UNIVERSIDADE FEDERAL DOS VALES DO JEQUITINHONHA E MUCURI

Programa de Pós-Graduação em Reabilitação e Desempenho Funcional

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ASSOCIAÇÃO ENTRE FATORES PERINATAIS E DOR MUSCULOESQUELÉTICA AO LONGO DA VIDA

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Dissertação apresentada ao programa de Pós-Graduação em Reabilitação e Desempenho Funcional da Universidade Federal dos Vales do Jequitinhonha e Mucuri, como requisito parcial para obtenção do título de Mestre.

Orientador: Prof. Dr. Hércules Ribeiro Leite
Coorientador: Prof. Dr. Vinícius Cunha de Oliveira

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ASSOCIAÇÃO ENTRE FATORES PERINATAIS E DOR MUSCULOESQUELÉTICA AO LONGO DA VIDA

Dissertação apresentada ao MESTRADO EM REABILITAÇÃO E DESEMPENHO FUNCIONAL, nível de MESTRADO como parte dos requisitos para obtenção do título de MESTRE EM REABILITAÇÃO E DESEMPENHO FUNCIONAL

Orientador (a): Prof. Dr. Hércules Ribeiro Leite

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DIAMANTINA

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“A única maneira de fazer um excelente trabalho é amando o que você faz. Se você ainda não encontrou, continue procurando. Não se acomode”.

Steve Jobs

RESUMO

Contexto: As condições musculoesqueléticas são problemas comuns de saúde com grande impacto nos indivíduos. Embora muitos fatores tenham sido associados ao desenvolvimento de dor musculoesquelética, como os fatores perinatais, sua etiologia ainda é pouco compreendida. **Objetivo:** Investigar sistematicamente se os fatores perinatais podem aumentar o risco de ter dor musculoesquelética ao longo da vida. **Métodos:** As bases de dados MEDLINE, CINAHL, Scopus, Web of Science e EMBASE foram pesquisadas desde o seu início até dezembro de 2017. Os descritores utilizados em nossa estratégia de busca foram relacionados a "fatores perinatais" e "dor musculoesquelética". Não houve restrições de idioma, idade, sexo ou data. Meta-análise foi usada para agrupar as estimativas de associação entre fatores perinatais e dor musculoesquelética. **Resultados:** Entre os seis artigos incluídos nesta revisão sistemática, três foram extraídos para a meta-análise. O agrupamento de três e dois estudos não mostrou associação entre dor musculoesquelética crônica e baixo peso ao nascer (OR 1.8, 95% IC 0,9-3.8, $I^2 = 0$; n = 157) ou nascimento pré-termo (OR 0.5, IC95% 0,0 -4,5; $I^2 = 78\%$; n = 374) em adultos, respectivamente. No geral, a qualidade das evidências após a aplicação da abordagem GRADE foi muito baixa em todos os estudos. **Conclusão:** Em adultos, nossa meta-análise não mostrou associação entre peso ao nascer ou prematuridade e dor musculoesquelética, e a qualidade da evidência foi muito baixa. Assim, a baixa qualidade da evidência e o número limitado de estudos não sugerem uma associação direta e clara. Outros estudos longitudinais de alta qualidade, e o controle de outros fatores de confusão mais relevantes, são necessários para entender melhor o complexo mecanismo que pode operar entre os fatores perinatais e a dor musculoesquelética.

Palavras-chave: cuidado perinatal; doença musculoesquelética; criança; adolescente; adulto.

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, I2=0; n=157) or pre-term birth (OR 0.5, 95% CI 0.0-4.5; I2=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 preterm 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.

Keywords: perinatal care; musculoskeletal disease; child; adolescent; adult.

SUMÁRIO

1 INTRODUÇÃO

1.1 Dor musculoesquelética

A dor musculoesquelética é descrita por experiências sensoriais desagradáveis e manifesta-se como consequência de lesões traumáticas cumulativas, lesões por esforço excessivo ou repetitivo e demais condições específicas que afetam o sistema locomotor, comprometendo os músculos, ossos, articulações, tendões e ligamentos (MACRAE; DAVIES, 1999). O mecanismo responsável por desencadear a dor musculoesquelética envolve a ativação dos nociceptores periféricos, os quais acionam fibras nervosas do tipo III (fibras Aδ) e tipo IV (fibras C) do sistema nervoso periférico (SNP). Esta ativação sensibiliza os neurônios nociceptivos no corno posterior da medula espinhal, a partir da atividade de neurotransmissores excitatórios, o que induz a instalação e a manutenção de modificações secundárias no sistema nervoso central (SNC) e, assim, contribui para o desenvolvimento da dor musculoesquelética (CAZZOLA *et al.*, 2014; GRAVEN-NIELSEN; ARENDT-NIELSEN, 2015).

As condições musculoesqueléticas dolorosas são consideradas como as principais responsáveis pela incapacidade na população mundial. Dados recentes demonstram que, entre os indivíduos com distúrbios musculoesqueléticos, aproximadamente 146 milhões (106 a 194 milhões) apresentaram incapacidade (VOS *et al.*, 2016). Diante deste cenário, é notável que a dor musculoesquelética contribui diretamente para um ônus substancial nas esferas sociais e econômicas (MARCH *et al.*, 2014). A dor musculoesquelética é capaz de resultar na limitação das práticas habituais, afetando a independência funcional, o estado mental e a qualidade de vida dos indivíduos. Assim, nota-se o maior uso dos recursos de assistência médica e o aumento dos custos para o sistema de saúde. Além disso, as condições musculoesqueléticas dolorosas comprometem as atividades ocupacionais, provocando a redução da produtividade, o absenteísmo e, consequentemente, o aumento dos custos aos empregadores. Neste aspecto, estima-se que, somente nos Estados Unidos, cerca de U$100 bilhões sejam gastos anualmente com o uso dos serviços de saúde e com as perdas de produtividade no trabalho em função de distúrbios musculoesqueléticos (GATCHEL; SCHULTZ, 2014; BRIGGS *et al.*, 2016).

A dor musculoesquelética pode ser classificada em aguda e crônica. A dor aguda está associada à sensibilização periférica dos nociceptores e apresenta-se como resultado de um estímulo provocado por disfunções ou lesões. Trata-se de uma dor autolimitada que pode durar até 4 semanas. Por outro lado, a dor crônica caracteriza-se pela sensibilização central dos

nociceptores e, neste caso, verifica-se a ausência de disfunções ou lesões identificáveis. Esta condição apresenta sinais de anormalidades sensoriais como a hiperalgesia generalizada e pode durar por 3 a 6 meses ou mais (WALSH *et al.*, 2008; ARENDT-NIELSEN *et al.*, 2011; LIDBECK, 2016).

Geralmente, a dor musculoesquelética ocorre ao longo da vida, podendo se manifestar desde a adolescência até a idade avançada (LEINO-ARJAS *et al.*, 2018). A dor lombar é considerada como uma das condições musculoesqueléticas mais frequentes e sua prevalência global é de aproximadamente 12%, sendo 23% ao mês, 38% ao ano e 40% ao longo da vida (HOY *et al.*, 2012). No Brasil, estimativas indicam que a prevalência de dor lombar crônica é de 4,2% para indivíduos com idade entre 24 e 39 anos, 19,6% para aqueles com idade entre 20 e 59 anos e 25,4% na população idosa com idade igual ou superior a 60 anos (MEUCCI *et al.*, 2015). Logo, é possível notar que a prevalência e o impacto das condições musculoesqueléticas dolorosas aumentam com o avanço da idade. Diante deste cenário, sabe-se que a transição demográfica acelerada e o consequente envelhecimento populacional tornaram-se responsáveis pelo aumento das doenças crônicas, o que tem resultado na adoção de estratégias para a manutenção de um estilo de vida ativo e para a redução do impacto das comorbidades. Entretanto, a dor musculoesquelética tem limitado profundamente a capacidade dos indivíduos em realizar mudanças no estilo de vida, favorecendo assim, o declínio funcional, a fragilidade, a perda de independência e a redução do bem-estar (BRIGGS *et al.*, 2016).

1.2 Fatores associados ao desenvolvimento da dor musculoesquelética

A literatura aponta inúmeros fatores que estão associados ao desenvolvimento da dor musculoesquelética e, entre eles, destacam-se os fatores biofísicos, psicológicos, sociais e genéticos. As alterações biofísicas provocadas no organismo contribuem para a dor musculoesquelética, entretanto, os aspectos envolvidos ainda não são totalmente compreendidos (HARTVIGSEN *et al.*, 2018). Os fatores psicológicos e sociais mostram-se relevantes no que se refere à ocorrência da dor musculoesquelética. Assim, verifica-se que a saúde mental, tal como a depressão, ansiedade e catastrofização da dor, por exemplo, influenciam negativamente a progressão da dor musculoesquelética em direção a um estado crônico. Além disso, o estresse psicossocial desencadeado por diferentes tipos de estressores vinculados às dificuldades e insatisfações na vida social, também é frequentemente associado

ao desenvolvimento da dor musculoesquelética (BUSCEMI *et al.*, 2017). Com relação aos fatores genéticos, sabe-se que a variabilidade genética é capaz de afetar as vias de neurotransmissão, sendo existentes associações significativas entre mutações e polimorfismos genéticos e o desenvolvimento da dor musculoesquelética (BUSKILA; SARZI-PUTTINI, 2006; VAN MEURS *et al.*, 2009; ZORINA-LICHTENWALTER *et al.*, 2016). No entanto, além dos fatores biofísicos, psicológicos, sociais e genéticos, os fatores perinatais também têm sido evidenciados como potenciais determinantes para o desenvolvimento da dor musculoesquelética.

1.2.1 Fatores perinatais associados à dor musculoesquelética

Os fatores perinatais são consequências de condições que ocorrem imediatamente antes, durante e após o parto, compreendendo o período entre 22 semanas completas de gestação (154 dias) e 7 dias completos após o nascimento (WHO, 2019). Estudos demonstram que entre os fatores perinatais responsáveis por desencadear a dor musculoesquelética ao longo da vida, pode-se citar a idade gestacional, o peso ao nascer e o escore de Apgar (HESTBÆK *et al.*, 2003; IVERSEN *et al.*, 2015; IVERSEN *et al.*, 2017).

A idade gestacional é o tempo decorrido entre o primeiro dia da última menstruação e o dia do parto, sendo expressa em semanas completas. Com base na idade gestacional, os neonatos são classificados em pré-termo (< 37 semanas), a termo (37 a 41 semanas) e pós-termo (≥ 42 semanas) (MENGESHA *et al.*, 2016; GOMELLA, 2018). O peso ao nascer trata-se da primeira medida de peso obtida logo após o nascimento, sendo definido como muito baixo (< 1500g), baixo (< 2500g), normal (≥ 2500g) e alto (> 4500g). Dentre as categorias definidas para o peso ao nascer, o muito baixo peso (< 1500g) é a condição que mais se associa à dor musculoesquelética (WHO, 2014; IVERSEN *et al.*, 2017). Já o escore de Apgar consiste em uma escala utilizada para a avaliação de 5 sinais objetivos do neonato: Aparência (cor da pele), Pulso (frequência cardíaca), Gesticulação (irritabilidade reflexa), Atividade (tônus muscular) e Respiração (esforço respiratório). Esta escala é aplicada no primeiro e no quinto minuto após o nascimento, atribuindo-se de 0 a 2 pontos para cada um dos sinais avaliados (Quadro 1). A somatória destes sinais confere aos neonatos um escore total que varia de 0 a 10, sendo os escores de 7 a 10 indicativos de boa adaptação à vida extra-uterina. Assim, para os neonatos com escore menor que 7, a aplicação da escala deve ser repetida a cada 5 minutos até

que um escore mínimo de 7 seja alcançado (APGAR *et al.*, 1958; SILBERT-FLAGG; PILLITTERI, 2017).

Quadro 1: Escore de Apgar

	ESCORE		
SINAIS	**0**	**1**	**2**
Frequência cardíaca	Ausente	Abaixo de 100	Acima de 100
Esforço respiratório	Ausente	Lento, irregular, choro fraco	Bom, choro forte
Tônus muscular	Flácido	Flexão das extremidades	Bem flexionado
Irritabilidade reflexa (Estimulação na sola do pé) (Cateter na narina)	Sem resposta Sem resposta	Algum movimento, careta Careta	Choro e retirada do pé Tosse ou espirro
Cor da pele	Azul, pálido	Corpo rosa, extremidade azul	Completamente rosa

Fonte: (APGAR *et al.*, 1958; SILBERT-FLAGG; PILLITTERI, 2017).

Adicionalmente, nota-se que fatores perinatais como tipo de parto, admissão na unidade de terapia intensiva neonatal, ventilação artificial e fatores relacionados ao sofrimento fetal são frequentemente investigados, entretanto, determinados estudos têm mostrado a ausência de associações significativas entre estes fatores e o desenvolvimento da dor musculoesquelética (MALLEN *et al.*, 2006).

1.2.1.1 Mecanismos de ligação entre fatores perinatais e dor musculoesquelética

A exposição às condições de estresse no início da vida é capaz de alterar a função do eixo Hipotálamo-Hipófise-Adrenal (HPA). O HPA é um dos principais sistemas de resposta aos estressores e relaciona-se a uma cascata de eventos centrais e periféricos, resultando na liberação de corticosteróides pelas glândulas supra-renais. A ativação do eixo HPA afeta o funcionamento do cérebro para garantir uma resposta comportamental adequada ao estressor, no entanto, essa adaptação induzida pela exposição às condições de estresse no início da vida pode gerar consequências futuras, aumentando o risco de desenvolvimento de determinadas patologias (VAN BODEGOM *et al.*, 2017).

Estudos revelam que os mecanismos subsequentes à alteração na função do eixo HPA associam-se à hiperalgesia e à dor musculoesquelética crônica (CHIKANZA *et al.*, 1992;

CROFFORD *et al.*, 1994; CLAUW; CHROUSOS, 1997; HEIM *et al.*, 1997; VAN UUM *et al.*, 2008; MEEUS *et al.*, 2015). Neste aspecto, verifica-se que os fatores perinatais podem modificar substancialmente a função do eixo hipotálamo-hipófise-adrenal (HPA), porém algumas das evidências disponíveis na literatura não indicam associações significativas entre os fatores perinatais e a dor musculoesquelética (GRUNAU; WEINBERG; WHITFIELD, 2004; GRUNAU *et al*., 2005; MALLEN *et al*., 2006; LITTLEJOHN *et al*., 2012; SPIEGLER *et al.*, 2017; VAN BODEGOM *et al*., 2017).

Adicionalmente, vale ressaltar que a exposição à dor durante o período neonatal leva a mudanças a longo prazo nos circuitos neurais. O nascimento prematuro e a consequente exposição do neonato aos múltiplos procedimentos invasivos dolorosos, durante a internação na unidade de terapia intensiva, geram uma inflamação localizada capaz de alterar permanentemente os circuitos neuronais responsáveis pelo processamento da dor na medula espinhal (ANAND, 2000). Segundo Ruda *et al*. (2000), o mecanismo relacionado ao desenvolvimento da dor ao longo da vida para aqueles indivíduos expostos a experiências dolorosas no período neonatal, baseia-se no aumento do número de fibras sensitivas primárias (aferentes) que saem do nervo ciático, fibras estas, que conectam-se com camadas superficiais do corno dorsal da medula espinhal envolvidas no processamento da dor (lâminas I / II). Essas fibras nervosas finamente mielinizadas ou não-mielinizadas também se estendem aos segmentos caudais da medula espinhal (L6 / S1) e, portanto, os neurônios do corno dorsal que recebem entrada destes terminais tornam-se hiperexcitáveis, apresentando uma atividade aumentada em repouso e em resposta a estímulos táteis ou nocivos, o que gera um aumento no comportamento de resposta à dor.

Estudos experimentais demonstram que crianças e adolescentes nascidos pré-termo com experiência em unidade de terapia intensiva neonatal apresentam maior sensibilidade e menor tolerância à dor, estando propensos a desenvolver síndromes dolorosas no futuro (BUSKILA *et al.* 2003; VEDERHUS *et al.,* 2012). Neste contexto, acredita-se que a sensibilização perceptiva aumentada nos nascidos pré-termo após estímulos dolorosos tônicos ou repetitivos resulta em uma sensibilização central, o que é indicativo de alterações neuroplásticas induzidas por atividade de longa duração nas vias centrais da dor (HERMAN *et al.,* 2006; LATREMOLIERE; WOOLF, 2009; HOHMEISTER *et al.*, 2010).

1.3 Fatores perinatais associados ao desenvolvimento de outras patologias

Atualmente, está bem consolidado na literatura que os fatores perinatais resultam em desfechos negativos capazes de comprometer a saúde do indivíduo a longo prazo (BARKER, 2004). Patologias como asma, diabetes *mellitus* tipos 1 e 2, hipertensão arterial e obesidade vem sendo investigadas como resultados da exposição do indivíduo a eventos estressores no início da vida (SIN *et al.,* 2004; CARDWELL *et al.,* 2008; THAVAGNANAM *et al.*, 2008; LI *et al.,* 2015a; LI *et al.*, 2015b; YUAN *et al.*, 2016).

No estudo conduzido por Sin *et al*. (2004), ao comparar crianças nascidas a termo (≥37 semanas) com peso normal e com alto peso, foi possível observar que aquelas com alto peso ao nascer tiveram maior risco de realizar consultas de emergência para asma nos primeiros 10 anos de vida (RR: 1,16; IC 95%: 1,04 - 1,29), sendo que para as crianças nascidas com peso acima de 4,5 Kg, houve um acréscimo de 10% do risco de realizar consultas de emergência para asma a cada aumento de 0,10 Kg (RR: aumento de 10%; IC 95%: 2% - 19%). Acredita-se que o mecanismo existente entre o alto peso ao nascer e o desenvolvimento da asma esteja associado ao estado pró-inflamatório gerado pela adiposidade, visto que os adipócitos regulam positivamente a produção de várias citocinas pró-inflamatórias, incluindo leptina, interleucina 6 e fator de necrose tumoral α, que podem se localizar no sistema pulmonar e exacerbar a inflamação das vias aéreas. Estes adipócitos podem ainda aumentar a produção e ativação de mastócitos em grandes vias aéreas, predispondo-as ao broncoespasmo (MOHAMED-ALI; PINKNEY; COPPACK, 1998). Logo, a adiposidade torna-se responsável pela diminuição das taxas de fluxo expiratório e consequente fechamento prematuro das vias aéreas periféricas, comprometendo assim, a função pulmonar (INSELMA; MILANESE; DEURLOO, 1993). Além disso, indivíduos obesos podem ter sua função muscular respiratória diminuída e o custo energético da respiração aumentado, resultando no agravamento dos sintomas da asma (KOENIG, 2001; LITTLETON, 2012).

Segundo Cardwell *et al.* (2008) e Li *et al.* (2015a), fatores perinatais como o parto cesáreo estão significativamente associados a diabetes *mellitus* tipo 1 (OR: 1,23; IC 95%: 1,15 - 1,32) e fatores perinatais como o baixo peso ao nascer apresentam associação significativa com diabetes *mellitus* tipo 2 (RR: 1,55; IC 95%: 1,46 - 1,64), respectivamente. Entre as teorias descritas para justificar o aumento do risco de diabetes *mellitus* tipo 1 nos indivíduos nascidos por parto cesáreo, considera-se que a microbiota intestinal desempenha um papel importante na

estimulação do desenvolvimento do sistema imunológico e, portanto, os nascidos por parto cesáreo ao serem expostos aos microorganismos provenientes do ambiente hospitalar adquirem uma composição microbiana intestinal diferente daqueles nascidos por parto normal que tem seu primeiro contato com os microorganismos maternos (GRÖNLUND *et al.*, 1999; GUARNER; MALAGELADA, 2003; SALMINEN *et al.*, 2004). Alternativamente, especula-se que qualquer risco aumentado de diabetes *mellitus* tipo 1 após cesariana pode ter relação causal com o estresse perinatal não específico (DAHLQUIST; KÄLLÉN, 1992). Por outro lado, o baixo peso ao nascer que trata-se de um parâmetro que reflete prematuridade ou restrição de crescimento intra-uterino é capaz de induzir o desenvolvimento deficiente das células β pancreáticas, o que resulta no decaimento da sua função e em uma menor capacidade secretora de insulina, promovendo assim, o desenvolvimento de diabetes *mellitus* tipo 2 (ERIKSSON *et al*., 2003; REMACLE *et al*., 2007*).*

Em seu estudo, Li *et al.* (2015b) confirmaram maior risco de hipertensão arterial ao longo da vida entre nascidos a termo com baixo peso (RR: 1,25; IC 95%: 1,14 - 1,37). Neste aspecto, presume-se que indivíduos com baixo peso ao nascer apresentam alterações persistentes na estrutura vascular durante o desenvolvimento fetal, o que resulta na perda de elasticidade nas paredes dos vasos e consequente predisposição à hipertensão arterial após o nascimento (BARKER, 1995; MENENDEZ-CASTRO; RASCHER; HARTNER, 2018). Além disso, o retardo do crescimento intra-uterino e o baixo peso ao nascer geram grande influência sobre o desenvolvimento renal, sendo observado um déficit de 30% no número de néfrons e consequente redução de 50% na taxa de filtração glomerular. Logo, os indivíduos que apresentam um número reduzido de néfrons tornam-se suscetíveis ao desenvolvimento de hipertensão arterial devido à alteração das curvas de pressão natriurética, o que requer a elevação da pressão sanguínea para manutenção do equilíbrio entre a ingestão normal de sódio e a excreção (ZIMANYI; BERTRAM; BLACK, 2000; HUGHSON *et al*., 2006).

Com relação à obesidade, Yuan *et al*. (2016) demonstraram que 15% dos indivíduos nascidos por cesariana foram mais propensos a se tornarem obesos do que aqueles nascidos por via vaginal (RR: 15%; IC 95%: 6% - 26%). Ao utilizar como parâmetro a comparação entre irmãos, o mesmo estudo sugere que indivíduos nascidos por parto cesáreo apresentam 64% de risco para o desenvolvimento da obesidade em relação aos seus irmãos nascidos por parto normal (RR: 64%; IC 95%: 8% - 148%). Neste aspecto, destaca-se que no parto cesáreo, a

ausência de contato com a secreção vaginal materna e a consequente exposição do indivíduo às bactérias da pele materna e do ambiente hospitalar resulta em alterações permanentes na microbiota gastrointestinal e no sistema imunológico do neonato, tornando-o suscetível a uma série de doenças crônicas a longo prazo, como é o caso da obesidade (BIASUCCI *et al.*, 2008; DOMINGUEZ-BELLO *et al.*, 2010; NEU; RUSHING, 2011; BARROS *et al*., 2012).

Finalmente, vale ressaltar que todas as patologias previamente descritas como resultados da exposição do indivíduo a eventos estressores no início da vida apresentam grande relevância para a comunidade científica, entretanto, o presente estudo tem como objetivo investigar especificamente a influência dos fatores perinatais sobre o desenvolvimento da dor musculoesquelética e conhecer a produção existente acerca do tema.

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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.

2.1 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 condi- tions. Although many factors have been associated with the develop- ment of musculoskeletal pain, its aetiology is still poorly understood (Clark and Horton, 2018). Current evidence suggests complex interac- tions 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.

2.2 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).

2.2.1 Identification of the studies

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

2.2.2 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).

2.2.3 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).

2.2.4 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.

2.2.5 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.

2.2.6 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).

2.2.7 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.

2.2.8 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).

2.3 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,

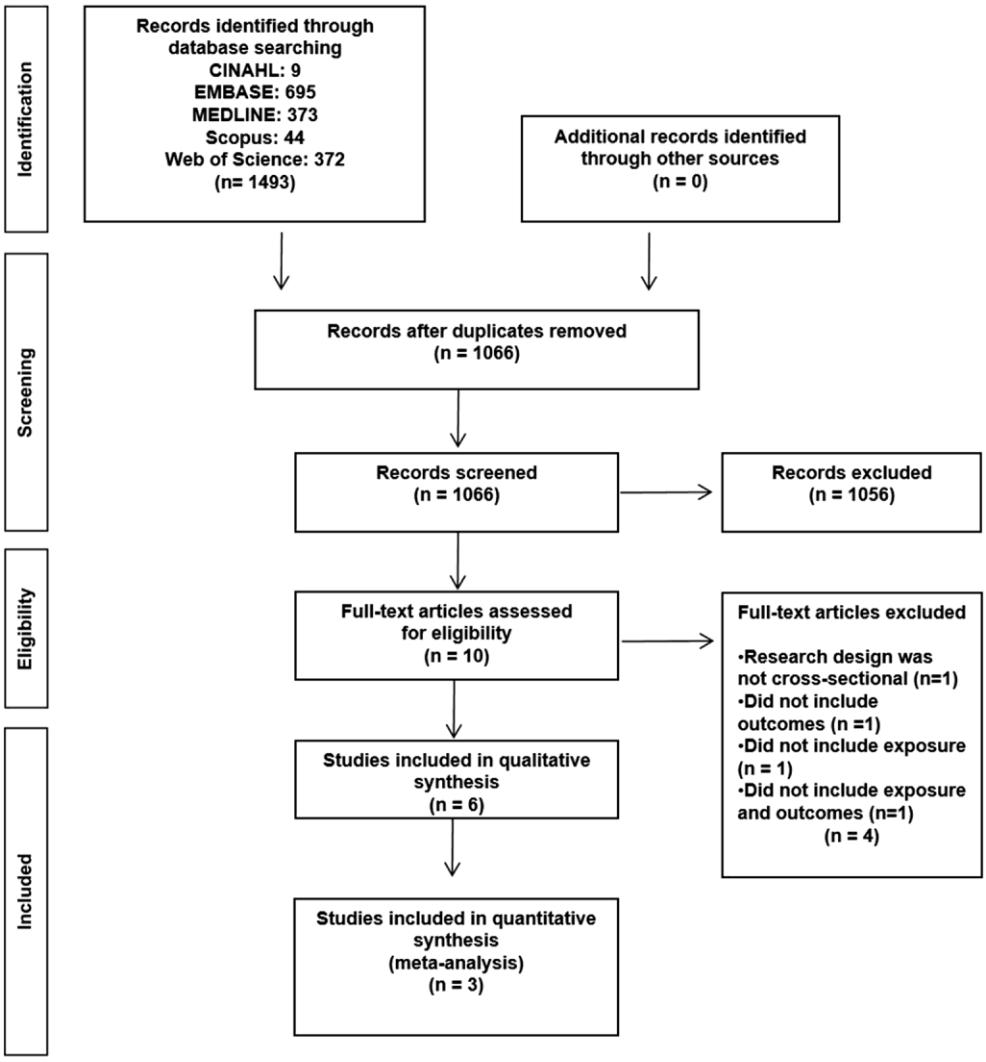

Fig. 1. Selection of the included studies.

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 (ado- lescents and young adults). The included studies were published be- tween 2003 and 2017. The total number of participants from studies that assessed musculoskeletal pain was 25,628. Included studies re- cruited 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.

2.3.1 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 fac- tors. Overall the risk of bias of the studies was moderate (63%).

2.3.2 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.

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 5y 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 . *

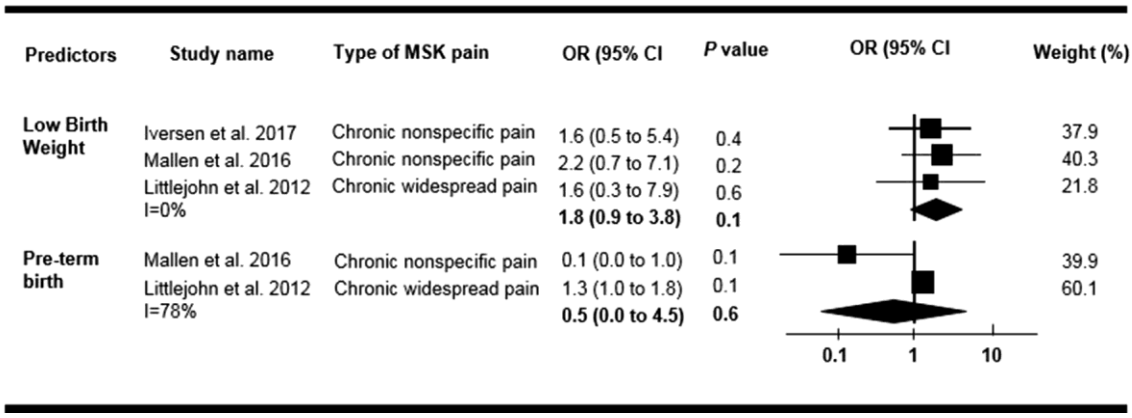

Fig. 2. Pooled and individual ORs of studies (adjusted or non-adjusted for confounding factors) that investigated the association between the perinatal factors, low birth weight (< 2500 g) and pre-term birth (< 37 wk), and chronic nonspecific pain. Squares represent individual studies. Diamonds represent 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.

2.3.3 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 in- cluded in two studies (Littlejohn et al., 2012; Mallen et al., 2006).

2.3.4 Qualitative synthesis

2.3.4.1 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 and 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).

2.3.4.2 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.

2.3.5 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).

2.4 Discussion

2.4.1 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.

2.4.2 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).

2.4.3 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.

2.4.4 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.

2.5 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.

Disclaimer statements

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3 ANEXOS

ANEXO I

Estratégia de Busca - Descritores

04/12/2017
Database: Ovid MEDLINE(R) <1946 to November Week 4 2017>
Search Strategy:

Medline
1. Musculoskeletal Pain/
2. back pain/ or low back pain/
3. neck pain/
4. chest pain/
5. shoulder pain/
6. ((back or neck or shoulder or thoracic or chest or arm or buttocks) and (pain* or ache*)).mp.
7. (low* and (back pain or backpain or backache or back ache)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
8. (upper limb* and (pain or ache)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
9. (widespread adj3 (pain or ache)).mp.
10. dors?algia.mp.
11. exp Perinatal Care/
12. perinatal*.mp.
13. exp Infant, Premature/
14. prematur*.mp.
15. exp birth weight/ or fetal weight/
16. birthweight.mp.
17. ((birth or f?etal or gestation*) adj3 weight).mp.
18. (gestation adj3 (birth or age or period or factor*)).mp.
19. (factor* adj3 birth).mp.
20. Gestational Age/
21. Apgar Score/
22. Premature Birth/
23. preterm.mp.
24. exp delivery, obstetric/ or cesarean section/ or cesarean section, repeat/ or extraction, obstetrical/ or vacuum extraction, obstetrical/ or labor, induced/ or vaginal birth after cesarean/ or version, fetal/
25. (c?esar?an or c-section*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
26. ((vaginal or normal) and birth*).mp.
27. Intensive Care, Neonatal/
28. (artificial* adj3 commence*).mp.
29. Fetal Distress/
30. f?etal distress.mp.
31. 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
32. Epidemiology/
33. epidemiolog*.tw.
34. observational study/
35. epidemiologic studies/ or case-control studies/ or cohort studies/ or follow-up studies/ or longitudinal studies/ or prospective studies/ or retrospective studies/

36. (epidemiolog* or cross-sectional or cohort or follow up or case control* or observational or longitudinal).mp. and stud*.tw. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
37. 32 or 33 or 34 or 35 or 36
38. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
39. 31 and 37 and 38
40. limit 39 to (humans and ("all child (0 to 18 years)" or "all adult (19 plus years)"))

Embase

Database Field Guide - Opens new tab Embase Classic 1947 to 1973, Database Field Guide - Opens new tab Embase 1974 to 2017 December 01

1. perinatal care/
2. perinatal care.mp. or perinatal care/
3. perinatal*.mp.
4. prematurity/
5. premature.mp.
6. prematur*.mp.
7. birth weight/
8. birthweight.mp.
9. ((birth or fetal) adj3 weight).mp.
10. (gestation adj3 (birth or age or period or factor*)).mp.
11. factor*adj3 birth.mp.
12. gestational age/
13. gestational age.mp.
14. apgar score/
15. cesarean section/
16. vaginal delivery/
17. vaginal birth.mp.
18. (c?esar?an or c-section*).mp.
19. ((vaginal or normal) and birth).mp.
20. newborn intensive care/
21. newborn intensive care.mp.
22. artificial*adj3 commence*.mp.
23. fetus distress/
24. fetal distress.mp.
25. f?etal distress.mp.
26. 1 or 2 or 3 or 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 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25
27. musculoskeletal pain/
28. backache/
29. back pain.mp.
30. musculoskeletal pain.mp.
31. (back pain or low back pain).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
32. neck pain/
33. shoulder pain/
34. ((back or neck or shoulder or thoracic or chest or arm or buttocks) and (pain* or ache*)).mp.
35. (low* and (back pain or backpain or backache or back ache)).mp.

35. (low* and (back pain or backpain or backache or back ache)).mp.
36. (upper limb* and (pain or ache)).mp.
37. (widespread adj3 (pain or ache)).mp.
38. dors?algia.mp.
39. 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38
40. epidemiology/
41. epidemiolog*.tw.
42. observational studies.mp. or observational study/
43. (epidemiolog* or cross-sectional or cohort or follow up or case control* or observational or longitudinal).mp. and stud*.tw.
44. 40 or 41 or 42 or 43
45. 26 and 39 and 44
46. limit 45 to human

Web of Science

(((perinatal care or perinatal* or prematur* or birth weight or fetal weight or birthweight or gestation age or gestation period or apgar score or premature birth or preterm or cesarean or vaginal delivery or c-section) and (musculoskeletal pain or back pain or low back pain or chest pain or shoulder pain or backache or back ache or widespread pain or upper limb pain) and (epidemiology or epidemiolog* or observational study or epidemiologic studies or case control studies or cohort studies or follow up studies or longitudinal studies or prospective studies or retrospective studies)))

Cinahl

S8	S3 AND S6 AND S37
S7	(MH " Prospective Studies+") OR (MH "Case Control Studies+") OR (MH "Epidemiological Research+") OR (MH "Cross Sectional Studies)
S6	S4 OR S5
S5	"musculoskeletal pain"
S4	(MH "Low Back Pain") OR (MH "Back Pain+") OR (MH "Chest Pain+") OR (MH "Shoulder Pain") OR (MH "Neck Pain")
S3	S1 OR S2
S2	(MH "Childbirth, Premature") OR (MH "Vaginal Birth After Cesarean") OR (MH "Infant, Low Birth Weight") OR (MH "Birth Weight") OR (MH "Infant, Very Low Birth Weight") OR (MH "Birth Weight") OR (MH "Infant, Very Low Birth Weight") OR (MH " Vaginal Birth") OR (MH "Infant, Small for Gestational Age") OR (MH "Term Birth") OR (MH "Cesarean Section, Effective") OR (MH "Infant, Large for Gestational Age")
S1	(MH "Perinatal Care") OR "perinatal care"

Scopus

(TITLE-ABS-KEY ("musculoskeletal pain" OR "back pain" OR "widespread pain") AND TITLE-ABS-KEY ("perinatal factor" OR "birth weight" OR "caesarean" OR "cesarean" OR "vaginal birth" OR "premature") AND TITLE-ABS-KEY ("cohort study" OR "cross sectional"))

ANEXO II

Newcastle-Ottawa Scale - NOS

S1 Text
NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
(adapted for cross sectional studies)

Selection: (Maximum 5 stars)

1) Representativeness of the sample:
   a) Truly representative of the average in the target population. * (all subjects or random sampling)
   b) Somewhat representative of the average in the target population. * (non-random sampling)
   c) Selected group of users.
   d) No description of the sampling strategy.
2) Sample size:
   a) Justified and satisfactory. *
   b) Not justified.
3) Non-respondents:
   a) Comparability between respondents and non-respondents characteristics is established, and the response rate is satisfactory. *
   b) The response rate is unsatisfactory, or the comparability between respondents and non-respondents is unsatisfactory.
   c) No description of the response rate or the characteristics of the responders and the non-responders.
4) Ascertainment of the exposure (risk factor):
   a) Validated measurement tool. **
   b) Non-validated measurement tool, but the tool is available or described.*
   c) No description of the measurement tool.

Comparability: (Maximum 2 stars)

1) The subjects in different outcome groups are comparable, based on the study design or analysis. Confounding factors are controlled.
   a) The study controls for the most important factor (select one). *
   b) The study control for any additional factor. *

Outcome: (Maximum 3 stars)

1) Assessment of the outcome:
   a) Independent blind assessment. **
   b) Record linkage. **
   c) Self report. *
   d) No description.
2) Statistical test:
   a) 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). *
   b) The statistical test is not appropriate, not described or incomplete.

This scale has been adapted from the Newcastle-Ottawa Quality Assessment Scale for cohort studies to perform a quality assessment of cross-sectional studies for the systematic review, "Are Healthcare Workers' Intentions to Vaccinate Related to their Knowledge, Beliefs and Attitudes? A Systematic Review".

We have not selected one factor that is the most important for comparability, because the variables are not the same in each study. Thus, the principal factor should be identified for each study.

In our scale, we have specifically assigned one star for self-reported outcomes, because our study measures the intention to vaccinate. Two stars are given to the studies that assess the outcome with independent blind observers or with vaccination records, because these methods measure the practice of vaccination, which is the result of true intention.

ANEXO III

Grading of Recommendations Assessment, Development and Evaluation – GRADE

Quality of evidence	Study design	Lower if *	Higher if *
High	Randomised trial	**Study quality**: -1-Serious limitations -2-Very serious limitations -1-Important **inconsistency** **Directness**: -1-Some uncertainty -2-Major uncertainty -1-**Sparse data** -1-High probability of **Reporting bias**	**Strong association**: +1-Strong, no plausible confounders, consistent and direct evidence** +2-Very strong, no major threats to validity and direct evidence*** +1-Evidence of a **Dose response** gradient +1-All **plausible confounders** would have reduced the effect
Moderate	Quasi-randomised trial		
Low	Observational study		
Very low	Any other evidence		

* 1 = move up or down one grade (for example from high to moderate)
2 = move up or down two grades (for example from high to low)
The highest possible score is High (4) and the lowest possible score is Very low (1). Thus, for example, randomised trials with a strong association would not move up a grade.
** A relative risk of >2 (< 0.5), based on consistent evidence from two or more observational studies, with no plausible confounders
*** A relative risk of > 5 (< 0.2) based on direct evidence with no major threats to validity

ANEXO IV

International Prospective Register of Systematic Reviews - PROSPERO

PROSPERO
International prospective register of systematic reviews

NHS
National Institute for
Health Research

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

Paulo Ferreira, Vinicius Oliveira, Fernando Siqueira, Amabile Dario, Alison Harmer, Hercules Leite

PROSPERO
International prospective register of systematic reviews

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

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Citation
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Review question
Are perinatal factors associated with musculoskeletal pain across life span?

Searches
Electronic searches will be conducted in MEDLINE, CINAHL, Scopus, Web of Science, and EMBASE databases. The full search strategy will be conducted on December 2017. In addition, citation tracking of the included studies and relevant systematic reviews will be conducted. No date or language restrictions will be applied.

Types of study to be included
Quantitative and observational studies will be included, such as cohort studies, case-control studies and cross-sectional studies.

Condition or domain being studied
Recent studies have suggested that early life conditions (e.g. low birth weight - LBW) may be associated with later morbidities, including hypertension (10), asthma (11), psychological distress (12) and musculoskeletal diseases (13). Low birth weight (<2,500 g) is the consequence of premature birth (before 37 weeks of gestational age) or intrauterine growth retardation (14). The link between LBW and adult chronic conditions has been explained by the "fetal programming theory", in which perturbations at critical stages of fetal growth and development lead to significant alterations in tissue structure and function (15, 16). In fact, LBW foetus responds increasing the glucocorticoids (e.g. cortisol) content, which in turn increases blood pressure and glucose to provide energy for vital organs, however the chronic cortisol levels lead to HPA axis dysregulation across lifespan (17, 18). Infants born with LBW have low basal cortisol concentration at 3 months, however they evidence significantly increased levels at 8 and 18 months (19). Long-term 're-setting' of endocrine stress responses (ref 19) seems to occur in children (ref 20) and adults (refs 21-23) as a result of low birth weight and HPA dysregulation(19). Despite the fact that chronic stress has been linked with hypocortisolism (24), inflammation and pain somatization disorders, including fibromyalgia (25, 26), whiplash-associated disorder (27) and low back pain (8), there is little and conflicting information regarding any link between chronic musculoskeletal pain and low birth weight.

Previous studies have shown an increased risk of self-reported chronic pain (OR, 2.6; 95% CI, 0.9-7.6) (13) or chronic musculoskeletal pain (OR, 2.1, 95% CI, 0.6-7.0) among adults (28) who had low birth weight, however confidence intervals were wide which leads to uncertainty about the risk. Further, there is considerable uncertainty regarding the relationship between LBW and chronic widespread pain in adults (RR, 1.4, 95 % CI, 0.4-5.2) (29), and LBW and chronic nonspecific pain (OR, 1.0, 95% CI, 0.7-1.3) (30) or low back pain in adolescents (OR, 1.2; 95% CI, 0.9-1.5) (31). These results demonstrate an uncertain risk and some inconsistency regarding the impact of LBW on non-specific back pain in adult life. Furthermore, a number of these studies were potentially limited by low numbers of participants with LBW or lack of adjustment for potentially confounding factors (28-30). For instance, previous twin studies have shown that heritability may explain 40–44% of the variance in liability to symptomatic non-specific back pain(32, 33), suggesting that genetics should be taken into account when studying the direct association between BP and other risk factors (34, 35).

Participants/population
Several criteria will be used to select eligible studies. We will include cross-sectional and longitudinal

observational studies that investigate the association between perinatal factors and musculoskeletal pain. Descriptors used in our search strategy will be related to "perinatal factors" and "musculoskeletal pain". There will not have language, age, sex and date restrictions. Studies will be excluded if they investigate specific conditions (fracture, cancer, and systemic diseases, osteoarthritis and sports injury) or pregnancy-related to musculoskeletal pain.

Intervention(s), exposure(s)
The exposure factors will be all perinatal exposure such as, period of gestation, birth weight, neonatal ITU admission, artificial commencement, foetal distress, Apgar scores and mode of delivery.

Comparator(s)/control
Not applicable.

Context

Main outcome(s)
The outcomes of interest will be prevalence of musculoskeletal pain (i.e, back pain and widespread pain) in cross-sectional studies and future occurrence (incidence) of chronic pain in longitudinal studies. All definitions for musculoskeletal pain will be accepted, as these varied significantly among studies.

Additional outcome(s)
Not applicable.

Data extraction (selection and coding)
Data will be extracted from each paper with customized data extraction forms. Attempts will be 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) will be 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 will 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 will be contacted by e-mail. For those studies for which we received no reply from the authors, the unadjusted value will be used. We will extract 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.

Risk of bias (quality) assessment
The Newcastle-Ottawa Scale (NOS) will be used to assess the quality of non-randomized studies, including cohort studies. A score for quality, modified from the Newcastle-Ottawa scale14 (adapted for cross-sectional studies), will be 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) will perform the quality appraisal. Disagreements were resolved by a third reviewer (VCO).

Strategy for data synthesis
A quantitative synthesis will be used if the included studies are sufficiently homogenous.

Analysis of subgroups or subsets
The results will be separated and explored by exposure (e.g birth weight, type of birth).

Contact details for further information
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PROSPERO
International prospective register of systematic reviews

NHS
National Institute for Health Research

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Anticipated or actual start date

07 December 2017

Anticipated completion date

31 July 2018

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None.

Conflicts of interest

Language

English

Country

Australia, Brazil

Stage of review

Review_Completed_not_published

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

Female; Humans; Musculoskeletal Pain; Parturition; Pregnancy

Date of registration in PROSPERO

11 December 2017

Date of publication of this version

29 May 2018

Details of any existing review of the same topic by the same authors

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes

Versions

11 December 2017

PROSPERO
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