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ORIGINAL ARTICLE

Early-life programming of pain sensation? Spinal pain in pre-adolescents with pain experience in early life

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Abstract

Neurobiological mechanisms can be involved in early programming of pain sensitization. We aimed to investigate the association between early-life pain experience and pre-adolescence spinal pain. We conducted a study of 29,861 pre-adolescents (age 11–14) from the Danish National Birth Cohort. As indicators of early-life pain, we used infantile colic and recurrent otitis media, reported by mothers when their children were 6 and 18 months. Self-reported spinal pain (neck, middle back, and/or low back pain) was obtained in the 11-year follow-up, classified according to severity. Associations between early-life pain and spinal pain in pre-adolescents were estimated using multinomial logistic regression models. To account for sample selection, inverse probability weighting was applied. Children experiencing pain in early life were more likely to report severe spinal pain in pre-adolescence. The association appeared stronger with exposure to two pain exposures (relative risk ratio, 1.31; 95% CI, 1.02–1.68) rather than one (relative risk ratio, 1.14; 95% CI, 1.05–1.24). We observed similar results when using headache and abdominal pain as outcome measures, underpinning a potential neurobiological or psychosocial link in programming of pain sensitization.

Conclusion: Experience of early-life pain is seemingly associated with spinal pain in pre-adolescence. The study highlights that early-life painful experiences can influence programming future pain responses.

What is Known:

- *Spinal pain in pre-adolescents is common, causes marked discomfort and impairment in everyday life, and may be an important predictor of spinal pain later in life.*
- *Neurobiological mechanisms have been suggested as involved in early programming of pain sensitization.*

What is New:

- *Pain exposure in early postnatal life in terms of infantile colic and recurrent otitis media is associated with spinal pain in pre-adolescence; thus, experience of such painful conditions in the early postnatal period may seemingly influence programming of future pain sensation.*

Keywords Back pain, · Spinal pain, · Pain sensitivity, · Pre-adolescence, · Epidemiology

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Abbreviations

DNBC	The Danish National Birth Cohort
DNBC-11	The 11-year follow-up in the Danish National Birth Cohort
IPW	Inverse probability weighting
ISCED	International Standard Classification of Education
RRR	Relative risk ratio
Spinal pain	Neck pain, middle back pain, and/or low back pain
YSQ	The Young Spine Questionnaire
95% CI	95% confidence interval

Introduction

Spinal pain (i.e., neck, middle back, and/or low back pain) is a prevailing problem among school-aged children [13, 26, 31]. The 6-month prevalence of severe spinal pain was recently estimated to 11% of 11-year-olds in Denmark increasing rapidly with age [26]. Spinal pain can cause marked discomfort and impairment in children's everyday life and have lifelong problems, physically and mentally [13, 17, 27, 47]. In addition, pediatric-onset of spinal pain is suggested as an important predictor of spinal pain in later life [20, 51]. However, little is known about the etiology and early-life factors predisposing to spinal pain, which makes effective and targeted prevention of spinal pain in young people difficult [13].

Mechanisms involved in pain susceptibility are still not well understood. Neurobiological mechanisms are involved in the production and perception of pain including the nociceptive system and the hypothalamic-pituitary-adrenal (HPA) axis (i.e., stress response) [7, 19, 44]. These mechanisms are particularly sensitive for programming and modulations in the perinatal period due to the ongoing maturation of the neurobiological systems and significant brain development [19, 32, 35]. Changes in the functioning of the nociceptive system can be induced by recurrent and persistent pain experience in early life [19, 44]. Such changes can persist well beyond infancy and result in profound and long-lasting effects on pain processing [19, 44] including decreased pain threshold [18], hyperalgesia [18, 50], and allodynia [1]. The HPA axis is a key mechanism underlying the link between early-life development and later-life disease [14, 40]. Childhood adversities and early-life stressors can lead to excessive activation of the HPA stress response. This, in turn, can result in long-term alterations in HPA axis responsiveness [7, 32, 35] and in enhanced susceptibility to the development of chronic pain in later life [7] for example fibromyalgia [41] and chronic back pain [54]. Thus, dysfunction of the HPA axis may also impact the nociceptive system [7].

Previous studies on the association between early-life pain and later-life pain sensation have primarily focused on experiences in the neonatal intensive care unit (NICU), typically present among preterm children, as proxy measures for pain exposures in early postnatal life. In NICUs, infants are most often exposed to physiological and environmental stressors in relation to e.g. neonatal illness, neonatal surgery, and noxious stimuli exposures (e.g., medical procedures) [18, 55].

It may be worth investigating pain complaints in relation to other painful conditions appearing in the early postnatal period. Two common conditions causing pain in infants are infantile colic and acute otitis media [11, 43]. Infantile colic is characterized by repeated episodes of excessive crying or fussing during the first months of life and affects 10–20 % of all infants [11, 59]. Acute otitis media is one of the commonest infections in early life with 60–70% of all children experiencing at least one episode. Before the age of 1 year, 10–20% will experience recurrent otitis media (≥ 3 episodes) and, accordingly, experience frequent acute ear pain, fever, and general illness [42, 53].

To investigate the impact of early-life pain experience on future pain responses, we aimed to study whether complete unrelated early-life pain experience in terms of infantile colic and recurrent otitis media was associated with self-reports of spinal pain in pre-adolescents, taking advantage of prospectively collected data in the large-scale Danish National Birth Cohort (DNBC).

Material and methods

Study population

The DNBC is a population-based cohort of mothers and their children born from 1996 to 2003 with follow-ups during pregnancy and through childhood and young adulthood [37]. Further details of the DNBC are described elsewhere [37]. The baseline population in the present study was DNBC-children born from singleton pregnancies in the period 1998–2003, and for whom mothers had provided information about infant pain experiences in the 6- and 18-month interviews. Of these, 29,861 children participated in the 11-year follow-up (DNBC-11) and provided full information on explanatory and outcomes measures (Fig. 1).

Approval of the study was obtained from the Danish Data Protection Agency through the joint notification of the Faculty of Health and Medical Sciences at the University of Copenhagen and the DNBC Steering Committee. All data were stored and processed at Statistics Denmark and no personally identifiable data were accessible.

Pain exposures in early life

Indicators for early-life pain experience were infantile colic and recurrent otitis media. Infantile colic was assessed in the first maternal interview postpartum when the children

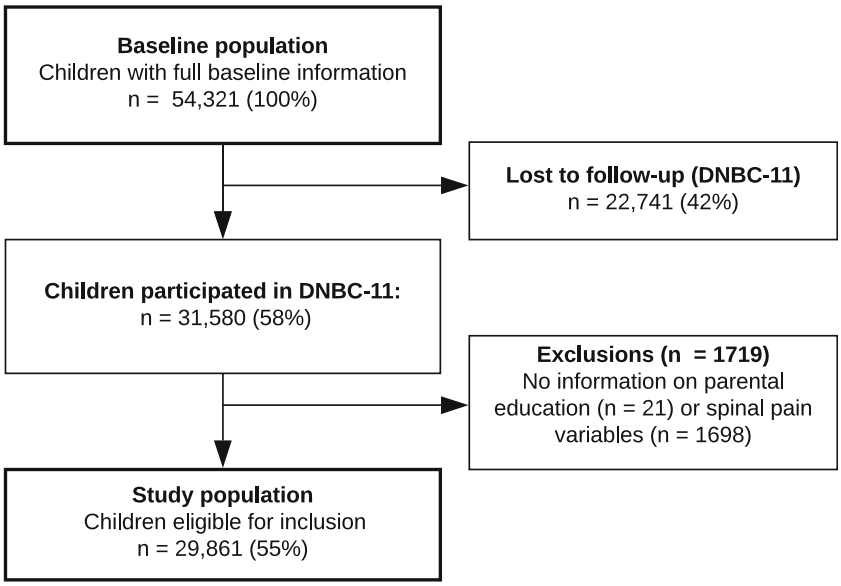

Fig. 1 Flowchart of the study population

were around 6 months of age. The mothers were asked to report hours of excessive crying per day and the number of days per week in which crying exceeded more than 3 h. Hence, infantile colic was defined as crying for more than 3 h a day and more than 3 days a week. This definition was adapted from the "Rule of three" originally proposed by Wessel and colleagues [59] and the Rome IV criteria [3]. Acute otitis media episodes were assessed by maternal reports at the 6- and 18-month interviews. Since otitis media is most prevalent after 6 months of age, we used data from the 18-month interview. Recurrent otitis media was defined as three or more episodes of acute otitis media [33, 42]. Subsequently, we conducted a measure of early-life pain experience categorized as no pain exposure, one pain exposure (infantile colic or recurrent otitis media), and both pain exposures (infantile colic and recurrent otitis media).

Spinal pain

The DNBC-11 included a subdivision of The Young Spine Questionnaire (YSQ), designed as a standardized tool of measuring back and neck pain in children age 9–11 [30]. The YSQ includes questions on pain frequency (often/once in a while/once or twice/never) and intensity (from 1 "no pain" to 6 "very much pain" based on the Faces Pain Scale-Revised (FPS-r)) of neck-, middle back-, and low back pain [21, 30].

We combined the pain frequency and intensity for each spinal region into no pain, moderate pain or severe pain [26]. No pain was defined as a report of no pain or a pain of 1 or 2 on FPS-r occurring "once in a while" or "once or twice." Severe pain was defined as pain of 4 or more on FPS-r and occurring at least "once in a while." Moderate pain was every combination of frequency and intensity in-between no pain and severe pain. Subsequently, we constructed the main outcome of interest *Spinal pain* as a composite variable including the three spinal regions categorized according to severity [26]. For further details regarding the data collection, exact classification of the applied pain groups and testing of a variety of additional case definitions of spinal pain, see the previous study by Joergensen et al. [26].

Covariates

Potential confounders selected a priori were child's sex, gestational age, parity, maternal age at childbirth, and parental educational level identified using the methods of causal diagrams [16]. Information on gestational age (term/preterm), parity (nulliparous/parous), and maternal age at childbirth (≤ 25, 26–30, 31–35, > 35 years) was obtained from the Danish Medical Birth Registry [4]. We obtained information on parental education at childbirth from the Danish population's education register [25]. Educational level was operationalized as the highest of the parent's ongoing or completed education and categorized into three groups according to the International Standard Classification of Education (ISCED) 2011: low (ISCED 0–2), medium (ISCED 3–4), and high (ISCED 5–8) [23]. All national registries applied were available at Statistics Denmark and linked to DNBC-data through the unique individual personal identification number assigned to all persons with a permanent residence in Denmark [52].

Statistical analyses

Statistical analyses were made using STATA v.15. We reported descriptive statistics by proportions and analyzed for heterogeneity using the chi-squared test. To examine associations between early-life pain experience and spinal pain at age 11–14, we applied crude and adjusted multinomial logistic

regression models to estimate and report relative risk ratios (RRR) and their corresponding 95% confidence intervals (CI) [22]. In all analyses, no spinal pain was considered as the reference outcome. Taking dependency between siblings in the sample (n = 2481) into account, we applied a robust standard error estimator [60]. Further, we used Wald tests to examine potential interactions between child's sex and early-life pain. Tests showed no signs of interactions ($p_{Moderate}$ = 0.76/p_{Severe} = 0.97); hence, the main regression analyses were simply adjusted for all the a priori identified potential confounders.

Almost half of the 54,321 eligible singletons at baseline did not participate in DNBC-11. To evaluate whether selection forces may have biased our results, we firstly performed a loss to follow-up analysis. Here we explored the extent to which the applied study population differentiated on several important characteristics from those lost to follow-up [24]. For this purpose, we applied the Danish registry data to obtain information on children lost to follow-up in DNBC-11. Secondly, we compared the original analyses with analyses using inverse probability weighting (IPW) accounting for selection from attrition [45]. Further, we conducted IPW-analyses to account for the study population being a selected sample of the source population using a reference population consisting of all children born in Denmark from 1998 to 2003 (n = 380,243). The probability of participating in the study was estimated for each individual using a given set of variables predicting selection into the cohort and loss to follow-up. We hereto estimated weight for each child (i.e., the inverse of the probability of selection) such that each participant was representing not only him/herself but also children with similar characteristics that did not participate in the study [34].

Finally, we performed a number of sensitivity analyses to examine the robustness of the findings including analyses using alternative definitions of spinal pain as well as additional somatic symptoms as outcome measures (for the definition of headache and abdominal pain, see Supplementary File 5).

Results

Almost 12% of pre-adolescents in the age range from 11 to 14 in the DNBC reported severe spinal pain and almost 30% reported moderate pain, most frequent among girls (Table 1). Pre-adolescents with early-life pain experience differed from their peers without pain experience in early life (Table 2). They were characterized by lower parental education, lower maternal age at childbirth, and they were more often born preterm. In addition, boys were more often exposed to otitis media in early life. In contrast, children with infantile colic were more often girls and firstborn.

Table 1 Prevalence of spinal pain among the 29,861 pre-adolescents included in the study population, stratified by child's sex (The Danish National Birth Cohort, born 1998–2003). (For prevalence based exclusively on DNBC-11, born 1996–2003 (N = 46,726), see Joergensen et al. [26])

	Total, N (%)	Boys, N (%)	Girls, N (%)
Spinal pain			
No pain	17,608 (59.0)	8789 (61.8)	8819 (56.4)
Moderate pain	8787 (29.4)	4059 (28.5)	4728 (30.2)
Severe pain	3466 (11.6)	1373 (9.7)	2,093 (13.4)

Association between early-life pain experience and pre-adolescence spinal pain

Results from the multinomial regression model showed that early-life pain experience increased the risk ratio of reporting spinal pain at age 11–14 (Table 3). The association was stronger for severe than for moderate pain. We observed a dose-response effect between the numbers of early-life pain exposures and the risk of pre-adolescence spinal pain. Examining the association for infantile colic and otitis media separately, we observed an association with spinal pain for both pain indicators of which infantile colic had a slightly stronger effect on spinal pain in pre-adolescents than otitis media (Table 3). We found no interaction with sex (for sex-stratified analyses, see Supplementary File 1).

Sensitivity analyses

For all analyses, we observed similar patterns to those of overall spinal pain analyzing neck, middle back, and low back pain separately (Supplementary Files 2–4). Likewise, using daily life consequences (refrainment of physical activity, school absenteeism, and care-seeking behavior) attributable to spinal pain as outcome measures of spinal pain, the results were in accordance with those of the applied definition of spinal pain. In term, the risk estimates were stronger (data not shown).

To add to the interpretation of the findings regarding spinal pain, we performed analyses using headache and abdominal pain as alternative somatic symptoms as outcome measures. These results were in line with those of spinal pain; however, results of abdominal pain were less robust (Supplementary File 5).

We further tested the impact of having had at least one episode of otitis media before 6 months (i.e., same period as infantile colic). This showed similar results to those of 18 months; however, the affected proportion of children were

Table 2. Characteristics of the 29,861 pre-adolescents included in the study population according to exposure status (early-life pain exposures, infantile colic, and otitis media) (The Danish National Birth Cohort, 1998–2003)

Characteristics	Early-life pain exposures[a]			Infantile colic[b]		Recurrent otitis media[c]	
	No pain exposure 22,158 (74.2)	One pain exposure 7120 (23.8)	Both pain exposures[d] 583 (2.0)	No 27,578 (92.4)	Yes 2283 (7.7)	No 23,858 (79.9)	Yes (≥ 3 episodes) 6003 (20.1)
Sex							
Boys	10,232 (46.2)	3665 (51.5)	324 (55.6)	13,176 (47.8)	1045 (45.8)	10,953 (45.9)	3268 (54.4)
Girls	11,926 (53.8)	3455 (48.5)	259 (44.4)	14,402 (52.2)	1238 (54.2)	12,905 (54.1)	2735 (45.6)
Gestational age[e]							
Term	21,338 (96.3)	6786 (95.3)	546 (93.7)	26,520 (92.2)	2150 (94.2)	22,942 (96.2)	5728 (95.4)
Preterm	820 (3.7)	334 (4.7)	37 (6.4)	1058 (3.8)	133 (5.8)	916 (3.8)	275 (4.6)
Parity[f]							
Nulliparous	10,266 (46.3)	3358 (47.2)	277 (47.5)	12,731 (46.2)	1170 (51.3)	11,159 (46.8)	2742 (45.7)
Parous	11,892 (53.7)	3762 (52.8)	306 (52.5)	14,847 (53.8)	1113 (48.8)	12,699 (53.2)	3261 (54.3)
Maternal age at childbirth (year)							
≤ 25	2374 (10.7)	850 (12.0)	75 (12.9)	3008 (10.9)	292 (11.8)	2592 (10.9)	708 (11.8)
26–30	9264 (41.8)	3165 (44.5)	252 (43.2)	11,679 (42.4)	1002 (43.9)	10,014 (42.0)	2667 (44.4)
31–35	7807 (35.2)	2398 (33.7)	190 (32.6)	9661 (35.0)	734 (32.2)	8351 (35.0)	2044 (34.1)
> 35	2712 (12.2)	707 (10.0)	66 (11.3)	3230 (11.7)	255 (11.2)	2901 (12.2)	584 (9.7)
Parental education at childbirth							
High	14,281 (64.5)	4368 (61.4)	307 (52.7)	17,654 (64.0)	1302 (57.0)	15,276 (64.0)	3680 (61.3)
Medium	7386 (33.3)	2578 (36.2)	252 (43.2)	9307 (33.8)	909 (39.8)	8043 (33.7)	2173 (36.2)
Low	491 (2.2)	174 (2.4)	24 (4.1)	617 (2.2)	71 (3.2)	539 (2.3)	150 (2.5)

[a] Variables were analysed with the chi-squared test of heterogeneity. The chi-squared tests were statistically significant for all variables except for parity ($p = 0.42$)

[b] Variables were analysed with the chi-squared test of heterogeneity. The chi-squared tests were statistically significant for all variables except for child's sex ($p = 0.065$)

[c] Variables were analysed with the chi-squared test of heterogeneity. The chi-squared tests were statistically significant for all variables except for parity ($p = 0.13$)

[d] Exposed to both infantile colic and recurrent otitis media

[e] Term ≥ 37-week gestation; preterm < 37-week gestation

[f] Maternal parity status in index pregnancy

markedly lower ($n = 1425$) and the results were not statistically significant (data not shown).

Selection of study participants

Children lost to follow-up constituted 45% (Fig. 1). They were more often boys, preterm born, born to parous mothers, and from families with lower educational and income status, and their mothers were younger at childbirth (Supplementary File 6). In IPW analyses accounting for selection from attrition, effect estimates were essentially unaffected (Supplementary File 7).

Finally, we performed sub-analyses in a reference population consisting of all children born in Denmark in the corresponding period, in which we applied IPW to account for selection both into the cohort and attrition. These estimates were also essentially unaffected by IPW (Supplementary File 8).

Discussion

In this study, we examined the impact of early-life pain experience on spinal pain in pre-adolescence. Children experiencing pain in early life were more likely to report spinal pain. The association appeared stronger with exposure to two pain exposures rather than one, and infantile colic was seemingly more strongly associated with spinal pain in pre-adolescents than otitis media.

Our results are concordant with our hypotheses. Pain experience results from a complex interplay of biological and psychosocial influences, and it is possible that the observed associations are attributable to specific characteristics of the children or the familial environment such as children's attention to pain, parental modeling of pain, or social learning [29, 49, 57] rather than or concurrently with a neurobiological impact of the pain experience itself. Nevertheless, there are biological reasons to suspect that pain experience in early postnatal life

Table 3 Relative risk ratio (RRR) of spinal pain according to pain experience in early life among the 29,861 pre-adolescents included in the study population (The Danish National Birth Cohort, born 1998–2003)

	No. of cases (moderate/severe)	Model 1[a,b]		Model 2[a,c]	
		Moderate pain RRR	Severe pain RRR	Moderate pain RRR (95% CI)	Severe pain RRR (95% CI)
Early-life pain exposures					
No pain exposure	6464/2510	Ref.	Ref.	Ref.	Ref.
One pain exposure	2149/875	1.07	1.12	1.08 (1.01–1.14)	1.14 (1.05–1.24)
Both pain exposures	174/81	1.08	1.30	1.09 (0.90–1.31)	1.31 (1.02–1.68)
Infantile colic					
No	8080/3165	Ref.	Ref.	Ref.	Ref.
Yes	707/301	1.12	1.21	1.12 (1.01–1.23)	1.20 (1.05–1.36)
Recurrent otitis media					
No	6997/2730	Ref.	Ref.	Ref.	Ref.
Yes (≥ 3 episodes)	1790/736	1.04	1.14	1.05 (0.98–1.12)	1.13 (1.03–1.23)

[a] Reference categories: for explanatory variables, no pain experience in early life (no infantile colic/no recurrent otitis media); and for outcome variables, not having reported moderate or severe spinal pain in DNBC-11 (no pain)

[b] Crude model

[c] Adjusted for child's sex, gestational age, parity, maternal age at childbirth, and parental education

affects both the nociceptive system and the HPA axis with both short- and long-term consequences on the pain sensation [7, 19, 44]. Thus, the findings of this study can be due to the amount of pain experience itself (i.e., affecting the nociceptive system) or the distress related to the pain experience (i.e., affecting the HPA axis), or both, making it difficult to disentangle and interpret the effects of physical versus psychological stress [7].

We observed slightly stronger associations for infantile colic than for otitis media. This may be explained by the first months of life being more sensitive to alterations in the neurobiological mechanisms or it may be related to the nature of infantile colic and otitis media. Applying the measure of otitis media at 6 months did not reveal timing as a main issue. However, since infantile colic exposes the child to longer cumulative pain duration compared with one episode of otitis media, we cannot exclude that timing constituted a main issue. Also, the subjective pain experiences caused by infantile colic and otitis media in terms of topography and intensity are likely to differ. Moreover, longitudinal studies have indicated that infantile colic is associated with inefficient sensory processing [12] and exhibited emotional and behavioral problems [6, 8]; hence, it is likely that otitis media does not have the same potential as infantile colic to sensitize children in terms of pain and distress.

Our analyses revealed no sex differences, which is in contrast to the existing literature regarding programming of the HPA axis [5, 9, 35, 58] and the nociceptive system [2, 46]. This may be explained by the complex interplay between biological and psychosocial influencing pain experience [2, 46, 56].

In addition to the main analyses of spinal pain, we found relevant correlations between early-life pain experience and additional somatic symptoms in terms of headache and abdominal pain. Thus, the early-life relation to spinal pain in pre-adolescents is seemingly not an exclusive correlation. However, it has become increasingly acknowledged that vulnerability to spinal pain develops and becomes apparent already in childhood and subsequently tracks into adult life [13, 20, 28, 51]. Therefore, further analyses are necessary to investigate whether the mechanisms involved in the development of spinal pain in pre-adolescents diverge from those of other somatic symptoms.

As mentioned, parental modeling of pain can be an important mechanism influencing children's pain perception and behavior. Parents are central in developing self-esteem, self-confidence, and effective coping mechanisms in their children. Parental modeling of pain behaviors is shown to affect children's own pain outcomes [15]. It is also theorized that within the family, a specific cognitive style exists for coping with pain that is associated with a child's response to pain experience [29]. In addition, parental pain behavior has been associated with children's report of spinal pain [10, 48]. Both infantile colic and recurrent otitis media induce a disproportional degree of parental concern and distress [11, 39, 43]. It could be speculated whether experience of having children with pain in early life makes parents exaggerate their children's pain, starting a trajectory where they amplify the pain,

which in turn increases the children's attention to pain. Accordingly, it is possible that pain catastrophizing and sensitization arise as a function of social learning and parental modeling of pain [6, 48, 49].

Strengths and limitations

By using data from the DNBC, we were able to perform a large-scale study of early-life programming of pain in children including maternal and self-reported variables that are not available in national registries. The prospective study design ensured temporality between early-life pain and spinal pain in pre-adolescents. Another strength of this study was the inclusion of both infantile colic and otitis media as pain indicators. Although they are pathologically very different conditions, occurring at different points during infancy and with different duration periods, the results were robust for both conditions. This validates both as being indicators for pain experience with similar mechanistic relations to pain sensitization.

Both exposures were based on maternal reports, which may have introduced misclassification. We believe this is mainly a concern for infantile colic. Acute otitis media can be considered more distinct and objective, whereas infantile colic is more likely to be biased due to parental pain modeling and distress. Additionally, it is difficult to disentangle whether infantile colic acts as an indicator of preexisting sensitive pain processing rather than a pain exposure itself; thus, a proxy related to children born with a certain susceptibility to pain.

We were able to adjust for several potential confounders; however, when assessing the potential effect of early-life pain on subsequent pain sensation, comprehensive inclusion of appropriate psychological and social factors is challenging [58]. For example, preexisting parental concern and parental pain modeling may represent an important role in the findings. The possibility of parental concern being an intermediate step arising from having a child exposed to painful conditions may also exist. Both of which, we were not able to take into account with the data at hand. We did, however, perform a number of sensitivity analyses to reinforce the existence of neurobiological mechanisms as involved in early programming of pain e.g. by applying headache and abdominal pain as alternative somatic outcome measures. Since the association was apparent for all somatic outcomes, it points to the existence of a neurobiological link. In contrast, if the association had been apparent for only one somatic symptom, the etiology of the specific conditions would probably have been more disease-specific or due to external factors.

Lastly, the risk of selection having biased our results cannot be disregarded due to DNBC-participants being a selected sample of the source population and to the large proportion of children lost to follow-up [24]. However, the weighted results did not reveal any essential changes to the estimates; therefore, we do not believe selection bias was a major problem for the findings in this study [24, 36, 38].

Conclusion

Children with pain experience in early life are seemingly more likely to report spinal pain in pre-adolescence. This study highlights that painful early-life experiences can influence programming of future pain responses; however, whether the influence is related to the nociceptive system, the stress response or psychosocial factors remain to be explored.

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Authors' Contributions Joergensen, MSc, conceptualized and designed the study, contributed to methods development, carried out data management and analyses and interpretation of results, and drafted the manuscript.

Prof. Nybo Andersen conceptualized and designed the study, contributed to methods development and to the interpretation of results and critical revision of the manuscript.

Dr. Hestbaek contributed to the conceptualization and design of the study, to methods development, to interpretation of results and to critical revision of the manuscript.

Dr. Lucas contributed to the conceptualization and design of the study, to methods development, to the interpretation of results and to critical revision of the manuscript.

Prof. Kragh Andersen supervised in statistical methods and analyses and contributed to the interpretation of results and critical revision of the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of this article.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval Approval of the study was obtained from the Danish Data Protection Agency through the joint notification of the Faculty of Health and Medical Sciences at the University of Copenhagen and the DNBC Steering Committee.

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