

In search of risk factors for chronic pain in adolescence:

a case-control study of childhood and
parental associations

Name:	Alies Coenders
Student number:	s1636960
Supervisor:	Associate Professor David Champion
Institute:	Department of Anaesthesia and Pain Medicine Sydney Children's Hospital
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1. Abstracts

1a. English

Background and aims:

Functional pain syndromes (FPS), including growing pains (GP), recurrent abdominal pain (RAP), migraine and non-migraine headaches, are prevalent and have some co-morbid interrelationships in childhood and adolescence. However, relationships between childhood FPS and chronic pain in adolescence have not been adequately examined. This study was designed to test the hypothesis that an individual and parental history of FPS will be found more often in adolescents suffering from chronic pain than in their pain-free peers.

Methods:

Our case-control study involved 101 adolescents aged 10 to 18 years. Cases (N=46, M=14.1 years, 66.7% female) were patients of the Chronic Pain Clinic at Sydney Children's Hospital with diverse chronic pain disorders. The controls consisted of 55 adolescent volunteers recruited by the Schools Liaison Officer (M=15.5 years, 65.5% female) who did not have chronic pain. Case and control participants, as well as their parents, filled out questionnaires covering demographic data and known and potential risk factors for chronic pain. Questions were included to assess various FPS, as well as restless legs syndrome (RLS). A validated questionnaire screened for a history of GP. Chi-squared-tests, T-tests and odds ratios were used to test the univariate associations between chronic pain in adolescence and the lifetime prevalence of FPS. Logistic regression was used to test the multivariate associations.

Results:

Migraine, non-migraine headaches, RAP and RLS were reported significantly more frequently in cases than controls (*P*-values 0.010, <0.001, 0.014 and 0.027, respectively). The results for GP were not significant, probably reflecting the relatively small sample size. Parental migraine, RAP and RLS were also found to be significantly related to adolescent chronic pain. Other statistically significant associations with chronic pain included adversity, having sustained serious injury, experiencing prolonged fatigue, being low in iron and vitamin D and suffering anxiety and depression. Further, parental depression and stress were significantly more common in cases. Logistic regression analyses, explaining 36-49% of the variance in chronic pain, showed that individual history of migraine, headaches, RAP, and parental history of RAP and depression were significant multivariate associations and potential predictors.

Conclusion:

The results indicate a significant association between chronic pain disorders and an individual history of FPS, particularly regarding migraine, non-migraine headaches, and RAP. Further, parental migraine, RAP and RLS were found to be associated with chronic pain in adolescence. Known univariate child and parental associations with adolescent chronic pain were also confirmed.

1b. Dutch

Achtergrond en doelstellingen:

Functionele pijnsyndromen, waaronder groeipijnen, periodieke buikpijn, migraine en hoofdpijn, zijn prevalent en comorbide in kindertijd en adolescentie. Echter, relaties tussen functionele pijnsyndromen in de kindertijd en chronische pijn in adolescentie zijn tot op heden niet voldoende onderzocht. Dit onderzoek test de hypothese dat een individuele voorgeschiedenis van functionele pijnsyndromen vaker wordt gevonden in adolescenten met chronische pijn dan in leeftijdsgenoten die geen pijn ervaren. Bovendien wordt onderzocht of ouders van patiënten met chronische pijn vaker functionele pijnsyndromen in hun voorgeschiedenis rapporteren.

Methoden:

Ons case-control onderzoek bestond uit een populatie van 101 adolescenten tussen 10 en 18 jaar. De cases (N=46, gemiddeld 14.1 jaar oud, 66.7% vrouw) waren adolescenten met chronische pijnklachten. De 55 adolescenten in de controle groep (gemiddeld 15.5 jaar oud, 65.5% vrouw) rapporteerden geen chronische pijn. Vragenlijsten met betrekking tot demografische data en bekende of potentiële risicofactoren voor chronische pijn werden ingevuld door zowel de adolescenten als hun ouders. Specifieke vragen waren toegevoegd om verscheidene functionele pijnsyndromen en het restless legs syndroom vast te stellen. Een gevalideerde vragenlijst beoordeelde bovendien een voorgeschiedenis van groeipijnen. Chi-kwadraat-testen, T-testen en odds ratio's werden gebruikt om de univariate associaties tussen chronische pijn in adolescentie en functionele pijnsyndromen te bepalen. Logistische regressie werd gebruikt om multivariate associaties te testen.

Resultaten:

Migraine, hoofdpijn, periodieke buikpijn en restless legs syndroom kwamen significant vaker voor in adolescenten met chronische pijn dan in leeftijdsgenoten zonder pijn (*P*-waarden respectievelijk 0.010, <0.001, 0.014 en 0.027). De resultaten voor groeipijnen waren niet significant, wat meest waarschijnlijk te wijten is aan de kleine onderzoekspopulatie. Migraine, periodieke buikpijn en restless legs syndroom in ouders waren ook significant geassocieerd met chronische pijn in adolescentie. Andere variabelen met een significante relatie tot chronische pijn waren een voorgeschiedenis van slechte ervaringen en ernstig letsel, vermoeidheid, ijzer- en vitamine D deficiëntie, depressie en angst. Bovendien kwamen depressie en stress significant vaker voor in de ouders van adolescenten met chronische pijnklachten, vergeleken met de ouders van de controle adolescenten. Met logistische regressie werd aangetoond dat een individuele geschiedenis van migraine, hoofdpijn en periodieke buikpijn, tezamen met een geschiedenis van periodieke buikpijn en depressie in de ouders significante geassocieerd waren met adolescentie chronische pijn.

Conclusie:

De resultaten lieten een significante associatie zien tussen chronische pijn in adolescentie en een individuele voorgeschiedenis van functionele pijnsyndromen, met in het bijzonder migraine, hoofdpijn en periodieke buikpijn. Migraine, periodieke buikpijn en restless legs in de ouders waren ook geassocieerd met chronische pijn in adolescentie.

2. Introduction

2a. Background

Adolescent chronic and recurrent pain disorders are an important problem, affecting approximately 15% - 37.3% of the population (1-5). Unexplained chronic pain is commonly referred to as functional pain, the most well known functional pain syndromes (FPS) being growing pains (GP), non-migraine headaches, recurrent abdominal pain (RAP), migraine, neck and back pains and chronic widespread pain and its subset fibromyalgia. Typically, the first three are the most common FPS in early childhood, affecting the lower limbs, head and abdomen (6-8). Aforementioned disorders are often co-morbid, with multiple pain disorders increasing the intensity of pain experience (5, 6, 9, 10). Restless legs syndrome (RLS), although uncommon in children, exhibits some co-morbidity with FPS individually and in the family.

While FPS are known to be multi-factorial, their exact aetiology remains poorly understood. Recent publications provide evidence for the combined effects of neurobiological, physiological and anatomical changes in the central nervous system while end-organ pathology is usually minimal (11,12). FPS are thought to share a specific susceptibility, commonly referred to as pain vulnerability or sensitivity (7, 11). This propensity to pain is characterised by genetic predispositions as well as pathogenetic mechanisms, and is influenced by environmental factors, impaired pain regulatory systems and sensory inputs into the central nervous system (12).

Apart from being highly prevalent, FPS carry significant morbidity. They impair daily activities and have a negative impact on everyday functioning, resulting in a lower quality of life (13, 14). Adolescents suffering from chronic and recurrent pain report increased utilisation of health care services and medication (9, 15, 16). Furthermore, chronic pain gives rise to financial and emotional problems, influencing not only the adolescent but the family as a whole (9, 14, 17).

Due to their high prevalence, co-morbidity and negative effect on quality of life, it is important to gain more insight into the aetiology of FPS. Identifying factors associated with the development of chronic pain in adolescence might be a first step in improving both prevention and treatment.

2b. Primary objective

There is now evidence to hypothesise that a history of FPS in childhood is predictive of pain disorders later in life (18-21). Furthermore, a parental history of FPS seems to be predictive of certain chronic pain syndromes, supporting the theory of genetics playing a role in the development of chronic pain (3, 22-30). However, there is not enough support to draw the same conclusions for a wide range of chronic pain syndromes in adolescence. Publications testing the three common early childhood FPS as potential risk factors for chronic pain in adolescence are lacking, as are studies testing the influence of a parental history of FPS.

In light of this, the primary objective of the current study was to investigate relations between chronic adolescent pain conditions and (earlier) FPS occurring in the individual and/or in parents. It was hypothesised that an individual history or parental history of FPS would be found more often in adolescents suffering from chronic pain than in their pain-free peers.

2c. Secondary objective

Apart from an individual and parental history of FPS, previous studies have addressed further possible and probable risk factors for the development of pain disorders in adolescence.

Firstly, certain socio-demographic factors (e.g. age, gender and academic level) seem predictive of chronic pain, leading to the belief that pubertal girls (3, 31), older children (32) and children with a higher academic level are more prone to developing pain syndromes. Interestingly, no relationships are found between age of menarche and chronic pain (33, 34).

Secondly, a wide range of early childhood factors and experiences are thought to relate to chronic pain. For instance, having a low birth-weight (35), being born prematurely (36), being hospitalised and having experienced serious injury, adverse life events such as parental death (37-40), and having suffered acute pain (22) may lead to the development of chronic pain later in life. It remains unclear whether childhood stresses, such as familial financial hardship and living away from home, lends any predictive contribution to FPS (3, 40, 41).

Thirdly, certain factors in adolescence could be regarded as predictive for chronic adolescent pain. Using excess health services and medication (9, 23, 42), sedentary activity such as using the computer or watching TV (7, 43) and suffering from prolonged fatigue (31, 33, 44) are all found to be associated with the development of chronic pain. Further, being low in vitamin D and suffering iron deficiency are related to several different FPS and share a connection with RLS (45-50). Whether hypermobility and excessive physical exercise are associated with chronic pain remains controversial in that comparable studies show these factors either to be correlated with chronic pain (20, 43, 51, 52) or having no effect on pain whatsoever (31, 33, 44).

Fourthly, previous studies give evidence of a co-morbid relationship between chronic pain and a range of psychological disorders, demonstrating higher rates of anxiety and depression in adolescents with chronic pain relative to their peers (53-59). Janssens and colleagues have even gone so far as to calling anxiety and depression risk factors for the development of pain syndromes (60). Interestingly, the parents of chronic pain sufferers are also more likely to experience certain psychological disorders (32, 61, 62).

Finally, further familial factors are found to be associated with chronic pain. For example, children from families that are poorer and suffer more financial stress are thought to experience pain more often than children from wealthy families (63, 64).

As a secondary objective, this study was conducted to identify aforementioned probable risk factors for chronic pain in adolescence.

2d. Tertiary objective

To extend and validate the results found with respect to the primary objective, we proposed a model using an individual history of FPS to predict chronic pain in adolescence. Relevant factors, other than FPS, that were found to be univariately associated with chronic pain in adolescence, were considered as potential confounders and were controlled for.

3. Materials and methods

3a. Participants

This research was carried out as a case-control study. Eligible cases included adolescents that were currently suffering from chronic pain or had been in the past, chronic pain being defined as having had pain for longer than 3 months (65). The control group consisted of adolescents that reported no previous or current chronic pain. Both the cases and the controls were between 12 and 18 years of age.

3b. Procedure

The protocol was reviewed and approved by the Human Research Ethics Committee of the South Eastern Sydney and Illawarra Area Health Service. Individual questionnaires were designed for both the adolescents and their parents, requiring informed consent.

Cases were recruited among past or current attendees of the Chronic Pain Clinic at Sydney Children's Hospital. Patients and their parents were approached in the waiting room, by post or by telephone, and were asked to fill out the questionnaires at home. These were completed either online or on hard-copy. A total of 96 potential cases were approached.

Control participants were recruited primarily at the hospital, where adolescents participating in a Community Service Program were contacted by the School Liaison Officer. Further controls were recruited by visiting secondary schools in the proximity of the hospital. Thirty minutes of the hospital program, or, alternatively, the science class, were allocated to filling in the questionnaires under supervision of the researcher. Hard-copies were taken home to be completed by the parents and to be returned to the hospital in a pre-paid envelope.

Questionnaire distribution occurred from September 2009 to February 2011.

3c. Data collection instruments

Adolescents' questionnaire

The adolescents' questionnaire pack firstly covered socio-demographic factors, such as age, gender, age of menarche, height and weight. Secondly, to assess the occurrence of chronic pain, the adolescents were asked whether they had ever had pain that lasted longer than three months. If yes, they were required to report the diagnosis, the age of onset and the location of their pain. Furthermore, these individuals were asked to describe the intensity and impact of their pain. Thirdly, the questionnaires covered the incidence of known and perceived factors associated with (early) childhood and adolescence, to enable confirming possible risk factors for chronic adolescent pain while controlling for known risk factors.

Pain diagnosis, location and impact

For the cases, a few pages of the questionnaire were designed to learn more about their chronic pain condition. Controls were asked to skip these questions.

Firstly, in order to establish their primary pain disorder, cases were asked to report the diagnosis first provided to them by their doctor. This primary diagnosis was later checked in their hospital files. Furthermore, a body chart was included to evaluate pain location in the cases. Body charts have been validated to be used independently by children from the age of

8 onwards (66). The chart showed a body divided in 21 parts, each allocated a different number (67). An accompanying legend was used to describe in words the body part that each number represented. Participants were required to colour those parts of the body that were painful and to circle the one that hurt most. A question was added to determine whether pain in the limbs was right sided, left sided or both.

Secondly, pain intensity was assessed using the Faces Pain Scale. This scale was first introduced in 1989 and has been validated as a measure for pain intensity in children (68, 69). The scale consists of seven gender-neutral drawings of faces, each with facial expressions differentiating various levels of pain. Participants were asked to circle the face that best represented the worst intensity of pain they had experienced in the past week.

Thirdly, different tests were used to identify the significance of pain in everyday life. The first was a numerical scale, where participants were asked to score on a scale of 0 to 10 how much of their awake time they were bothered by pain (0 being *no time*, 10 being *every moment*). Secondly, the adolescents were asked to report how many days a week they were pain-free or not bothered by pain. Finally, the impact of pain on daily functioning was monitored using the Functional Disability Inventory (FDI). This survey was developed to monitor illness-related limitations in activity and social functioning and has been validated for use in children and adolescents (69-71). It consists of 15 questions assessing difficulties in carrying out everyday activities. Disability is rated on a scale of 0 to 5, where 0 is *no trouble* and 5 is *impossible*. For analysis purposes, all 15 questions were added to form a total FDI score. The FDI was regarded as clinically significant when the total score was equal to or bigger than 11.

Factors in childhood and adolescence

Adolescents were asked to report their medical history, including medical services they had attended, medication use, hospitalisation and serious injuries. Furthermore, information was obtained concerning adverse life events, such as death of a family member and parental divorce.

Questions were included to assess the occurrence of RLS and hypermobility. RLS was identified using a simple screening question: '*When you try to relax in the evening or sleep at night, do you ever have unpleasant, restless feelings in your legs that can be relieved by walking or movement?*'(72). Hypermobility was assessed with two questions, ('*Can you place the palms of your hands on the floor when your knees are straight?*') and '*Can your knees be straightened/extended beyond the normal straight?*') requiring a positive answer to both. Participants were also asked to report the amount of hours spent on physical exercise and sedentary activity, such as watching TV or playing on the computer.

To gain information on anxiety and depression, the Depression Anxiety Stress Scales (DASS-21) and the Anxiety Sensitivity Inventory (ASI-3) were used. The former is a 21-question survey that is capable of distinguishing depression and anxiety from general distress (73). Questions are designed to measure negative emotional states of depression, anxiety and general stress in the last week and are scored on a scale from 0 (*Did not apply to me at all*) to 3 (*Applied to me very much of the time*). It has been validated for use in both adolescents and adults (74, 75). The questions are scored into the three different subscales and multiplied by

two. The total scores are then compared to the full range of scores in a population, to define the severity of depression, anxiety and stress [Table 1].

The ASI-3 was included to assess the more overall functioning of the adolescents and their anxiety sensitivity. This survey uses 18 questions to enquire about physical, cognitive and social concerns. The answers are scored from 0 to 4, depending on how much the different statements apply to the participant (ranging from 0-*very little* to 4-*very much*). The questions are scored into the three different subscales and the totals compared with mean scores obtained in the general population (76). The ASI-3 has been validated and recommended for use in children and adults aged 12 and above (77, 78).

Table 1: DASS severity ratings			
	Depression	Anxiety	Stress
Normal	0 – 9	0 – 7	0 – 14
Mild	10 – 13	8 – 9	15 – 18
Moderate	14 – 20	10 – 14	19 – 25
Severe	21 – 27	15 – 19	26 – 33
Extremely severe	28+	20+	34

Parents’ questionnaire

The parents’ questionnaire pack was designed to serve two different purposes. For one, parents were asked to report early childhood factors in their child’s life in order to minimise inadequate and biased recall in the adolescents. Secondly, the parent’s version addressed further possible associated factors in family history.

Factors in (early) childhood

Parents were asked to confirm and report early childhood factors for their children, including prematurity, birth weight, serious injuries, hospitalisation, adverse life events, prolonged fatigue, acute pain problems, living away from home, low iron and low vitamin D.

Furthermore, they were asked to score their child’s academic performance on a scale of 0 (*far below average*) to 4 (*far above average*).

Questions were included to assess for both pain disorders (such as migraine, non-migraine headaches, RLS and RAP) and psychological disorders (anxiety, depression, eating disorder) in the adolescents. A validated screening measure was used to determine the presence of GP, requiring a minimum of three essential criteria with no excluding factors being met [Table 2](79).

Table 2: Screening measure to determine growing pains (GP)	
Questionnaire variables:	Essential Criteria
A) Pain was in both legs	1. A OR K
B) Pain persisted at least 3 months	2. C AND/OR pain worse at night (E AND/OR intensity scales that showed pain worse at night)
C) Pain started between ages 3-12 years	3. At least one of more general descriptive characteristics of GP (B, D, F, G)
D) Periods of days, weeks or months without leg pains	If the above three criteria were met, with no excluding factors, GP were determined likely.
E) Pain typically occurred at end of day or during night	
F) Pain was not a problem in the morning	Exclusion Criteria:
G) No significant limitation of activity and no limping	
H) No associated lack of well-being (except tiredness if sleep impaired)	1. Pattern of pain severity not consistent with GP
I) No evidence leg pains caused by definite orthopaedic disorder	2. Any indication of a definite orthopaedic disorder (I)
J) No abnormalities on specific testing	3. Any abnormalities on specific testing (J)
K) Doctor diagnosed the leg pains as growing pains	

Parental and familial factors

To gain information on possible factors associated with chronic adolescent pain occurring in the family, parents were asked to fill out some questions regarding the biological mother and biological father of the child concerned. For both parents, questions were included to determine marital status, financial hardship, employment, adverse events and chronic medical conditions.

To establish the occurrence of FPS, parents were asked whether they had ever experienced migraine, non-migraine headaches, RAP, fibromyalgia and RLS requiring medical consultation. GP was determined by applying the criteria in Table 2. To assess for psychological conditions, parents were required to report having ever suffered from depression, stress, anxiety, problems with alcohol and/or problems with drugs. Furthermore, DASS-21 and ASI-3 were added to the parents' questionnaire pack.

3d. Data analysis

Missing and inconsistent data

Missing values in both cases and controls were left blank and excluded from analysis of that particular variable. A cut-off point of 20% was used, whereby questions that 20% of participants failed to answer were excluded from analysis. Fortunately, this was only the case for the ASI-3 survey.

In the parent's questionnaires, the parent filling in the questionnaire often failed to include data on the other parent. For this reason, new variables were made to assess whether at least

one of both parents reported a certain factor. All parental factors were analysed using these new 'either parent' variables.

In certain questionnaires, parents' and adolescents' questionnaires contained inconsistencies regarding adversity, hospitalisation, injury and having RLS. Where this was the case, analysis was conducted using data obtained from the parents' questionnaire only, as these data were regarded as more reliable.

Statistical tests

Descriptive statistics were used to determine the frequencies, mean and standard deviation (SD) of different variables. To assess differences between cases and controls, Chi-squared tests were used for categorical variables and Independent T-tests for continuous variables. When numbers were small, and Chi-squared tests contained cells with an expected count of less than 5, Fisher's Exact tests were used. Associations were termed significant when a *P*-value of less than 0.05 was reached.

With regards to the tertiary objective, logistic regression was conducted to develop a model of multivariate associations as potential predictors of chronic pain in adolescence. Other relevant variables that were previously univariately found to be statistically associated to chronic pain were tested as possible confounders. These variables were entered into the model step by step, and excluded from the model if they did not significantly influence the relationship between chronic pain and an individual history of FPS. Bearing in mind the assumptions of logistic regression, care was taken not to include too many variables in the model, nor to include multicollinear variables (80)(81)(82).

In analysing the association between chronic pain and the occurrence of additional FPS, the primary diagnoses reported by cases were not included in analysis. Furthermore, when the primary diagnosis was an extension of an earlier FPS, such as migraine and non-migraine headaches, that particular FPS was not included in the analysis.

For all statistical analysis SPSS for Windows, version 17, was used.

4. Results

4a. Descriptives

Characteristics of study population

The questionnaires yielded a total response of 51 potential cases, with a response rate of 53%. Of the potential controls, 58 returned the questionnaire. Participation rates were not calculated for controls, as there was no record of the number of adolescents recruited in the science classes. After evaluating the responses, 6 potential cases and 2 potential controls were excluded on grounds of age or withdrawal of consent. Resultantly, analysis was done with a total of 45 cases and 56 controls.

The total study population was characterised according to the variables in Table 3 and Table 4. The case group and control group were relatively similar regarding gender and age. Adolescents in both groups seemed to come from more or less the same socio-economic class, judging by comparable data on financial difficulties and having at least one currently employed parent.

Table 3: Characteristics of study population (1)

	Cases N(%)	Controls N(%)
Total	45 (44.6)	56 (55.4)
Gender		
Male	15 (33.3)	21 (37.5)
Female	30 (66.7)	35 (62.5)
Either parent working	45 (100)	52 (92.9)
Either parent reported financial difficulty	10 (22.2)	6 (10.7)

Table 4: Characteristics of study population (2)

	Cases			Controls		
	Mean	Range	SD	Mean	Range	SD
Age (years)	14.1	10 - 18	2.16	15.5	13 - 17	1.32
Height (cm)	161.8	140 - 185	10.54	168.5	150 - 188	7.92
Weight (kg)	57	31 - 90	13.1	60	39 - 120	12.61

Characteristics of cases

Primary diagnosis

Table 5 presents the primary diagnoses that were reported by the cases. RAP was the FPS most commonly reported as primary diagnosis. These pains were most frequently attributable to Crohn's disease, gastro oesophageal reflux, inflammatory bowel syndrome and having an elongated bowel.

A total of 27 cases reported a syndrome other than GP, migraine, non-migraine headaches, RAP and RLS. In this category, the most common pain syndromes reported were chronic widespread pain/fibromyalgia, chronic regional pain/limb pain and neuropathic pain. As these were not the FPS of primary interest, they have been classified under 'Other'. Finally, for 3 cases the primary diagnosis was still unknown at the time the questionnaires were filled out.

Table 5: Primary diagnosis

	Cases N (%)
Growing pains (GP)	1 (2.2)
Migraine / Non-migraine headaches	5 (11.1)
Recurrent abdominal pain (RAP)	9 (20.0)
RLS (RLS)	0 (0)
Other	27 (60)
Unknown	3 (6.7)

Pain location

The vast majority of cases reported more than one body location in which they were experiencing pain. The lower limbs and abdomen were most frequently reported. The number of cases reporting a certain pain location are summarised in Table 6.

Table 6: Pain location

	Cases N(%)
Head/face	11 (24.4)
Upper limbs	10 (22.2)
Lower limbs	17 (37.8)
Abdomen	13 (28.9)
Chest	2 (4.4)
Back	7 (15.6)
Pubic area	4 (8.9)
Widespread (> 3 of the above)	7 (15.6)

Impact of pain

Adolescent cases reported a significant impact of pain on their everyday life [Table 7]. The average intensity reported using the Faces Pain Scale was 4 out of 7. With regards to the pain frequency, adolescents reported to experience pain almost half of the time, with an average of 2.69 pain-free days per week. The mean score for the Functional Disability Inventory was relatively high, as a score above 11 is regarded as clinically significant.

Table 7: Impact of pain

	Mean	SD	Range
Pain intensity (Faces Pain Scale)	4.03	1.89	1 - 7
Time bothered by pain (0-10 scale)	4.51	3.37	0 - 10
Days a week pain-free	2.69	2.78	0 - 7
Functional Disability Score	13	11.79	0 - 46

4b. Primary objective

Individual history of FPS

Amount of FPS

The results demonstrate that cases suffered from other FPS that could not be attributed to the primary diagnosis provided to them by their doctors. Some controls also reported an individual history of one or multiple FPS. The total number of FPS that the controls reported can be found in Table 8. For the cases, Table 8 shows the amount of FPS that they reported after excluding their primary diagnosis.

For both cases and controls the mean number of additional FPS was calculated. When comparing these means, a significant difference was found between cases, reporting on average 1.31 FPS apart from their primary diagnosis, and controls, reporting on average 0.30 FPS (independent t-test= 5.294, 95% CI= 0.61-1.41, *P*-value <0.001).

Reporting a total of any 3 FPS (including RLS) was found to be significantly associated with chronic pain in adolescence, while a total of any 2 FPS was not [Table 9].

Table 8: Number of FPS reported by individuals

	Cases N (%)	Controls N (%)
0	13 (28.9)	45 (80.4)
1	17 (37.8)	6 (10.7)
2	5 (11.1)	4 (7.1)
3	7 (15.6)	1 (1.8)
4	2 (4.4)	0 (0)

Table 9: Multiple FPS reported

	Cases N (%)	Controls N (%)	X²	P-value	OR	95% CI
Any 2 FPS	5 (11.1)	4 (7.1)	0.12	0.507 †	1.63	0.41 - 6.45
Any 3 FPS *	7 (15.6)	1 (1.8)	4.74	0.021 †	10.13	1.20 - 85.74

* Significant result

† Fisher's Exact test

Specification of FPS

When comparing cases to controls, a difference was found in the specific FPS that they reported [Table 10]. After excluding their primary diagnoses and additional FPS that were directly related to the chronic pain diagnosis, the most common additional FPS in the case group was non-migraine headaches (28.9%), closely followed by RAP (24.4%). Controls most commonly reported GP (7.1%).

Case adolescents reported an individual history of migraine, headache, RAP and RLS significantly more often than the controls. No significant results were found between chronic pain in adolescence and having a history of GP or other FPS, such as chronic widespread pain.

Table 10: Specific FPS reported

	Cases N (%)	Controls N (%)	X²	P-value	OR	95% CI
Growing pains (GP)	8 (17.8)	4 (7.1)	1.78	0.183	2.81	0.79 - 10.03
Migraine *	10 (22.2)	2 (3.6)	6.60	0.010	7.71	1.59 - 37.33
Non-migraine headaches *	13 (28.9)	1 (1.8)	13.16	<0.001	22.34	2.79 - 178.9
Recurrent abdominal pain (RAP)*	11 (24.4)	3 (5.4)	6.10	0.014	5.72	1.49 - 22.00
Restless legs syndrome (RLS)*	10 (22.2)	3 (5.4)	4.91	0.027	5.05	1.30 - 19.65
Other	5 (11.1)	4 (7.1)	0.12	0.507 †	1.63	0.41 - 6.45

* Significant result

† Fisher's Exact test

Parental history of FPS

The parents of adolescents with chronic pain were significantly more likely to report having migraine, RAP or RLS currently or in the past [Table 11].

Significant relationships were not found between adolescent chronic pain and parental GP, non-migraine headaches, fibromyalgia or other pain syndromes. Of the parents who reported experiencing another pain syndrome, it was found that arthritis (37.5%) and back pain were the most common (37.5%).

Table 11: Parental history of FPS

	Cases N (%)	Controls N (%)	X²	P-value	OR	95% CI
Growing pains (GP)	7 (15.6)	5 (8.9)	0.51	0.475	1.88	0.55 - 6.38
Migraine *	23 (51.1)	15 (27.3)	5.00	0.025	2.79	1.21 - 6.41
Non-migraine headaches	9 (20.0)	10 (18.2)	<0.001	1.000	1.13	0.41 - 3.06
Recurrent abdominal pain (RAP) *	18 (40.0)	6 (10.9)	9.94	0.002	5.44	1.93 - 15.35
Restless legs syndrome (RLS) *	12 (26.8)	4 (7.3)	5.56	0.018	4.64	1.38- 15.60
Fibromyalgia	1 (2.2)	2 (3.6)	<0.001	1.000 †	0.60	0.05 - 6.87
Other	7 (15.6)	7 (12.7)	0.01	0.908	1.26	0.41 - 3.91

* Significant result

† Fisher's Exact test

4c. Secondary objective

Socio-demographic factors

A significant association was found between chronic pain in adolescence and both age (independent t-test= 3.76, 95% CI= 0.67-2.20, *P*-value <0.001) and academic level [Table 12]. Cases were more likely to be younger and to have a lower academic level than controls.

No significant relationship was found between chronic pain and gender, since this was determined by recruitment. Further, chronic pain in adolescence was not significantly associated with an early onset of menarche.

Table 12: Socio-demographic factors

	Cases N (%)	Controls N (%)	X²	P-value	OR	95% CI
Gender (female)	30 (66.7)	35 (62.5)	0.05	0.822	0.83	0.37 - 1.90
Menarche (early (<13 years))	13 (76.5)	15 (51.7)	1.81	0.178	3.03	0.80 - 11.54
Academic level (below average) *	15 (33.3)	8 (14.3)	4.12	0.042	0.33	0.13 - 0.88

* Significant result

† Fisher's Exact test

Factors in (early) childhood and adolescence

Significant associations

Chi-square and Fisher's Exact tests revealed a number of (mostly early) childhood factors to be significantly associated with chronic pain in adolescence [Table 13]. These included a history of injury and adversity, the use of medication, experiencing prolonged fatigue, iron deficiency and being low in vitamin D.

Of all the adolescents having sustained a serious injury, the most common was suffering from fractures (62.5% of cases and 66.7% of controls). Adversity was mostly specified as experiencing the death of a family member (61.8%), followed by parental divorce (17.6%) and serious illness of a family member (11.8%). Fatigue followed a flu-like illness in 38.9% of cases and in 50% of controls suffering from fatigue.

Non significant associations

There was a link between chronic pain and watching TV for more than 2.5 hours a day, with the association approaching significance. The same can be said for playing a musical instrument for longer than 5 hours a week. More controls than cases reported spending more than 2.5 hours on exercise each week.

Adolescents in the case group were 1.69 times more likely to have ever been hospitalized, though the association with chronic pain failed to reach significance. Of all the reported reasons for hospitalization, surgery was the most common (69.6% of cases, 50% of controls), followed by illness (47.8% of cases, 27.3% of controls) and injury (17.4% of cases, 36.4% of controls).

Table 13: Factors in (early) childhood and adolescence

	Cases N (%)	Controls N (%)	X ²	P-value	OR	95% CI
Birth weight (low (<2.5 grams))	4 (9.1)	3 (6.4)	0.01	0.708 †	0.68	0.14 - 3.24
Prematurity	6 (13.3)	4 (7.1)	0.49	0.484 †	2.00	0.53 - 7.57
Hospitalisation	23 (52.3)	22 (39.3)	1.20	0.274	1.69	0.76 - 3.76
Injury *	10 (22.2)	3 (5.4)	4.91	0.027	5.05	1.30 - 19.65
Adversity *	21 (46.7)	13 (23.2)	5.14	0.023	2.89	1.23 - 6.79
Acute pain	24 (49.5)	26 (46.6)	0.24	0.624	1.32	0.60 - 2.90
Living away from home	5 (11.1)	5 (8.9)	0.00	0.748 †	1.28	0.35 - 4.71
Medication *	28 (66.7)	5 (9.8)	30.09	<0.001	18.4	5.98 - 56.62
Using the PC (>2.5 hrs a day)	13 (31.0)	11 (21.2)	0.71	0.398	1.67	0.66 - 4.25
Watching TV (> 2.5 hrs a week)	9 (21.4)	3 (5.8)	3.81	0.051	4.46	1.12 - 17.69
Playing instrument (> 5 hrs a week)	2 (4.8)	7 (13.5)	1.15	0.181 †	0.32	0.06 - 1.64
Fatigue *	20 (44.4)	6 (10.7)	13.14	<0.001	6.67	2.38 - 18.69
Low iron *	11 (24.4)	4 (7.3)	4.46	0.035	4.13	1.21 - 14.03
Low vitamin D *	6 (13.3)	1 (1.8)	3.43	0.043 †	8.31	0.96 - 71.80
Hypermobility	3 (7.1)	4 (7.7)	<0.001	1.000 †	0.92	0.20 - 4.37
Physical exercise (> 2.5 hrs a week)	26 (61.9)	38 (73.1)	0.87	0.351	0.60	0.25 - 1.43

* Significant result

† Fisher's Exact test

Child psychological factors

DASS-21

The results of the DASS-21 survey were analysed using two different approaches. Firstly, the total scores for the three different subscales were added and the means of cases and controls were compared [Table 14]. Secondly, the number of cases scoring moderate, severe or extremely severe ratings (based on the distinction shown in table 1) was compared to the number of controls scoring moderate, severe or extremely severe on the three subscales [Table 15]. The cases and controls scoring normal or moderate were disregarded from this analysis.

Both methods of analysis showed no significant associations. However, the relationship between chronic pain in adolescence and having moderate to extremely severe depression approached significance.

Parent report

When looking at the results of parent report, both depression and anxiety showed a significant association with chronic pain in adolescence [Table 15]. No significant results were found for ADD/ADHD, eating disorders and other psychological factors, such as obsessive/compulsive disorder.

Table 14: Child psychological factors: total DASS scores

	Cases			Controls			t-test		
	Mean	SD	Range	Mean	SD	Range	Levene's	t-value	P-value
Depression	7.45	9.19	0 – 32	4.85	5.88	0 - 26	< 0.001	1.56	0.123
Anxiety	6.16	6.23	0 – 24	6.42	6.29	0 - 30	0.73	1.98	0.843
Stress	9.21	7.01	0 – 30	8.23	7.42	0 - 36	0.90	0.63	0.528

* Significant result

Table 15: Child psychological factors: DASS ratings and parent report

	Cases N (%)	Controls N (%)	X ²	P-value	OR	95% CI
DASS rating (moderate to extr. severe)						
Depression	10 (25.0)	5 (9.6)	2.88	0.090	3.13	0.98 - 10.07
Anxiety	12 (31.6)	12 (23.1)	0.44	0.510	1.54	0.60 - 3.94
Stress	3 (7.7)	4 (7.7)	<0.001	1.000 †	1.00	0.21 - 4.75
Reported by parent						
Depression *	10 (22.2)	2 (3.6)	6.60	0.010	7.71	1.59 - 37.33
Anxiety *	13 (28.9)	6 (10.7)	4.27	0.039	3.39	1.17 - 9.81
ADD/ADHD	1 (2.2)	1 (1.8)	<0.001	1.000 †	1.25	0.08 - 20.56
Eating disorder	0 (0)	1 (1.8)	<0.001	1.000 †	0.55	0.46 - 0.66
Other	2 (4.4)	1 (1.8)	0.04	0.584 †	2.56	0.22 - 29.16

* Significant result

† Fisher's Exact test

Parental psychological factors

DASS-21

As can be seen in Table 16, there was no significant difference between the mean total scores of DASS-21 in cases and controls. However, the mean of the subscales depression and stress in cases were found to be higher than in controls. For anxiety, controls scored higher than cases.

The DASS-21 ratings of moderate, severe or extremely severe depression, anxiety and stress also failed to reach significance [Table 17].

Self report

Judging by self report, the parents of cases experienced significantly more depression and stress than did the parents of controls [Table 17]. The reported anxiety was also higher, but not significantly so.

Table 16: Parental psychological factors: total DASS scores

	Cases			Controls			t-test		
	Mean	SD	Range	Mean	SD	Range	Levene's	t-value	P-value
Depression	3.41	4.72	0 – 16	2.80	4.76	0 – 26	0.39	0.62	0.540
Anxiety	2.39	4.39	0 – 20	2.68	3.74	0 – 18	0.59	0.34	0.739
Stress	7.90	5.98	0 – 22	6.82	7.51	0 – 32	0.39	0.77	0.447

* Significant result

Table 17: Parental psychological factors: DASS ratings and self report

	Cases N (%)	Controls N (%)	X ²	P-value	OR	95% CI
DASS rating (moderate to extr. severe)						
Depression	3 (7.3)	2 (4.3)	0.05	0.655 †	1.88	0.30 - 11.83
Anxiety	3 (7.3)	4 (8.0)	<0.001	1.000 †	0.91	0.19 - 4.31
Stress	3 (7.3)	4 (8.0)	<0.001	1.000 †	0.89	0.19 - 4.22
Self report						
Depression *	18 (40.0)	7 (13)	8.13	0.004	4.48	1.66 - 12.08
Anxiety	10 (22.2)	5 (9.3)	2.28	0.131	2.80	0.88 - 8.91
Stress *	21 (46.7)	13 (24.1)	4.60	0.032	2.76	1.17 - 6.49

* Significant result

† Fisher's Exact test

Further familial factors

In testing the link between chronic pain in adolescence and further familial factors, such as financial problems, unemployment, adverse events, chronic disorders and abuse of alcohol in parents, significant associations were only found with the latter two variables [Table 18].

The chronic disorders most frequently reported by the parents were asthma, diabetes, arthritis and hypertension. Alcohol abuse most commonly occurred in the father.

Table 18: Further familial factors

	Cases N (%)	Controls N (%)	X ²	P-value	OR	95% CI
Financial problems	10 (23.3)	6 (11.3)	1.65	0.199	2.37	0.79 - 7.17
Unemployment	0 (0)	2 (3.7)	0.34	0.499 †		
Adverse events	18 (40.0)	18 (34.0)	0.17	0.684	1.30	0.57 - 3.00
Chronic disorder *	21 (46.7)	8 (15.1)	10.18	0.001	4.92	1.90 - 12.77
Abuse of alcohol *	5 (11.1)	0 (0)	4.22	0.017 †		

* Significant result

† Fisher's Exact test

4d. Tertiary objective

Explanation of the model

A model was designed to predict chronic pain in adolescence using an individual history of FPS, while controlling for confounders.

The model included an individual history of RAP, migraine and non-migraine headaches. GP was left out of the model, as its correlation with chronic pain in adolescence was not sufficient. RLS in individual history was not included, because preliminary regression tests demonstrated that this variable correlated directly with RAP. This multicollinearity could have a negative influence on the predictive model.

The independent variables that did not significantly influence the relationship between chronic pain in adolescence and an individual history of FPS were injury, adversity, fatigue, depression, anxiety, parental RLS, parental migraine and parental stress. Subsequently, only parental RAP and parental depression were included in the model.

Predictive ability of the model

The model, using the aforementioned predictors, was shown to sufficiently predict chronic pain outcomes in adolescence, as tabulated in Table 19. The highly significant value of the Omnibus Test of Model Coefficients and the relatively large value of the Hosmer and Lemeshow Test are both indicative of the high predictive ability of the model. Further, the model was able to explain between 36.4% and 48.7% of the variance of chronic pain in adolescence, and could correctly classify 77.8% of all cases and controls. This last result was opposed to 54.5% of the study population being correctly classified when the independent variables were not included in the model.

The contribution of each of the independent variables is displayed in Table 20. As previously mentioned, all variables significantly contributed to the predictive ability of the model.

Table 19: Significance of the model

	X²	df	P-value
Omnibus tests of model coefficients *	44.83	5	<0.001
Hosmer and Lemeshow test **	7.70	4	0.103

* Significant result

** Significant result when > 0.05

Table 20: Variables in the model

	B	SE	Wald	P-value	Exp. (B)	95% CI
Individual history of:						
Migraine *	2.05	0.93	4.82	0.028	7.77	1.25 - 48.40
Non-migraine headaches *	2.91	1.14	6.52	0.011	18.28	2.00 – 170.0
Recurrent abdominal pain (RAP) *	2.11	0.81	6.86	0.009	8.24	1.70 - 40.0
Parental history of:						
Recurrent abdominal pain (RAP) *	1.62	0.67	5.83	0.016	5.05	1.36 - 18.79
Depression *	1.49	0.62	5.87	0.015	4.44	1.33 - 14.85

* Significant result

5. Discussion

5a. Primary objective

Individual history of FPS

When comparing controls to the sample of case adolescents, the results indicated a significant association between chronic pain in adolescence and an individual history of functional pain syndromes (FPS). Associations with chronic adolescent pain were found particularly regarding migraine, non-migraine headaches, and recurrent abdominal pain (RAP). An association with restless legs syndrome (RLS) was also shown.

As this is the first study that tests FPS as potential risk factors for chronic pain in adolescence, no direct comparison can be made to similar findings in previous research. However, in a recent study, Walker and colleagues found that 35% of their population that suffered from childhood RAP continued to have chronic pain in adulthood (18). Similarly, two studies reported that early RAP and chronic widespread pain increase the likelihood of chronic pain symptoms on 1-year and 4-year follow-up (19, 21). These findings that link certain FPS with chronic pain later in life are in agreement with our results.

Furthermore, our results are concordant with publications that have found FPS to be highly co-morbid (6, 10). Of our population of cases, 64.9% reported more than two FPS (including their primary diagnosis), while Perquin and colleagues found multiple pain sites in almost half of their participants (5). Likewise, a recent German study showed 54% of their population to report two or more sites of recurrent pain and attributed this finding to an underlying pain vulnerability (9).

Due to the small sample size associations between chronic adolescent pain and an individual history of growing pains (GP) did not reach statistical significance. However, as GP is shown to be related to RLS, a significant association may be expected (83). This expectation can be further underlined by the relatively large odds ratio found regarding GP in individual history (OR = 2.81). However, a larger research population might be needed to validate this proposed association.

Parental history of FPS

Regarding a parental history of FPS, associations with chronic pain in adolescence were found for parental migraine, RAP and RLS. These findings are supported by Russell and colleagues, who reported that first-degree relatives of migraine patients increase their chances of developing migraine 2 to 3-fold (30). Likewise, parental RAP and parental RLS are shown to be risk factors for persisting pain in children (26, 28). Further, our results underline the belief that pain syndromes are genetically influenced and share heritable vulnerability traits, as supported by multiple studies (7, 11, 12).

No significant associations could be found with respect to parental GP, non-migraine headaches and other FPS. These results are surprising when compared to previous research on this topic. For example, parental GP and a family history of fibromyalgia have both been found to predispose to chronic pain in children (23-25, 27). Furthermore, studies found parental headaches to be associated with the frequency of headaches in children and

adolescents (3, 29). Regarding a parental history of GP, the most probable explanation for the lack of significant findings in our study is the small sample size. However, there is no satisfactory explanation for the fact that we were unable to find a comparable association with non-migraine headaches.

5b. Secondary objective

Socio-demographic factors

Regarding the secondary objective of this study, associations were found between chronic pain in adolescence and the variables age and academic level. However, these relationships were unexpected and not in agreement with literature (32). In our study, cases were found to be younger and their academic levels lower compared to controls. An explanation for these surprising results may lie in the recruitment of the controls, as they were approached while volunteering in the hospital or attending science classes. These students primarily came from older grades and talented/gifted classes, owing to the fact that their schedules allowed more time for extra-curricular activities. Not only could this account for the fact that the controls were older than the cases, these adolescents may also be regarded as being high achievers and having perfectionist traits, thereby influencing results.

The female predominance in the case group was typical and reflects the results of previous research. Two comparable studies found that girls report higher frequencies of recurrent pain and co-morbidity of pain syndromes than boys, particularly after menarche (3, 31). Stanford and colleagues proposed that hormonal and biochemical mechanisms underlie these sex differences. Unfortunately, our results were not able to confirm this theory, as no significant association was found between age of menarche and chronic pain in adolescence.

The gender distribution was no different in the controls, where a similar female predominance was found. This large number of girls in the control group could be attributable to the fact that girls are more likely to be responders. However, the lack of statistical significance between the amount of females in cases and controls was an advantage in the current study, as it ensured a more homogenous study population, thus avoiding gender influences on the data.

Factors in (early) childhood and adolescence

Several associations were found between (mostly early) childhood factors and chronic pain in adolescents. Among these were use of medication, injury, adversity, fatigue, iron deficiency, low vitamin D and low academic level.

The associations found with regards to injury and adversity were in accordance with the literature. Boey and colleagues described more patients with abdominal pain having experienced adverse life events, while Kopec and McBeth demonstrated the same association regarding chronic back pain and chronic widespread pain, respectively (37, 38, 41). Jones and colleagues extended this research and, by using multivariate analysis, revealed that the association with widespread pain was not biased by confounders such as psychological distress (40). Similarly, when compared to literature, our results regarding low iron and low vitamin D can be regarded as likely to be valid. Studies demonstrate that being low in vitamin D is related to RLS, non-migraine headaches and musculoskeletal pain (45-47), while iron deficiency is associated with fibromyalgia and RLS (48-50).

Previous research found that chronic pain in adolescence is invariably linked to the use of medication and experiencing prolonged fatigue (23, 31, 33, 44). The link with medication is surely attributable to the fact that cases are generally prescribed analgesics and other medications in order to cope with their pain, rather than their pain being caused by an excess use of medication. Similarly, chronic pain could contribute to children's fatigue, instead of fatigue being a predictive factor for current chronic pain, although a bidirectional relationship could well occur. It is therefore difficult to draw conclusions about causality in regards to these variables.

In contrast to the literature, this study did not find a significant association between chronic pain in adolescence and low birth weight, prematurity, sedentary activity and living away from home. This was contrary to worldwide studies reporting that these childhood factors predispose to chronic pain (3, 35, 36, 40, 41). Our conflicting results could be held attributable to the small sample size, which accounted for a very small number of participants to report positive answers for these variables.

A significant association with a history of hospitalisation was also not found. This is surprising, as multiple studies found hospitalisation and in particular hospitalisation following injury to be predictive of chronic pain (37, 38, 40). As these studies were either longitudinal or based on hospital files, our conflicting results may be due to our study design. This research was retrospective and relied on self report, possibly giving rise to biased recall. Following the same line of thought, it is possible that participants used different interpretations of the word 'hospitalisation'. For example, parents of cases, who compared to parents of controls are more accustomed to seeking medical advice, might be more inclined to under report and trivialise hospital visits, thereby influencing our results.

While not significantly associated with chronic pain in adolescence, cases seemed to report less hours of physical exercise than did controls, contradicting previous research on this topic (20, 32, 33, 40). A possible explanation is that our questionnaire assessed the amount of hours usually spent on exercise, as opposed to specifically requesting the time spent on exercise before having pain problems. As a consequence, our data might represent exercise as a consequence rather than a predictor of chronic pain, indicating that pain prevents adolescents from engaging in physical exercise.

Finally, previous research reported inconsistencies regarding associations between chronic pain and hypermobility. El-Metwally and colleagues conducted a research on the topic in 2004, concluding that musculo-skeletal pain is indeed associated with later chronic pain outcomes (20). However, when repeating the study in 2007, the association was lost (44). The same occurred in studies conducted by Mikkelsen in 1998 and 2008 (32, 51). Judging by the fact that the research population was vastly bigger in both the latter studies, one might argue that these results are more convincing. The conclusion that hypermobility does not relate to chronic pain is in agreement with the non significant findings in our current study.

Contradictory results are also found regarding the predictive ability of living away from home, with a British study confirming an association with chronic pain and a comparable Canadian study finding no significant relationship (40, 41). Again, our results are consistent with the studies that failed to show a significant association regarding these variables.

Psychological factors

The findings on psychological factors in both individual and parental history strengthen conclusions drawn by others: both individual anxiety and depression and parental depression and stress were found to be significantly associated with chronic pain in adolescence. In previous research, these associations were particularly found for migraine, non-migraine headaches and RAP, and were explained by describing models of shared vulnerability, genetic pathways and altered pain perception (53-57). Our results do not shed light on the etiology nor on the direction of the association, though there is evidence to suggest that psychological factors have significant effect on pain syndromes as well as being the consequence of chronic pain (60).

Surprisingly, DASS-21 scores obtained from both the adolescents' and the parents' questionnaire could not support an association between psychological variables and chronic pain. On the contrary, the anxiety score in adolescents seemed to be higher in controls than in cases, though this difference failed to reach significance. These discrepancies could be explained by the fact that the DASS-21 measures thoughts of depression, anxiety and stress in the last week, as opposed to assessing an overall tendency to these psychological disorders. Furthermore, it could be possible that adolescents were hesitant and embarrassed to report their true ideas on the DASS-21 survey, while their parents would have less difficulty reporting psychological disorders in their children.

Further familial factors

Either parent reporting a chronic disorder or having a history of alcohol abuse was found significantly more often in cases than in controls. These factors might have caused significant childhood stress, potentially leading to or aggravating chronic pain in adolescence. Contrary to the literature, no significant association was found with low socio-economic status and financial hardship (63, 64). These results might be biased by a certain level of social desirability, whereby participants are hesitant to openly report difficult and personal issues.

5c. Tertiary objective

A noteworthy strength of this present study is that logistic regression was used to verify whether the associations found with regards to the primary objective were correct or whether they were biased by confounding factors. A model was proposed, in which an individual history of FPS was tested as a predictor of chronic pain in adolescence, while controlling for possible confounders.

The model showed that an individual history of migraine, non-migraine headaches and RAP, along with parental RAP and parental depression, were the major factors multivariately associated with chronic adolescent pain and might represent independent predictors. These findings are in line with our expectations and with the literature, as discussed earlier (subheading 5a. Primary objective).

5d. Limitations

This study had several weaknesses that should be considered when interpreting the results. Firstly, the relatively small sample size might have reduced our ability to detect statistically significant differences between the cases and controls, resulting in a Type-2 error of rejecting the hypothesis when it is in fact correct.

Secondly, the method of data collection might be a limitation. Data were obtained using questionnaires and were primarily based on self-report. Therefore, the data might have been subject to social desirability or inadequate recall. While steps were undertaken to minimise biased recall, such as having parents report and confirm early childhood factors in their children, results might still be influenced by this method of data collection. Furthermore, the questionnaires contained missing data, most likely owing to the fact that the researcher was not always present when parents and case adolescents filled out the survey. Missing data were particularly important in regard to the time course of FPS and other factors, and ruled out our ability to relate trajectories of FPS to adolescent chronic pain.

Thirdly, the study sample was not completely representative with regards to the socio-demographic population. The study samples seemed to primarily come from middle and upper socio-economic classes. To minimize bias arising from socio-demographic differences, special care was taken to match controls and cases in regards to age, gender and socio-economic status. The slightly older age of controls might have biased against the testing of associations between FPS and chronic pain in that the controls would have had longer to have acquired a FPS.

Fourthly, one could question whether the recruitment of controls was completely unbiased. As previously mentioned, approaching controls through higher classes and predominantly talented/gifted classes might have accounted for their higher age and academic level. Further, controls having a family member with chronic pain might have been more interested in participating in the study, as opposed to adolescents that had no previous association with chronic pain. However, this may in fact have acted to strengthen our findings, as cases still reported significantly more FPS in individual and parental history than did controls.

Fifthly, it is possible that this study was influenced by an overestimation of associations with adolescent chronic pain. The fact that cases attended the Chronic Pain Clinic at Sydney Children's Hospital might have increased the probability of them being diagnosed with additional FPS. Further, the other probable risk factors might be influenced by the primary diagnosis of chronic pain that was provided to them by their doctor (84). For example, cases might have undergone tests to determine the nature of their pain, providing them with information on their iron and vitamin D levels. Healthy controls would arguably visit their doctor less regularly and might not be aware of potential iron and vitamin D deficiencies.

Sixthly, the limitations of case-control studies in general need to be acknowledged. The method of selection of suitable controls is always an issue, and limitations occur because the research has to be within the bounds of practicable recruitment. Case-control studies cannot determine causal direction of associations. Rather, the associations found are hypothesis generating guiding testing by higher order methods. In the area of observational studies, that usually means prospective cohort designs.

Finally, participants were notified of the background and objectives of the study beforehand in order to receive informed consent. For this reason, the data might have been subject to a certain level of information bias.

5e. Implications and directions for future research

The current study lays the foundation for further examination of childhood predictors for chronic pain in adolescence. Research on this subject might result in a better understanding of FPS and their etiology, eventually leading to improved prevention, earlier intervention and better treatment.

Future research should aim to achieve a larger sample size and a more unbiased method of data collection. It should include designs to determine the trajectory and inter-relationships between childhood FPS, by obtaining the exact age of onset of these disorders. Furthermore, FPS should be tested as independent risk factors for chronic pain in adolescents and adults. The most optimal study design to achieve these goals is a prospective and population-based design, which will enable researchers to find trajectories and to adequately study the existence of symptoms (84).

6. Conclusion

The current case-control study was able to find significant associations between chronic pain in adolescence and both an individual history and a parental history of FPS, taking in consideration the limitations.

Adolescents suffering from chronic pain were more likely to report a history of migraine, non-migraine headaches and RAP than their pain-free peers. Furthermore, an association with RLS was found. With regards to a parental history of FPS, more migraine, RAP and RLS were found in the parents of the cases.

A multivariate model was tested using an individual history of FPS, parental RAP and parental depression to predict chronic pain in adolescence. This model was found to have strong predictive ability of chronic pain in adolescence and controlled for confounding factors (parental RAP and parental depression).

When comparing cases to controls, several other associations were found with chronic pain in adolescence. These included adversity, having sustained serious injury, experiencing prolonged fatigue, being low in iron and vitamin D and suffering anxiety and depression. Furthermore, having parents with depression or stress was significantly associated with chronic pain in adolescence, as were parental chronic disorders and parental alcohol abuse.

In summary, this study has contributed to a better understanding of factors associated with and potentially predictive of chronic pain in adolescence. Further research is needed to test an individual and parental history of FPS as risk factors for chronic adolescent pain, as this might lead to better prevention and earlier intervention of chronic pain syndromes.

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8. Attachments

8a. Abstract as submitted to the Australian Pain Society 31st Annual Scientific Meeting

Please note: as the deadline for submitting this abstract was relatively early, this abstract has been written on the basis of preliminary analysis. Therefore, the title and exact numbers do not correspond with those of the definitive analysis found in this thesis.

ASSOCIATIONS BETWEEN CHRONIC PAIN DISORDERS IN ADOLESCENTS AND HISTORY OF FUNCTIONAL PAIN SYNDROMES: a case-control study

Coenders, A.¹, Champion, D.^{2,3}, Hannaford, P.², Jaaniste, T.³, Qiu, W.³ RijksUniversiteit Groningen¹, Groningen, Netherlands, University of NSW², Kensington, NSW, Australia, Sydney Children's Hospital³, Randwick, NSW, Australia

Background and aims

Functional Pain Syndromes (FPS), including growing pains (GP), recurrent abdominal pain (RAP), and non-migraine headaches, are prevalent and co-morbid in early childhood, while migraine is more frequent in adolescents than in younger children. However, relationships between childhood FPS and chronic pain in adolescence have not been adequately examined.

This study was designed to test the hypothesis that a history of FPS will be found more often in adolescents suffering from chronic pain than in their pain-free peers.

Method

Our case-control study involved 101 adolescents aged 10 to 18 years. Cases (N=46, median age 14, 65.2% female) were adolescents who were patients of the Chronic Pain Clinic with diverse chronic pain disorders. The controls consisted of 55 adolescents (median age 16, 63.6% female) who did not have chronic pain, recruited by our Schools Liaison Officer.

Case and control participants filled out questionnaires covering demographic data and known and potential risk factors for chronic pain. The diagnoses of cases were determined by self-report and chart review. To minimise inadequate or biased recall, parents were asked to report and confirm early childhood history and risk factors in their children. Questions were included to assess various FPS, as well as restless legs syndrome (RLS). A validated questionnaire screened for a history of GP.

χ^2 -tests and odds ratios were used to test the associations between chronic pain in adolescence and the lifetime prevalence of FPS. Cases in which the primary diagnosis was an extension of a FPS, e.g. migraine preceding chronic headache, were not included in the analysis. Multiple regression will be applied to control for other associations with chronic pain as confounders.

Results

Migraine, headache, RAP and RLS were reported significantly more frequently in cases than controls, as tabulated. The results for GP were not significant, probably reflecting the relatively small sample size.

FPS in cases and controls					
	Migraine	Headache	RAP	GP	RLS
Cases (N=46)	12 (26.1%)	14 (30.4%)	11 (23.9%)	9 (19.6%)	10 (21.7%)
Controls (N=55)	2 (3.6%)	1 (1.8%)	3 (5.5%)	3 (5.5%)	3 (5.5%)
Odds Ratio	9.35	23.63	5.45	4.22	4.82
χ^2, P-value	8.8, P=0.003	14.0, P<0.001	5.7, P=0.017	3.5, P=0.06	4.5, P=0.014

Other statistically significant associations with chronic pain included anxiety, depression, fatigue, adversity, injury, low iron and low vitamin D.

Conclusion

When comparing controls to the sample of adolescents, the results indicate a significant association between chronic pain disorders and FPS, particularly regarding migraine, non-migraine headaches, and RAP. An association with RLS was also shown, but with this sample size GP association did not reach statistical significance.

Future research should include designs to determine the trajectory and inter-relationships between childhood FPS and testing them as independent risk factors for chronic pain in adolescents and adults.

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