6) and chronic pain in boys and girls, respectively; and no clear association between low birthweight OR 0.8 (95% CI 0.6–1.2) and 1.0 (95% CI 0.7–1.3); and chronic pain complaints in boys and girls, respectively. Post-term birth was associated with higher OR 1.8 (95% CI1.3–2.6) of having chronic multisite pain and daily pain in boys. A low Apgar score in girls was strongly associated with increased OR 2.6 (95% CI 1.1–5.8) of reporting chronic daily pain in girls.	The results did not change after adjusting for multiple possible confounders (total income, parents' education and age, mother's parity and adolescent's age)
Iversen et al. (2017)	Cross-sectional	Preterm infant admitted to the Neonatal Intensive Care at the University Hospital in Trondheim, Norway aged at 19 y at baseline N = 216 Sex: not reported	Very low birth weight ≤1500 g) Small for gestational age (born at term) Days admitted to the neonatal intensive care admission Days on ventilator Days with supplemental O_2 treatment 1- or 5 min Apgar scores	Pain intensity (bodily pain during the last 4 weeks) Chronic nonspecific pain (defined as bodily pain which has lasted for more than 6 months)	Very low birth weight was associated to chronic pain and intensity of pain, OR 2.8 (95% CI 1.2–6.4) and 2.6 (0.9–7.6), respectively. In the very low birth weight group the number of days in neonatal intensive care admission, on ventilator, with supplemental O_2 treatment, and 1- or 5-min Apgar scores were not associated with self-reported pain (duration and intensity). The small for gestational age group showed a significantly higher risk of having moderate to very severe pain (OR 3.9, 95% CI 1.7–8.7) and chronic musculoskeletal pain (OR 3.6, 95% CI 1.3–9.9) in adult life.	Very low birth weight was not associated with chronic pain and pain intensity when adjusted for: Anxiety, depression, maternal smoking, sex and maternal age for chronic and intensity pain, OR 1.6 (95% CI 0.4–5.4) and 1.7 (95% CI 0.7–4.3), respectively. Small for gestational age was not associated with pain intensity and chronic pain after adjustment for confounders (sex, maternal age and intelligent quotient at 26 years in participants with data on anxiety and depression), OR 2.5 (95% CI 1.0–6.2) and 2.6 (95% CI 0.8 to 8.5), respectively.
Littlejohn et al. (2012)	Cross-sectional	The 1958 British Cohort Study (or National Child Development Child Study); participants aged at 45 y N = 8572 Sex: not reported	Gestational age (full term, ≥ 37; and preterm, < 37 wk) Birth weight (full birth, ≥2500; low birth, 1500–2500; and very low birth weight, < 1500 kg)	Chronic widespread pain (pain present for three months or more, both above and below the waist, on both left and right sides of the body, and in the axial skeleton)	Preterm birth was not associated with chronic widespread pain RR 1.26 (95% CI 0.95–1.67) Low birthweight was not associated with an increased risk of pain RR 1.01 (95% CI 0.78–1.32). Very low birth weight was not associated to chronic widespread pain, RR 1.48 (95% CI 0.42–5.22, $p > 0.05$)	The increased risk of pain with preterm birth weight decreased after adjustment (sex, social class at birth and age 42, childhood behavior problems at 11 y, and adult psychiatric disorder), RR 0.85 (95% CI 0.56–1.27) The risk of pain with very low birth weight did not change after adjustment for sex and social class at birth, RR 1.41 (95% CI 0.39–5.15).
Mallen et al. (2006)	Cross-sectional	Young adults (18–25 y) registered at the time of survey in Stoke-on-Trent N = 580 Sex: 58.6% female	Period of gestation (< 37 wk) Birth weight (< 2500 g) Neonatal intensive care admission	Chronic nonspecific pain (defined as pain lasting for over three months in the previous six months)	Prematurity OR 0.14 (95% CI 0.0–1.1), foetal distress 0.80 (95% CI 0.4–1.8), artificial commencement of labour 1.04 (95% CI 0.6–1.8), or non-vaginal delivery 1.03 (95% CI	Adjustments for age and gender made minimal differences to the odds ratios.

(*continued on next page*)

Table 1 (*continued*)

Study	Design	Study population	Perinatal factors	Musculoskeletal pain	Results	Results after adjusting for confounders
			Artificial commencement Fetal distress Non-vaginal delivery		0.5–2.0), neonatal intensive care admission OR 1.6 (95% CI 0.4–7.4) were not associated with chronic pain. The risk tended to be higher for pain status with low birth weight OR 2.2 (95% CI 0.6–7.0), but not associated.	
Spiegler et al. (2017)	Cross-sectional	German neonatal network cohort at 5 y N = 862 Sex: 50% female	Very low birth weight (< 1500 g)	Multisite pain (frequency of pain during the last 12 months)	The frequency of pain was: Leg pain: 13% Back pain: 2% Arm pain:3% Leg pain: 13% Thoracic pain:1%	Not adjusted

LBP Low Back pain; *BMI* Body Mass Index.

Table 2
Risk of bias assesment of included studies.

Study	Selection (max 5 stars)				Outcome (max 3 stars)		Comparability (max 2 stars)	Quality score
	Representative Sample[a]	Sample size[b]	Non-respondents[c]	Ascertainment of the exposure[d]	Assessment of the outcome[e]	Statistical Test[f]	Statistical adjustment[g]	Total score
Hestbaek et al., 2003	*	*	*	**	**	*	**	10/10
Iversen et al., 2015	*	*	*	**	*	N	*	7/10
Iversen et al., 2017	*	N	*	*	*	*	*	6/10
Littlejohn et al., 2012	*	*	*	*	*	*	*	7/10
Mallen et al., 2006	N	N	N	**	***	N	*	6/10
Spiegler et al., 2017	N	N	N	**	N	N	N	2/10
Mean score								6.3

*Star score, N = No star.
[a] Truly representative of the average in the target population (all population or random sampling)*; somewhat representative of the average in the target population*.
[b] Justified and satisfactory*.
[c] Comparability between respondents and non-respondents' characteristics is established, and the response rate is satisfactory*.
[d] Validated measurement tool**; no-validate measurement tool, but the tool is available or described*.
[e] Independent blind assessment**; record linkage*; self-report*.
[f] The statistical test used to analyze the data is clearly described and appropriate, and the measurement of the association is presented, including confidence intervals and the probability level (*p* value).
[g] The study controls for the most important factor*; or/and the study control for any additional factor*.

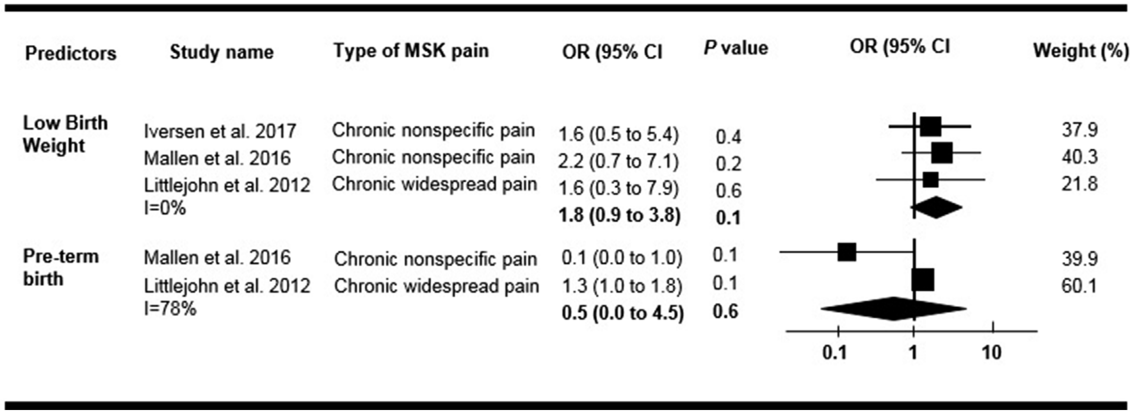

Fig. 2. Pooled and individual ORs of studies (adjusted or non-adjusted for confounding factors) that investigated the association between the perinatal factors, low birth weight (< 2500 g) and pre-term birth (< 37 wk), and chronic nonspecific pain. Squares represent individual studies. Diamonds represent the pooled effect. Weight % represents the influence of each study in the overall meta-analysis. OR, odds ratio; CI, confidence interval; I^2, heterogeneity of studies; MSK, Musculoskeletal.

et al., 2015; Littlejohn et al., 2012; Mallen et al., 2006), followed by 1–5 min Apgar score (Hestbaek et al., 2003; Iversen et al., 2015, 2017). The cut-points used in each study are provided in Table 1.

3.3. Assessment and definition of musculoskeletal pain

The most common musculoskeletal pain conditions included was chronic nonspecific pain (Iversen et al., 2015, 2017; Mallen et al., 2006), followed by widespread/multisite pain (Iversen et al., 2015; Littlejohn et al., 2012; Spiegler et al., 2017) and low back pain (Hestbaek et al., 2003) (Table 1). Pain was assessed by questionnaires (Hestbaek et al., 2003; Iversen et al., 2015, 2017; Littlejohn et al., 2012; Mallen et al., 2006; Spiegler et al., 2017), with a body chart also included in two studies (Littlejohn et al., 2012; Mallen et al., 2006).

3.4. Qualitative synthesis

3.4.1. Perinatal factors and musculoskeletal pain in childhood and adolescence

One study (Spiegler et al., 2017) described the year prevalence of multisite musculoskeletal pain among five-year old children in a cohort with very low birth weight, compared to a healthy birth-weight cohort (Table 1). There was a low frequency of multisite pain in these cohorts, and the frequency of pain was not statistically different between those born with very low birth weight and healthy controls.

One study (Hestbaek et al., 2003) described the association between low back pain and perinatal factors among a cohort of 8000 Danish adolescent twins, aged 12–22 years old. The OR (adjusted for age) for the lifetime prevalence of low back pain increased from 1.22 (0.94–1.56) for a birth weight of 2000–2500 g, to 1.97 (1.35–2.88) for a birth weight of > 3500 g, compared to the smallest weight group (< 2000 g) in males, but not in females. The same pattern was evident for one-year prevalence of low back pain. However, the co-twin control study (i.e., one twin report back pain while the other did not, which permits to adjust for familiar factors, such as genetic and environment) showed no associations between low back pain and birth weight. Furthermore, no associations were found between low back pain and other birth factors (e.g. 1–5 min Apgar score and gestational age) (Table 1).

One study (Iversen et al., 2015) (Young-HUNT) reported the association between chronic pain and perinatal factors in 8200 adolescents aged 13–19 years. The authors found no consistent association between pre-term birth and chronic pain and no clear association between birth-weight and chronic musculoskeletal complaints in adolescence. However, post-term birth in boys (OR 1.8, 95% CI 1.3–2.7) and 5-min Apgar score (< 7) in girls (OR 2.7, 95% CI 1.1–6.6) was associated with increased odds of reporting chronic daily pain, adjusted for confounders (Table 1).

3.4.2. Perinatal factors and musculoskeletal pain in adulthood

One study (Iversen et al., 2017) investigated the relationship between self-reported pain (moderate to very severe pain in the last four weeks) in adults and the following perinatal variables: days admitted to the neonatal intensive care unit (OR 1.0, 95% CI 1.0–1.0; p = 0.5), days on a ventilator (OR 1.0, 95% CI 0.9–1.1; p = 0.5), days with supplemental oxygen (OR 1.0, 95% CI 1.0–1.0; p = 0.9) and 1 (OR 1.0, 95% CI 0.8–1.3) −5 min Apgar score (OR 1.1, 95% CI 0.8–1.5) (Table 1). Similarly, in a study of young adults (18–25 years) (Mallen et al., 2006), after adjustment for age and gender, artificial commencement of labour (OR 1.0, 95% CI 0.6–1.9), fetal distress (OR 0.8; 95% CI 0.3–1.8) and non-vaginal delivery (OR 1.0; 95% CI 0.5–2.0), were not associated with increased odds of reporting chronic musculoskeletal pain, although non-significant trends were observed for neonatal intensive care unit admission (OR 1.7, 95% CI 0.3–8.0).

One study demonstrated a higher risk of moderate to very severe pain (in the last four weeks) in a group with very low birth weight (OR 2.8, 95% CI 1.2–6.4) (Iversen et al., 2017). However, this result was attenuated and disappeared after adjustment for potential confounding factors such as mental health (OR 1.7, 95% CI 0.7–4.3). The "small for gestational age" (but not premature) group had a significantly higher risk of having moderate to very severe pain (OR 3.9, 95% CI 1.7–8.7) and chronic musculoskeletal pain (OR 3.6, 95% CI 1.3–9.9) in adult life, but the ORs were attenuated to 2.5 (95% CI 1.0–6.2) and 2.6 (95% CI 0.8–8.5), respectively, after adjustment for confounders.

3.5. Meta-analysis

Three studies were included in the meta-analysis. The non-homogeneous data (RR) from one (Littlejohn et al., 2012) study was transformed to OR. Three homogeneous studies (Iversen et al., 2017; Littlejohn et al., 2012; Mallen et al., 2006) investigated the association between low birth weight and chronic nonspecific pain. Pooled data of three studies (Iversen et al., 2017; Littlejohn et al., 2012; Mallen et al., 2006) (Fig. 2) revealed a very-low quality of evidence that low birth weight was not significantly associated with chronic nonspecific pain reported in adulthood (OR 1.8, 95% CI 0.9–3.8; n = 157; p = 0.1). Furthermore, pooled of two studies (Littlejohn et al., 2012; Mallen et al., 2006) showed a very-low quality of evidence that pre-term children had no greater association of reporting chronic nonspecific pain in adult life (OR 0.5; 95% CI 0.0 to 4.5; n = 374; p = 0.6) (Fig. 2).

4. Discussion

4.1. Main findings

Early life distress seems to impact on health across the lifespan and has been associated with increased susceptibility to poor health outcomes (e.g. mental health disorder, pain, obesity and asthma) (Thavagnanam et al., 2008; Cardwell et al., 2008; Sin et al., 2004; van Bodegom et al., 2017). Our review aimed to summarize the evidence of the association between perinatal factors and musculoskeletal pain across the lifespan. Evidence from all individual studies showed that perinatal factors (e.g. birth weight, gestational age, unit care admission and Apgar) were associated with musculoskeletal pain. Nevertheless, most of these associations were attenuated and rendered non-significant after adjusting for confounders. For two perinatal factors, the association remained significant even adjusting for confounders revealing that post-term birth in boys and low Apgar score in girls were associated with the risk of reporting musculoskeletal pain later in life. Furthermore, our meta-analysis did not find any association between low birth weight and pre-term with the report of nonspecific musculoskeletal pain in adult life. Overall the quality of the evidence by using GRADE classification was very low for all the associations.

4.2. Mechanism linking perinatal factors and musculoskeletal pain

Our findings revealed a greater risk of having nonspecific musculoskeletal pain in boys born post-term or girls with low Apgar score. We speculated that these findings could at least partially explain due to being exposed to stress earlier in life. It has been suggested that early life conditions (e.g., birth weight, gestational age and mode of delivery) can substantially modify hypothalamic pituitary adrenal (HPA) axis function (van Bodegom et al., 2017; Grunau et al., 2004, 2005). In fact, there is an inverse association between post-term birth (Neu et al., 2007; Nwosu et al., 1975) and Apgar score and cortisol levels of infants (Neu et al., 2007). HPA axis dysregulation has been linked to chronic musculoskeletal pain (Heim et al., 1997; Chikanza et al., 1992; Clauw and Chrousos, 1997; Crofford et al., 1994; Van Uum et al., 2008; Meeus et al., 2015) and hyperalgesia (Al'Absi et al., 2002), although it's not clear if these changes in early life are associated with cortisol disruption and higher risk of musculoskeletal pain later in life (Sveinsdottir et al., 2016).

Although the theoretical model linking early life stress and musculoskeletal pain is normally accept, evidence from our meta-analyses and other epidemiological studies are not in full agreement. One study included in this review showed no significant difference between those who had low birth weight and a control group regarding the prevalence of musculoskeletal pain at age five (Spiegler et al., 2017). Furthermore, the individual included studies failed to show any significant association (after adjustment for confounders) between having been small for gestational age (but born at term) and low birth weight (but pre-term) and musculoskeletal pain across adolescence and adult life (Iversen et al., 2015, 2017). Additionally, the meta-analysis did not support this association, because infants classified as low birth weight (OR 1.8, CI 0.9–3.8) did not have higher risk of having musculoskeletal pain in adult life. Surprising, high birth weight was significantly associated with chronic musculoskeletal pain (low back pain) in male adolescents. However, the association was attenuated after comparing twins within pairs, which suggests that genetics may be a plausible confounder. In fact, it has been shown that complaints of pain were higher among offspring of a parent with chronic pain, and when both parents report chronic pain (Higgins et al., 2015). Children of mothers with chronic pain were more likely to experience adverse birth conditions, such as low birth weight, pre-term delivery, caesarean section, intensive care admission and mortality (Higgins et al., 2015).

It has also been speculated that early repeated and prolonged pain exposure, such as exposure in neonatal intensive care, might contribute to DNA alterations (i.e., epigenetics alterations of imprinted and stress related genes) (Provenzi et al., 2018) which could be associated with pain processing disruption in childhood (Grunau et al., 1994). However, our results do not support this theory. The individuals studies included in this review did not reveal significant associations between musculoskeletal pain and fetal distress (Mallen et al., 2006), artificial ventilation (Iversen et al., 2017), neonatal admission and days admitted to the unit care after adjusting for confounders (Iversen et al., 2017; Mallen et al., 2006).

4.3. Interpretation and implications for clinical practice and research

Currently there is uncertainty regarding the impact of perinatal factors as risk factors for musculoskeletal pain later in life. Inadequate sample size (e.g., birth weight and gestational age), low number of studies with heterogeneous exposures and outcomes, and inadequate control for important confounders, such as familial factors (except for one study) (Hestbaek et al., 2003) are possible explanation for conflicting and limited results found in our systematic review. Musculoskeletal pain is associated with a complex interaction between diverse risk factors, such diabetes (Molsted et al., 2012), obesity (Smith et al., 2014; Dario et al., 2015), cardiovascular (Fernandez et al., 2016) and mental health (Fujii et al., 2018; Pinheiro et al., 2018). Also related to those comorbidities are perinatal factors (Yuan et al., 2016; Li et al., 2015; Mathewson et al., 2017), which in turn may impact on musculoskeletal pain (Hestbaek et al., 2003; Iversen et al., 2015, 2017). Further studies need to address this complex interaction, because there are no firm limits among these factors and they all interact with each other.

The results of this review provide a different perspective on the relationship between perinatal factors and musculoskeletal pain across the lifespan. Further studies accounting for genetics and the role of the environment may clarify new mechanisms underlying this association and could, in turn, lead to effective early life interventions for those newborns presenting perinatal risk factors. We highlight that future high-quality longitudinal studies, particularly using a within-pair twin case-control design, is an appropriate method to comprehend this association more precisely. For example, the link between HPA axis dysregulation in early life and musculoskeletal pain later in life needs to be better clarified using well designed studies.

4.4. Strengths and limitations

This is the first systematic review to evaluate associations between perinatal factors and nonspecific musculoskeletal pain in childhood, adolescence and adult life. Unfortunately, the limited number of included studies and the high heterogeneity of measures of perinatal factors precluded pooling of data in this review, except for birth weight and gestational age. Also, this review just included cross-sectional studies.

5. Conclusion

Our results showed no association between birth weight or pre-term birth and musculoskeletal pain in adults. Moreover, the quality of evidence after applying GRADE approach was very low across all the studies. Thus, the very low quality of evidence and limited number of studies do not suggest a direct clear association. Further longitudinal studies accounting for more relevant confounders are needed to better understand the complex mechanism among perinatal factors and nonspecific musculoskeletal pain.

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