Programa Doutoral em Saúde Pública

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PEDIATRIC PAIN IN THE GENERATION XXI BIRTH COHORT:

A clinical perspective on population-based data from childhood to early adolescence

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E D I T A L

DOUTOR JOSÉ HENRIQUES DIAS PINTO BARROS, PROFESSOR CATEDRÁTICO DA FACULDADE DE MEDICINA DA UNIVERSIDADE DO PORTO

Faço saber que o júri da prova de Doutoramento em Saúde Pública, requerida pela mestre **Vanessa Alexandra Oliveira Gorito**, em reunião de 11 de abril de 2025, deliberou marcar o ato respeitante àquela prova para o **dia 29 de maio de 2025, às 10:00 horas**, a decorrer na Aula Magna da Faculdade de Medicina da Universidade do Porto.

A discussão e defesa de uma tese original subordinada ao título **"Pediatric Pain in the Generation XXI Birth Cohort: A clinical perspective on population-based data from childhood to early adolescence"**, terá como arguentes a Doutor José António Pereira da Silva, professor catedrático da Faculdade de Medicina da Universidade de Coimbra e o Doutor André Laboreiro Ferreira Mendes da Graça, professor associado convidado da Faculdade de Medicina da Universidade de Lisboa.

Participam ainda como elementos do júri os Doutores Maria João Lopes Marques, investigadora auxiliar da Escola Nacional de Saúde Pública da Universidade Nova de Lisboa, Liane Maria Correia Rodrigues da Costa Nogueira Silva, professora associada convidada com agregação do Instituto de Ciências Biomédicas Abel Salazar da Universidade do Porto, Raquel Lucas Calado Ferreira, investigadora principal com agregação do Instituto de Saúde Pública da Universidade do Porto e orientadora da tese e Carla Maria de Moura Lopes, professora catedrática da Faculdade de Medicina da Universidade do Porto.

E para constar, lavrou-se o presente edital que vai ser afixado nos lugares de estilo.

Faculdade de Medicina da Universidade do Porto, 14 de abril de 2025.

O Presidente do Júri

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"...make pain matter,

make pain understood,

make pain visible,

and make pain better."

The Lancet Child & Adolescent Health Commission on Children's Pain, 2020

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ABBREVIATIONS AND ACRONYMS

APPT: Adolescent Pediatric Pain Tool

BAPQ: Bath Adolescent Pain Questionnaire

BPI: Brief Pain Inventory

CRPS: Complex Regional Pain Syndrome

CI: Confidence Interval

EDIN: Échelle De Douleur Et d'Inconfort Du Nouveau-Né

FLACC: Face, Legs, Activity, Cry, Consolability Scale

FLACC-R: Face, Legs, Activity, Cry, Consolability – Revised

FPS-R: Faces Pain Scale – Revised

FPS: Functional Pain Syndromes

GCPS: Generalized Chronic Pain Syndrome

HICP: High-Impact Chronic Pain

IASP: International Association on the Study of Pain

IL: Interleukin

IBS: Irritable Bowel Syndrome

JIA: Juvenile Idiopathic Arthritis

LR: Likelihood Ratio

LPQ: Luebeck Pain Screening Questionnaire

MPQ: McGill Pain Questionnaire

NHS: National Health System

NICU: Neonatal Intensive Care Unit

NIPS: Neonatal Infant Pain Scale

NIMP: Noninflammatory Musculoskeletal Pain

NRS: Numerical Rating Scale

OR: Odds Ratio

PedsQL: Pediatric Quality of Life Inventory

PIPP-R: Premature Infant Pain Profile-Revised

PPIS: Pediatric Pain Interference Scale

PPQ: Varni/Thompson Pediatric Pain Questionnaire

PROMIS: Patient Reporting Outcomes Measurement Information System

QST: Quantitative Sensory Test

RR: Relative Risk

TNF: Tumor necrosis factor

VAS: Visual Analog Scale

WHO: World Health Organization

ABSTRACT

Background:

Pediatric pain represents a frequently misunderstood, underdiagnosed, and undertreated medical challenge. Committees and organizations have intensified their efforts to enhance the understanding, assessment, and management of pain worldwide.

Given its considerable prevalence within the pediatric population, pain exerts a significant impact on children's lives, with chronic pain conditions constituting a major contributor to the global burden of disease. A comprehensive understanding of the development of pain susceptibility profiles during childhood and their potential determinants may enable the stratification of chronic pain risk within the population, extending beyond the identification of organic etiologies.

Elucidating the epidemiology of pediatric pain is the first step in reshaping the overall pain experience. However, long-term follow-up data remain limited and inconclusive, thereby restricting our capacity to modify the trajectory of chronic pain and associated behaviors.

Therefore, the utilization of large population-based prospective studies presents a unique opportunity to characterize pain experienced throughout the first decade of life. This approach facilitates the early identification of children exhibiting a heightened propensity to develop lifelong pain phenotypes.

Aims:

For the present thesis our objectives were:

1. To estimate a point prevalence of pain complaints at 7 years of age (Paper I)
2. To describe differences between children's and parent's reports of pain at 7 years of age (Paper I)
3. To estimate a point prevalence of pain complaints, triggers and impact on children's daily life at 10 years of age (Paper II)
4. To characterize children's utilization of health care services for pain and the medical diagnoses associated with it (Paper II)
5. To explore atopy-like symptoms as early determinants of pain in early life and their association with pain reports at 10 years of age (Paper III)

6. To stratify the risk of multisite pain at 13 years according to the reported pain experience in the first decade of life (Paper IV)

Methods:

The objectives of this thesis were achieved through the analysis of data obtained from Generation XXI, a prospective population-based birth cohort study, with recruitment at birth in 2005/2006 in the five public maternity units from metropolitan area of Porto; and follow-up assessment waves at 4, 7, 10 and 13 years of age.

Consecutive subsamples of babies were examined at 6 and 15 months and we collected information about health in early life. We used standardized questionnaires to ask parents about atopic-like symptoms their child had experienced since birth. Data on history of pain according to parents and children were collected at the 7 and 10-years follow-up waves, while data on adolescents´ report of pain was collected at 13 years.

In the 7 and 10-years evaluations, parents completed a Portuguese version of the Luebeck Pain Screening Questionnaire (LPQ) on behalf of their child. The first (screening) question was, "Did your child complain of pain in the last 3 months?" If the answer was affirmative, the parent was asked to select the anatomical sites where the child felt pain and to indicate the principal pain site. When a recurrent pain was reported, the parent was asked about its: duration, frequency, and intensity. The parent was also asked about the impact on the child's daily living. Pain triggers and context of the first episode were also reported. Family history of chronic pain was considered present if the parent reported, at either age 7 or 10, that any of the parents or siblings of the index child had a chronic pain condition. Parents were also asked about the intake of medication, health care use, and medical diagnosis of child's recurrent pain.

Specifically in 7 year-evaluation, parents and children were separately asked about the presence of any pain in the child at the time of the interview. If pain complaints were identified by parents or by the children as being present when filling out the questionnaire, respondents were asked to identify the child's anatomical pain site(s) in a body chart.

At 10 years, using a similar questionnaire, children answered questions about their pain experience in the previous week: the presence of any pain, pain intensity and the number of pain sites, using the same body chart.

In the 13-years evaluation, trained interviewers applied a short version of the LPQ to each adolescent as part of the face-to-face evaluation. Due to the sequential design of the LPQ,

the choice of multisite pain as the outcome also allowed to optimize the number of adolescents with valid information on pain experience.

Results:

Paper I: At 7 years of age, 499 children [8.8% (95% CI (8.1–9.6)] reported having pain at the time of the interview. Of those, 44.1% had high-intensity pain [3.9% (95% CI (3.4–4.4) of the whole sample] and 12.4% reported pain in two or more sites [1.1% (95% CI 0.8–1.4) of the whole sample]. In this community setting, pain prevalence and intensity were lower when collected from parents. Parental report had sensitivity below 20% and specificity above 95% but its positive predictive value was at most 25%.

Paper II: Of the 3725 children reporting pain, 26.7% had a parent-reported impact on at least one of their daily activities, with no differences between boys and girls. An impact on daily activities was more likely in children with more frequent pain [OR 1.35 (1.26-1.46)], longer-lasting pain [OR 1.59 (1.48-1.69)], pain that required medication use [OR 2.12 (1.24-4.23)], higher-intensity pain [OR 1.82 (1.73-2.0)], or multisite pain [OR 2.04 (1.43-2.92)]. Among children with pain, 17.0% sought health care and 12.5% obtained a medical diagnosis as a result. The most frequent diagnosis categories were musculoskeletal (34.4%), gastroenterological (13.5%), and psychological conditions (12.0%). Health care use was associated with higher pain frequency [OR 1.18 (1.09-1.27)], duration [OR 1.26 (1.17-1.36)], and use of pain medications [OR 1.70 (1.53-1.90)].

Paper III: At 10 years of age, 1302 of the 1555 children evaluated at 6 months and 874 of the 1043 children evaluated at 15 months had both parent and child reports of pain.

Considering the parental report of pain, children with reported atopic dermatitis-like episodes at 15 months had higher risk of multisite pain at age 10 [42% vs 30%; RR 1.67 (1.18–2.37)]. Children with food-allergy-like symptoms at 15 months had a higher risk of reported pain at age 10. Presence of rhinitis-like symptoms at 15 months was borderline associated with any and intense pain. As for child report of pain, atopic dermatitis-like symptoms at 6 months had higher risk of reporting any pain in the previous week at 10 years of age than those without atopic dermatitis [37% vs 25%; RR 1.75 (1.15–2.66)]. Children with wheezing episodes at 6 months had slightly higher risk of any pain, but not intense or multisite pain at age 10.

Paper IV: At age 13, 39.2% of girls and 27.2% of boys reported multisite pain in the previous three months. The risk was higher among girls with multisite and recurrent pain

at ages 7 and 10 than in girls without those adverse features, especially if psychosocial triggers were also present [(RR 1.87; CI 95% 1.36–2.36); (LR 3.49; CI 95% 1.53–7.96)]. Boys with recurrent pain of higher frequency and causing activity restrictions at ages 7 and 10 had a higher risk of multisite pain at 13 [(RR 2.05; IC 95% 1.03–3,05); (LR 3.06; IC 95% 1.12–8.39)]. Earlier adverse experiences were more predictive of future pain in girls than in boys.

Conclusion:

Our population-based study suggests that parental report is useful to exclude major pains but has limited sensitivity to identify children's pain at 7 years of age. This reinforces the importance of listening to children's reports, collecting its specific attributes to avoid the underestimation of pediatric pain and ultimately to allow fast-track evaluation, diagnosis, and treatment.

At 10 years, despite the higher frequencies of pain, chronic pain, intense pain, and multisite pain among girls, we identify a similar impact on daily activities between boys and girls. Our results question stereotypical sex interpretations suggesting a higher female burden in terms of the effects of pain on children's lives, as well as care-seeking profiles. The main diagnoses of pain at 10 years of age (musculoskeletal, gastroenterological, and psychological) raise the possibility that they constitute the first manifestation of a spectrum of chronic functional pain syndromes. As expected, most pediatric pain is managed without resorting to health care, but tracking their future trajectories may be useful to estimate early diagnosis gaps.

Atopic dermatitis symptoms in early life are linked to an increased likelihood of experiencing pain at the age of 10, which suggests that exploring the potential for sensitization is a worthwhile area of investigation, avoiding possible long-term consequences of this process.

We identify sex-specific pain features that can be collected by practitioners in the first decade of life to improve the stratification of children in terms of their future risk of a maladaptive pain experience in adolescence. Early multisite pain and psychosocial triggers are relevant predictors of future multisite pain in girls, whereas repeated reports of high-frequency pain leading to activity restrictions are predictive of adolescent multisite pain in boys.

RESUMO

Introdução:

A dor pediátrica representa um desafio médico frequentemente mal compreendido, subdiagnosticado e subtratado. Comités e organizações têm intensificado os seus esforços para melhorar a compreensão, avaliação e gestão da dor na população pediátrica a nível mundial.

Dada a sua considerável prevalência na população pediátrica, a dor exerce um impacto significativo na vida das crianças, sendo as condições de dor crónica um dos principais contribuintes para a carga global de doença. Uma compreensão abrangente do desenvolvimento dos perfis de suscetibilidade à dor durante a infância e dos seus potenciais determinantes pode permitir a estratificação do risco de dor crónica na população, para além da identificação de etiologias orgânicas.

Elucidar a epidemiologia da dor pediátrica é o primeiro passo na reformulação da experiência global da dor. No entanto, os dados de seguimento a longo prazo permanecem limitados e inconclusivos, restringindo assim a nossa capacidade de modificar a trajetória da dor crónica e dos comportamentos associados.

Portanto, a utilização de grandes estudos prospetivos de base populacional apresenta uma oportunidade única para caracterizar a dor experienciada ao longo da primeira década de vida. Esta abordagem facilita a identificação precoce de crianças que exibem uma propensão aumentada para desenvolver fenótipos de dor ao longo da vida.

Objetivos:

Para a presente tese, os nossos objetivos foram:

1. Estimar a prevalência pontual de queixas de dor aos 7 anos de idade (Artigo I)
2. Descrever as diferenças entre os relatos de dor das crianças e dos pais aos 7 anos de idade (Artigo I)
3. Estimar a prevalência pontual de queixas de dor, gatilhos e impacto na vida diária das crianças aos 10 anos de idade (Artigo II)
4. Caracterizar a utilização dos serviços de saúde pelas crianças devido a dor e os diagnósticos médicos associados (Artigo II)
5. Explorar sintomas típicos de atopia como determinantes precoces da dor e sua associação com relatos de dor aos 10 anos de idade (Artigo III)

6. Estratificar o risco de dor múltipla aos 13 anos de acordo com a experiência de dor relatada na primeira década de vida (Artigo IV)

Métodos:

Os objetivos desta tese foram alcançados através da análise de dados obtidos da Geração XXI, um estudo prospetivo de coorte de nascimentos de base populacional, com recrutamento à nascença em 2005/2006 nas cinco maternidades públicas da área metropolitana do Porto; e com avaliação de acompanhamento aos 4, 7, 10 e 13 anos de idade. Subamostras consecutivas de bebés foram examinadas aos 6 e 15 meses e foram colhidas informações sobre o estado de saúde no início da vida. Utilizámos questionários padronizados para perguntar aos pais sobre sintomas semelhantes aos da atopia que seus filhos apresentavam desde o nascimento. Os dados sobre história de dor segundo pais e filhos foram coletados nas avaliações de acompanhamento aos 7 e 10 anos, enquanto os dados sobre relato de dor dos adolescentes foram inquiridos aos 13 anos. Nas avaliações dos 7 e 10 anos, os pais preencheram uma versão em português do questionário de rastreio da dor de Luebeck (LPQ) em nome dos seus filhos. A primeira pergunta (de triagem) foi: "O seu filho queixou-se de dor nos últimos 3 meses?" Se a resposta fosse afirmativa, solicitava-se aos pais que selecionassem os locais anatómicos onde a criança sentia dor e indicassem o principal local da dor. Quando uma dor recorrente foi relatada, os pais foram questionados sobre: duração, frequência e intensidade. Os pais também foram questionados sobre o impacto na vida diária da criança. Os gatilhos da dor e o contexto do primeiro episódio também foram inquiridos. A história familiar de dor crónica foi considerada presente se o pai relatasse, aos 7 ou 10 anos de idade, que algum dos pais ou irmãos da criança índice tinha uma condição de dor crónica. Os pais também foram questionados sobre a ingestão de medicamentos, uso de cuidados de saúde e diagnóstico médico de dor recorrente da criança.

Especificamente na avaliação dos 7 anos, pais e filhos foram questionados separadamente sobre a presença de alguma dor na criança no momento da entrevista. Se fossem identificadas queixas de dor pelos pais ou pelas crianças no preenchimento do questionário, os entrevistados foram solicitados a identificar o(s) local(is) anatómico(s) de dor da criança num gráfico corporal.

Aos 10 anos, utilizando um questionário semelhante, as crianças responderam a perguntas sobre a experiência de dor na semana anterior: a presença de alguma dor, a intensidade da dor e o número de locais de dor, utilizando o mesmo gráfico corporal.

Na avaliação de 13 anos, entrevistadores treinados aplicaram uma versão resumida do LPQ a cada adolescente como parte da avaliação presencial. Devido ao desenho sequencial do LPQ, a escolha da dor múltipla como resultado também permitiu otimizar o número de adolescentes com informações válidas sobre a experiência de dor.

Resultados:

Artigo I: Aos 7 anos de idade, 499 crianças [8,8% (IC 95% 8,1–9,6)] relataram sentir dor no momento da entrevista. Destes, 44,1% tiveram dor de alta intensidade [3,9% (IC 95% 3,4–4,4) de toda a amostra] e 12,4% relataram dor em dois ou mais locais [1,1% (IC 95% 0,8–1,4) de toda a amostra]. Neste estudo populacional, a prevalência e intensidade da dor foram menores quando mencionadas pais. O relato dos pais apresentou sensibilidade abaixo de 20% e especificidade acima de 95%, mas seu valor preditivo positivo foi no máximo de 25%.

Artigo II: Das 3725 crianças que relataram dor, 26,7% tiveram um impacto relatado pelos pais em pelo menos uma das suas atividades diárias, sem diferenças entre meninos e meninas. O impacto nas atividades diárias foi mais provável em crianças com dor mais frequente [(OR) 1,35 (1,26-1,46)], mais duradoura [OR 1,59(1,48-1,69)], que exigiu uso de medicação [OR 2,12 (1,24-4,23)], dor de maior intensidade [OR 1,82 (1,73-2,0)] ou dor múltipla [OR 2,04 (1,43-2,92)]. Entre as crianças com dor, 17,0% procuraram atendimento de saúde e 12,5% obtiveram diagnóstico médico. As categorias diagnósticas mais frequentes foram musculoesqueléticas (34,4%), gastroenterológicas (13,5%) e psicológicas (12,0%). O uso de cuidados de saúde foi associado a maior frequência de dor [OR 1,18 (1,09-1,27)], duração [OR 1,26 (1,17-1,36)] e uso de medicamentos para a dor [OR 1,70 (1,53-1,90)].

Artigo III: Aos 10 anos de idade, 1302 das 1555 crianças avaliadas aos 6 meses e 874 das 1043 crianças avaliadas aos 15 meses tiveram dor relatada por pais e filhos. Considerando o relato de dor dos pais, as crianças com relatos de sintomas compatíveis com dermatite atópica aos 15 meses apresentaram maior risco de dor múltipla aos 10 anos [42% vs 30%; RR 1,67 (1,18–2,37)]. Crianças com sintomas compatíveis com alergia alimentar aos 15 meses apresentaram maior risco de dor relatada aos 10 anos. A presença de sintomas compatíveis com rinite aos 15 meses apresentou uma associação limítrofe à presença de qualquer dor intensa. Quanto ao relato de dor nas crianças, os sintomas compatíveis com dermatite atópica aos 6 meses tiveram maior risco de relatar qualquer dor na semana anterior aos 10 anos de idade do que aqueles sem dermatite atópica [37%

vs 25%; RR 1,75 (1,15–2,66]]. Crianças com episódios de sibilância aos 6 meses apresentaram risco ligeiramente maior de qualquer dor, mas não de dor intensa ou múltipla aos 10 anos.

Artigo IV: Aos 13 anos, 39,2% das meninas e 27,2% dos meninos relataram dor em vários locais nos últimos três meses. O risco foi maior entre meninas com dor múltipla e recorrente aos 7 e 10 anos de idade do que em meninas sem essas características adversas, especialmente se os gatilhos psicossociais também estivessem presentes [(RR 1,87; IC 95% 1,36–2,36); (LR 3,49; IC 95% 1,53–7,96)]. Meninos com dor recorrente de maior frequência e causando restrições de atividades aos 7 e 10 anos tiveram maior risco de dor múltipla aos 13 anos [(RR 2,05; IC 95% 1,03–3,05); (LR 3,06; IC 95% 1,12–8,39)]. Experiências adversas anteriores foram mais preditivas de dor futura nas meninas do que nos meninos.

Conclusão:

O nosso estudo de base populacional sugere que o reporte dos pais é útil para excluir dores graves, mas tem sensibilidade limitada para identificar a dor das crianças aos 7 anos de idade. Isto reforça a importância de ouvir os reporte das crianças, recolhendo os seus atributos específicos para evitar a subestimação da dor pediátrica e, em última análise, permitir avaliação, diagnóstico e tratamento precoces.

Aos 10 anos, apesar das maiores frequências de dor, dor crónica, dor intensa e dor múltipla entre as meninas, identificamos impacto semelhante nas atividades diárias entre meninos e meninas. Os nossos resultados questionam as interpretações sexuais estereotipadas, sugerindo uma maior carga feminina em termos dos efeitos da dor na vida das crianças, bem como nos perfis de procura de cuidados. Os principais diagnósticos de dor aos 10 anos de idade (musculoesquelético, gastroenterológico e psicológico) levantam a possibilidade de constituírem a primeira manifestação de um espectro de síndromes dolorosas funcionais crónicas. Como esperado, a maior parte da dor pediátrica é tratada sem recurso a cuidados de saúde, mas acompanhar as suas trajetórias futuras pode ser útil para estimar lacunas no diagnóstico precoce.

Os sintomas da dermatite atópica no início da vida estão associados a uma maior probabilidade de sentir dor aos 10 anos de idade, o que sugere que explorar o potencial de sensibilização é uma área de investigação valorizável, evitando possíveis consequências a longo prazo deste processo.

Identificamos características de dor específicas do sexo que podem ser coletados pelos profissionais na primeira década de vida para melhorar a estratificação das crianças em termos de risco futuro de uma experiência de dor mal adaptativa na adolescência. A dor precoce em vários locais e os gatilhos psicossociais são preditores relevantes de futura dor múltipla em meninas, enquanto reportes repetidos de dor de alta frequência que levam a restrições de atividades são preditivos de dor múltipla na adolescência em meninos.

1) INTRODUCTION

1.1) Definitions and general concepts

The experience of pain is a multidimensional phenomenon that can be seen simultaneously as a complex web of biological mechanisms, an all-too-common clinical symptom, a psychosocial distress sign, and even a cultural representation (1).

The International Association on the Study of Pain (IASP) has been the leading global organization in pain research and management since 1974. Over the last decades, the IASP has developed comprehensive definitions of pain, which have become standard for clinicians and researchers worldwide (2).

Pain is defined by the IASP as “an unpleasant sensory and emotional experience associated with, or resembling that associated with actual or potential tissue damage". This definition emphasizes several key aspects: subjectivity (pain is inherently subjective and varies significantly among individuals), sensory and emotional components (pain involves both physical sensations and emotional responses), and association with tissue damage (pain often results from actual tissue damage but can occur in its absence) (2, 3)**.**

Pain can be classified into different types, each with characteristics and mechanisms. (4). Chronic pain is characterized by its persistence or recurrence beyond the expected healing time, typically defined as lasting for more than three to six months, and is often associated with significant psychosocial impact. Multisite pain refers to pain experienced in multiple anatomical locations simultaneously or sequentially, which may indicate widespread or systemic involvement. Recurrent pain describes episodic or intermittent pain episodes that occur over time, alternating between flare-ups or exacerbations and periods of relief (2, 5, 6).

In recent years, the IASP has emphasized special considerations for pediatric pain. Pediatric pain is influenced by biological, psychological, social, and developmental aspects. Children may experience pain differently from adults due to their immature nervous systems, limited communication skills, and evolving cognitive and emotional development. As a result, assessing and managing pediatric pain requires specialized knowledge and approaches tailored to the child's age, developmental stage, and individual needs (7).

The IASP underscores the importance of a biopsychosocial perspective in understanding

pediatric pain, recognizing the interplay between biological factors (e.g. underlying medical conditions, neurobiological mechanisms), psychological factors (e.g. stress, anxiety, coping strategies), and social factors (e.g. family dynamics, cultural influences, and socioeconomic status) (7).

Moreover, the IASP highlights the need for multidisciplinary and family-centered approaches to pediatric pain management. Collaboration among health care providers, including physicians, nurses, psychologists, physical therapists, and social workers, is essential for addressing the complex needs of pediatric patients. Involving families and caregivers in the assessment and treatment process enhances shared decision-making, treatment adherence, and overall outcomes (2, 7).

1.2) Pain process and the life course of pain

1.2.1) Pain mechanisms

Evidence suggests that nociceptive pathways form during fetal development, with functional nociceptors and spinal cord circuits emerging by the second trimester (8). Although debates exist on the conscious pain perception in utero, fetal responses to noxious stimuli, such as changes in heart rate and motor activity, indicate a primitive form of nociception (9). Exposure to painful stimuli during gestation may impact neurodevelopment and alter pain processing mechanisms later in life (8).

Nociceptors, specialized sensory neurons, are crucial for detecting noxious stimuli and initiating the nociceptive process. These neurons express receptors and ion channels sensitive to various mechanical, thermal, and chemical stimuli, allowing them to detect tissue damage and transmit nociceptive signals to the central nervous system (10). Upon activation, nociceptors release neurotransmitters, such as substance P and glutamate, initiating a cascade of events leading to pain perception (11). In response to tissue injury or inflammation, nociceptors can become sensitized, resulting in increased responsiveness to noxious stimuli. Peripheral sensitization involves alterations in nociceptors' excitability, such as receptor and ion channel upregulation, leading to enhanced sensitivity and reduced activation thresholds (12). This phenomenon contributes to hyperalgesia and allodynia, where normally non-painful stimuli evoke pain responses, further amplifying the nociceptive process.

Nociceptive signals are transmitted to the central nervous system, where they undergo

extensive processing and modulation. At the spinal cord level, nociceptive signals are relayed to higher brain regions via ascending pathways, where they are integrated and interpretated (11). Simultaneously, descending modulatory pathways originating from supraspinal structures, such as the brainstem and cortex, exert inhibitory or facilitatory influences on nociceptive processing, modulating pain perception and behavior (13).

1.2.2) From the nociceptive process to chronic pain

Chronic pain is characterized by a pathological and histological basis, resulting from persistent acute pain experiences that cause long-lasting changes to the central nervous system. Usually, unpleasant stimuli diminish as healing advances, and pain perception decreases until little or no pain is felt. On the other hand, chronic pain triggers secondary neural mechanisms in both peripheral and central nervous systems, leading to allodynia, hyperalgesia, and hyperpathia, which can impair normal function. Sensitization of first-order spinal neurons to cyclo-oxygenase-2 and interleukin (IL) 1β are upregulated in the peripheral system. These modifications subsequently sensitize second-order spinal neurons by activating N-methyl-d-aspartic acid channels and inducing alterations in neuronal cytoarchitecture through microglia signaling. Prostaglandins, endocannabinoids, ion-specific channels, and scavenger cells are all important in the progression from acute to chronic pain through these mechanisms (Figure 1) (14, 15).

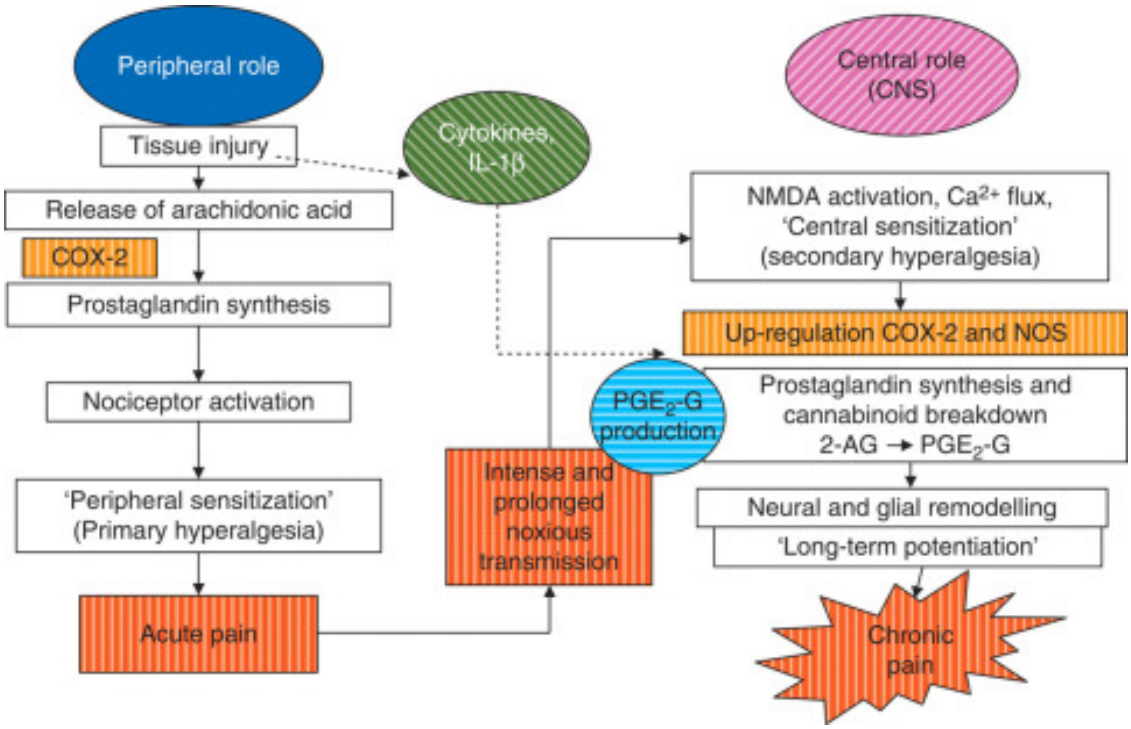


Figure 1: Peripheral and central roles of prostaglandins and cyclo-oxygenase-2 (COX-2) in pain perception and sensitization.
Legend: 2-arachidonoylglycerol (2-AG); prostaglandin E_2 subtype G (PGE_2-G); Interleukin-1 beta (IL-1β), *N*-methyl-d-aspartate receptor (NMDA), calcium (Ca^{2+}), nitric oxide synthetase (NOS).
Reproduced from: Voscopoulos C, Lema M (2010) When does acute pain become chronic? British Journal of Anaesthesia 105:i69–i85 (15)

1.2.3) From the nociceptive process to amplified and multiple pain

The nociceptive process involves the transmission of noxious stimuli from peripheral nerves to the central nervous system, ultimately leading to the perception of pain. However, nociceptive pathways can undergo sensitization, a phenomenon characterized by heightened responsiveness to stimuli, resulting in increased pain sensitivity and intensity. This increased sensitivity is due to the release of inflammatory mediators like prostaglandins, bradykinin, and cytokines, which reduce the threshold for nociceptor activation. As a result, even normally non-painful stimuli can become painful, a phenomenon known as allodynia (12, 16). The familiar phenomenon of hyperalgesia is defined as the enhanced sensitivity and responsivity to stimulation of the area around the damaged tissue. Central sensitization occurs at the level of the spinal cord and brain, involving alterations in synaptic transmission, neuronal excitability, and neuroplasticity. This process leads to the amplification of pain signals and the spread of sensitivity to surrounding tissues, resulting in hyperalgesia and allodynia (17).

The literature identifies three types of pain: nociceptive pain, caused by damage to body tissue; neuropathic pain, reflecting both peripheral and central sensitization mechanisms; and nociplastic pain, defined by the IASP as *"pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain"* (2). Nociplastic pain is characterized by pain in multiple body regions, fatigue, sleep disturbances, cognitive dysfunction, multisensory hypersensitivity, depression and anxiety. Individuals experiencing nociplastic pain are often diffusely tender — indicative of hyperalgesia and/or allodynia (18).

Alterations in the central nervous system, particularly in brain regions situated within the default mode, salience, and somatosensory networks, have been reported in many chronic pain conditions with nociplastic features. Despite the exact etiopathogenesis of nociplastic pain remaining unknown, being female, early-life stressors, trauma, poor sleep, heightened somatic awareness and physical inactivity increase the risk for nociplastic pain (19).

1.2.4) Pain and immunity - a lifelong interaction

Pain and the immune system engage in complex and bidirectional interactions that begin in early development and continue to influence health and disease processes into adulthood. The relationship between the nervous and immune systems involves several key mechanisms. Cytokines and chemokines can directly influence nociceptors, increasing pain sensitivity. Pro-inflammatory cytokines like IL-1β, IL-6 and tumor necrosis factor (TNF-α), are known to increase nociceptive transmission and contribute to pain hypersensitivity (20). In the central nervous system, glial cells, including microglia and astrocytes, play an important role in pain modulation. Activation of these cells in response to injury or inflammation can release additional cytokines and chemokines, perpetuating a cycle of pain and inflammation (21). Additionally, nerve fibers release neuropeptides, such as substance P and calcitonin gene related peptide, which contribute to local inflammatory responses and enhance pain signaling (22).

Chronic pain is often associated with persistent immune activation and dysregulation. Patients with chronic pain conditions frequently exhibit elevated levels of pro-inflammatory cytokines and reduced anti-inflammatory cytokines, suggesting an imbalance in immune regulation (23).

1.2.5) Early development as a sensitive period for pain experience

During early life, the central nervous system exhibits high levels of plasticity, allowing for significant changes in response to nociceptive input. Synaptic connections are continuously formed and refined based on sensory experiences. This plasticity means that early pain experiences can have lasting effects on pain perception and sensitivity (22, 24). Central nociceptive pathways begin to develop early in gestation. By the second trimester, the basic structures for pain processing, including the spinal cord, thalamus, and cortex, are formed and start to function. Nociceptive neurons in the dorsal horn of the spinal cord transmit pain signals to the brain, where they are processed and interpreted (22). As children grow, their pain pathways mature, through the strengthening of synaptic connections and the increased specificity of pain pathways. The balance between excitatory and inhibitory signals also becomes more refined, helping in accurate nociceptive information processing (25). Descending modulatory pathways, originating in the brain and traveling down to the spinal cord, play a crucial role in regulating pain. These pathways begin to develop during the prenatal period and continue to mature into adolescence (26).

Early life experiences, including pain and stress, can influence the maturation of these pathways. Also, positive experiences, such as effective pain management, can enhance the development of inhibitory pathways, leading to better pain control. Conversely, repeated or poorly-managed pain can lead to maladaptive changes, increasing the risk of chronic pain (27).

1.2.6) Early life determinants of pediatric pain

Recent research has shed light on various factors that influence the development and expression of pain in pediatric populations. Genetic predisposition plays a significant role in shaping individual differences in pain sensitivity and vulnerability to pain disorders (28). Variations in the genes that encode pain-related neurotransmitters, receptors, and ion channels, can influence nociceptive processing and modulate pain sensitivity (29). Genetic conditions, such as Ehlers-Danlos syndrome and Marfan syndrome, are associated with connective tissue abnormalities and increased pain sensitivity, predisposing affected individuals to chronic pain conditions (30). Additionally, genetic polymorphisms have been implicated in the development of specific pain conditions (31). Organic conditions may also be intrinsically associated with pain processes during

childhood. Neurological disorders, such as cerebral palsy, spina bifida, and epilepsy, can disrupt normal sensory processing pathways, leading to altered pain perception and greater pain sensitivity (32). Chronic inflammatory diseases like juvenile idiopathic arthritis (JIA) and inflammatory bowel disease can heighten pain sensitivity through peripheral and central sensitization mechanisms, contributing to chronic pain states (33, 34). Orthopedic conditions often result in chronic musculoskeletal pain due to nociceptive input from affected tissue and secondary changes in pain processing (35).

Early life experiences, including prenatal and perinatal factors, can influence the development of pain sensitivity and pain-related outcomes in childhood (36). Perinatal factors, such as birth trauma, prematurity, and neonatal intensive care unit (NICU) experiences, can also impact pain sensitivity and contribute to the development of chronic pain conditions later in life (37).

Early life stress and trauma, including physical abuse, emotional neglect, and parental separation, can have long-lasting effects on pain perception and pain-related outcomes (38). Moreover, adverse childhood experiences have been associated with heightened pain sensitivity, increased risk of chronic pain conditions, and changes in pain processing pathways (39). Chronic exposure to stress hormones, such as cortisol, during critical periods of brain development, can lead to dysregulation of the hypothalamic-pituitary-adrenal axis and alterations in pain modulation systems (40).

Parental factors, including parental pain history, parenting behaviors, and family dynamics, can shape children's pain experiences and coping strategies, as well as model maladaptive pain behaviors (41, 42). Parental responses to children's pain, such as showing concern, minimizing, or catastrophizing, can influence pain outcomes and contribute to the development of pain-related disability (43).

Furthermore, emerging research suggests a potential link between alterations in gut microbiota composition (dysbiosis) and pediatric pain conditions, including functional abdominal pain disorders and irritable bowel syndrome (IBS) (44). The gut microbiota and stressful experiences impact neurobehavioral development in preterm infants during their NICU hospitalization (45).

Dysregulation of the immune system during early life, such as imbalances in pro-inflammatory and anti-inflammatory cytokines, may influence pain sensitivity and contribute to the development of chronic pain disorders (46). Atopic diseases, characterized by immune system hypersensitivity to environmental triggers, represent an emerging early determinant of pediatric pain. Conditions, such as eczema, asthma, and

allergic rhinitis, commonly manifest in childhood and can significantly impact pain experiences through various mechanisms (47). The pain associated with atopic diseases arises from inflammation-induced sensitization of nociceptors, tissue damage from scratching or rubbing, and psychological distress related to chronic symptoms (48-50).
Additionally, comorbid conditions, such as sleep disturbance, anxiety, and depression commonly observed in children with atopic diseases, can worsen pain perception and lead to functional impairment (48, 51).

1.3) Chronic pain syndromes in childhood

Chronic pain syndromes, commonly referred to as functional pain syndromes (FPS), can present in different ways, but often share common underlying processes, such as central sensitization and genetic and environmental interactions (52, 53). These processes contribute to the persistence of acute and lasting pain states – as illustrated in the proposed model of Figure 2 (52).
Central sensitization, associated with the development and endurance of chronic pain, is a core mechanism in many pediatric chronic pain syndromes (23).
Genetic predispositions and environmental factors, such as early life stress and injury, combine to influence the development of chronic pain syndromes. These factors can affect pain processing pathways and contribute to varied pain experiences among children (54).
Individuals have genetic susceptibility through a polygenic mix of common polymorphisms in genes, such as Catecol O-Metiltransferase, serotonin transporter, and beta-2 adrenergic receptor. This vulnerability does not automatically lead to central sensitivity syndrome. A complex network of epigenetic and gene-environment interactions leads to sensitization (54).
Environmental triggers may play a key role in which phenotypic facet of central sensitivity syndrome is presented to the health care system. Increased peripheral input from the affected organ system, coupled with central sensitization, results in the development of predominant symptoms in that system (55).

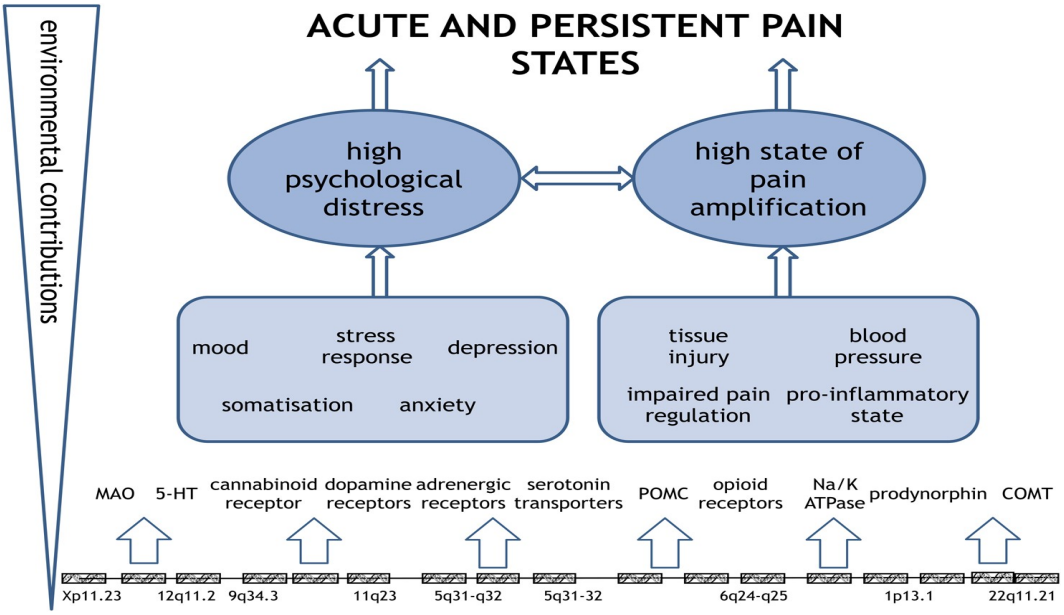


Figure 2. Model depicting likely determinants that contribute to the risk of onset and maintenance of acute and persistent pain states.
Reproduced by: Crabtree D, Ganty P (2016) Common functional pain syndromes. *BJA Educ*, Volume 16, Issue 10, October 2016, Pages 334–340 (52)

1.3.1) Specific pain syndromes

1.3.1.1) Musculoskeletal Pain Syndromes

– **Noninflammatory musculoskeletal pain (NIMP):** NIMP is characterized by pain in muscles, bones, or joints that is not associated with inflammation or a detectable injury. It often presents as diffuse, widespread pain and may be accompanied by symptoms, such as fatigue and sleep disturbances. Unlike inflammatory conditions, NIMP does not show clinical signs of swelling, redness, or warmth (56). Studies suggest that it affects a significant portion of the pediatric population, with prevalence rates varying depending on the population and diagnostic criteria used (57, 58).

- **Generalized Chronic Pain Syndrome (GCPS) / Juvenile Fibromyalgia:** GCPS, previously known as Juvenile fibromyalgia, is characterized by widespread musculoskeletal pain, fatigue, and sleep disturbances. It predominantly affects adolescent girls and, on examination, is associated with tenderness. This condition is believed to involve abnormalities in pain processing pathways and neurotransmitter systems. Management typically includes physical therapy, cognitive-behavioral therapy, and medications, such as antidepressants

or anticonvulsants (59). GCPS is often associated with psychological stress and can significantly impact a child's quality of life (60).

- **Growing Pains:** Growing pains are a benign form of NIMP that typically occurs in the legs of children aged 3-12 years. The pain often occurs at night and is not associated with physical activity. The exact cause is unknown, but it is hypothesized to relate to the rapid growth and development of bones and muscles during childhood (59, 61).
- **Myofascial Pain Syndrome:** Myofascial pain syndrome involves pain and tenderness in specific muscle groups, often associated with trigger points that can cause referred pain. This condition is thought to result from muscle overuse, injury, or stress, leading to the formation of taut bands of muscle fibers that are painful upon palpation (62).
- **Overuse Syndromes:** Also known as repetitive strain injury or cumulative trauma disorder, results from repetitive movements, awkward postures, or sustained force that leads to microtrauma and inflammation in muscles, tendons, nerves, and other soft tissues. Common overuse syndromes include Osgood-Schlatter disease and Sever's disease. Symptoms include localized pain and tenderness, often exacerbated by activity. Treatment focuses on rest, physical therapy, and anti-inflammatory medications (59).

  Both myofascial pain syndromes and overuse syndromes are commonly seen in adolescents who are involved in repetitive activities or sports (63).
- **Benign Hypermobility Syndrome:** Benign hypermobility syndrome is characterized by joint pain and increased flexibility without signs of inflammation. It is more common in girls and tends to decrease with age. Pain is usually localized in the knees, ankles, and feet. Management includes education, strengthening exercises, and sometimes orthotic devices (59).

- **Complex Regional Pain Syndrome (CRPS):** CRPS is a severe, chronic pain condition that typically affects one limb after an injury. It is characterized by distinct clinical features, including allodynia, hyperalgesia, sudomotor and vasomotor abnormalities, and trophic changes. The pain experienced is disproportionate to the degree of tissue injury and persists beyond the expected time for tissue healing. The pathophysiology of CRPS is multifactorial and not fully understood but is thought to involve dysregulation

of the nervous system (59). CRPS is classified into two subtypes: type I (formerly known as reflex sympathetic dystrophy), which occurs in the absence of nerve trauma, and type II (formerly known as causalgia), which occurs with nerve trauma. Clinically, these subtypes can be indistinguishable and follow a regional rather than a dermatomal or peripheral nerve distribution, with common spread to the proximal or contralateral limb. CRPS can further be categorized into "warm" versus "cold" types and “sympathetically-maintained” versus “sympathetically-independent”, which may affect prognosis and treatment options (64, 65). The condition not only impacts function, sleep, and activities of daily living but also has significant mental and psychosocial implications (66). Treatment requires a multidisciplinary approach, including physical therapy, pain management, and psychological support (59).

1.3.1.2) Other Functional Pain Syndromes

- **Chronic Abdominal Pain:** Chronic or recurrent abdominal pain, including conditions like IBS or functional dyspepsia, are common in children. These conditions are often classified as functional, with no identifiable organic cause. They are thought to result from dysregulation of the brain-gut axis, involving both central and peripheral mechanisms. The persistence of pain into adulthood may be linked to psychiatric conditions (67).
- **Headaches and Migraines:** Chronic headaches, including migraines, are prevalent among children and adolescents. These conditions are influenced by genetic factors, hormonal changes, and environmental triggers. Migraines are associated with central sensitization and may be accompanied by symptoms, such as nausea and visual disturbances (68).
- **Temporomandibular dysfunction:** This condition is frequently associated with regional pain symptoms like cervicalgia, migraine, and trismus. No single external cause or trigger has been identified. Instead, a complex interaction between environmental influences and genetic predispositions may lead to psychological distress and increased pain, regardless of the specific cause (52, 69).
- **Chronic cardiac chest pain:** Chronic cardiac chest pain is a visceral, poorly-defined FPS with no universal clinical definition. It represents a minor element within the

broader spectrum of cardiac chest pain and is less common in the pediatric population than adults (52).

Psychological comorbidities, such as anxiety and depression, often accompany chronic pain syndromes in children. These conditions can exacerbate pain, complicate treatment, and have long-term psychological consequences in adulthood (70, 71).
The social and family context plays a crucial role in the experience and management of chronic pain. Supportive family environments and positive social interactions can mitigate the negative impacts of chronic pain, while family stress and social isolation may worsen outcomes (72).

1.4) Pain impact on pediatric age

1.4.1) Impact on children's lives

The impact of pain experienced on children's lives is undeniable. For this reason, progressive tools have been developed to make pain visible through measurement tools that assess both pain characteristics and their impact on multiple domains of life. Systematic reviews of measures of pain impact (73), pain-related anxiety (74), sleep disturbances (75), observational/behavioral measures of pain (76), and self-report measures of pain for very young children (77), are available. More research exists on the impact of pain in adolescents than in younger children, perhaps justifiably, because pain is more prevalent with increasing age and easier to measure in adolescents.
Although studies are not as conclusive regarding sex differences in the impact of pain as in other characteristics, some studies indicate that pain can significantly impact the daily functioning of girls (78, 79). Girls report higher levels of pain-related disability and interference with daily activities compared to boys (80).
Pain problems negatively affect many aspects of children's and adolescents' lives. Although many children with pain conditions cope well, a subgroup of children and adolescents with chronic pain experiences poor school attendance, reduced participation in athletic and social activities, and sleep disturbances (81,82).
Sleep disturbances may occur in all pediatric age groups, with more than half of a school survey in Norway reporting this problem, and a higher prevalence among girls (83). These disturbances can *per se* impact children's lives in various ways, for instance, absence

from school and poor school performance, emotional state, and relationships with friends (83). Studies have shown an association between pain and disturbed sleep (84, 85).

Furthermore, a study among adolescents with chronic pain found that they often report disabilities, including reduced everyday physical activities like walking and sitting unaided, needing more rest than usual, and disturbances in self-management behaviors, such as eating and washing (86). Adolescents with pain engage less in tasks and activities than their peers, leading to lifelong drawbacks (87, 88). Unwelcome changes in social and schooling/occupational activities are also common (89, 90). Recurrent or chronic pain contributes to school absenteeism, with studies showing high rates of absenteeism (higher in girls) and frequent absences linked to higher overall pain burden and stress levels. Adolescents who indicated missing school were more often girls, slightly older, and had a higher overall pain burden and stressor levels. Adolescents absent from school are at higher risk of school dropout, behavioral and social problems (91, 92). School-aged children with pain are absent from school more often than their pain-free peers and those with other chronic diseases (80, 93). Pain affects social and physical functioning (94), with adolescents reporting negative changes in affective domains, such as depression and anxiety (95, 96), and specific changes in psychosocial functioning, such as anxious sensitivity to a range of physical sensations (97). Children with pain also report lower quality of life and higher levels of distress, anxiety, and depression (81, 82). The co-occurrence of chronic pain and mental health conditions (posttraumatic stress disorder, anxiety, and depressive disorders) is high (71).

This mix of physical, social, and psychological domains affected by chronic pain is classified as chronic pain syndrome. The biopsychosocial model of pain provides a framework for understanding how different diseases are related through an assessment of sensorial, cognitive/affective, and interpersonal factors.

Considering this framework (Figure 3), it has been demonstrated that chronic pain is often associated with other processes that can affect how pain is perceived (98). In this line of reasoning, the concept of high-impact chronic pain (HICP) has been proposed to better identify individuals with significant levels of life interference due to chronic pain. A Spanish cross-sectional study on HICP in children found a prevalence rate of 5%. The study revealed that these children experienced worse physical, psychological, and cognitive functioning compared to those with chronic pain, which was also associated with worse school performance (99). Moreover, individuals with HICP account for the largest share of the economic costs of chronic pain (100).

Although the prevalence of HICP is higher in girls, the differences in how pain affects daily life based on sex are not well-established and should be interpreted with caution (101).

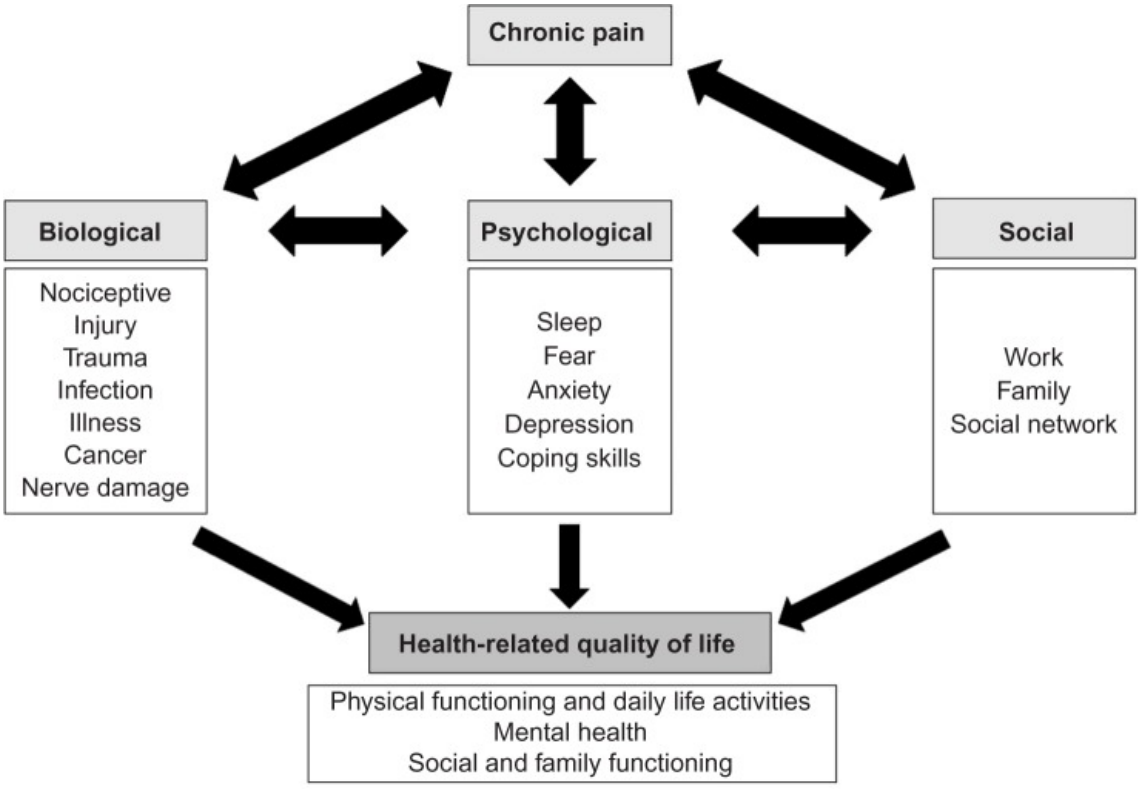


Figure 3: Biopsychosocial model of pain and consequences on the quality of life. Reproduced from: Dueñas M, Ojeda B, Salazar A, Mico JA, Failde I. A review of chronic pain impact on patients, their social environment and the health care system. J Pain Res. 2016 Jun 28;9:457-67. Doi: 10.2147/JPR.S105892. PMID: 27418853; PMCID: PMC4935027 (98).

1.4.2) Use of Health Care Services

Recent research has focused on the use of health care services by children increasingly experiencing pain, particularly chronic pain and primary pain disorders (FPS), and its economic impact (58) (102). However, only a subset of children is evaluated in health services, and primary pain disorders are often undiagnosed and untreated (103). A school survey in Norway found that only 11% of children and adolescents received a medical diagnosis for their pain (83).

There are various factors influencing health care use. The severity and impact of pain on daily functioning often influence the likelihood of seeking health care. In general,

increasing age, pain intensity, and duration predict higher health care utilization rates (104). There is a strong association between pain-related disability and increased health care service use (105).

Parents may seek medical care more frequently if they perceive their child's pain as severe or if it persists despite home management strategies. Parents with low health literacy are more likely to overestimate the severity of illness and seek care sooner to gain answers about the illness and treatment options (106). Socioeconomic status can also impact access to specialized care services, with children from lower-income families facing barriers (107).

A USA study by Groenewald and their colleagues concluded that pediatric pain-related conditions were associated with $11.8 billion in incremental health care payments, similar to those for attention deficit and hyperactivity disorder, but more than for asthma and obesity (108).

Other studies from the Netherlands, Malaysia, and the USA have identified increased health care service use due to pediatric pain-related conditions but did not calculate associated costs (109, 110, 111).

Health care services include primary care and hospitals (level II and III). Information on pediatric health care services profiles is limited, but studies in adults reported that chronic pain patients visited their doctor between two and nine times in the months prior to the study, with 11% visiting at least ten times (112). A recent study in Portugal reported an average of six medical consultations per year among chronic pain patients, double the mean seen in the general Portuguese population, with only a minority attended by pain specialists (113).

A cross-sectional observational study in pediatric primary care found a prevalence of around 15% for pediatric pain (114). Despite this, in a population-based survey in the USA, children estimated that chronic pain was not associated with increased odds of primary care or mental health care use, but was associated with greater odds of using other specialty and emergency care. The higher likelihood of emergency care use in this group raises the question if better multidisciplinary management of pediatric chronic pain could reduce emergency department use (115). Mental health services, such as counseling and cognitive-behavioral therapy, are crucial for addressing the psychological aspects of pain and promoting coping skills (71).

Specialized pain clinics and multidisciplinary programs are increasingly recognized as essential for the comprehensive care of children with complex pain conditions (116, 117).

A recent study evaluating all children with pain referred to a pediatric rheumatology division found that more than 75% were diagnosed with non-rheumatic conditions, primarily non-specific musculoskeletal pain (62%) and somatic conditions (12%) (118).
A primary care study in Spain reported that musculoskeletal pain is responsible for approximately 6% of primary care visits for children aged 3-14 years, rising to over 10% for adolescents (119). This increases to 20–33% in adults according to the World Health Organization (WHO) (120).
A cohort study on the impact of undiagnosed diffuse musculoskeletal pain found that 29% of children had at least one emergency visit and 5% were hospitalized. Even before the diagnosis, these children had high levels of health care use, diagnostic testing, and medical costs (121).

1.5) Pediatric pain: prevalence, perception and measurement

1.5.1) Overall prevalence

Pediatric pain affects a significant portion of children worldwide. Epidemiological studies have shown that chronic pain affects between 11% and 38% of children and adolescents globally, depending on definitions and measurement tools (57, 58, 122, 123). Acute pain is even more common, with nearly all children experiencing it at some point due to injury, illness, or medical procedures (124). A prospective study among the Dutch pediatric population (ages 0-18 years) found that 54% had experienced pain within the previous 3 months, and a quarter of the respondents reported chronic pain. The prevalence of chronic pain appears to increase with age, peaking during adolescence. (125). The first systematic review and meta-analysis on pediatric chronic pain in low- and middle-income countries reported a prevalence lower than 10% (126). However, the most recent systematic review and meta-analysis by Chambers et al. found that the global prevalence of chronic pain in children and adolescents remains around 20% (127). Cross-sectional and clinical studies often report higher prevalence rates compared to cohort studies due to differences in population characteristics. For example, a cross-sectional study conducted in Spain reported that nearly 50% of children had chronic pain conditions (99).
In Portugal, pain has been studied mainly in adults and clinical settings (12, 128). A nationwide cross-sectional epidemiological study conducted by Azevedo et al. reported a prevalence of chronic pain of 36.7% (128). Despite that, the overall presence of pain among healthy Portuguese children needs further investigation. Four cross-sectional

studies among adolescents (aged 12-19 years) compared school surveys conducted in different regions of our country (129). The most studied age group was adolescents, with participants ranging from 11 to 19 years old. The prevalence of chronic pain varied between 29.1% and 34.1% in two Portuguese studies using the same chronic pain definition and questionnaire – (130, 131) – with a total of 423 participants. More recently, prospective birth cohort studies are ongoing investigated non-specific and chronic pain in the healthy pediatric population to estimate the point prevalence of pain more accurately among Portuguese children and adolescents (132, 133).

1.5.2) Anatomical distribution of complaints

The prevalence of pain in different parts of the body varies worldwide depending on methodological approaches and the population in analysis. Despite these differences, data consistently identify headache, abdominal pain, and musculoskeletal pain (limbs and back) as the main anatomical pain locations among children and adolescents (57, 58, 99, 104, 125, 127, 134). An international study with 749 healthy children and adolescents reported prevalence rates of 60.5% for headaches, 43.4% for abdominal pain, 33.6% for limb pain, and 30.3% for back pain (30.2%) (104).

Abdominal pain is often chronic and is estimated to affect between 3.8 and 53.4%, and is more common in girls and younger children (58). Other studies estimate that the 3 to 6-month prevalence of recurrent abdominal pain in children and adolescents from 6 to 17 years of age ranges from 6% to 41%, decreasing with age (135, 136, 137). Musculoskeletal pain, including limb pain and back pain, is also highly prevalent in about 40% of children and adolescents (138, 139), with limb pain affecting approximately 10% to 20% of children (58). Back pain is increasingly reported in older children and adolescents, with prevalence rates ranging from 10% to 25% (57, 58, 123, 134, 140).

The most recent systematic review and meta-analysis, published in 2024, reported prevalence rates of around 25% for headache, 17% for abdominal pain, 26% for musculoskeletal pain, and 20% for back pain (127).

In line with international data, a Portuguese study reported headaches (33.6%), abdominal pain (16.8%), and limb pain (12.8%) as the most prevalent among adolescents with pain (131).

Moreover, pediatric populations often report pain in different anatomical sites. The prevalence of multiple pain varies according to definitions and/or methodological

approaches, ranging between 20 and 50% worldwide (125, 127). A recent study in patients with psychiatric comorbidities found a higher prevalence, above 75% (141). Gobina et al. collected information on multisite pain in 42 countries and estimated an overall prevalence of 20.6%, higher than the Portuguese subsample (13.8%) (142).

1.5.3) Pain perception triggers

The real causes of pain are known only after detailed medical evaluation and diagnosis. However, several recent studies have examined pain triggers through self-assessment and self-perception. The results show the subjective views of children, adolescents, and parents, and indicate the complex processing of psychosocial circumstances that trigger pain symptoms (143).

Roth-Isigkeit et al. found that the most frequent triggers for pain among German children and adolescents were external factors, such as changes in weather conditions (33%), illness (30.7%), and physical exertion from sports and other physical activities (21.9%). Additionally, 12.8% of participants reported that their pain was triggered by television or computer use, and lack of sleep was perceived as a trigger in 16.2% of children (104).

A recent cross-sectional qualitative study among Spanish school-age children showed a variety of reasons for pain, including pathologies and injuries (45.95%), ergonomic issues (22.60%), and psychological issues (15.95%). Psychological factors included personal anger states, arguments, agitation, stress at school, schoolwork, family situations, and overall sadness (144).

Other studies have linked media exposure (e.g., television and computers), lack of sleep, and daytime sleepiness to back pain among adolescents (145, 146). Schoolwork and the school environment have also been self-reported as pain triggers in children (83). Nutrition has been associated with headaches in the pediatric population (147, 148, 149). These findings underscore the importance of considering the biopsychosocial model when evaluating pain experiences.

1.5.4) Sex differences in pain experiences

Sex differences in pediatric pain experiences are influenced by biological, psychological, and social factors, manifesting differently across various pain types and developmental stages.

Studies consistently show that girls report higher pain prevalence compared to boys. For

instance, Perquin et al. found that girls were more likely to report chronic pain than boys, particularly during adolescence (125). A systematic review by King et al. confirmed higher chronic pain prevalence in girls, with conditions, such as headaches, abdominal pain, and musculoskeletal pain more common (58).

Girls are more prone to headaches and migraines compared to boys, with prevalence rates increasing during adolescence (150, 151). Similarly, girls report higher instances of functional abdominal pain and IBS (152). The prevalence of musculoskeletal pain is also higher in girls, especially during periods of rapid growth and physical activity (58, 153). A recent systematic review and meta-analysis by Chambers et al. found that girls have a higher prevalence of chronic pain (18.3%) compared with boys (12.7%) (127).

The self-reported triggers for pain also vary between sexes. Girls more frequently report weather conditions (39% vs 25%), acute illness, anger/disputes (20.9% vs 11.9%), family conditions (12.1% vs 5.2%), and sadness (11.9% vs 3.4%) as triggers. In contrast, boys stated more often than girls that their pain was triggered by physical exertion (28% vs 17.2%) (104).

Girls generally report lower pain thresholds and higher pain sensitivity compared to boys. This has been observed in both experimental and clinical settings (154, 155). Experimental studies show that girls are more sensitive to thermal, pressure, and ischemic pain stimuli than boys (156). Additionally, girls report higher pain intensity and greater emotional distress associated with pain (99). This difference is particularly notable during adolescence when hormonal changes may worsen pain experiences (157).

The role of hormones, particularly estrogen and progesterone, in modulating pain sensitivity, is well-documented. Pubertal changes in girls are associated with increased pain sensitivity and higher pain prevalence (158). Menstrual cycles can influence pain perception, with many girls reporting fluctuations in pain severity related to their menstrual phases (159). For example, Kløven et al. found that early menarche is associated with higher odds of chronic pain in adolescence (160), while Hebert et al. showed that advanced puberty is associated with more spinal pain (161).

Genetic predispositions also play a role in how pain is felt between the sexes. Certain genes related to pain perception and modulation are expressed differently in boys and girls, contributing to different pain experiences (162).

Psychological and social factors further influence these sex differences. Girls are more likely to use emotion-focused coping strategies, such as seeking social support and expressing emotions, which can affect their pain experiences and reports (163). Boys, on

the other hand, may use more problem-focused coping strategies, potentially leading to underreporting of pain or different pain management outcomes (164).

Social and cultural expectations also play a role in how boys and girls perceive and report pain. Girls may be more encouraged to express pain and seek help, while boys may be socialized to endure pain without complaint (165).

Thus, sex differences in pediatric pain experiences result from a complex interplay of biological, hormonal, psychological, and social factors. Girls are generally more likely to develop chronic pain and report multiple pain sites (166).

1.5.5) Discrepancies between children's and parents' reports

Assessing pediatric pain is complex, with significant discrepancies often observed between children's self-reports and their parents' perceptions of their pain.

Although research has shown that children can report their own pain experiences using validated instruments from as early as 3 years old (167-170), parental reports have traditionally been relied upon for clinical history due to practical reasons, such as easy access, and rapid memory recollection. Numerous studies over the past two decades have compared children's and parents' reports yielding different results. A study by Chambers et al. found that parents tend to underestimate the intensity of their child's pain, particularly in cases of chronic pain (171). Palermo et al. highlighted that parents' assessments of their child's pain are often influenced by their observations of the child's behavior rather than verbal reports (172). This reliance on behavioral cues can be problematic, as children might not always display outward signs of pain, especially in chronic conditions where they may have adapted to living with discomfort. Kozlowski et al. revealed that discrepancies are more pronounced in younger children due to communication barriers, compared to adolescents who can more accurately articulate their pain (173). In 2016, Kamper et al. described poor agreement between children's self-reports and parents' reports of pain, with closer agreement for high-intensity and persistent pain (168).

Parents' emotional states and stress levels can also influence their perceptions of their child's pain. For example, Logan and Scharff found that parents who reported higher levels of anxiety and stress were more likely to overestimate their child's pain (174). Jaaniste et al. found that in various clinical settings, parents' reports of their child's pain often did not match the child's own pain ratings, particularly in acute pain situations, such

as post-surgical pain, where the dynamic nature of pain might make it harder for parents to gauge accurately (175).

A study combining data across children experiencing pain due to surgery, medical procedures or chronic diseases showed a better correlation between parental and child reports (176). Another study comparing adolescents' self-reports and mothers' proxy-reports of adolescents' chronic pain-related functioning suggests that there is greater agreement for observable and shared disabilities, whereas more contradiction is noted for internal experiences (177).

Nevertheless, a national study comparing the agreement between parents, nurses, and children regarding children's pain concluded that both nurses and parents tend to underestimate pain intensity reported by children (178).

Cultural factors also play a role in pain reporting differences. For instance, a cross-cultural study by Zhou et al. found that cultural norms regarding pain expression and stoicism can influence how parents perceive and report their child's pain (170).

Despite that, some studies reinforce the good agreement between children and parents. A study on children's pain after surgery found good levels of agreement between child and parental reports of pain intensity (169). A cross-sectional study involving children aged 3–15 years treated at emergency departments concluded that parents and children had moderate agreement regarding the presence of pain (167). These studies included children with conditions associated with hospital admission, outpatient care or emergency room visits (167, 169).

Less is known about parental accuracy in assessing pain on a wider spectrum, particularly in healthy children. A cross-sectional study in Norway showed that many parents are unaware of the pain experienced by their children and adolescents aged 8–18 years (83). Symptoms reported by children aged 7 to 14 were significantly more frequent and severe than those reported by parents, according to a German epidemiological study (179). Sundblad et al. and Waters et al. used community-based surveys to investigate the harmony between parent and child pain reports, finding poor agreement overall and noting that children reported more regular and more intense pain than their parents (180, 181).

A study among Zimbabwean adolescents found that most parents of school children with recurrent non-specific low back pain were unaware of their children's pain status (182). A Danish Cohort study, evaluating healthy children separately from their parents, also showed poor agreement between parents and children regarding musculoskeletal pain in

the previous week (168).

Discrepancies between child and parent reports can have significant implications for pain management and treatment outcomes, potentially leading to unnecessary medical interventions and increased anxiety for both the child and the parent (183).

1.5.6) Pain experiences according to age group

Cohort studies, systematic reviews, and meta-analyses consistently show that the overall prevalence of pain increases with pediatric age (58, 99, 127, 184).

However, the prevalence varies according to the anatomical location of pain. Headache prevalence is estimated to be between 52% to 69% and tends to increase with age (185, 186). The 3 to 6-month prevalence of recurrent abdominal pain in children and adolescents aged 6 to 17 years ranges from 6% to 41%, decreasing with age (135-137). Back pain prevalence in the previous month is approximately 20% in children and adolescents aged 8 to 18 years, with increased prevalence in older adolescents (123, 140). Musculoskeletal pain is present in about 40% of children and adolescents aged 9 to 18, with higher prevalence in older adolescents (138, 139).

Despite the overall increase in prevalence with age, studies have shown that even newborns experience pain responses to various stimuli. Stevens et al. highlighted that procedural pain is prevalent in NICU, particularly during routine medical procedures (187).

From ages 3-4 years, children can verbalize pain to some extent, though their communication skills are still developing. Research by Stinson et al. demonstrated that toddlers and preschoolers often experience pain related to injuries, illnesses, and medical procedures (188). Chronic conditions like recurrent abdominal pain are also prevalent in this age group, as shown in a study by Campo et al. (189).

School-aged children become increasingly capable of expressing their pain experiences. Studies by King et al. and Huguet et al. have highlighted the prevalence of various types of pain in this age group, including headaches, musculoskeletal pain, and pain related to sports injuries (58, 190). Psychological factors, such as anxiety and stress, can also contribute to pain prevalence (191).

Adolescence is a critical period characterized by physical, emotional, and social changes, influencing pain frequency. Forgeron et al. showed that adolescents commonly experience pain, including headaches, menstrual pain, and chronic conditions like

fibromyalgia (72). Factors, such as peer relationships and academic stress, can exacerbate pain experiences, as observed by Eccleston et al. (192). A prevalence study involving 42 countries and regions found that pain prevalence increased with age, with 44.2% of adolescents reporting chronic weekly pain during the last six months (142).

1.5.7) Assessing pain in pediatric age

1.5.7.1) Validated tools/rating scales to assess pain

The development and constant adaptation of tools and scales for assessing pain in pediatric populations are crucial for obtaining accurate and reliable pain measurements across different age groups (193-203).

Several validated tools are available to assess pain in children, each tailored to different developmental stages and types of pain. These tools help clinicians and researchers obtain reliable and consistent measurements of pain intensity, quality, and impact (204).

Multiple tools and scales are used to evaluate pain in children, depending on their cognitive development and age. A systematic review of pain and sedation scales in neonates and preverbal children, which included 65 scales, concluded that clinicians should consider using scales validated for at least construct validity, internal consistency, and interrater reliability. This should be combined with information about the population of interest and the construct the scale is intended to measure (205).

Another meta-review analyzing 36 pain assessment tools concluded that no single pain assessment tool could be recommended as the gold standard due to limited availability and quality of evidence supporting their validity, reliability, and clinical utility. This meta-review aims to collate available evidence to assist clinicians in deciding on the most appropriate tool to use in their clinical practice. Researchers must adopt a standard approach to evaluating the psychometric properties of pain assessment tools and their clinical utility to use the highest level of evidence to guide tool selection (206).

In Portugal, several guidelines/clinical guidance standards have been developed in recent years. These guidelines present recommendations for pain control in various age groups and the validated, adapted and recommended pediatric pain scales for assessing pain in the Portuguese pediatric population (207). These guidelines can be consulted in detail in supplementary files (Supplementary material A).

- **Neonates: Preverbal age/ behavior scales**

a) Échelle de Douleur et d'Inconfort du Nouveau-Né (EDIN)

The EDIN scale is a one-dimensional behavioral scale based on the assessment of five items: facial expression, body movements, quality of sleep, quality of contact with nurses, and consolability. Each item is scored from 0 to 3, and EDIN scores greater than 6 are considered indicative of pain (208**).** Factors, such as gestational age, pain process, illness severity or prolonged sedation may affect the results and contribute to the underestimation and undertreatment of pain (209, 210).

The Portuguese version of this scale was adapted and validated for use in Portuguese neonates by Batalha et al. (211).

b) Neonatal Infant Pain Scale (NIPS)

Primarily used in NICU for preterm and full-term infants, the NIPS assesses pain based on facial expressions, crying, breathing patterns, arm and leg movements, and arousal state. This scale uses body language to help determine if a child is in pain. A child is given a score of 0 or 1 in each category based on their behavior, and a score greater than 3 usually indicates that a child is likely experiencing pain or discomfort (197). It is recommended for use in acute and postoperative pain (212). A national version of this scale was adapted and validated for use in Portuguese neonates by Batalha et al. (213).

c) Premature Infant Pain Profile-Revised (PIPP-R)

The PIPP-R evaluates pain in premature and term neonates based on three behavioral items (facial actions: brow bulge, eye squeeze, nasolabial furrow), two physiological items (heart rate and oxygen saturation), and two contextual items (gestational age and behavioral state). Each item is numerically scaled and scored on an empirically based 4-point scale (0, 1, 2, 3) reflecting increasing changes in each variable from baseline values. The scores obtained for the seven items are added together for a total pain intensity score (201, 214). It is suitable for assessing pain during procedures like heel lancing and venipuncture. The Portuguese version of this scale was adapted and validated for use in Portuguese neonates by Batalha et al. (213).

- **Infants: Preverbal age/ cognitive impairment/ behavior scales**

a) Face, Legs, Activity, Cry, Consolability Scale (FLACC Scale)

The FLACC scale assesses pain based on five criteria: facial expression, leg movement, activity, cry, and consolability, with scores ranging from 0 to 10. A score of 1-3 indicates mild pain/discomfort, 4-6 moderate pain/discomfort, and 7 or higher indicates severe pain/discomfort. This scale is particularly useful for non-verbal children and those unable to self-report pain. However, the interpretation of pain behaviors and treatment decisions require careful consideration of the context in which the pain behaviors are observed (199).

The cultural adaptation and validation were performed in Portugal by Batalha et al. in 2009 (215).

b) Face, Legs, Activity, Cry, Consolability – Revised (FLACC-R)

The revised FLACC-R is a behavioral pain assessment scale designed for children who are unable to self-report their pain due to developmental disabilities. The scale rates the child on five measurement categories: face, legs, activity, cry, and consolability. Each category is scored from 0 to 2, and the total score ranges from 0 to 10. For awake patients, the assessment involves observation for at least 1-3 minutes, with legs and body uncovered, noting activity and body tenseness and tone. For patients who are asleep, observation should be conducted for at least 5 minutes, with similar criteria and, if possible, with the patient in different positions. This scale can be used for all non-verbal children but is particularly valid for use in children with cognitive impairment (216).

Batalha et al. adapted and validated the Portuguese version of FLACC-R in 2013 (217).

- **Children/adolescents: Verbal age/ quantitative scales**

a) Faces Pain Scale – Revised (FPS-R)

The FPS-R is a self-report measure of pain intensity developed for children, adapted from the Faces Pain Scale (218). It uses a series of cartoon faces ranging from no pain to the worst pain, scored as 0, 2, 4, 6, 8 or 10. This scale is particularly recommended for children aged 3-4 years. The absence of smiles and tears in this scale may be advantageous for more accurate pain assessment (195).

b) Wong-Baker Faces Pain Rating Scale

This scale uses a series of six faces ranging from a smiling face (no pain) to a crying face (worst pain) for children to choose from. The faces can be numbered from 0 to 5 **(**0: does not hurt at all; 1: hurts just a little bit, 2: hurts a little bit more; 3: hurts even more; 4: hurts a whole lot and; 5: hurts as much as you can imagine, although you do not have to be crying to have this worst pain).

Alternatively, the faces can be numbered by 0 (does not hurt at all), 2 (hurts just a little bit), 4 (hurts a little bit more), 6 (hurts even more), 8 (hurt a whole lot) and 10 (hurts as much as you can imagine, although you do not have to be crying to have this worst pain). It is suitable for children aged 3 years and older (203, 219).

c) Visual Analog Scale (VAS)

The VAS measures pain intensity using a 100 mm line anchored by "no pain" on one end and "worst pain imaginable" on the other. Children mark a point on the line representing their pain intensity, with the score determined by measuring in millimeters from the left-hand end of the line to the point that the patient marks. It can be applied to access pain in school-aged children (198). There are various ways in which the VAS has been presented, including vertical lines and lines with additional descriptors (220) which provide an informative discussion of the benefits and shortcomings of different VAS styles.

Although the VAS was initially developed for assessing chronic pain, it is often used in studies of postoperative pain (221). Pain intensities on the VAS can be categorized into no pain (0-4-mm), mild pain (5-44 mm), moderate pain (45-74 mm), and severe pain (75-100 mm) (222).

d) Numerical Rating Scale (NRS)

The NRS is a numeric version of the VAS, suitable for school-age children, and measures pain intensity on a scale from 0 (no pain) to 10 (worst pain possible). This type of scale can be administered verbally. It can also be administered via paper to be completed physically (202). The patient is asked to make three pain ratings corresponding to current, best, and worst pain experienced over the past 24 hours. The average of the three ratings represents the patient's level of pain, with a final score of 1-3 indicating mild pain, 4-6 moderate pain, and 7-10 severe pain (223).

1.5.8) Assessing the multiple dimensions of pain

It is recommended to assess pain not only in terms of intensity but also in terms of its multidimensional impact, especially in older children and adolescents. Various international tools assess the impact of pain on multiple domains of daily life (physical, emotional, social, and interpersonal). However, in Portugal, there is still no nationally validated document (*guideline*) that recommends their use and under what circumstances.

a) **Adolescent Pediatric Pain Tool (APPT)**

   The APPT assesses pain intensity, location, and quality using a body outline for marking pain areas and a list of descriptive words for pain level. It is suitable for adolescents to provide a comprehensive pain assessment (224).

   Jacob et al. found good evidence for the construct validity, reliability, and sensitivity of the APPT for measuring pediatric pain. The APPT has been used to measure pain in children with different conditions, such as cancer, sickle cell disease, orthopedic and traumatic injuries, and during allergy testing (225).

b) **McGill Pain Questionnaire (MPQ)**

   The MPQ is a self-report measure designed to assess pain across several diagnoses. It evaluates both the quality and intensity of subjective pain by examining sensory, affective, and evaluative dimensions of pain through a series of descriptive words and intensity scales. Initially developed for adults, the MPQ has been validated for use in older children and adolescents, particularly those experiencing pain due to different chronic diseases (226-228).

c) **Brief Pain Inventory (BPI)**

   The BPI evaluates pain severity and the impact of pain on daily functions, including mood, walking, and work. It is particularly useful for adolescents experiencing chronic pain (194, 229).

d) **Bath Adolescent Pain Questionnaire (BAPQ)**

   The BAPQ is a self-report questionnaire validated for adolescents aged 11–18 years, assessing the impact of pain across multiple domains of life. The BAPQ may offer a comprehensive way to assess the widespread harmful impact of adolescent chronic pain in both a research and clinical setting (230).

   There is a version for parents, assesses the functioning and development of the adolescent from the parents' perspective (231).

e) **Varni/Thompson Pediatric Pain Questionnaire (PPQ)**

The PPQ is a comprehensive (parent and child) screening tool used for assessing pain in children and adolescents. It evaluates pain intensity, as well as sensory, affective, and evaluative dimensions of pain, including its location. Developed for children aged 4 to 16 years (232), the PPQ has been used with children up to 18 years old (233). This tool is designed to assess pain experiences across different cognitive and developmental stages and is available in three forms: for children, adolescents, and adults. Originally developed for children with conditions, such as rheumatoid arthritis and spina bifida, it has been applied to various types of musculoskeletal pain (234, 235). The PPQ includes a VAS, color-coded body diagram, and open-ended questions to provide a comprehensive assessment of pain (232).

f) **Patient Reporting Outcomes Measurement Information System (PROMIS) Pediatric Pain Interference Scale (PPIS)**

The PPIS is a tool designed to assess the impact of chronic pain on daily activities in children. Initially developed for adults aged 18 to 65 years (236), a pediatric version was later created for children aged 8 to 17 years (237). The tool has been condensed from a 39-item bank to an 8-item short form, which evaluates pain interference with physical, psychological, and social functioning over the past seven days (236).

g) **Pediatric Quality of Life Inventory (PedsQL)**

The PedsQL is a modular instrument for measuring health-related quality of life in children and adolescents ages. The PedsQL 4.0 Generic Core Scales consist of 23 items that assess physical, emotional, social, and school functioning. These scales are used for both self-report by children and proxy-report by parents. The PedsQL 4.0 can be integrated with Disease-Specific Modules to provide a comprehensive assessment for various health conditions, including both acute and chronic health issues (238).

Considering the biopsychosocial model, assessing the multidimensions of pain is an essential step to clarify and to improve pediatric pain, through a multidisciplinary approach incorporating specific drugs, physiotherapy, cognitive-behavioral therapy, and other psychological interventions that can be effective in managing all comorbidities and improving pain outcomes (239-241).

2) OBJECTIVES

Using data from the prospective birth cohort Generation XXI, the global objective of this thesis was to address several unanswered questions regarding children's pain experience in the first decade of life to improve the risk stratification of maladaptive pain in adolescence.

To achieve this, the study-specific objectives included:

1. To estimate a point prevalence of pain complaints at 7 years of age (Paper I)

2. To describe differences between children's and parent's reports of pain at 7 years of age (Paper I)

3. To estimate a point prevalence of pain complaints, triggers, and impact on children's daily life at 10 years of age (Paper II)

4. To characterize children's utilization of health care services for pain and the medical diagnoses associated with it (Paper II)

5. To explore atopy-like symptoms as early determinants of pain in early life and their association with pain reports at 10 years of age (Paper III)

6. To stratify the risk of multisite pain at 13 years according to the reported pain experience in the first decade of life (Paper IV)

3) METHODS

The objectives of this thesis were achieved through the analysis of data obtained from Generation XXI, a prospective population-based birth cohort study, with recruitment at birth and follow-up assessment waves at ages 4, 7, 10 and 13 years.

Specifically, data on pain history according to parents and children were collected at the 7- and 10-year follow-up, while data on adolescents' reports of pain were gathered at age 13. Consecutive subsamples of babies were examined at 6 and 15 months and we collected information about health in early life.

An overview of the Generation XXI participants and data collection procedures is provided below. Additional details about the study have been published elsewhere (132, 133). The selection of eligible participants for each article analysis depends on the specific objectives of the research and is described in detail in the methods sections of each individual chapter.

Figure 4 presents a conceptual scheme of the main investigative line of this thesis to accomplish the specific objectives mentioned above.

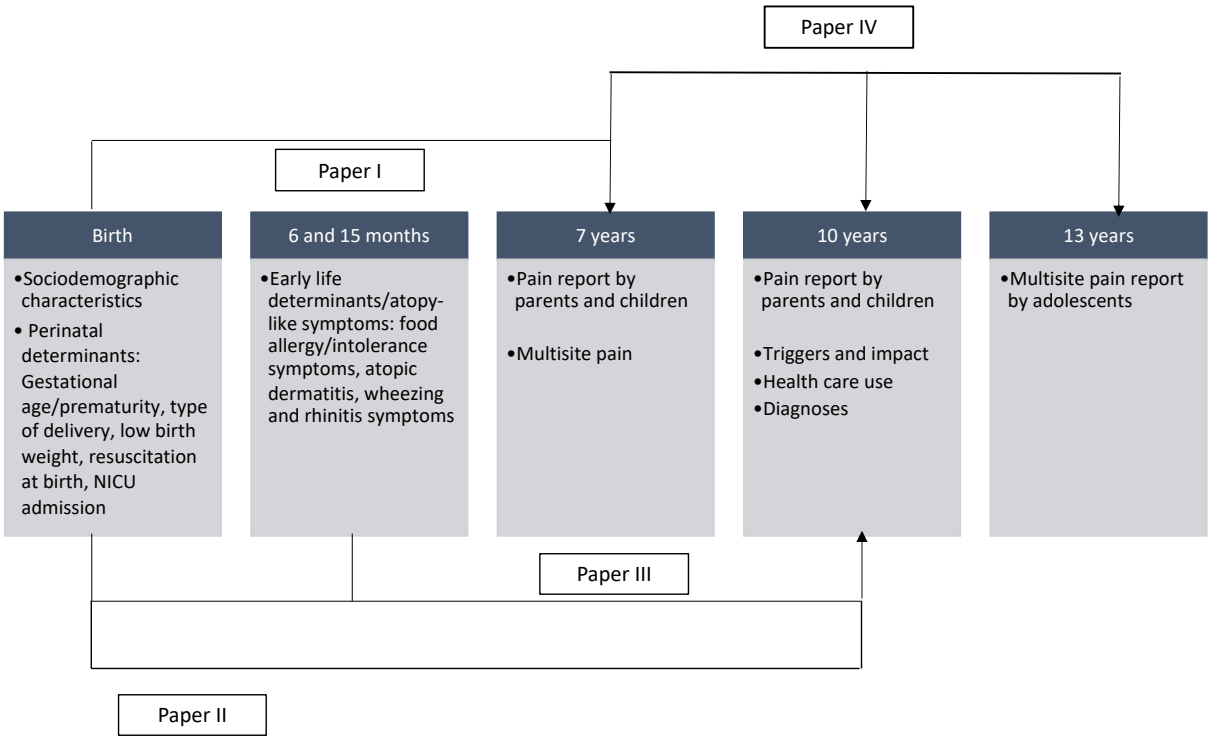


Figure 4: Conceptual scheme of investigative line with main exposures, outcomes, and evaluation waves considered in each paper. Legend: NICU – Neonatal Intensive Care Unit

3.1) The Generation XXI cohort study

Generation XXI is the first Portuguese birth cohort study. The cohort met during 2005 and 2006 in the Porto Metropolitan Area. It was established as a multipurpose prospective population cohort that aims to characterize prenatal and postnatal growth and development and identify its determinants in order to better understand health in childhood and later in adolescence and adulthood, thereby contributing to advances in health among the population.

3.1.1) Participants

Recruitment took place between April 2005 and August 2006 in the five public maternity units providing obstetric and neonatal care and covering, at that time, the metropolitan area of Porto, Portugal. The five maternity hospitals included in the study were the Centro Hospitalar de Vila Nova de Gaia, the Centro Hospitalar do Porto - Maternidade de Júlio Dinis, the Hospital de São João, the Centro Hospitalar do Porto - Hospital de Santo António and the Unidade Local de Saúde de Matosinhos - Pedro Hispano Hospital.

To be eligible to participate, women had to reside in Porto Metropolitan Area (Figure 5) - and deliver a live-born child with more than 23 weeks of gestation in one of the mentioned units, during the recruitment period. Seventy percent of the eligible mothers were invited and, of these, 91.4% accepted to participate. A total of 8495 mothers and their infants (n=8647) were enrolled in the cohort study.

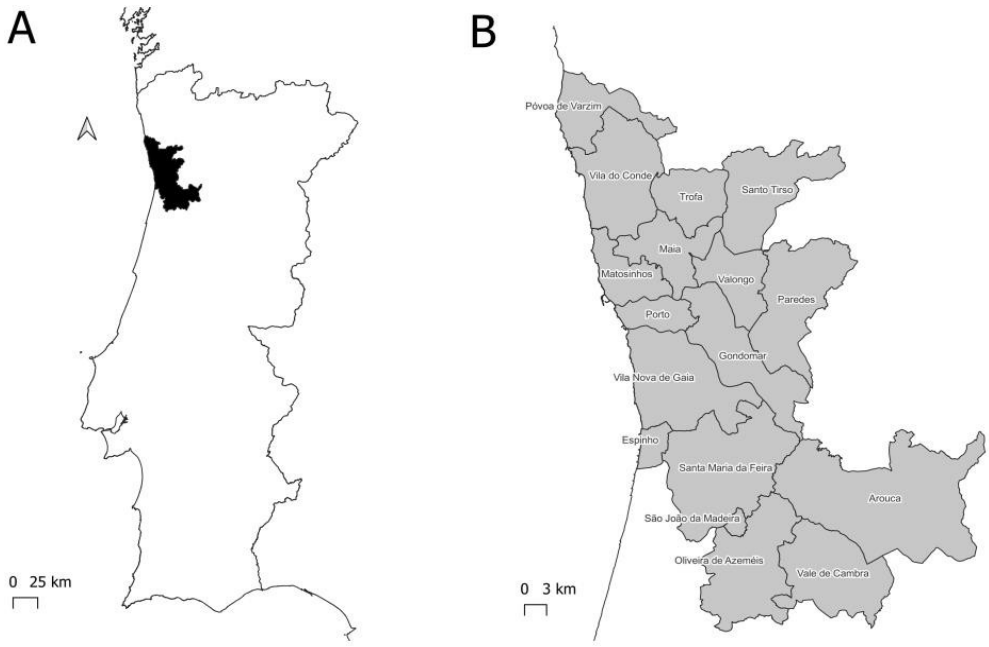


Figure 5. Representation of population-based birth cohort assembled in the Porto Metropolitan Area, Portugal

3.1.2) Ethical considerations

Generation XXI study protocol complies with the Ethical Principles expressed in the Declaration of Helsinki and was approved by the Ethics Committee of the Hospital de São João and the University of Porto Medical School. The study protocol also conforms to national legislation and is registered with the Portuguese Data Protection Authority. Procedures were developed in order to guarantee data confidentiality and protection. All participants received an explanation on the purposes and design of the study. Written informed consent was obtained from all parents or legal guardians, and oral assent was obtained from children at each evaluation. Alternatively, verbal consent was explicitly solicited for the telephone interviews.

3.1.3) Data collection

At baseline, within the first 24 to 72 hours after delivery during the hospital stay, trained interviewers located at the five hospitals were responsible for presenting the Generation XXI study and inviting mothers to participate. Data were collected in a face-to-face interview and clinical records at birth were reviewed by the trained interviewers.

Subsamples of the cohort were evaluated at the ages of 6 months, 15 months and 2 years (n=1555, n=1043 and n=855, respectively). Four years after birth, between April 2009 and July 2011, a follow-up evaluation of the entire cohort was conducted, and 7459 children, corresponding to 86.3% of the cohort, were re-evaluated. Of these, 5987 children (69.2% of the cohort) were assessed in a face-to-face interview while for 1472 children (17.0% of the cohort), who were unable to attend an in-person evaluation, a shorter version of the questionnaire was completed by legal guardians in a telephone interview. Between April 2012 and April 2014, all families were again invited to attend the 7-year follow-up of the cohort. Overall, 6889 children were reassessed (79.7% of the entire cohort), of which 5849 children (67.6% of the cohort) were evaluated in-person and 1040 (12.0% of the cohort) provided information via telephone interview. A subsequent evaluation of the cohort took place between July 2015 and July 2017, when children were 10 years of age, and 6397 children (74.0% of the cohort) were reevaluated. At 13 years of age, between 2018 and 2020, 4640 adolescents and their families (53.7% of the cohort) participated in the last evaluation wave.

Figure 6 shows the participation rates during the follow-up evaluations of the cohort. These evaluations took place at Departamento de Ciências da Saúde Pública e Forenses, e Educação Médica in the University of Porto Medical School. Standard procedures were established and adopted in all evaluations. A multidisciplinary team of interviewers and health professionals, periodically trained and supervised by the Generation XXI scientific committee, is responsible for administering structured questionnaires, performing the physical examination of parents and children, and extracting information from clinical records and the National Health Service (NHS) official health books.

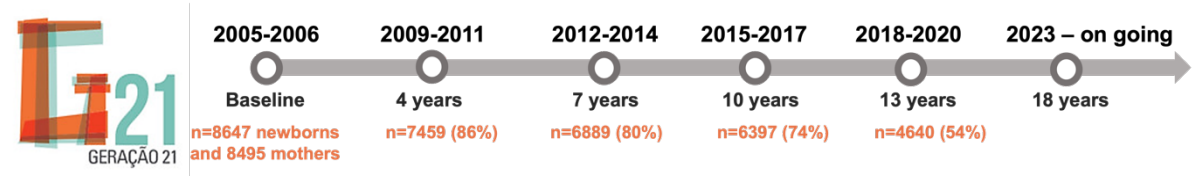


Figure 6. Generation XXI birth cohort baseline and follow-up assessments

The following description of procedures refers specifically to the data collection sections from the baseline, six-month, fifteen-month, seven-year, ten-year, and thirteen-year follow-up evaluations, as these were the cohort assessment waves from which data were retrieved to accomplish the objectives of this thesis.

a) Questionnaires

Face-to-face interviews, using structured questionnaires designed by a multidisciplinary team, were conducted in order to obtain information on the following areas:

- Sociodemographic characteristics: including caregivers' date of birth, educational level, marital status and socioeconomic indicators.
- Child and family medical history: including existence of chronic diseases, child neurodevelopmental and behavioral problems and maternal gynecologic and obstetric history.
- Early life atopic-like symptoms: At 6 and 15 months, subsamples of 1555 and 1043 babies were randomly selected from the whole cohort and examined, respectively. We used standardized questionnaires and asked parents to report atopic-like symptoms experienced by the child since birth, as described below. At 6 months, the personal history of food allergy/intolerance-like symptoms, atopic dermatitis-like symptoms and wheezing-like symptoms were evaluated through the following questions: "Did your baby ever have an episode of wheezing, whistling or rattling in the chest?", "Did your baby ever have an episode of food allergy/intolerance?", and "Did your baby ever have an episode of itchy skin changes/eczema?".

  At 15 months, the child's history of food allergy-like symptoms, atopic dermatitis-like symptoms and wheezing-like symptoms were repeated, and an additional question was included: "Did your baby ever have "persistent symptoms such as sneezing, nasal itching, rhinorrhea or nasal congestion without a cold/flu?".
- Pain questionnaire at age 7 and 10 years: In the 7- and 10-year-evaluations, parents answered a structured questionnaire focused on the child's health and surrounding context, including the child's experience of pain. To assess the pain experience, parents completed a Portuguese version of LPQ on behalf of their child (104). The first (screening) question was, "Did your child complain of pain in the last 3 months?" If the answer was affirmative, the parent was asked to select the

anatomical sites where the child felt pain and indicate the principal pain site based on their assessment. *Recurrent pain* was considered present if the parent reported that their child experienced two or more episodes of the principal pain in the previous 3 months. When recurrent pain was reported, the parent was asked about its: duration, frequency, and intensity, using both the original version of the Wong-Baker Faces Pain Rating Scale (203) and a VAS ranging from 0 (indicating "hardly noticeable pain") to 100 mm (indicating "strongest conceivable pain"). The parent was also asked about the impact on the child's daily living (missing school, being unable to meet with friends or engage in leisure time activities, having trouble eating or sleeping). Pain triggers and context of the first episode were also reported. A family history of chronic pain was considered present if the parent reported, at either age 7 or 10, that any of the parents or siblings of the index child had a chronic pain condition. Additionally, parents were also asked about the intake of medication, health care use, and medical diagnosis of the child's recurrent pain.

Specifically in 7-year-evaluation, parents and children were separately asked about the presence of pain in the child at the time of the interview. If pain complaints were identified as present by either the parents or the children at the time of the questionnaire, respondents were asked to identify the child's anatomical pain site(s) in a body chart.

Using a brief questionnaire at age 10, children also answered questions about their pain experience in the previous week: the presence of some pain, pain intensity (intense pain was considered if face 4 or higher was selected) and the number of pain sites, using an age-appropriate body chart.

- Pain at age 13 – adolescents report: Trained interviewers applied a short version of the LPQ to each adolescent as part of the face-to-face evaluation at age 13. Due to the sequential design of the LPQ, the choice of multisite pain as the outcome also allowed for the optimization of the number of adolescents with valid information on pain experience. *Multisite pain* was defined using the same list of anatomical sites and was characterized as pain reported in two or more body sites in the previous 3 months.

  Pain questionnaires applied are presented as supplementary files for more complete information (Supplementary material B).

b) Review of clinical records, and the National Health Service official pregnancy and children's health book

At the baseline evaluation, obstetric clinical records were reviewed at the maternity units and the NHS official pregnancy booklet—a record of check-ups, ultrasounds, tests, and medical notes provided as part of routine primary care for all pregnant women.

These records were examined to retrieve only the data missing from the baseline questionnaire, including information on prenatal care, pregnancy complications, pregnancy anthropometrics, and delivery and neonatal characteristics such as birth weight, length, gestational age, type of delivery, need for resuscitation at birth, and admission to a NICU.

During each follow-up evaluation, legal guardians were asked to bring their children's NHS official health and vaccination booklets to abstract data on the child's development. Specifically, from the children's health booklet, which contains records obtained as part of routine pediatric health care, the research team abstracted all length/height and weight measurements taken during each medical visit to a health professional.

4) RESULTS

This thesis resulted in the following papers:

Paper I: Gorito V, Monjardino T, Azevedo I, Lucas R (2022) Potentially unrecognized pain in children: population-based birth cohort study at 7 years of age. J Paediatrics Child Health 58:474–480. https://doi.org/10.1111/jpc.15749

Paper II: Gorito V, Talih M, Fernandes F, Navasardyan N., Azevedo I, Lucas R. The burden of pediatric pain: triggers, impact on daily life and health care utilization – a cohort study [Submitted]

Paper III: Gorito V, Brandão M, Azevedo I, Moreira A, Lucas R (2024) Atopic dermatitis in early life and pain at 10 years of age: An exploratory study. Eur J Pediatr 183:2239–2249. https://doi.org/10.1007/s00431-024-05439-0

Paper IV: Lucas R, Brandão M, Gorito V, Talih M (2022) Refining the prediction of multisite pain in 13-year-old boys and girls by using parent-reported pain experiences in the first decade of life. European Journal of Pain 26:695–70. https://doi.org/10.1002/ejp.1898

4.1) Paper I

Potentially unrecognised pain in children: Population-based birth cohort study at 7 years of age

Vanessa Gorito, Teresa Monjardino, Inês Azevedo, Raquel Lucas

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ORIGINAL ARTICLE

Potentially unrecognised pain in children: Population-based birth cohort study at 7 years of age

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Aim: To estimate agreement in the point prevalence of any pain, high-intensity pain and pain in two or more sites according to parental and child report.

Methods: We conducted a prospective study of 5639 children from a Portuguese birth cohort – Generation XXI, where parents and 7-year-old children answered the same questions at the same time. We assessed the accuracy of parental report, considering children's self-report as the gold standard.

Results: At 7 years of age, 499 children (8.8% (95% confidence interval (CI) 8.1–9.6)) reported having pain at the time of the interview. Of those, 44.1% had high-intensity pain (3.9% (95% CI 3.4–4.4) of the whole sample) and 12.4% reported pain in two or more sites (1.1% (95% CI 0.8–1.4) of the whole sample). In this community setting, pain prevalence and intensity were lower when collected from parents. Parental report had sensitivity below 20% and specificity above 95% but its positive predictive value was at most 25%.

Conclusion: Our findings support that, outside acute care, parents have a specific but not sensitive report of children's pain at the age of 7 years. Their report seemed useful to exclude major complaints but limited to screen children's pain. This limitation was higher for more severe pain, that is two or more sites or high-intensity pain. Children should be asked directly about pain to avoid under-estimating paediatric pain.

Key words: accuracy; agreement; paediatric pain; population-based study.

What is already known on this topic

1 Parental report is commonly used by paediatricians to identify and characterise children's complaints.
2 Pain has both sensory and emotional dimensions and children are able to report their pain since pre-school age.
3 Agreement studies between parent and children's report have variable results.

What this paper adds

1 Parental report is useful to exclude major complaints but limited to screen children's pain.
2 Parents did not accurately identify pain with multiple location or intense pain and these observations may contribute to under-diagnosed pain experiences in children.
3 Children should be asked directly about pain to avoid under-estimating paediatric pain.

As the fifth vital sign, pain has itself become a major focus of clinical research. It is also a rising concern in the public health agenda, mainly since the United States Congress declared 2001–2011 the 'Decade of Pain Control and Research'.[1,2] However, paediatric pain is often neglected and not managed correctly, which may lead to short- and long-term consequences.[3] One of the possible reasons behind this lies in the observation that children often experience pain that is not reported by parents.[4] Therefore, valuing and considering children's self-report is essential to avoid the underestimation of paediatric pain, as well as late diagnosis and treatment. Research has shown that children are able to report on their own pain experiences, through validated instruments, since age 3 years.[5–8]

Given that pain has both sensory and emotional dimensions, children should be uniquely able to describe their internal experiences.[9–18] Nevertheless, parental report has traditionally been interpreted as a key source of clinical history for paediatricians, mainly due to practical reasons such as easy access, rapid memory elicitation and willingness of parents to contribute to the collection of clinical history. This highlights the importance of confronting pain assessments obtained by questioning care givers with children's report of their pain experience, using child report as the gold standard. However, only a few studies have evaluated this. A study about children's pain after surgery found good agreement between child and parental report of pain intensity ($\kappa = 0.72$).[7] A cross-sectional study involving children aged 3–15 years treated at the emergency department, concluded that

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parents and children had a moderate agreement ($\kappa = 0.55$) for the presence of pain.[5] These studies have included children with a disease and/or complaint associated with hospital admission, outpatient care or emergency room visit.[5,7,19]

Less is known on the accuracy of parents to assess child pain in a wider spectrum, that is upstream from health-care-seeking behaviour. Population-based investigations have shown that parents and children rate paediatric pain differently. A cross-sectional study in randomly selected schools in a region of Norway showed that many parents are unaware of the pain experienced by their children and adolescents (age 8–18 years) ($\kappa = 0.20$).[20] Symptoms reported by children between the age of 7 and 14 were significantly more frequent and severe in all health domains when compared to reports made by their parents, according to an epidemiological study conducted in Germany.[21] Another study among Zimbabwean adolescents concluded that most parents of school children with recurrent non-specific low back pain are unaware of the pain status of their children.[22] A Danish Cohort study including two samples of healthy children evaluated at school and separately from their parents, showed a poor agreement ($\kappa = 0.20$) between parents and children regarding the experience of musculoskeletal pain in the previous week.[6] Since the frequency of self-reported pain in children is high and care-seeking behaviour is strongly determined by parental assessment of severity, measuring parental accuracy outside the clinical setting may provide an estimate of the extension of children's pain that goes uncared for.

Therefore, using a large population-based sample of children, where parents and children answered the same questions at the same time, we aimed to estimate the point prevalence of any pain, high-intensity pain, and pain in two or more sites according to parental and child report, and to assess the accuracy of parental report, considering children's self-report as the gold standard.

Methods

The Generation XXI (G21) cohort study

We used data from Generation XXI (G21), a prospective population-based birth cohort assembled in Porto, Portugal.[23,24] All live infants with more than 23 weeks of gestation born in one of the five public maternity units in the Porto Metropolitan Area between April 2005 and August 2006 were eligible to participate in the cohort. A baseline evaluation was done during the hospital stay (24–72 h after the delivery). The whole cohort was invited to participate in re-evaluations at 4, 7, 10 and more recently at 13 years. In each evaluation, written informed consent from parents or legal guardians and oral assent from children was obtained. The study protocol complies with the Declaration of Helsinki and was approved by the Ethics Committee of the University of Porto Medical School/Hospital de São João, Porto, Portugal and is registered with the Portuguese Data Protection Authority.

Participants and data collection

For the present study, data from the 7-year-old evaluation wave were used. During this evaluation, the accompanying parent was asked to answer a structured questionnaire focused on the child's health and surrounding context. Specifically, parents and children were separately asked about the presence of pain in the child at the time of the interview. In case pain complaints were identified by parents or children as present at the time of the questionnaire, respondents were asked to identify the child's anatomical pain site(s) in a body chart. We defined multiple pain as the presence of pain in at least two anatomical sites. Respondents were asked to select the anatomical site of the most disturbing pain. Pain intensity on that site was assessed using the original version of the Wong-Baker Faces Pain Scale, a validated tool to screen the presence of pain.[10,11] The faces in the scale are numbered by 0 (does not hurt at all), 2 (hurts just a little bit), 4 (hurts a little bit more), 6 (hurts even more), 8 (hurt a whole lot) and 10 (hurts as much as you can imagine, although you do not have to be crying to have this worst pain). Low- to moderate-intensity pain was considered in faces 2 or 4 and high-intensity pain was defined as faces 6, 8 or 10.

In this evaluation wave, parents were also asked about the child's pain in the previous 3 months using a Portuguese version of the Luebeck Pain Screening Questionnaire.[20,25] As a whole, those results are outside the scope of the present paper, since here we aimed specifically at assessing the agreement between parents and children with regard to pain at the moment of the questionnaire. However, we used the Luebeck Questionnaire to extract information on any medical diagnosis that could account for the child's pain, when they reported that the child had felt pain more than once in the previous 3 months, here labelled as recurrent pain.

Statistical analysis

Descriptive statistics include point prevalence and 95% confidence intervals (95% CI) of pain features according to children and parents. Assuming child report as the gold standard, we calculated sensitivity and specificity of parental report of pain presence and attributes. A sensitivity analysis to assess the impact of including all care givers, rather than mothers alone, as respondents on the estimate of the accuracy of proxy report, was carried out by excluding children whose respondent care giver was not the mother.

Using child-reported pain as the gold standard, we calculated predictive values to estimate the probability of parents correctly identifying children with pain (positive predictive value) and also of identifying children without complaints as having no pain (negative predictive value). Cohen's kappa was applied to evaluate the agreement between the report of children and parents. The result was interpreted as follows: values ≤0 as indicating no agreement, 0.01–0.20 as none to slight, 0.21–0.40 as poor or fair, 0.41–0.60 as moderate, 0.61–0.80 as good or substantial, and 0.81–1.00 as almost perfect agreement.[26]

All statistical analyses were conducted using Stata® 15 software (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC).

Results

Of the invited mothers, 91.4% accepted to participate and their 8647 infants were enrolled in the cohort study. Seven years after birth (April 2012 to April 2014), all G21 participants were invited to a follow-up evaluation and, of the initial cohort, 5849 (67.6%) were interviewed face to face. Among the 5849 children evaluated in-person at 7 years of age, 5720 answered one or more questions about pain features. From these, 5639 had complete information about all pain questions composing our study

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Table 1 Socio-demographic characterisation of the sample according to proxy respondent

Socio-demographic characterisation	Children with parental report ($n = 5720$), n (%)
Child's gender	
Female	2782 (48.6)
Male	2938 (51.4)
Parental marital status	
Living together	4937 (86.3)
Separated	777 (13.6)
Siblings	
No	2208 (38.6)
Yes	3512 (61.4)
Care giver educational level	
Basic	2292 (40.1)
Secondary	1729 (30.2)
Higher	1697 (29.7)
Monthly household income (Euro)	
≤1000	1626 (28.4)
1001–2000	2628 (45.9)
2001–3000	975 (17.0)
>3000 €	347 (6.1)
Parental work participation	
Full-time employed	3928 (68.7)
Part-time employed	443 (7.7)
Unpaid	1340 (23.4)
Concern about household expenses	
Never or rarely	326 (5.7)
Sometimes or a lot of times	1253 (21.9)
Almost always or always	4092 (71.5)
Child's school type	
Private	544 (9.5)
Public	5149 (90.0)

sample. Participants without complete information were excluded. Of those, the respondent was the mother for 96.3%.

Socio-demographic data, including family context and monthly household income, are characterised in Table 1. At 7 years of age, 499 children (8.8% (95% CI 0.081–0.096)) reported having pain at the time of the interview. Of those, 44.1% had high-intensity pain (3.9% (96% CI 3.4–4.4) of the whole sample) and 12.4% reported pain in two or more sites (1.1% (95% CI 0.8–1.4) of the whole sample). Around 6.1% (95% CI 5.6–6.9) of the parents reported pain complaints in their children, and approximately 2.2% (95% CI 1.8–2.7) described pain of high intensity. The prevalence of 1.0% (95% CI 0.8–1.3) for pain in two or more sites reported by parents was similar to the estimate of 1.1% obtained from child interviews (Table 2).

Agreement for the presence of any pain

Of the 499 children who reported pain at the time of the interview, only 88 parents (17.6%) reported the presence of pain in their child.

Among parents of the 5140 children that reported having no pain, 4878 (94.9%) agreed in reporting no pain in their children (Fig. 1). The sensitivity of parental report to detect pain in their children was 17.6% (95% CI 14.3–20.9) and specificity was 94.9% (95% CI 94.3–95.5). The positive predictive value of parental report was 25.1% (95% CI 21.2–29.6) and the negative predictive value was 92.2% (95% CI 91.9–92.5) (Table 2).

Agreement for the presence of high-intensity pain

Among the 220 (3.9%) children who reported high-intensity pain, only 20 (9.2%) were identified as having high-intensity pain by their parents. Among 5411 (95.6%) children without high-intensity pain, 101 (1.8%) parents reported that their child had high-intensity pain while the remaining 5310 (94.2%) parents agreed with their children in pain intensity characterisation (low or moderate intensity) (Fig. 1). The sensitivity of parent's report to identify intense pain in children was 8.8% (95% CI 5.0–12.6) and its specificity was 98.1% (95% CI 97.8–98.5). The positive predictive value of parent report of high-intensity pain was 15.8% (95% CI 10.5–23.2) and the negative predictive value was 96.4% (95% CI 96.3–96.6) (Table 2).

Agreement for the presence of pain in two or more sites

Of the 5632 (99.9%) children without multiple pain locations, 5579 (98.9%) were correctly identified by parents and 53 (0.9%) were reported by parents to have pain in two or more sites. In the group of 62 (1.1%) children that reported pain in at least two sites, 59 (1.0%) were described by parents as having no multiple pain (Fig. 1). The sensitivity of parental report was 4.8% (95% CI −0.5 to 10.2) and the specificity was 99.1% (95% CI 98.8–99.3) (Table 2). We calculated a positive predictive value of 5.4% (95% CI 1.8–14.9) and a negative predictive value of 98.9% (95% CI 98.9–99.0) for parental report to identify pain in two or more sites in children (Table 2). Cohen's kappa showed poor agreement, with all estimates below 0.2, between parents and children report of pain presence, high-intensity pain and pain in at least two sites (Table 2).

As seen in Table 3, even in children with pain in two or more sites, 83.9% of the parents were not able to report any pain and there was low overall concordance between parents and children according to the weighted Cohen's Kappa. Among children with pain (both one site or two or more sites), more than 80% were identified by parents as having no pain complaints. Parents were more likely to identify pain in one site (16.6%) than pain in two or more sites (4.8%). Although 95% of the parents of children with no pain complaints identified them correctly, only 13.4% correctly identified children with low-intensity pain and 9.2% of parents reported correctly high-intensity pain (Table 3). Estimates of weighted kappa demonstrated poor concordance between parental and child reports. Sensitivity analysis excluding children whose care giver respondent was not the mother ($n = 207$) did not materially affect our results.

Among 2602 children with recurrent pain in the previous 3 months, as reported by their parents, only 514 reported a history of organic disease or a known medical diagnosis that accounted for pain complaints (19.8%). The most frequently

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Table 2 Prevalence, agreement, sensitivity and specificity of pain report according to children and parents

	Children point prevalence, %	Parents point prevalence, %	Observed agreement, %	Cohen's kappa (95% CI)	Specificity, % (95% CI)	Sensitivity, % (95% CI)	Positive predictive value, % (95% CI)	Negative predictive value, % (95% CI)	Likelihood ratio+	Likelihood ratio−
Presence of pain	8.8	6.1	88.1	0.14 (0.120–0.170)	94.9 (0.943–0.955)	17.6 (0.143–0.209)	25.1 (0.212–0.296)	92.2 (0.919–0.925)	3.46	0.88
High-intensity pain	3.9	2.2	94.7	0.09 (0.060–0.110)	98.1 (0.978–0.985)	8.8 (0.050–0.126)	15.8 (0.105–0.232)	96.4 (0.963–0.966)	4.71	0.93
Two or more sites	1.1	1.0	98.0	0.04 (0.010–0.070)	99.1 (0.988–0.993)	4.8 (−0.005–0.102)	5.4 (0.018–0.149)	98.9 (0.989–0.990)	5.14	0.96

CI, confidence interval.

reported diagnoses were: growth pains (4.0%), dental issues (3.6%), gastrointestinal disorders (3.3%), otorhinolaryngology problems (2.5%), musculoskeletal problems (1.5%) and psychological distress (1.2%).

Discussion

We found that parental report was highly specific to exclude overall pain, pain of high intensity and pain in two or more sites. However, the sensitivity of parent reports to predict pain complaints in their children was limited, especially regarding high-intensity pain and pain at least in two sites. A positive predictive value of at most 25.1% means that when care givers reported pain in their child there was only a 25.1% probability that the child actually had pain. Care givers frequently missed the identification of pain complaints in children mainly in high-intensity pain (positive predictive value: 15.8%) and pain in two or more sites (5.4%). The low prevalence of complaints reported in this sample (we found 8.8% prevalence of pain, 3.9% of high-intensity pain and 1.1% of multiple pain according to children report) largely accounts for low positive predictive values and high negative predictive values, above 90%.

Although several studies have shown that, at the age of 7, children can interpret a face pain scale,[16–19] self-report by children has often been underutilised.[5–8] Recent research has compared children's and parents' perspectives about children's pain complaints. In 2016, Kamper *et al*. described poor agreement between children's self-report and parents' report on pain in the child.[6] In this study, participants aged 10–14 years experienced pain that was not always reported by parents, but the agreement was better for high-intensity and persistent pain.[6]

Kroner-Herwig *et al*.,[21] Sundblad *et al*.[27] and Waters *et al*.[28] all used community-based surveys of children to investigate the concordance between parents' and children's pain report. These studies reported an overall poor agreement between parent and child ratings and found that children reported pain more often (and of greater intensity) than their parents, corroborating our results. On the other hand, a meta-analysis combining data from studies in children experiencing pain due to surgery, medical procedure or chronic diseases showed a better correlation between parental and child reports.[29,30] Nevertheless, a study comparing the agreement of parents, nurses, and children in the report of children's pain concluded that nurses and parents underestimate pain intensity.[19] Considering previous evidence suggesting poor parent–child agreement and acknowledging pain as a subjective and emotional experience, where the children's report is the gold standard, our study reinforces the importance of assessing the child's experience to avoid the underestimation of paediatric pain.

The lack of sensitivity may translate a parental limitation in recognising characteristics that could be interpreted by clinicians as red flags and be associated with a high burden of pain. However, we did not perform a clinical evaluation of participating children that could be correlated with the parents' report of the child's pain. Therefore, our study lacked medical validation of children's complaints during the report as well as a measure of prognosis or clinical course of pain from the time of evaluation. We did collect information on known medical diagnoses for pain, which were present only for a minority of children and pointed

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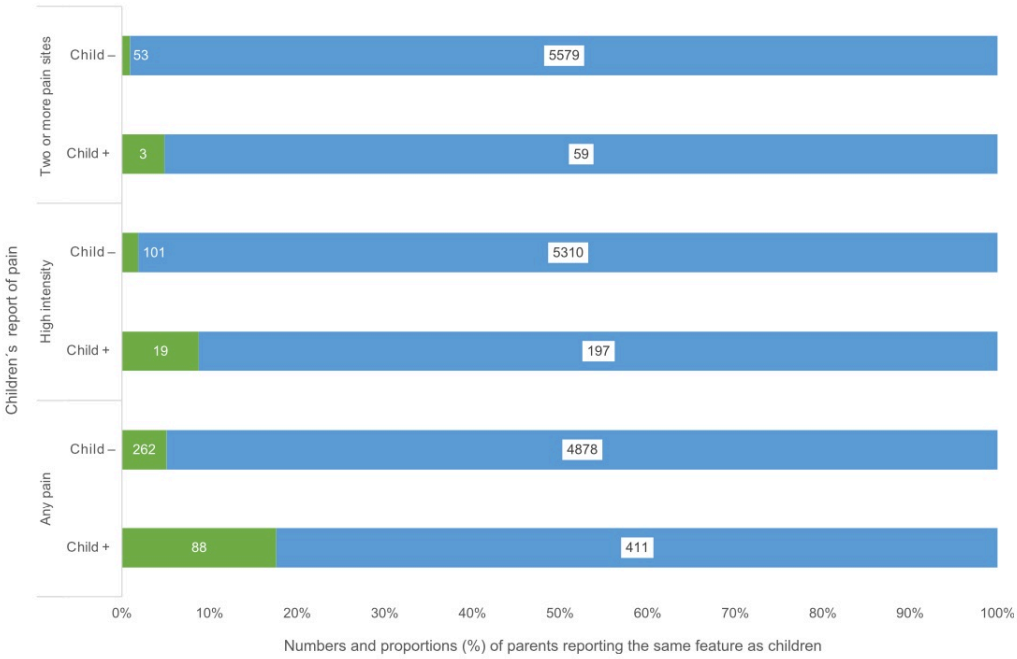


Fig 1 Distribution of parental report according to children's report of pain. Child–, child reported no present pain; Child+, child reported present pain; Parent–, parent reported no present pain; Parent+, parent reported present pain. (■), Parent+; (■), parent−.

Table 3 Concordance between parents and children report of pain according to pain intensity and location

Parents	Children					
	No pain, %	Low- to moderate-intensity pain, %	High-intensity pain, %	Weighted kappa (CI 95%)	Expected agreement	Observed agreement (CI 95%)
No pain	95.0	82.3	83.0	0.128 (0.093–0.164)	0.861	0.879 (0.870–0.888)
Low- to moderate-intensity pain	3.3	13.4	7.9		0.022	0.080 (0.058–0.109)
High-intensity pain	1.8	4.3	9.2		0.062	0.063 (0.039–0.096)

	No pain, %	One site, %	Two or more sites, %	Weighted kappa (CI 95%)	Expected agreement	Observed agreement (CI 95%)
No pain	95.0	82.4	83.9	0.131 (0.777–0.165)	0.971	0.880 (0.871–0.888)
One site	4.1	16.0	11.3		0.664	0.106 (0.084–0.132)
Two or more sites	0.9	1.6	4.8		0.903	0.026 (0.007–0.080)

CI, confidence interval.

mostly to non-specific complaints. It seems a source of concern that parents did not acknowledge pain in multiple regions or high-intensity pain, which might have interfered with the child's daily living. To better characterise the burden of pain on children's lives, it would have been interesting to measure the persistence or impact of pain from the child's perspective, which is

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important to quantify the potential relevance and stability of complaints. This is particularly important in children, as they may not always verbalise their complaints spontaneously.[31] It is expected that, at 7 years of age, children express their pain through multiple behaviours such as refusal to perform physical activity or to remain in the orthostatic position, or eviction of daily living activities.[4] Parents were less accurate in identifying pain with multiple locations or of higher intensity in children, and these observations may contribute to underdiagnosed pain complaints in paediatric age.

We should also note that, although the latest evidence supports the use of the Faces Pain Scale-Revised, our assessment used the Wong-Baker Faces Pain Rating Scale, which is not ideal but also a validated face scale for children.[10,11,19] Additionally, it should be noted that we did not take the degree of neurodevelopment of each child into account and a fraction of children may be less capable of describing their pain.

In this study, we included participants from a population-based cohort, regardless of pain complaints, which allowed us to screen pain in a generally healthy population and avoid the spectrum bias common to accuracy studies that can affect samples in clinical settings. Considering that age and puberty may influence pain complaints,[32] having participants of the same chronological age of 7 strengthens our findings as it allows a comparison between children at similar stages of physical development in a prepubertal stage. Another main advantage of our study is the possibility to compare pain reports from children and their parents through the same evaluation tool assessing the same period of time.

Conclusion

In conclusion, our study suggests that parents have a specific but not sensitive report of children's pain. Their report is useful to exclude major complaints but limited to identify children's pain at 7 years of age. This limitation is higher in multisite pain (two or more sites) and high-intensity pain. This highlights the importance of listening to children's complaints, collecting its specific attributes to avoid the underestimation of paediatric pain and ultimately to allow fast-tracking, evaluation, diagnosis and treatment.

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4.2) Paper II

The burden of pediatric pain: triggers, impact on daily life and health care utilization – a cohort study

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[Submitted]

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Ethical approval: The study protocol complied with the Declaration of Helsinki and was approved by the Ethics Committee of the University of Porto Medical School/Hospital de São João, Porto, Portugal. At each evaluation, written informed consent was obtained from legal guardians and oral assent from minor participants.

Conflict of interests: No financial or non-financial benefits have been received or will be received from any party related directly or indirectly to the subject of this article.

Contributors' statement: All authors of this study made significant contributions to the conception and design, data analysis, and interpretation of the results.

The initial draft of the manuscript was prepared by V. Gorito using a study design conceived by V. Gorito, I. Azevedo and R. Lucas. Subsequent revisions for important intellectual content were made by

M. Talih, F. Fernandes, N. Navasardyan, I. Azevedo and R. Lucas. Finally, all authors provided the final approval of the manuscript for publication.

Abstract

Background: Pain has an important impact on children's current and future life, leading frequently to health care seeking. We aimed to characterize pain frequency, triggers, impacts on children's daily activities, health care use and medical diagnoses, focusing on sex differences.

Methods: Using data from the Generation XXI birth cohort at 10 years, we selected children with parent-reported pain in the previous 3 months (Luebeck Pain Screening Questionnaire). Parents were asked about perceived triggers and restrictions to daily activities. Health care-seeking behavior was inquired and medical diagnoses were categorized by organs and systems. Logistic regressions were performed to predict activity restrictions and use of health care services. Results are expressed as odds ratios (OR) and 95% confidence intervals (CI).

Results: Of the 3725 children reporting pain, 26.7% had a parent-reported impact on at least one of their daily activities, with no differences between boys and girls. An impact on daily activities was more likely in children with more frequent pain (OR 1.35, 1.26-1.46), longer-lasting pain (OR 1.59(1.48-1.69)), pain that required medication use (OR 2.12, 1.24-4.23), higher-intensity pain (OR 1.82, 1.73-2.0), or multisite pain (OR 2.04, 1.43-2.92). Among children with pain, 17.0% sought health care and 12.5% obtained a medical diagnosis as a result, more frequently boys. The most frequent diagnosis categories were musculoskeletal (34.4%), gastroenterological (13.5%), and psychological conditions (12.0%). Health care use was associated with higher pain frequency (OR 1.18, 1.09-1.27), duration (OR 1.26, 1.17-1.36), and use of pain medications (OR 1.70, 1.53-1.90).

Conclusion: Despite the higher prevalence of pain among girls, we highlight a similar impact in both sexes. As expected, most pediatric pain is managed without resorting to health care, but tracking their future trajectories may be useful to estimate early diagnosis gaps.

Introduction

Pain is a common problem in children and adolescents that can potentially have extensive negative effects on many aspects of their lives. It can also contribute to the establishment of chronic pain phenotypes in adult life[1]. As with adults, children can experience pain due to various reasons, including injury, illness, medical procedures, or chronic conditions. A recent study evaluating all children with pain referred to a pediatric rheumatology division concluded that about 75% of patients were diagnosed with non-rheumatic conditions, with non-specific musculoskeletal pain more commonly implied (62%)[2]. Notably, musculoskeletal pain is the top contributor to the burden of years lived with disability in Europe[3,4].

Epidemiological studies have increased over the past years to evaluate triggers and diagnoses for pain among children.[5-9] Psychological causes seem to determine clinical presentation as well as future somatization and psychologization of distress.[10] For both sexes, sports and lack of sleep have been identified as the most frequent self-reported triggers of pain.[6] School-work and the school environment have also been self-reported triggers of pain in children[29].

Sex differences in pain experiences become apparent also in pediatric ages, with girls generally showing a higher frequency and intensity of pain, being more likely to transition to chronicity, and more frequently reporting multiple pain sites [30,31,32]. However, less is known about possible differences between girls' and boys' impact on daily life activities, including health services use. A school survey in Norway found that only 11% of children and adolescents obtained a medical diagnosis for their pain. [29.] Pediatric pain stems from a wide range of conditions that usually affect muscle, bone, joint, head, or abdomen and in certain cases requires specific pain management strategies, such as analgesics or physiotherapy[17]. Other studies support this finding[5-7]. There is evidence that children who report persistent musculoskeletal pain are at increased risk of adverse pain phenotypes, including amplified musculoskeletal pain syndrome (AMPS), as well as chronic pain in adulthood [11-14, 17-20].

There is a strong association between pain-related disability and increased use of health care services[27]. A study showed that children who complain often of aches and pains use more health

services, have more psychosocial problems, miss school more often, and perform worse academically[28]. To reduce the burden of lifelong pain conditions, it is important to further characterize pediatric pain—especially musculoskeletal pain—across diverse populations and sociocultural contexts.

Using a large population-based cohort of Portuguese children, we aimed to describe the triggers of pain and the impact of pain on children's daily activities. In addition, we aimed to describe the profile of children using health care and the medical diagnoses assigned. Finally, we aimed to study potential differences in pain experience according to sex.

Methods

Generation XXI

The study included participants from the Generation XXI (G21) Portuguese birth cohort. The G21 cohort enrolled 8647 newborns, born between April 2005 and August 2006, in the five public maternity hospitals covering the metropolitan area of Porto.[15,16] An initial evaluation was done during hospitalization (24-72 hours after delivery). The whole cohort was invited to participate in re-evaluations at the ages of 4, 7, 10 and 13 years.

At each evaluation wave, a team of trained health professionals interviewed families who agreed to participate and conducted an extensive physical examination. Questionnaires included information about demographic and socioeconomic characteristics, clinical history, common childhood symptoms including pain, eating habits, physical activity, and use of health care.

The study protocol complied with the Declaration of Helsinki and was approved by the Ethics Committee of the University of Porto Medical School/Hospital de São João, Porto, Portugal, and was registered with the Portuguese Data Protection Authority. At each evaluation, written informed consent was obtained from legal guardians and oral assent from child participants.

Pain assessment – participants and data collection

About 75% of the enrolled cohort participated in the 10-year evaluation wave - 6397 parents were invited to answer a structured questionnaire focused on the child's health and his/her surrounding

context, including the Luebeck Pain Screening Questionnaire (LPQ), which is a structured questionnaire specifically designed for epidemiologic investigations of pain characteristics among children and adolescents. Parents answered on behalf of their child about the presence of pain in the preceding three months. [17] If they had not experienced any pain during that period, no further questions were asked. If pain was reported, respondents were asked to answer questions about the anatomical site(s) of the child´s pain and to select a main pain site. Multisite pain was defined by the presence of at least two pain sites. If pain in the main pain site had occurred only once in the past three months, no further questions were asked. If pain occurred more than once in the past three months (i.e., recurrent pain), respondents were asked about the intensity and frequency of pain, as well as its triggers and impact on daily activities. Intense pain was defined by the selection of faces 4, 5, or 6 using the original 6-faces version of the Wong-Baker Faces Pain Scale[18]. Parents were asked about the presence of any triggers of the recurrent pain from a list including: sports, anxiety, food habits, new challenges, lack of sleep, weather changes, interpersonal conflicts, acute illness/cold, homework, school, computer use, TV use, sadness, family distress, noise, loneliness, other triggers, no perceived trigger.

The impact of the recurrent pain on the child's daily activities was assessed with questions related to limitations at school and home. These included needing to rest due to pain, experiencing loss of appetite, sleep disturbances, interference with hobbies, school absenteeism, interference with friends' meets, and the need for the parent to take day(s) off for childcare. We considered that impact on daily activities to be present if the participants answered "yes" to one or more of these questions.

Parents were also asked about the use of pain relief medications and whether their child had undergone medical evaluations due to pain complaints. Medical diagnoses of child's recurrent pain reported by parents were divided into categories/groups of disorders: musculoskeletal, gastrointestinal, psychological, ENT (Ear, Nose, and Throat), neurological, respiratory, infectious, ophthalmic, injury, rheumatic (immune-mediated), genetic, endocrine or other cause.

Statistical analysis

Descriptive statistics included prevalence according to parents' characterization of the child's pain. Logistic regression was performed to predict the impact on children's daily activities (no impact vs. at least one daily activity affected) and the use of health care services, according to parents' characterization of pain: frequency (fewer vs at least 3 times per month); duration (less vs at least 3 months), intensity (low to moderate vs intense) and multisite pain (one vs at least 2 anatomical regions affected).

Results are expressed as odds ratios (OR) and 95% confidence intervals.

Results

Of all the participants at 10 years (n= 6397), whose sample characteristics are summarized in Table 1, 3725 children (57.5%) had parent -reported pain in the three months preceding the evaluation. Among children with reported pain, 886 (23.6%) had recurrent intense pain, 974 (26.1%) had recurrent pain that lasted more than 3 months (i.e., chronic pain), and 842 children (22.6%) had multisite pain. Girls mentioned more frequently any pain (60.7% vs 53.9%, $p<0.001$), chronic pain (29.1% vs 22.2%, $p<0.001$), intense pain (25.5% vs 21.6%, $p=0.001$) and multisite pain (23.8% vs 18.9%, $p<0.001$) than boys. Although girls sought slightly more health care services (18.0% vs 16.0%, $p=0.037$), boys were more frequently diagnosed with pain complaints (13.1% vs 11.9%, $p=0.043$) (Figure 1).

1- Triggers of pain

As shown in Table 2, sports, anxiety, food habits, new challenges, lack of sleep, weather changes, conflicts, acute illness/cold, homework, and school were the most frequently perceived triggers of pain in children. In addition, computer use, TV use, sadness, family distress, noise, and loneliness were also mentioned as pain triggers. Sixty-nine participants did not identify any trigger for their pain. Lack of sleep was a more prevalent trigger among girls (1.7% vs 0.2%, $p<0.01$) than among boys, while boys mentioned sports (5.1% vs 6.5%, $p<0.01$), TV use (0.8% vs 1.3%, $p=0.008$), computer use (0.6% vs 1.2%, $p<0.01$) more often than girls. Weather changes

also affected boys slightly more than girls (1.8% vs 2.0%; p=0.037) (Table 2).

2- Impact on daily activities

Of the 3725 children with pain, 993 (26.7%) were reported by parents to have had an impact on at least one of their daily activities. Needing to rest due to pain (22.3%), loss of appetite (10.0%), sleeping problems (9.7%), interference with hobbies (7.4%), school absenteeism (7.2%), and care provided by parents (5.5%) were the most frequently implied (Figure 2).

In general, there were no differences in the impact on daily activities between boys and girls. Only sleep problems (10.9% vs 8.4%, p=0.013) and the need to rest due to pain (22.8% vs 21.7%, p=0.016) were more prevalent among girls.

The odds of reporting an impact on daily activities were higher in children with more frequent pain (OR 1.35, 1.26-1.46), longer-lasting pain (OR 1.59, 1.48-1.69), higher-intensity pain (OR 1.82, 1.73-2.0), multisite pain (OR 2.04, 1.43-2.92), and in those who took pain relief medication (OR, 1.59 1.48-1.69) (Table 3).

3- Health care use and medical evaluation of pain

Among children with reported pain, 633 (17.0%) sought health care, resulting in a medical diagnosis for pain in 465 cases (12.5%). Despite girls sought slightly more health care services and boys were more frequently diagnosed with pain complaints (Figure 1). No other differences were found between sex in stratified analysis.

Health care use was not associated with pain intensity (OR 0.96 [0.89-1.03]) but there was a borderline association between health care use and the presence of multisite pain (OR 2.07, 0.99-1.03). Higher frequency (OR, 1.18 1.09-1.27) and longer duration of pain (OR 1.26, 1.17-1.36) were associated with increased health care service utilization. The use of medication for pain was associated with the use of health services (OR 1.70 [1.53-1.90]), although the temporal sequence is unclear.

The most frequent medical categories among participants with pain reports were: musculoskeletal (34.4%), gastrointestinal (13.5%), psychological (12.0%), endocrine (9.8%), ENT (9.0%),

neurological (7.1%), respiratory (5.4%), infectious (2.8%), ophthalmic (2.2%), injury (0.9%), rheumatic/immune-mediated (0.9%), genetic (0.4%), or other causes (2.6%) (Figure 3).

Among the 160 children with pain of musculoskeletal origin, the major diagnoses were: growing pains (61.9%), muscle/tendon lesion (18.1%), scoliosis (5.6%), Sever's Disease (5.0%), varus and valgus foot (4.3%), Osgood-Schlatter disease (2.5%), varus and valgus knee (1.9%), Köhler's disease (1.3%), benign tumor (1.2%) and osteochondritis dissecans (0.6%) (Table 4).

Discussion:

In our cohort study, around a quarter of participants had intense, chronic, or multisite pain. We found a higher prevalence of pain among girls, but a similar impact in both sexes. However, boys had more frequently a medical diagnosis for pain complaints and there were no relevant differences in the impact on daily activities between boys and girls. The most common pain triggers were sports activities, anxiety/new challenges, and food habits, which is consistent with the literature[6].

More than a quarter of children experiencing pain were affected in at least one daily activity, with a greater impact observed in children with longer, more frequent, more intense, or multisite pain. Previous studies have shown a variable impact of pain on daily

activities, ranging from 5 to 45%, including school absenteeism and impaired physical activity reported by adolescents[20]. Roth-Isigkeit and colleagues concluded that only the intensity of pain was predictive of the degree of restrictions in daily activities attributable to pain [6], while in our study we found that pain that was more frequent, longer-lasting, higher intensity, multisite, or managed with medication was associated with increased odds of impacting children's daily activities. These differences can be justified by the use of different populations with different age groups and also by sociocultural differences and pain behaviors that have changed over the last decades.

About 17% of G21 children with pain sought health care. Of these, around three-quarters received a medical diagnosis for their pain, primarily related to musculoskeletal, gastroenterological, or psychological issues, while the remaining cases had no obvious etiology. More than one-third of

children were diagnosed with musculoskeletal conditions, consistent with studies in other countries[21-24]. This is concerning, as a prospective study on musculoskeletal symptoms with formal rheumatologic evaluation over a 3-year interval showed persistence of musculoskeletal pain during the teenage period; 54.3% of the subjects, mostly pre-pubertal, were still symptomatic after 3 years of follow-up[21].

Among musculoskeletal complaints, we found muscle/tendon tenderness and arthralgia to be the most frequent cause of pain, in line with international data[21]. The main symptoms reported were lower limbs arthralgia and myalgia. This location of pain at weight-bearing anatomical structures is probably due to the greater joint overload that causes disruption of the capsule-ligamentous structures and muscle contractures. Myalgia was very common, typically manifesting as cramping growing pains[21].

Increased health care use was associated with pain of higher frequency or longer duration, as well as with medication intake. These numbers may indicate an appropriate use of health care services, reflecting a profile typical of children with chronic, intense pain who use medication to relieve their symptoms (by medical prescription or before that). Despite that, it is worrying that most children with pain did not seek health care and may be underdiagnosed and consequently undertreated. A direct physical examination allows the doctor to complement parents' perception with clinical data, thus minimizing the risk of over- or under-estimation of the symptoms. Clinical examination also allows the detection of inflammatory or systemic diseases, such as arthritis or enthesitis, which may present as unspecific musculoskeletal complaints at onset but may require early pharmacological management[22].

In a cohort study evaluating the impact of undiagnosed diffuse musculoskeletal pain, 29% of children had at least one emergency visit and 5% were hospitalized.[23] Even before the diagnosis, they had high levels of health care use, diagnostic testing, and medical costs. Early recognition of disability and faster referral to trained subspecialists may improve the prognosis, reduce unnecessary testing, and reduce the overall costs of health care[23]. A study in a primary care setting in Spain reported that musculoskeletal pain is responsible for approximately 6% of the primary

care visits for children aged 3-14 years, and more than 10% for adolescents[24]. This ascends to 20–33% in adults according to World Health Organization (WHO)[25].

Childhood and adolescence are periods of growth and development of the musculoskeletal system with changes in structural properties, biomechanics, and motor control before the system stabilizes in adulthood. Similarly, substantial cognitive, emotional and social development occurs during this period, and hormonal changes regulate mood and emotions differently from adulthood[26]. Sex differences in pain experiences become apparent also in pediatric ages, with girls generally showing a higher frequency of pain, being more likely to transition to chronicity, and more frequently reporting multiple pain sites[31,32]. Multiple mechanisms underlying sex differences are plausible, alone or combined, including biological—namely genetic, hormonal and neurophysiological differences—and psychosocial factors—including coping strategies, catastrophizing, self-efficacy, gender roles and sociocultural beliefs[33]. In our study girls also presented higher frequencies of pain, chronic pain, intense pain and multisite pain, in line with international data [34,35,36]. However, boys had more frequently a medical diagnosis for pain complaints and mainly there were no differences in the impact on daily activities between boys and girls. Our results differ from common conceptions that suggest a higher female burden in terms of the effects of pain on children's lives, as well as care-seeking profiles; our results question stereotypical gendered interpretations and highlight the need for further investigation in this area.

We acknowledge that our study may be subject to some degree of information bias, particularly because it relies on parent-reported data regarding diagnoses and pain experiences without direct clinical validation. Besides, pain was analyzed without children's report. According to our previous research parent-reported pain was very specific, but not sensitive, so it is expected that pain prevalence is underestimated at these ages[30]. Moreover, pain characteristics are frequently clustered by parents (usually those who report higher frequencies of pain, also report higher frequencies of multisite, intense or chronic pain) [37].

Like most interval cohorts, the composition of the G21 sample has been affected by nonparticipation or dropouts during the evaluation waves. Additionally, our results were obtained

from a single cohort, and we cannot be sure that they are applicable to external populations. Likewise, we do not have information about long-term outcomes reproducibility until adulthood. Our study provides prospective evidence from a large cohort of children of the same chronologic age who were recruited at birth, and regularly reassessed, independently of their health status, concerning multiple pain features, providing valuable information not only on the impact of pediatric pain, but also on health care seeking due to pain, highlighting the absence of sex differences in these consequences.

In conclusion, pain has an important impact on children's lives, but only a subset of children with pain is evaluated in health care services. Girls sought slightly more health care services, but boys had more frequently a medical diagnosis. Musculoskeletal disorders are the most frequent diagnoses. Despite the higher prevalence of pain among girls, we highlight the similar impact in both sexes. As expected, the vast majority of pediatric pains are managed without resorting to health care, but tracking their future trajectories may be useful to estimate early diagnosis gaps, and consequently to decrease the risk of chronicity and amplification of pain, particularly musculoskeletal.

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Table 1. Sample characteristics of G21 cohort participants at 10 years (N=6397)

	N (%)
Sex at birth	
Female	3135 (49%)
Male	3262 (51%)
Maternal age at the child's birth (years)	
< 26	1663 (26%)
26-35	3964 (62%)
≥ 36	770 (12%)
Maternal education	
< 10th grade	3135 (49%)
10th - 12th grade	1727 (27%)
> 12th grade	1535 (24%)
Monthly household income (EUR)	
≤ 1000	2198 (35%)
1001 to 2000	2460 (38%)
≥ 2000	856 (13%)
No inforrmation	883 (14%)
History of child chronic disease[a]	
Yes	863 (14%)
No	5534 (86%)
BMI z score[b]	
Underweight and normal weight	3220 (50%)
Overweight	867 (14%)
Obese	1291 (20%)
No inforrmation	1019 (16%)

[a] History of child chronic disease was recoded based on the predefined diagnosis (asthma, epilepsy, diabetes, heart disease, and kidney failure) as "no" if child does not have any of these diagnoses and "yes" if at least one diagnosis was present).
[b] BMI z-score was recoded as Underweight/Normal weight (≤ 1 Standard Deviation (SD)); Overweight (>1SD to <2SD), and Obesity (≥2SD) based on the World Health Organization recommendations.

Table 2 – Frequency (%) of each trigger of pain according to parental report at 10 years evaluation

Trigger of pain	Girls n = 3135* (%)	Boys n = 3262* (%)	Total n = 6397*	p-value
Weather changes	58 (1.8)	67 (2.0)	125 (1.9)	0.037
Lack of sleep	54 (1.71)	73 (0.2)	127 (1.9)	0.002
Noise	19 (0.6)	19 (0.5)	38 (0.5)	0.872
New challenges	197 (6.1)	84 (2.5)	191 (2.9)	0.605
Conflicts	59 (1.9)	66 (2.0)	125 (1.9)	0.281
Acute illness/cold	58 (1.8)	62 (1.8)	120 (1.8)	0.317
Familiar distress	24 (0.7)	21 (0.6)	45 (0.7)	0.741
Sports/ physical activity	162 (5.1)	217 (6.5)	379 (5.8)	<0.001
School problems	52 (1.6)	44 (1.3)	96 (1.4)	0.669
Tv use	27 (0.8)	45 (1.4)	72 (1.1)	0.008
Computer use	19 (0.6)	63 (1.9)	82 (1.2)	<0.001
Anxiety	174 (5.5)	151 (4.5)	325 (5.0)	0.920
Loneliness	11 (0.3)	7 (0.2)	18 (0.2)	0.816
Homework	60 (1.9)	48 (1.4)	108 (1.6)	0.921
Food habits	125 (3.9)	89 (2.6)	214 (3.3)	0.355
Sadness	26 (0.8)	20 (0.6)	46 (0.7)	0.765
Not defined	42 (1.3)	27 (0.8)	69 (1.0)	0.197

*Percentages considering all the Cohort participants

Table 3 – Associations (odds ratios, OR, and 95% confidence intervals, 95% CI) between pain attributes and pain impact on daily activities (at least one dimension) and use of health services, as reported by parents

	Association with impaired Daily Activities		Association with Health Services Use	
	OR (crude)	95 % CI	OR (crude)	95 % CI
Frequency				
< 3 times/week[a]	1		1	
≥ 3 times/week	1.35	1.26-1.46	1.18	1.09-1.27
Duration				
< 3 months[a]	1		1	
≥ 3 months	1.59	1.48-1.70	1.26	1.17-1.36
Intensity				
- Low to moderate[a]	1		1	
- Intense	1.86	1.73-2.00	0.96	0.89-1.03
Medication				
- Not used[a]	1		1	
- Used	2.12	1.24-4.23	1.70	1.52-1.90
Multisite				
< 2 sites[a]	1		1	
≥ 2 sites	2.04	1.43-2.92	2.07	0.99-4.31

[a] reference category

Table 4 - Classification of Musculoskeletal pain:

Musculoskeletal pain	**n=160 (100%)**
Growth pains	99 (61.9)
Muscle/tendon tenderness	25 (15.6)
Scoliosis	9 (5.6)
Sever's disease	8 (5.0)
Varus and valgus foot	7 (4.3)
Osgood-Schlatter disease	4 (2.5)
Varus and valgus knee	3 (1.9)
Kohler's disease	2 (1.3)
Benign tumor	2 (1.3)
Osteochondritis dissecans	1 (0.6)

Figure 1. Frequency (%) of each pain feature at the 10-years evaluation by sex, according to the parent's report, considering as denominator children with pain in the previous 3 months (n=3725)

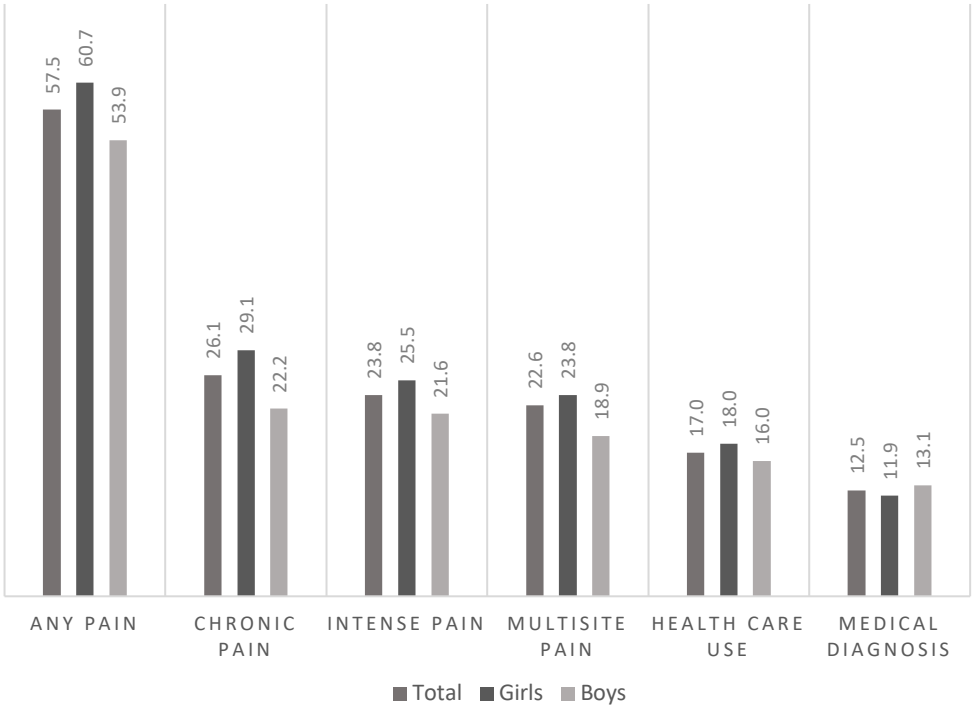


Figure 2 - Impact on daily activities due to pain at age 10 years – number of children reporting each of the limitations in their routine

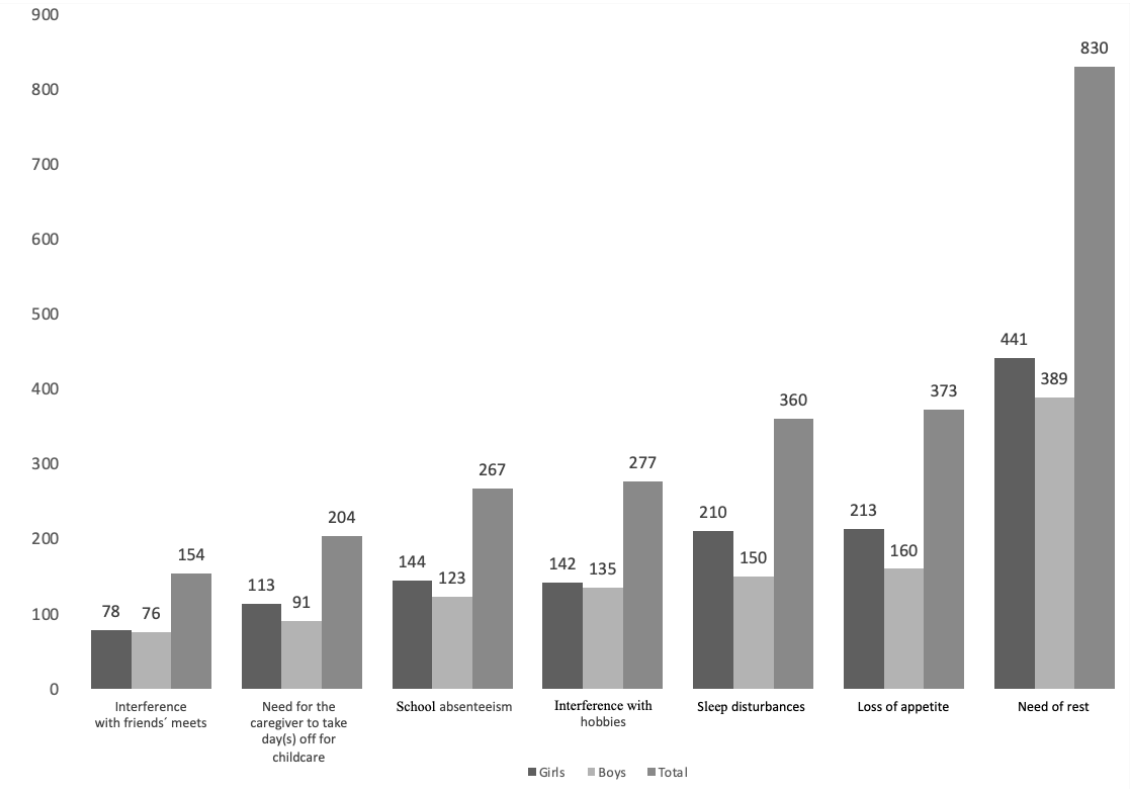
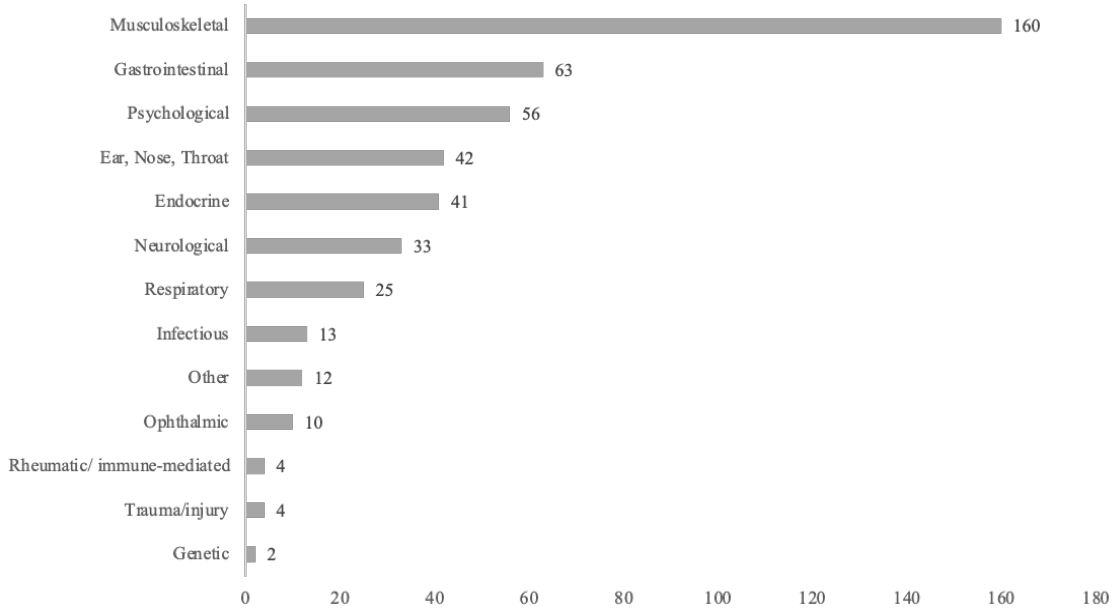


Figure 3 – Categorization of Pain after Medical Evaluation



4.3) Paper III

Atopic dermatitis in early life and pain at 10 years of age: An exploratory study

Vanessa Gorito, Maria Brandão, Inês Azevedo, André Moreira, Raquel Lucas

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RESEARCH

Atopic dermatitis in early life and pain at 10 years of age: An exploratory study

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Abstract

Pain is a distinctive burden in atopic dermatitis and recognized as an important and highly prevalent symptom. It is unknown if the presence of atopic disease may sensitize children to adverse pain profiles in the long term. We aimed to assess the impact of early-life atopic dermatitis-like symptoms on pain at 10 years of age. We used data from 1302 and 874 participants of the Generation XXI birth cohort evaluated at 6 and 15 months, respectively, and 10 years. Atopy-like symptoms since birth, including atopic dermatitis, were collected at ages 6 and 15 months by interviewing parents. Pain history in the last 3 months at age 10 was collected from parents and children using structured questionnaires. We computed relative risks (RR) and respective 95% confidence intervals of pain features at age 10 according to each atopic-like symptom at 6 and 15 months. Children whose parents reported atopic dermatitis-like symptoms at 6 months and at 15 months had higher risk of reporting any pain (RR 1.75 [1.15–2.66]) and multisite pain, respectively (RR 1.67 [1.18–2.37]) at 10 years of age.

Conclusion: Atopic dermatitis symptoms in early life were associated with a higher risk of pain at age 10, suggesting that potential for sensitization during the first decade of life and highlighting the importance of improving the health care of children with atopic dermatitis is worth investigating.

What is Known:
- *Atopic disorders have been associated with many non-atopic comorbidities, including chronic pain.*
- *Pain and atopic dermatitis share common inflammatory pathways. Inflammation, injury to the skin from scratching, fissures, and intolerance to irritants related to atopic dermatitis can cause pain.*

What is New:
- *Atopic dermatitis in early life is linked to an increased likelihood of experiencing pain at the age of 10, which suggests that exploring the potential for sensitization is a worthwhile area of investigation.*
- *Our proof-of-concept study highlights the potential benefit of studying management targets and improving itching and relieving skin pain as quickly as possible, avoiding potential long-term consequences of the sensitization process.*

Keywords Atopy · Atopic dermatitis · Sensitization · Pediatric pain · Cohort study · Child health

Introduction

Atopic disorders have been associated with many non-atopic comorbidities, including chronic pain [1, 2]. It is thought that nociceptive pain events in the first years of life can partly trigger amplified pain syndromes [3]. In recent years, there has been a growing focus on the burden of pain in patients with atopic dermatitis, one of the most frequent chronic skin diseases of childhood[1,2] that affects around 20% of children in high-income countries [1, 4].

Atopic dermatitis has been described as inducing significant somatic suffering and psychological disturbance (sleep disorders, depression, anxiety) with massive economic burden [5]. Epidermal barrier disruptions and skin inflammation are cornerstones of atopic dermatitis pathophysiological processes. A consequence of the interaction between a compromised barrier and a type 2 immune

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Key message: Atopic dermatitis symptoms in early life are linked to an increased likelihood of experiencing pain at the age of 10, which suggests that exploring the potential for sensitization is a worthwhile area of investigation.

Extended author information available on the last page of the article

environment is the promotion of percutaneous allergic sensitization [6]. Although itch is the most prominent symptom, the pain has recently been considered a nonnegligible burden in atopic dermatitis [5, 6]. Inflammation, injury to the skin from scratching, fissures, and intolerance to irritants related to atopic dermatitis can cause pain that ranges in intensity from aggravating to agonizing. Huet et al. in an investigation published recently revealed that among adult participants with atopic dermatitis, more than a half dealt with pain issues at least once a week and five percent had pain daily [7]. Silverberg et al. found that about half of the adults and adolescents with atopic dermatitis in the study experienced pain [8].

Pain and atopic dermatitis share common inflammatory pathways. IL-1β has been implicated in painful and inflammatory processes, namely promoting hyperalgesia [9]. Elevating the inflammatory cytokines IL-1β, IL-6, and TNF-α in fibromyalgia suggests an inflammatory component in the induction of widespread pain [2]. Besides, serum levels of IL-8, TNF-α, and IL-6 may be important markers of disease severity and for the follow-up of children with atopic disorders [10].

We hypothesized that atopic dermatitis may have a prospective influence on pain experiences in children. Also, in large-scale population-based studies, without a clinical evaluation, atopic-like symptoms can be used as a proxy of atopy, even if not optimally specific. Therefore, we used prospective data from a population-based cohort to study the association between early-life atopic dermatitis, among other atopic-like symptoms, and pain experiences in school-age children.

Materials and methods

The Generation XXI (G21) cohort study

Generation XXI is a birth cohort study that enrolled 8647 newborns, in 2005–2006, in the five public maternities covering the metropolitan area of Porto, Portugal. A baseline evaluation was done during the hospital stay (24–72 h after the delivery) with a 91.4% participation proportion. Consecutive subsamples of babies were examined at 6 and 15 months and the whole cohort was invited to participate in evaluations at 4, 7 and 10 years. In each evaluation wave, questionnaires collected extensive information, including demographic and socioeconomic characteristics, clinical history, common childhood symptoms, and pain experiences [11, 12].

We present the sociodemographic and clinical characteristics of our sample on Table 1.

Data collection

Early life atopic-like symptoms at 6 months and 15 months

At 6 and 15 months, subsamples of 1555 and 1043 babies were randomly selected from the whole cohort and examined, respectively. We used standardized questionnaires and asked parents to report atopic-like symptoms experienced by the child since birth, as described below. At 6 months, personal history of food allergy/intolerance-like symptoms, atopic dermatitis-like symptoms and wheezing-like symptoms were evaluated through the following questions: "Did your baby ever have an episode of wheezing, whistling or rattling in the chest?", "Did your baby ever have an episode of food allergy/intolerance?", and "Did your baby ever have an episode of itchy skin changes/eczema?".

At 15 months, the child's history of food allergy-like symptoms, atopic dermatitis-like symptoms and wheezing-like symptoms were repeated, and an additional question was included: "Did your baby ever have "persistent symptoms such as sneezing, nasal itching, rhinorrhea or nasal congestion without a cold/flu?".

Pain at 10 years of age

In the 10 years of evaluation, about 74% of all the cohort had been evaluated; 6397 parents and 4752 children answered a structured questionnaire focused on the child's health and surrounding context, including the child's experience of pain. The whole cohort was invited to participate, including participants with diagnosed chronic conditions reported by parents, namely atopic disorders, independently of flare symptoms at 10 years evaluation.

From all cohort, we used information provided for 83% of the subsample evaluated at 6 months and 84% of the subsample evaluated at 15 months who had complete information about pain at 10 years of follow-up.

To evaluate the pain experience, a Portuguese version of the Luebeck pain screening questionnaire was applied [13]. The first (screening) question was, "Did your child complain of pain in the last 3 months?" If the answer was affirmative, the parent was asked to select the anatomical sites where the child felt pain and indicate the principal pain site according to parental assessment [14]. We considered multisite pain to be present if two or more anatomical regions (among head, chest, abdomen, pelvis, back, upper limb, lower limb, throat, ear, teeth or other) were selected and chronic pain if the child had at least one recurrent pain with a duration over 3 months. Pain intensity was assessed using the original six-point Faces Pain Scale (FPS). Intense pain was considered if FPS4 or higher was selected [15].

Table 1 Sociodemographic and clinical characteristics of G21 participants who were included in this study

	Evaluated at 6 months and 10 years ($N = 1302$)	Evaluated at 15 months and 10 years ($N = 874$)
Sex at birth		
Female	638 (49%)	442 (51%)
Male	664 (51%)	432 (49%)
Maternal age at the child's birth (years)		
< 26	274 (21%)	171 (20%)
26–35	859 (66%)	583 (67%)
≥ 36	169 (13%)	120 (13%)
Maternal education		
< 10th grade	520 (40%)	391 (45%)
10th–12th grade	379 (29%)	240 (27%)
> 12th grade	403 (31%)	243 (28%)
Monthly household income (EUR)		
Under 1000	408 (31%)	324 (37%)
1000 to 2000	650 (50%)	413 (47%)
Above 2000	244 (19%)	137 (16%)
Type of delivery		
Eutocic	645 (50%)	416 (48%)
Forceps	15 (1.2%)	9 (1.0%)
Vacuum	195 (15%)	122 (14%)
Cesarean	447 (34%)	327 (37%)
Gestational age at child's birth		
< 37 weeks	115 (8.8%)	75 (8.6%)
≥ 37 weeks	1187 (91%)	799 (91%)
Low birth weight (< 2500 g)		
Yes	108 (8.3%)	79 (9.0%)
No	1194 (92%)	795 (91%)
Child neonatal resuscitation[a]		
Yes	117 (8.9%)	85 (9.7%)
No	1185 (91%)	789 (90%)
Admission to neonatal intensive care unit		
Yes	94 (7.2%)	69 (7.9%)
No	1208 (93%)	805 (92%)

[a]Defined as the set of interventions at the time of birth to support the establishment of breathing and circulation

Using a brief questionnaire, children also answered questions about their pain experience in the previous week: the presence of some pain, pain intensity (intense pain was considered if FPS4 or higher was selected) and the number of pain sites, using an age-appropriate body chart. Multisite pain was considered present if two or more anatomical regions were selected (among head, chest, abdomen, back, hip, shoulder, arm, hand, leg, foot or other) [14].

Statistical analysis

We describe variable distributions using proportions by categories and computed risks of pain features at age ten reported by parents and children according to the presence of each atopic-like symptom at 6 and 15 months, using data of participants with complete information on all relevant variables.

We compared sociodemographic and clinical characteristics at the baseline of participants that fulfilled the inclusion criteria with all other participants of the G21 cohort to assess losses to follow-up. The following variables were collected from clinical records at childbirth: sex at birth (female or male); maternal age at birth (< 26 years, 26–35 years, ≥ 36 years); type of delivery (eutocic, forceps, vacuum or cesarean section); gestational age at birth (< 37 weeks; ≥ 37 weeks); low birth weight (below 2500 g

vs 2500 g or above); need for resuscitation at birth (yes or no); admission to a neonatal intensive care unit (yes or no). Maternal education (< 10th grade, 10th–12th grade, > 12th grade) and household monthly income (under EUR 1000, EUR 1000 to 2000, or above EUR 2000) were collected by questioning the mother at birth using standardized questionnaires applied by trained interviewers up to 72 h after delivery.

Non-eligible participants had similar sex distribution, maternal education, household income, type of delivery and birth weight proportions. However non-eligible participants are more frequently premature (9.1%) and admitted in the Neonatal Intensive Care Unit (8.9%) (Table 1 — Supplementary information).

As atopic dermatitis may cause a predisposition to additional atopic illnesses in pediatric age and the presence of these illnesses correlates with poor disease control, we created a dichotomous variable "*multiple atopic symptoms*" based on the presence/absence of two or more atopic-like symptoms at 6 months or 15 months [31, 32]. The magnitude of the associations between reported symptoms and pain features was estimated using relative risks (RR) and asymptotic confidence intervals (95% CI). We adjusted associations for potential confounding factors, through a multivariable regression model including as co-variates sex, maternal education, household income, type of delivery and gestational age at birth.

All statistical analyses were performed using SPSS version 27 and we used a significance threshold of $p = 0.05$.

Results

Cohort characterization

Of the 1555 children evaluated at 6 months of age, as reported by parents, 396 (26%) had at least a wheezing episode, 340 (22%) had an atopic dermatitis-like episode, and 129 (8.1%) had food allergy-like symptom. Of the 1043 children evaluated at 15 months of age, parents reported wheezing episodes in 474 (45%), atopic dermatitis-like symptoms in 160 (15%), food allergy-like symptoms in 199 children (19%), and rhinitis-like symptoms in 131 (13%) (Fig. 1).

At 10 years of age, 1302 of the 1555 children evaluated at 6 months and 874 of the 1043 children evaluated at 15 months had both parent and child reports of pain. Among those who were evaluated at 6 months and 10 years

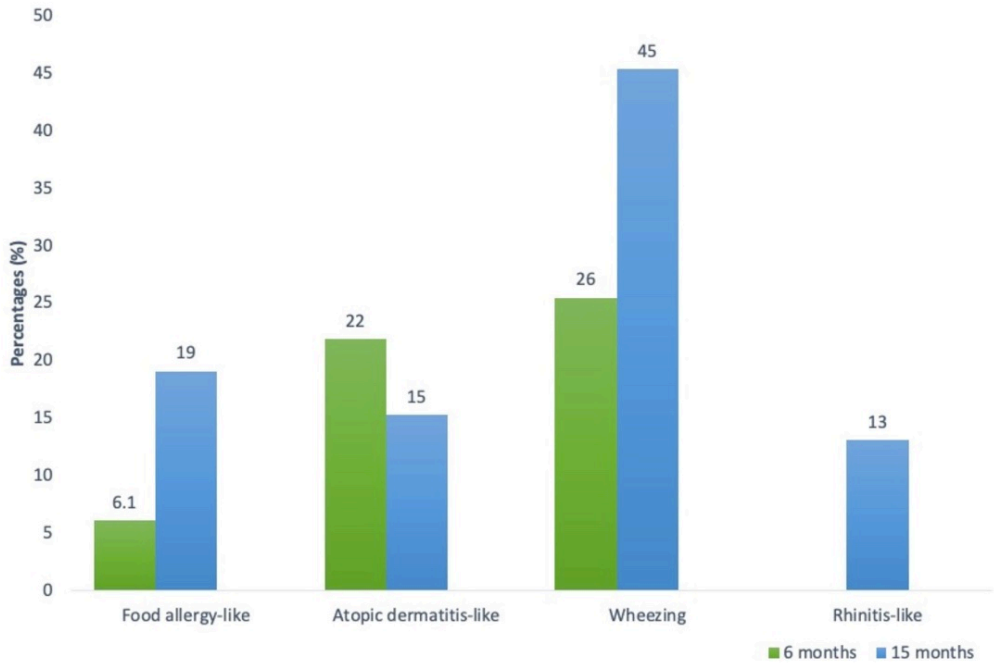


Fig. 1 Frequencies (%) of atopic-like symptoms in evaluations at 6 months and 15 months

of age, 333 (26%) children reported having some pain, 82 (6.3%) intense pain, and 98 (7.5%) multisite pain in the week before the evaluation. According to parents, 721 (55%) of those children had some pain, 172 (13%) chronic pain, 57 (4.4%) intense pain and 307 (24%) multisite pain in the three months preceding the evaluation (Fig. 2). Of the subsample evaluated at 15 months and 10 years of age, 253 (29%) children reported having some pain, 67 (7.7%) intense pain, and 49 (5.6%) multisite pain in the week before the evaluation. According to parents, 522 (60%) children had some pain, 141(16%) had chronic pain, 49 (5.6%) had intense pain and 208 (24%) had multisite pain during the previous three months (Fig. 2).

Atopic dermatitis-like symptoms and pain

Considering the parental report of pain, children with reported atopic dermatitis-like episodes at 15 months had higher risk of multisite pain at age 10 (42% vs 30%; RR 1.67 [1.18–2.37]). Atopic dermatitis-like episodes at 15 months were not associated to the presence of any pain (62% vs 59%; RR 1.16 [0.86–1.55]), intense (26% vs 23%; RR 1.16 [0.59–2.28]), and chronic pain reported by parents (67% vs 64%; RR 1.13 [0.62–2.06]). No associations were found between atopic dermatitis at 6 months and reported pain by parents at 10 years (Table 2).

Considering the children report of pain, atopic dermatitis-like symptoms at 6 months had higher risk of reporting any pain in the previous week at 10 years of age than those without atopic dermatitis (37% vs 25%; RR 1.75 [1.15–2.66]); but not intense pain (26% vs 24%; RR 1.08 [0.50–2.33] or multisite pain (8.30% vs 10%; RR 0.80 [0.35–1.89). Atopic dermatitis-like at 15 months was not associated with reports of intense or multisite pain at 10 years by children (Table 3).

We adjusted the relative risks for potential confounding factors, through a multivariable regression model including sex, maternal education, household income, type of delivery and gestational age. No major differences were found in findings after adjustment for both parents (Table 2) and children (Table 3) reports of pain.

Other atopic dermatitis-like symptoms and pain

Considering parental report of pain, wheezing episodes and food-allergy symptoms at 6 months had weak or no associations with pain, chronic pain, multisite and intense pain at 10 years. Children with food-allergy-like symptoms at 15 months had a higher risk of reported pain at age 10 (Table 2). Presence of rhinitis-like symptoms at 15 months was borderline associated with any and intense pain, but not with chronic or multisite pain at 10 years. There was no clear association between the presence of two or more atopy-like symptoms at 6 and 15 months and pain at 10 years of age (Table 2).

As for child report of pain, children with wheezing episodes at 6 months had slightly higher risk of any pain, but not intense or multisite pain at age 10. No clear associations were found between food allergy symptoms at 6 months

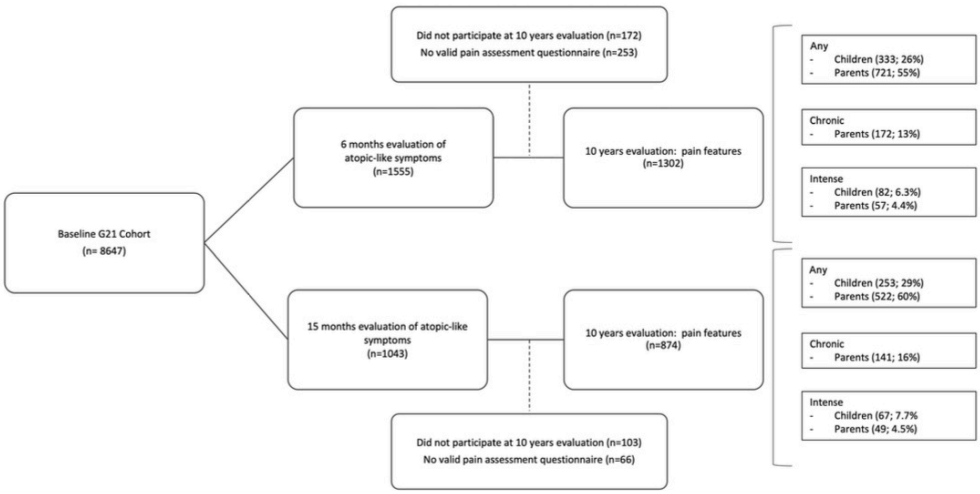


Fig. 2 Characterization of the pain experience at 10 years, considering subsamples of children consecutively selected from the whole cohort and evaluated at 6 months and 15 months for presence of atopy-like symptoms

Table 2 Association between diagnosed atopic-like symptoms in children evaluation at 6 months and 15 months and presence of any chronic, intense and multisite pain according to parents' report at 10 years

	Any pain			Chronic pain			Intense pain			Multisite pain		
N **= 1302** 6-months	%	RR [95% CI][b]	RR [95% CI] adjusted[a]	%	RR [95% CI][b]	RR [95% CI] adjusted[a]	%	RR [95% CI][b]	RR [95% CI] adjusted[a]	%	RR [95% CI][b]	RR [95% CI] adjusted[a]
Food allergy-like												
-Yes	61	1.08	0.68	68	1.29	1.49 [0.61–3.56]	27	1.32 [0.55–3.13]	1.10 [0.42–3.35]	25	0.94	0.76
-No	59	[0.72–1.63]	[0.28–1.62]	62	[0.58–2.86]		22			26	[0.58–1.50]	[0.42–1.39]
Atopic dermatitis-like												
-Yes	57	0.91	0.96	64	1.06	0.92 [0.41–2.24]	21	1.00 [0.38–2.61]	1.02 [0.35–1.44]	28	1.14	1.22
-No	59	[0.61–1.35]	[0.41–2.24]	63	[0.47–2.41]		21			26	[0.70–1.85]	[0.62–2.44]
Wheezing												
-Yes	57	0.88	0.71	67	1.25	0.98 [0.54–1.75]	21	1.03 [0.51–2.74]	1.00 [0.48–2.09]	26	1.05	0.63
-No	60	[0.68–1.14]	[0.38–1.30]	61	[0.70–2.22]		20			25	[0.78–1.42]	[0.42–1.02]
Atopic factors												
-0–1	58	1.06	1.02	13	1.53	1.01 [0.57–1.31]	21	1.08 [0.43–2.67]	0.99	25	1.38	1.12
-≥2	60	[0.72–1.57]	[0.61–1.37]	19	[0.93–2.51]		22		[0.54–1.75]	31	[0.91–2.10]	[0.64–1.75]
N **= 874** 15-months	%	RR [95% CI][b]	RR [95% CI] adjusted[a]	%	RR [95% CI][b]	RR [95% CI] adjusted[a]	%	RR [95% CI][b]	RR [95% CI] adjusted[a]	%	RR [95% CI][b]	RR [95% CI] adjusted[a]
Food allergy-like												
-Yes	68	1.59	1.70	65	1.1	1.67	32	1.79	0.49	31	0.96	0.44
-No	58	[1.12–2.27]*	[1.14–2.54]*	53	[0.58–2.08]	[0.36–7.76]	21	[0.88–3.64]	[0.22–1.13]	34	[0.63–1.46]	[0.06–3.44]
Atopic dermatitis-like												
-Yes	62	1.16	1.19	67	1.13	1.01	26	1.16	0.56	42	1.67	1.22
-No	59	[0.86–1.55]	[0.59–2.40]	65	[0.62–2.06]	[0.39–2.64]	23	[0.59–2.28]	[0.22–1.13]	30	[1.18–2.37]*	[1.15–2.43]*
Wheezing												
-Yes	67	1.64	1.56	64	1.06	1.07	22	0.89	0.85	38	1.43	1.58
-No	54	[1.25–2.17]**	[1.15–2.11]**	63	[0.61–1.85]	[0.56–2.06]	24	[0.47–1.70]	[0.41–1.78]	30	[1.02–2.01]*	[1.17–2.15]**
Rhinitis-like												
-Yes	66	1.38	0.75	70	1.41	0.60	32	1.91	0.59	31	0.93	0.35
-No	58	[0.98–1.94]	[0.38–2.4]	62	[0.75–2.64]	[0.27–1.29]	20	[0.96–3.79]	[0.27–1.23]	34	[0.63–1.40]	[0.02–2.33]
Atopic factors												
-0–1	57	1.67	1.27	14	1.82	1.37	14	1.50	1.07	45	0.15	0.37
-≥2	60	[0.36–7.76]	[0.43–4.21]	23	[0.21–15.76]	[0.53–5.11]	33	[0.23–1.83]	[0.53–1.71]	31	[0.02–1.51]	[0.12–2.13]

RR Relative Risk, *CI* Confidence Interval

*$p < 0.05$; **$p < 0.001$

[a]Model adjusted for: sex, maternal education, household income, type of delivery and gestational age

[b]Reporting pain features

Table 3 Association between diagnosed atopic-like symptoms in children evaluation at 6 months and 15 months and presence of any chronic, intense and multisite pain according to children´s report at 10 years

	Any pain			**Intense pain**			**Multisite pain**		
N **= 1302** 6-months	%	RR [95% CI][b]	RR [95% CI] adjusted[a]	%	RR [95% CI][b]	RR [95% CI] adjusted[a]	%	RR [95% CI][b]	RR [95% CI] adjusted[a]
Food allergy-like									
-Yes	29	1.21 [0.78–1.88]	0.74 [0.47–1.16]	29	1.22 [0.58–	0.92 [0.38—	11	1.12 [0.56–	0.22 [0.09–0.59]
-No	25			24	2.99]	2.21]	10	2.23]	
Atopic dermatitis-like									
-Yes	37	1.75 [1.15–	1.75 [1.14–	26	1.08 [0.50–	0.91 [0.41–2.01]	8.3	0.80 [0.35–	1.13 [0.41–3.10]
-No	25	2.66]**	2.69]*	24	2.33]		10	1.89]	
Wheezing									
-Yes	29	1.25 [0.94–1.67]	1.18 [0.67–2.24]	26	1.32 [0.75–	1.18 [0.63–2.24]	10	1.01 [0.61–	0.48 [0.19–1.21]
-No	24			21	2.33]		10	1.66]	
Atopic factors									
-0–1	25	1.29 [0.84–1.96]	1.14 [0.77–1.76]	22	1.06 [0.46–	1.02 [0.29–2.47]	10	0.31 [0.31–	0.58 [0.29–1.41]
-≥ 2	30			23	2.46]		7.5	1.55]	
N **= 874** 15-months	%	RR [95% CI][b]	RR [95% CI] adjusted[a]	%	RR [95% CI][b]	RR [95% CI] adjusted[a]	%	RR [95% CI][b]	RR [95% CI] adjusted[a]
Food allergy-like									
-Yes	27	0.91 [0.63–1.33]	1.11 [0.72–1.69]	30	1.24 [0.62–	0.68 [0.29–1.60]	9.9	1.34 [0.67–	1.84 [0.40–8.22]
-No	29			25	2.50]		7.6	2.65]	
Atopic dermatitis-like									
-Yes	28	0.94 [0.69–1.29]	1.03 [0.32–3.33]	28	0.75 [0.40–	0.68 [0.21–2.17]	6.9	0.85 [0.40–	0.37 [0.08–1.70]
-No	29			23	1.39]		9.0	1.42]	
Wheezing									
-Yes	31	1.17 [0.87–1.56]	0.83 [0.60–1.15]	24	0.81 [0.46–	1.48 [0.76–2.89]	8.2	1.01 [0.56–	0.63 [0.24–1.63]
-No	28			28	1.44]		8.1	1.80]	
Rhinitis-like									
-Yes	31	1.12 [0.78–1.60]	0.88 [0.59–1.31]	30	1.27 [0.66–	1.22 [0.56–2.64]	7.5	0.94 [0.46–	0.97 [0.31–3.02]
-No	229			25	2.45]		7.9	1.95]	
Atopic factors									
-0–1	29	1.02 [0.19–5.47]	1.00 [0.17–3.16]	12	1.45 [0.19–	1.12 [0.19–1.47]	0.9	1.09 [0.03–	1.07 [0.10–1.25]
-≥ 2	29			31	1.77]		8.1	1.15]	

RR Relative Risk, *CI* Confidence Interval

*$p < 0.05$; **$p < 0.001$

[a]model adjusted for: sex, maternal education, household income, type of delivery and gestational age

[b]reporting pain features

and child reports of any pain or multisite pain at age 10 (Table 3). Food allergy-like symptoms at 15 months were not associated with reports of intense or multisite pain at ten years. There were no differences in the risk of any type of pain between children with and without wheezing episodes at 15 months. No clear associations were found between rhinitis-like symptoms and any, intense, or multisite pain (Table 3). We found no clear association between the presence of multiple atopic symptoms at 6 months and the presence of intense or multisite pain. Reports of any pain by children were slightly more common when two or more atopic symptoms were present at 6 months. The presence of two or more atopic symptoms at 15 months was not associated with the risk of any pain, intense pain, or multisite pain (Table 3).

We adjusted the relative risks for potential confounding factors, through a multinomial regression model including sex, maternal education, household income, type of delivery

and gestational age. No differences were found in calculated risks after this adjustment for both parents (Table 2) and children (Table 3) reports of pain.

Discussion

Our prospective cohort study partly confirms our hypothesis, given that atopic dermatitis seemed to increase the risk of pain reported by children, as well as the report of multisite pain according to parents. Besides the increased risk of pain associated with atopic dermatitis in early life, food allergy-like symptoms and wheezing episodes at 15 months were also associated with future pain reported by parents, but those results were less robust.

Atopic dermatitis can negatively affect sensorimotor and cognitive development, behavior, pain responses, pharmacological requirements, and long-term health status of the children [15, 16]. Multisite pain is one of the most consensual indicators of adverse pain experiences in pediatric ages [17] and associations with atopy-like symptoms were slightly more robust with multisite and intense pain than with chronic pain.

Atopic skin with an impaired barrier, neurogenic inflammation mediators, and peripheral and central sensitization of pain processing pathways may possibly explain nociplastic pain mechanisms in atopic dermatitis [18]. Skin pain is increasingly recognized as an impactful symptom in atopic atopic dermatitis because of its association with patient discomfort, disease burden, and reduced quality of life [6, 7]. Although the nature of skin pain in atopic atopic dermatitis has not been systematically studied and is therefore not well understood, patients report soreness, discomfort, and tenderness that may reflect peripheral and central pain sensitization [8, 18]. Research suggests that peripheral inflammatory mediators contribute to pain [19, 20]. For instance, Cathepsin S activates T CD4+ cells, resulting in neuropathic pain [19] and IL-33 has been demonstrated to boost inflammation and pain [20]. Both inflammatory mediators are reported to be overexpressed in atopic dermatitis [20]. Nerve growth factor (NGF) is implicated in chronic pain conditions by primary pain afferents and the level of NGF was confirmed to be increased in atopic dermatitis patients [21].

Considering peripheral sensitization to pain, G protein-coupled receptors (GPCRs) and transient receptor potential (TRP) channels, contribute to skin sensation [22]. TRP vanilloid 1 (TRPV1), TRP ankyrin 1 (TRPA1), and transient receptor melastatin member 8 (TRPM8) are detected at high levels in atopic lesions [23]. Activation of TRPV1 results in increased levels of proinflammatory neuropeptide substance P, accelerating neurogenic inflammation [24]. Mas-related GPCRs (Mrgprs) are expressed by primary sensory neurons for peripheral skin sensations [25]. Mas-related GPCR D (MrgprD) is likely to be involved in neuropathic pain mechanisms as a nociceptor and mediate pain signaling [26].

Considering central sensitization of pain, the endothelin-1/endothelin receptor type B (ET-1/EDNRB) pathway was implicated in an atopic mouse model to explain the correlation between neuropathic pain and allergic inflammation, as also supported by an enhanced level of ET-1 in atopic patients [27]. The activation of spinal microglia boosts the expression of cytokines including IL-1β and TNF-α and brain-derived neurotrophic factor [28]. Besides, chronic pain-associated brain areas are activated in the anterior cingulate cortex, insula, and dorsolateral prefrontal cortex of the brain in atopic dermatitis patients, as observed by brain imaging [29].

The sensitization process that can lead to the perception of non-nociceptive stimuli as painful, as well as exaggerated (prolonged and generalized) perception of pain from noxious stimuli [6, 7] seems to be even more intense in early life, which justifies examining the associations between atopic dermatitis in early life and the occurrence of pain at age 10 years.

Strengths of the study

Our study examined atopy-like symptoms in early life as potential contributors for pain experiences at 10 years using a large population-based sample of children during their childhood. As far as we know this is the first prospective study of this association in a population-based sample of children, evaluated prospectively in different stages and selected independently of symptoms or healthcare seeking behavior.

We found associations between atopic dermatitis and both children and parental pain reports, even after adjustment for sociodemographic and perinatal confounders (sex, maternal education, household income, type of delivery and gestational age) contributing to making our hypothesis more plausible. Although children are able to report their pain at 10 years, and should be always asked about their pain, parents give valuable information to complement children's report. Parents are likely to notice any discomfort or change in children's behavior related to atopy-like symptoms and pain complaints, although our previous investigation in this cohort suggests that parental report is more useful to rule-in than to rule-out the child's pain [30]. We consider the use of both records (children and parents) a major strength of this study.

Limitations of the data

Our study may be limited because it is based on reports, without doctors' information/clinical validation of the diagnosis of atopy and without a clinical attribution for

pain reports, e.g. pain at age 10 could be directly related to an atopic disease flare and not a result of cumulative sensitization. We measured atopic-like symptoms in the first 15 months of life as reported by parents and not the prevalence of established/diagnosed atopic diseases, which would likely be lower if validated using clinical records. For instance, food allergy-like symptoms are often confused with food intolerances or isolated symptoms, and many respiratory infections can cause wheezing. Atopic dermatitis can also be mistaken for a nonspecific rash that may appear in early childhood. We conducted our study by selecting sub-samples of children with early-life atopic events from a population cohort and our results may be influenced by bias related to non-participation and/or attrition. It should also be noted that parents who report atopic-like symptoms may be more likely to report pain experiences due to being more health-conscious or more vulnerable to physical complaints, which could induce an association between atopy and pain due to surveillance bias.

Future approaches

There are different scales/questionnaires to assess the impact of atopic dermatitis on patients' lives [33]. In the near future, it would be advantageous to screen the pain complaints/discomfort routinely in appointments to improve the prevention measures and to diagnose and to treat flares earlier. The current evidence and advances for the potential treatment of atopic dermatitis have been studied by targeting specific interleukin (p.e IL1, IL33), common in both inflammatory pathways pain in atopic dermatitis [34]. Pharmacological treatment targeting these specific interleukines (p.e canakinumab) may be a potential treatment in atopic dermatitis especially associated with pain [34]. Nevertheless, ours is an exploratory study and a lot remains to be clarified regarding the complex early life influences on chronic pain in the general population, as seen, e.g. in a recent cohort study where preterm birth was associated with less severe spinal pain in pre-adolescence among girls [35].

Conclusion

In our population-based study, atopic dermatitis symptoms in early life were associated with a higher risk of pain at age 10, which could be a starting point to bring together the study of atopic dermatitis and pain sensitization in children. We highlight the potential benefit of studying strategies to address itching and skin pain to avoid pain sensitization processes that may contribute to long-term chronic pain phenotypes and to improve the care of children with atopic dermatitis.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00431-024-05439-0.

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Authors' contributions VG carried out the initial analyses, performed statistical analyses, contributed to interpreting the results and drafted the first version of the manuscript. MB, IA, AM, and RL contributed to understanding the results and critically reviewed the manuscript. RL coordinated and supervised data collection, contributed to the study conception and design and reviewed and revised the manuscript. VG and RL contributed to the study conception, design and the, interpretation and discussion of the data. All authors have seen and approved the final manuscript as submitted and take full responsibility for the manuscript.

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Data Availability Data are made available upon request, after submission of the scientific proposal to the executive committee of the cohort (info@geracao21.com).

Declarations

Ethics approval The protocol complied with the Declaration of Helsinki and was approved by the joint Ethics Committee of the São João Hospital and University Centre and the University of Porto Medical School. Families were considered participant if legal guardians signed a written informed consent form and children provided oral assent.

Conflict of interest The authors declare no competing interests.

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4.4) Paper IV

Refining the prediction of multisite pain in 13-year-old boys and girls by using parent-reported pain experiences in the first decade of life.

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ORIGINAL ARTICLE

Refining the prediction of multisite pain in 13-year-old boys and girls by using parent-reported pain experiences in the first decade of life

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Abstract

Background: We evaluated different pain profiles as prospective predictors of multisite pain in 13-year-old adolescents (1300 girls and 1457 boys) enrolled in Generation XXI, a birth cohort study in Portugal.

Methods: Pain history was queried using the Luebeck Pain Questionnaire through parent proxy- (ages 7 and 10) and adolescent (age 13) self-reports. We estimated the risk of multisite pain (2 or more pain sites) at age 13, according to previous pain experiences, including accumulation and timing. We defined five profiles that combined adverse features at ages 7 and 10 (recurrence, multisite, frequency, duration, intensity, triggers, activity restrictions, passive coping, and family history) and estimated their relative risks (RR) and likelihood ratios (LR) for adolescent multisite pain.

Results: At age 13, 39.2% of girls and 27.2% of boys reported multisite pain in the previous three months. The risk was higher among girls with multisite and recurrent pain at ages 7 and 10 than in girls without those adverse features, especially if psychosocial triggers were also present (RR 1.87; 95% confidence interval 1.36, 2.36 and LR 3.49; 1.53, 7.96). Boys with recurrent pain of higher frequency and causing activity restrictions at ages 7 and 10 had a higher risk of multisite pain at 13 (RR 2.05; 1.03, 3.05 and LR 3.06; 1.12, 8.39). Earlier adverse experiences were more predictive of future pain in girls than in boys.

Conclusions: Different profiles were useful to rule in future multisite pain in boys and girls. This provides clues for early stratification of chronic pain risk.

Significance: We identified sex-specific pain features that can be collected by practitioners in the first decade of life to improve the stratification of children in terms of their future risk of a maladaptive pain experience in adolescence. Using

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a prospective population-based cohort design, we show that early multisite pain and psychosocial triggers are relevant predictors of future multisite pain in girls, whereas repeated reports of high-frequency pain leading to activity restrictions are predictive of adolescent multisite pain in boys.

1 | INTRODUCTION

Chronic pain conditions are the leading cause of the disability burden worldwide (GBD 2016, 2017). These conditions raise complex prevention and management challenges since they frequently have unclear or nonspecific aetiology. Instead, they are physical manifestations of syndromes that result from multiple influences that act and interact throughout life, at different levels (Edwards et al., 2016). Understanding the development of pain susceptibility profiles that magnify and prolong the effects of serious or minor lesions is essential to stratify the risk of chronic pain in the population beyond the identification of organic causes (Dunn et al., 2013).

Over the last two decades, several longitudinal studies have expanded our understanding of pain susceptibility over time. They have shown that pain experiences track over time and across settings and that they can be described using trajectory archetypes, in adults as well as children (Dunn et al., 2011; Kongsted et al., 2016). Redirecting the trajectory of chronic pain and related suffering is essential to reshaping pain experience, and doing so requires the early identification of individuals with a higher propensity to develop lifelong pain phenotypes. It is therefore imperative to refine the prediction of adverse pain experiences, by identifying distinctive features that can prospectively predict maladaptive pain trajectories (Holley & Palermo, 2018). Still, relatively little is known on how to best use reported early pain experiences to stratify the risk of future chronic pain trajectories.

Adolescence is marked by extensive biological and psychosocial changes and is seen as a crucial stage for the embodiment of pain phenotypes, which build up throughout childhood and commonly track into adulthood (Coenen et al., 2017; Hestbaek et al., 2006; Isensee et al., 2018). Overall, pain experiences increase in frequency throughout adolescence and their topography shifts towards the musculoskeletal system (Gobina et al., 2019), with adult prevalence levels seemingly established by 18 years of age (Jeffries et al., 2007). It is also well-known that sex differences in pain experiences become apparent with pubertal development and widen throughout adolescence (King et al., 2011; Stanford et al., 2008). Sex differences include not only large disparities in prevalence but also in complementary dimensions of the whole pain experience, such as associated morbidity and resilience (Beales et al., 2012; Skrove et al., 2015).

Adverse pain experiences in adolescence are likely intermediate steps toward chronic pain trajectories and can therefore be regarded as undesirable outcomes. Specifically, multisite pain is an early and stable marker of severity, prognosis and distress in youth (Auvinen et al., 2017; Hoftun et al., 2013; Kroner-Herwig et al., 2011; Larsson & Sund, 2007) that extends into adulthood (Carnes et al., 2007; Kamaleri et al., 2009). Therefore, predicting multisite pain in adolescents by tracking previous pain features during the first decade of life can be a useful contribution to risk stratification, especially if sex differences are captured. Relevant features include not only symptom attributes and combinations thereof but also the timing and repetition of pain reports during the first decade of life. Identifying early predictors of adolescent multisite pain can also contribute to clarifying hypotheses addressing the accumulation of risk or sensitive periods as part of life course etiologic models (Dunn et al., 2013). Population-based prospective cohorts are ideal for this investigation since they follow children before pain phenotypes are established.

In this study, we aimed to evaluate different pain profiles at ages 7 and 10—pain features, and timing and accumulation of pain experiences—as prospective predictors of multisite pain in a population-based cohort of 13-year-old boys and girls.

2 | METHODS

2.1 | Study participants

This study was conducted using data from Generation XXI, a prospective population-based birth cohort study set up in Porto, Portugal, and described in detail elsewhere (Alves et al., 2012; Larsen et al., 2013). At the recruitment stage, all women who delivered live-born children with more than 23 gestation weeks, in all public units providing level III care (basic, specialty and subspecialty maternal care, comprising care for more complex maternal medical conditions, obstetric complications, and foetal conditions, according to the American College of Obstetrics and Gynecology classification) in the Metropolitan Area of Porto, between April

2005 and August 2006, were eligible. In 2004, the selected maternity units were responsible for 91.6% of the deliveries in the whole catchment population. Of those invited, 91.4% accepted to participate yielding a cohort of 8647 children enrolled from birth (when sex assigned was recorded). Cohort participants were invited, typically up to 8 weeks after their birthdays, to attend follow-up assessments at ages 4, 7, 10 and 13 years (86.3%, 79.6%, 73.9% and 48.6% participation, respectively). The 13-year evaluation wave was initiated in August 2018 and planned to end in late 2020 but was suspended in March 2020 due to the emergence of the COVID-19 pandemic, which originated unusually low participation in this wave, though this did not impact the study findings; see 'Nonparticipation and sensitivity analysis' section. Each follow-up evaluation included face-to-face interviews to collect information about the family (demographic and socioeconomic characteristics, family structure, and parental medical history) and the index child, that is, the cohort participant whose birth defined eligibility and timing of recruitment (medical history, physical symptoms, and health-related behaviours and circumstances). A comprehensive physical examination of the child was also conducted. Ethical approval was obtained from the Ethics Committee of *Hospital de São João* and the University of Porto Medical School. The study is registered with the Portuguese Data Protection Authority and conforms to the Helsinki Declaration. At each evaluation, written informed consent was obtained from legal guardians and oral assent from children. The original (Portuguese) versions of the questionnaires are available for download at the cohort website (https://www.geracao21.com/pt/projeto/#avaliacoes under tabs '7 anos', '10 anos' and '13 anos').

Data on pain experiences have been regularly collected starting at age 7, by inquiring of an accompanying adult, at ages 7 and 10, and the adolescent, at age 13 years. We considered eligible for the present study all children with completed pain assessment questionnaires in all three waves (n = 3697 children; 42.8% of the initial cohort). In the analysis, we included children whose father or mother served as proxy-respondent to the pain questionnaires at ages 7 and 10, who lived with the parent respondent, whose reported site of principal pain at ages 7 and 10, when applicable, was one of the sites of interest (see below), and who self-reported on their own pain experiences at age 13 (n = 2774), and further restricted the analytic sample to those with complete or imputable data on pain features (n = 2757, 1300 girls and 1457 boys). Children were considered eligible for the analysis regardless of whether their birth was single or multiple; our final analytic sample included 91 adolescents who were twins (n = 44 pairs) or triplets (n = 1); see Figure 1 and the 'Missing data' section, for more details on the selection of the analytic sample.

2.2 | Pain experience at ages 7 and 10

Parents completed a Portuguese version of the Luebeck pain screening questionnaire (LPQ) on behalf of their child (Roth-Isigkeit et al., 2005). The first question was 'Did your child complain of pain in the last 3 months?', which was used to define the dichotomous variable *Any pain*. If the answer was affirmative, the parent was asked to select all the sites where the child felt pain from a list of predefined anatomical sites (head, back, ears, abdomen, pelvis, arms, legs, chest, throat, teeth), as well as an additional open field to describe any 'other' site(s), and to indicate the site of the principal pain, subjectively assessed by the respondent as 'the most important pain among those selected'. After excluding the anatomical sites where pain is more likely due to acute self-limited illness (ears, nose, throat, teeth, mouth) as well as unspecified or ill-defined regions (e.g., skin), the pain sites selected for this paper were the following: head, back, neck/shoulders, upper limbs, chest, abdomen, pelvis, hips and lower limbs. *Multisite pain* was considered present if the parent indicated 2 or more of the sites selected for this paper. In addition, specific mention of 'generalized' or 'general' pain, or 'multiple' or 'various' sites in the open field were also interpreted to signify multisite pain. *Recurrent pain* was considered present if the parent reported that their child experienced two or more episodes of the principal pain in the previous 3 months.

Because of questionnaire design, which emulates the sequence of a clinical interview, features of pain other than the number of sites (duration, frequency, intensity, impact on daily living, triggers, context, passive coping and family history of chronic pain) were assessed only if the child was reported to have recurrent pain and only in reference to the principal pain site indicated by the parent. Consequently, analyses were restricted to those children whose reported principal pain site at ages 7 and 10, when applicable, was one of the aforementioned eligible sites for defining multisite pain. When a recurrent pain was reported, the parent was asked about its: duration, recoded as short (≤3 months) versus medium to long (>4 months); frequency, recoded as low (at most once a month) versus medium to high (more than once a month); and intensity, reported using both the original version of the Wong-Baker six-point Faces Pain Scale (FPS) (Wong & Baker, 1988) and a visual analogue scale (VAS) ranging from 0 ('hardly noticeable pain') to 100 mm ('strongest conceivable pain'). Intensity was recoded as low (FPS 1–3 and VAS < 30) versus medium to high (FPS ≥ 4 or VAS ≥ 30). The parent was also asked about the impact

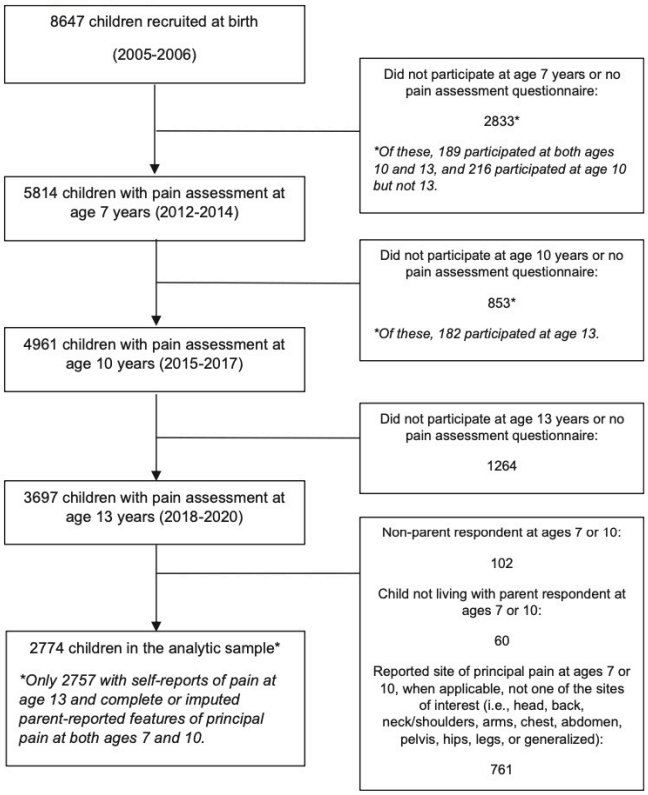


FIGURE 1 Selection of analytic sample for the Generation XXI cohort

on the child's daily living (missing school, not being able to meet with friends or engage in leisure time activities, having trouble eating or sleeping). Passive coping was briefly assessed by asking parents whether the child needed to rest or lie down due to pain, irrespective of whether resting or lying down was initiated by the child or directed by a parent. Pain triggers and context of the first episode were also reported. Triggers and context were analysed in combination and dichotomized as any psychosocial (any mention of interpersonal or psychological distress) versus no psychosocial trigger/context reported. Family history of chronic pain was considered present if the parent reported, at either age 7 or 10, that any of the parents or siblings of the index child had a chronic pain condition.

2.3 | Multisite pain at age 13

Trained interviewers applied a short version of the LPQ to each adolescent as part of the face-to-face evaluation at age 13. From the LPQ we selected multisite pain, that is, pain reported in two or more body sites in the previous 3 months, as our outcome measure. Multisite pain was defined using the same list of anatomical sites as before (i.e., head, back, neck/shoulders, upper limbs, chest, abdomen, pelvis, hips, lower limbs or generalized). In addition to the documented prognostic value of multisite pain, from our experience with the face validity of questionnaire items, adolescents typically found it easier to identify pain sites than to quantify other attributes, such as duration, frequency, or intensity. Finally, due to the sequential design of the LPQ, the choice of multisite pain as the outcome also allowed to optimize the number of adolescents with valid information on pain experience.

2.4 | Statistical analysis

We estimated prevalence ratios and 95% confidence intervals of different pain features at ages 7 and 10 between

boys and girls. We calculated absolute risks with 95% confidence intervals of multisite pain at age 13, according to pain features at ages 7 and 10. We combined follow-up waves to assess the relationship between different pain features at ages 7 and 10 and multisite pain at age 13, assuming that pain experiences were more severe if they were reported more than once—as a proxy for accumulation—or if they were first reported in the earlier examination—as a proxy for timing. Each pain feature was therefore categorized as: absent at ages 7 and 10, present only at age 10, present only at age 7, and present at both ages 7 and 10. Absolute risks were compared conservatively by assessing the overlap of confidence intervals.

Since pain features are not mutually exclusive, we examined the risk of multisite pain at age 13 according to profiles that aggregated complementary features. Each individual may be profiled according to their response to each specific feature at each age, resulting in a contingency table formed by sex, multisite pain at age 13, and the dichotomized pain features at ages 7 and 10, that consisted of 2^21 cells. Because the LPQ emulates a clinical history collection, most features were collected only when recurrent pain was reported. Also, more severe pain experiences are comparatively less frequent. As a result, the full contingency table was very sparse (over 93% of cells consisting of structural zeroes and 6% of sampling zeroes) and only the so-called 'all two-way interactions' log-linear model could be adequately estimated (Whittaker, 1991), whereas interactions among features (i.e., profiles) would not be estimable or reliably estimated. Instead of adopting such a limited model-based approach, we selected and grouped the features that identified subsets of adolescents with a higher risk of multisite pain at age 13, defined by at least 50% higher risk when the feature was present at ages 7 and 10 versus absent at both ages, an approach which was concordant with the preliminary results from the log-linear model described above. We did not use duration or intensity to build the profiles since none improved prediction when compared to recurrence alone. We then defined the following five profiles combining those features: (1) multisite and recurrent pain; (2) multisite and recurrent pain with psychosocial triggers; (3) multisite and recurrent pain with a family history of chronic pain; (4) multisite and recurrent pain that required rest; and (5) recurrent, medium- to high-frequency pain leading to activity restrictions. We calculated likelihood ratios (LR) with 95% confidence intervals to measure the accuracy of each profile in predicting multisite pain at age 13. Each LR is the ratio between the probabilities of that particular profile among adolescents with versus without multisite pain at age 13 (i.e., how much more or less likely that profile is among adolescents with multisite pain than among those without it) and we interpret it in terms of the impact of the LR on the change from the prior to the posterior probabilities of multisite pain at age 13. Analyses were stratified by sex at birth.

2.5 | Missing data

Our initial analytic sample consisted of 2774 adolescents (Figure 1). For 17 adolescents, data on the features of the principal pain, including its recurrence, were unavailable (e.g., skipped questions or 'don't know' responses), so the corresponding questionnaires were excluded from the analysis, resulting in a final analytic sample of 2757. Among those, a group of 53 children had missing data on at most two of the following six features: number of sites, duration, frequency, intensity, causal attributions, and resulting activity restrictions. To impute these missing data, we first constructed the age- and sex-specific contingency table formed by those six features using only the complete questionnaires, then we randomly drew the categories of the missing feature (e.g., for intensity: 'recurrent, low intensity', 'recurrent, medium intensity', or 'recurrent, high intensity') according to their estimated probabilities given the specific combination of the remaining five features for the index child in question. This procedure is equivalent to applying a Poisson regression model to predict missing feature categories (Allison, 2002).

2.6 | Nonparticipation and sensitivity analysis

As shown in Figure 1, children were considered eligible for the current study only if they had participated in pain assessment questionnaires at the 7-, 10- and 13-year evaluation waves with completed pain assessment questionnaires in all three waves. Comparisons of baseline characteristics between Generation XXI participants with pain assessment questionnaires at the 7-, 10- and 13-year evaluations ($n = 3697$) and those with pain assessment at ages 7 and 10 but no pain assessment at age 13 ($n = 1264$) revealed that the latter were born to younger mothers, with lower educational attainment and slightly higher parity, and were more likely to have had a low birthweight or been born prematurely (Table S1). These findings were consistent with baseline comparisons between those with assessments of pain experience at ages 7 or 10 and those with no such assessments (Lucas et al., 2021). However, none of these baseline characteristics were associated with multisite pain at age 13 (our response variable; see Table S2), and, with the exception of maternal education, there were no clear associations between baseline characteristics and pain features at ages 7 or 10 (Lucas et al.,

2021). In our sensitivity analysis, there were no relevant differences in the dose-response relation between feature severity at ages 7 and 10 and multisite pain at age 13 when estimates were stratified by maternal educational level. Finally, a comparison of pain features at ages 7 and 10 between children included in the final analytic sample (n = 2757) and those who were excluded (n = 915 meeting relevant inclusion criteria and with complete pain assessment at ages 7 and 10 but not 13) reveals only slightly higher prevalences of recurrent pain of medium to high frequency or intensity, or with activity restrictions, among those excluded than those included, leaving our findings unchanged (Table S3).

3 | RESULTS

3.1 | Pain features at ages 7 and 10

Table 1 presents and compares the frequencies of each parent-reported pain feature in girls and boys, at ages 7 and 10. At both ages, girls were more likely than boys to have any pain, as well as each of the pain features, examined. At age 7, point estimates for prevalence ratios (PR) between sexes varied between 1.23 (1.07, 1.41) for multisite pain and 1.38 (1.12, 1.70) for recurrent pain with psychosocial triggers, and at age 10 between 1.22 (1.08, 1.38) for multisite pain and 1.48 (1.19, 1.84) for recurrent pain with activity restrictions.

3.2 | Accumulation and timing of previous pain experiences and multisite pain at age 13

At age 13, the crude prevalence of self-reported multisite pain in the previous three months was 39.2% (36.6, 41.9) in girls and 27.2% (24.9, 29.5) in boys (PR 1.44; 1.27, 1.65). As seen in Table 2, in general, the risk of multisite pain was lowest among adolescents with no previous pain or previous pain of lower severity (only one report at ages 7 and 10 or report at age 10 only) and highest in those adolescents with each adverse feature at both ages 7 and 10. However, there was heterogeneity between sexes in the features that were the most predictive of multisite pain, as well as in the relation with the timing of previous pain experiences.

Compared to when each feature was absent at both ages 7 and 10, girls were more likely to report multisite pain at age 13 if they had repeated reports, at both ages 7 and 10, of any pain (absolute risk 48.8%; 43.7, 53.9), multisite pain (55.8%; 48.0, 63.7), recurrent pain (52.1%; 44.5, 59.7), pain of medium to high frequency (56.5%; 46.4, 66.7), pain with psychosocial triggers (61.5%; 46.3, 76.8)

TABLE 1 Frequencies, n (%), in girls and boys, and prevalence ratios (girls:boys) with 95% confidence intervals (95% CI) of the different pain features reported by parents at ages 7 and 10

	Girls (n = 1300)		Boys (n = 1457)		Prevalence ratios (95% CI) Girls:Boys	
	Age 7	Age 10	Age 7	Age 10	Age 7	Age 10
Any pain	529 (40.7%)	749 (57.6%)	520 (35.7%)	716 (49.1%)	1.14 (1.04, 1.25)	1.17 (1.09, 1.26)
Multisite pain	336 (25.8%)	388 (29.8%)	306 (21.0%)	357 (24.5%)	1.23 (1.07, 1.41)	1.22 (1.08, 1.38)
Recurrent pain	372 (28.6%)	378 (29.1%)	334 (22.9%)	323 (22.2%)	1.25 (1.10, 1.42)	1.31 (1.15, 1.49)
Recurrent pain of medium–high frequency	249 (19.2%)	257 (19.8%)	205 (14.1%)	209 (14.3%)	1.36 (1.15, 1.61)	1.38 (1.17, 1.63)
Recurrent pain of medium–long duration	272 (20.9%)	255 (19.6%)	235 (16.1%)	219 (15.0%)	1.30 (1.11, 1.52)	1.31 (1.11, 1.54)
Recurrent pain of medium–high intensity	255 (19.6%)	312 (24.0%)	230 (15.8%)	262 (18.0%)	1.24 (1.06, 1.46)	1.33 (1.15, 1.54)
Recurrent pain with psychosocial triggers	174 (13.4%)	156 (12.0%)	141 (9.7%)	128 (8.8%)	1.38 (1.12, 1.70)	1.37 (1.09, 1.70)
Recurrent pain with activity restrictions	170 (13.1%)	169 (13.0%)	142 (9.7%)	128 (8.8%)	1.34 (1.09, 1.66)	1.48 (1.19, 1.84)
Recurrent pain with need to rest	197 (15.2%)	203 (15.6%)	169 (11.6%)	171 (11.8%)	1.31 (1.08, 1.58)	1.33 (1.10, 1.61)

TABLE 2 Absolute risks (%) and 95% confidence intervals for multisite pain at age 13, in girls and boys, according to pain features reported at 7 and 10 years of age

	Girls				Boys			
	Not 7 or 10	10 only	7 only	7 and 10	Not 7 or 10	10 only	7 only	7 and 10
Any pain	33.0 (28.3, 37.7)	34.5 (29.7, 39.3)	43.8 (36.1, 51.4)	48.8 (43.7, 53.9)	25.0 (21.3, 28.6)	25.5 (21.2, 29.9)	27.6 (21.3, 33.9)	32.6 (27.5, 37.7)
Multisite pain	34.4 (30.9, 37.8)	37.6 (31.4, 43.8)	46.7 (39.5, 54.0)	55.8 (48.0, 63.7)	24.8 (22.0, 27.6)	30.3 (24.4, 36.2)	31.1 (24.3, 37.9)	33.3 (25.1, 41.6)
Recurrent pain	34.5 (31.1, 38.0)	37.1 (30.6, 43.6)	47.3 (40.5, 54.1)	52.1 (44.5, 59.7)	25.8 (23.0, 28.7)	24.7 (18.7, 30.8)	28.7 (22.6, 34.8)	38.4 (29.9, 46.9)
Recurrent pain of medium–high frequency	36.7 (33.5, 39.9)	37.0 (29.6, 44.3)	45.9 (38.1, 53.7)	56.5 (46.4, 66.7)	25.7 (23.1, 28.3)	24.0 (17.3, 30.8)	36.0 (28.3, 43.7)	41.8 (28.8, 54.9)
Recurrent pain of medium–long duration	35.5 (32.3, 38.7)	45.8 (38.2, 53.4)	46.4 (39.2, 53.7)	48.3 (37.9, 58.7)	25.6 (23.0, 28.2)	29.3 (21.9, 36.6)	32.5 (25.3, 39.7)	34.7 (23.7, 45.7)
Recurrent pain of medium–high intensity	36.8 (33.5, 40.1)	37.9 (31.4, 44.5)	46.1 (38.2, 54.0)	51.5 (41.7, 61.2)	25.9 (23.3, 28.6)	25.4 (19.1, 31.7)	32.7 (25.2, 40.1)	37.7 (26.8, 48.5)
Recurrent pain with psychosocial triggers	36.6 (33.6, 39.5)	41.0 (32.1, 49.9)	51.1 (42.7, 59.5)	61.5 (46.3, 76.8)	26.2 (23.7, 28.7)	29.8 (20.5, 39.0)	32.7 (23.8, 41.6)	38.2 (21.9, 54.6)
Recurrent pain with activity restrictions	36.6 (33.7, 39.6)	43.8 (34.6, 52.9)	47.8 (38.6, 57.0)	59.6 (46.9, 72.4)	26.1 (23.6, 28.5)	26.3 (17.6, 34.9)	35.4 (26.6, 44.2)	44.8 (26.7, 62.9)
Recurrent pain with need to rest	36.7 (33.7, 39.8)	41.2 (32.9, 49.4)	48.1 (39.5, 56.6)	53.0 (41.0, 65.1)	26.3 (23.8, 28.9)	26.2 (18.6, 33.7)	30.5 (22.5, 38.4)	43.9 (28.7, 59.1)
Recurrent pain with family history	36.6 (33.8, 39.5)	40.8 (29.4, 52.3)	62.5 (49.8, 75.2)	54.0 (43.6, 64.5)	26.3 (23.9, 28.8)	31.0 (20.2, 41.7)	32.1 (19.9, 44.4)	34.3 (23.2, 45.4)

or pain leading to activity restrictions (59.6%; 46.9, 72.4). Multisite pain at age 13 was also more likely when girls had a family history of chronic pain and recurrent pain was also present, only at age 7 (62.5%; 49.8, 75.2) or at both ages (54.0%; 43.6, 64.5).

Boys, on the other hand, were more likely to report multisite pain at age 13 if, at both ages 7 and 10, they had recurrent pain (38.4%; 29.9, 46.9), medium- to high-frequency pain (41.8%; 28.8, 54.9), medium- to high-intensity pain (37.7%; 26.8, 48.5), pain with psychosocial triggers (38.2%; 21.9, 54.6), pain leading to activity restrictions (44.8%; 26.7, 62.9) or pain that required rest (43.9%; 28.7, 59.1). In general, the risk of multisite pain at age 13 was not as clearly elevated in boys with earlier adverse pain experiences as it was in girls.

3.3 | Previous pain experience profiles and multisite pain at age 13

Table 3 presents absolute and relative risks of multisite pain at age 13 according to the five previously defined profiles that aggregated different features. The risk of multisite pain was higher among girls who had experienced multisite and recurrent pain at both ages 7 and 10 (RR 1.66; 95% CI 1.35, 2.00) or only at age 7 (RR 1.43; 1.18, 1.69), and increased when psychosocial triggers were also present at both ages (RR 1.87; 1.36, 2.36) or only at age 7 (RR 1.40; 1.13, 1.69). The risk was also higher when multisite and recurrent pain with the need to rest was reported at both ages (RR 1.44; 0.99, 1.91), only at age 7 (RR 1.43; 1.16, 1.71) or only at age 10 (RR 1.29; 1.02, 1.58). Higher risk was also observed among girls with a family history of chronic pain together with multisite and recurrent pain at age 7 (RR 1.66; 1.30, 2.02) or at both ages (RR 1.54; 1.17, 1.94), as well as among girls who had recurrent pain of medium to high frequency with activity restrictions at both ages (RR 1.75; 1.30, 2.22).

Among boys, the risk of multisite pain was higher among those who had multisite and recurrent pain at both ages 7 and 10 (RR 1.54; 1.09, 2.03), and increased when pain also required rest at both ages (RR 1.81; 1.04, 2.58). The relative risk of multisite pain at 13 was particularly elevated when boys had recurrent pain with medium to high frequency and activity restrictions at both ages 7 and 10 (RR 2.05; 1.03, 3.05) and also when this profile was present only at age 7 (RR 1.64; 1.21; 2.12).

Figure 2 presents likelihood ratios that summarize the accuracy of the pain profiles to classify multisite pain at age 13. None of the pain profiles examined were relevant to *rule out* multisite pain at age 13, with LR estimates very close to 1 when features were absent in both waves, that is, profiles where the selected features were absent at 7 and 10 were about as common among adolescents with multisite pain at age 13 as in those without it. Instead, profiles were more useful to *rule in* future multisite pain. In girls, the absolute risk of multisite pain at age 13 increased from an *a priori* probability of 39.2% (the prevalence in the whole sample) to 69.2% if participants had multisite and recurrent pain with psychosocial triggers at both ages 7 and 10 (Table 3); that profile was 3.5 times as likely among girls with multisite pain at age 13 than in those without it (LR 3.49; 95% CI 1.53, 7.96). Also, girls with multisite pain at age 13 were more than twice as likely to have had recurrent pain with medium to high frequency and activity restrictions at ages 7 and 10 (LR 2.96; 1.44, 6.08), family history of chronic pain together with multisite and recurrent pain only at age 7 (LR 2.47; 1.47, 4.17) or at both ages (LR 2.05; 1.19, 3.53), multisite and recurrent pain with need to rest only at age 7 (LR 2.13; 1.33, 3.40) or at both ages (LR 2.19; 1.34, 3.59), or multisite and recurrent pain at ages 7 and 10 (LR 2.14; 1.42, 3.21). In all of those cases, the risk of multisite pain at age 13 increased by 33% or more, from the 39.2% prior probability, if that profile was present. Earlier complaints in isolation among girls were generally more predictive of pain at age 13 than later reports, contrary to boys. In boys, reports of recurrent pain of medium to high frequency with activity restrictions at ages 7 and 10 increased the risk of multisite pain at age 13 by 96.0%, from an *a priori* probability of 27.2% to 53.3% (LR 3.06; 1.12, 8.39). Multisite recurrent pain with the need to rest at both ages 7 and 10 also increased the probability of later multisite pain, by 76.5% (LR 2.10; 1.25, 3.52).

4 | DISCUSSION AND CONCLUSIONS

In our study, adolescent girls had a higher risk of multisite pain when adverse experiences were reported from age 7, namely multisite and recurrent pain, and even higher if psychosocial triggers were also present. Among boys, those features of earlier pain experience were not as highly predictive of the risk of multisite pain at age 13. Instead, for boys, the presence, at ages 7 and 10, of recurrent pain of medium–high frequency with activity restrictions or multisite recurrent pain with passive coping were the most predictive of future multisite pain.

In this cohort, 39% of girls and 27% of boys aged 13 self-reported multisite pain in the 3 months prior to interview. Sex differences in pain experiences become apparent in paediatric ages, with girls generally showing a higher frequency of pain (King et al., 2011), being more likely to transition to chronicity (Holley et al., 2017), and more frequently reporting multiple pain sites during childhood (Petersen et al., 2006) and adolescence

TABLE 3 Absolute and relative risks (95% confidence intervals) of multisite pain at 13 years of age in girls and boys, according to selected pain profiles combining different features reported at ages 7 and 10 years

		Girls			Boys		
		n	Absolute risk of multisite pain at age 13 (in per cent; with 95% CI)	Relative risk of multisite pain at age 13 (with 95% CI)	*n*	Absolute risk (%) and 95% CI of multisite pain at age 13	Relative risk and 95% CI of multisite pain at age 13
Multisite and recurrent pain	Not 7 or 10	881	34.8 (31.7, 38.0)	1	1102	26.2 (23.6, 28.8)	1
	10 only	160	41.9 (34.2, 49.5)	1.20 (0.96, 1.46)	140	25.7 (18.5, 33.0)	0.98 (0.70, 1.29)
	7 only	171	49.7 (42.2, 57.2)	1.43 (1.18, 1.69)	143	29.4 (21.9, 36.8)	1.12 (0.83, 1.44)
	7 and 10	88	58.0 (47.6, 68.3)	1.66 (1.35, 2.00)	72	40.3 (28.9, 51.6)	1.54 (1.09, 2.03)
Multisite and recurrent pain with psychosocial triggers	Not 7 or 10	1077	37.0 (34.1, 39.8)	1	1284	26.7 (24.3, 29.1)	1
	10 only	91	42.9 (32.7, 53.0)	1.16 (0.88, 1.46)	70	27.1 (16.7, 37.6)	1.02 (0.63, 1.42)
	7 only	106	51.9 (42.4, 61.4)	1.40 (1.13, 1.69)	81	29.6 (19.7, 39.6)	1.11 (0.74, 1.51)
	7 and 10	26	69.2 (51.5, 87.0)	1.87 (1.36, 2.36)	22	45.5 (24.6, 66.3)	1.70 (0.93, 2.53)
Multisite and recurrent pain with need to rest	Not 7 or 10	1050	36.6 (33.7, 39.5)	1	1243	26.5 (24.1, 29.0)	1
	10 only	104	47.1 (37.5, 56.7)	1.29 (1.02, 1.58)	93	28.0 (18.8, 37.1)	1.05 (0.71, 1.43)
	7 only	109	52.3 (42.9, 61.7)	1.43 (1.16, 1.71)	92	29.3 (20.0, 38.7)	1.11 (0.76, 1.48)
	7 and 10	36	52.8 (36.5, 69.1)	1.44 (0.99, 1.91)	25	48.0 (28.4, 67.6)	1.81 (1.04, 2.58)
Multisite and recurrent pain with family history	Not 7 or 10	1127	36.9 (34.1, 39.7)	1	1300	26.5 (24.1, 28.9)	1
	10 only	60	45.0 (32.4, 57.6)	1.22 (0.87, 1.57)	58	31.0 (19.1, 42.9)	1.17 (0.74, 1.66)
	7 only	57	61.4 (48.8, 74.0)	1.66 (1.30, 2.02)	45	31.1 (17.6, 44.6)	1.18 (0.67, 1.74)
	7 and 10	51	56.9 (43.3, 70.5)	1.54 (1.17, 1.94)	47	38.3 (24.4, 52.2)	1.45 (0.94, 2.03)
Recurrent pain of medium–high frequency with activity restrictions	Not 7 or 10	1104	37.5 (34.6, 40.4)	1	1295	26.0 (23.6, 28.4)	1
	10 only	83	48.2 (37.4, 58.9)	1.29 (0.98, 1.59)	72	26.4 (16.2, 36.6)	1.01 (0.63, 1.45)
	7 only	81	43.2 (32.4, 54.0)	1.15 (0.86, 1.46)	75	42.7 (31.5, 53.9)	1.64 (1.21, 2.12)
	7 and 10	32	65.6 (49.2, 82.1)	1.75 (1.30, 2.22)	15	53.3 (28.1, 78.6)	2.05 (1.03, 3.05)

Note: Not 7 or 10: combination of features absent at both 7- and 10-year evaluation waves; 10 only: combination of features present only at 10-year evaluation wave; 7 only: combination of features present only at 7-year evaluation wave; 7 and 10: combination of features present at both 7- and 10-year evaluation waves.

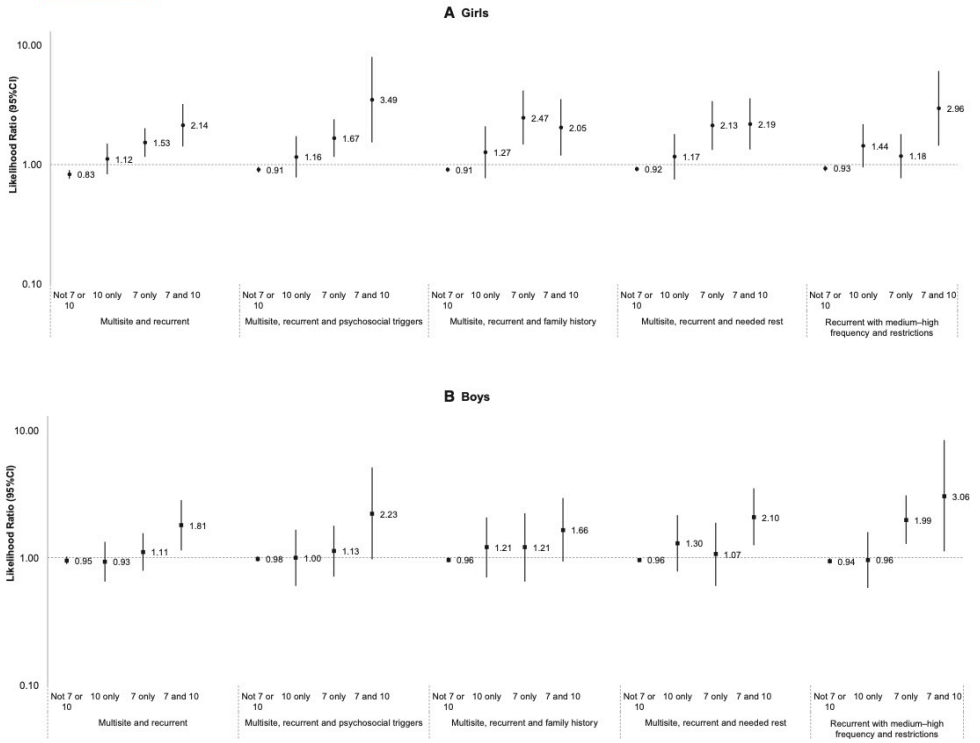


FIGURE 2 Likelihood ratios and 95% confidence intervals of different childhood pain profiles (parent-reported pain at ages 7 and 10) to predict self-reported multisite pain at age 13 in girls (panel a, circles) and boys (panel b, squares). Legend: Not 7 or 10: combination of features absent at both 7- and 10-year evaluation waves; 10 only: combination of features present only at 10-year evaluation wave; 7 only: combination of features present only at 7-year evaluation wave; 7 and 10: combination of features present at both 7- and 10-year evaluation waves

(Auvinen et al., 2017). Multiple mechanisms underlying sex differences are plausible, alone or combined, including biological—namely genetic, hormonal and neurophysiological differences—and psychosocial factors—including coping strategies, catastrophizing, self-efficacy, gender roles and sociocultural beliefs (Bartley & Fillingim, 2013). The timing when those disparities become established is unclear. Sex differences in experimental pain sensitivity seem modest up until early adolescence (Blankenburg et al., 2011), whereas late-adolescent girls have greater pain sensitivity (Tham et al., 2016). Sex differences in reported pain history seem to widen earlier, as shown in the present study where we found a 23% higher prevalence of multisite pain among girls at age 7 and a 44% higher prevalence at age 13. We built on those differences in the expression of pain as a rationale to stratify prediction by sex.

We refined the prediction of multisite pain in adolescents by testing different parent-reported pain experiences in childhood. Our findings suggest that individual profiles that included multisite pain, and pain with psychosocial triggers were useful to rule in future multisite pain in girls. In contrast, in boys, the profile that included repeated reports of the pain of medium–high frequency that led to activity restrictions seemed more relevant to rule in future multisite pain. Reports of passive coping, that is, rest, or family history of chronic pain also improved the prediction of adolescents' multisite pain, similarly in both sexes, but two of the sex-specific profiles were more accurate. Our findings are in agreement with previous evidence that the correlates of pain experiences are appreciably different in boys and girls. For instance, in a German study, multiple pain sites were associated with interpersonal conflict and internalizing

symptoms only among girls, whereas they correlated with externalizing symptoms among boys and with dysfunctional coping in both sexes (Kroner-Herwig et al., 2011). In Australian adolescents, musculoskeletal pain was associated with anxiety and depression among girls but with behavioural disorders in boys (Beales et al., 2012). Associations with depressive symptoms were also restricted to girls in a Finnish study (El-Metwally et al., 2005). Predominance of internalizing may explain the relevance of psychosocial attributions as predictors among girls in our study, whereas verbal expressions of high frequency and activity restrictions may be more closely related to externalizing among boys.

In general, the presence of two reports of previous pain (ages 7 and 10) was more strongly associated with future multisite pain than one report across different features. Repeated pain reports may reflect a single longstanding pain condition detected as early as age 7, which is captured again at ages 10 and 13. In this case, strong associations are expected given that they reflect the same underlying phenotype at different points in time. Alternatively, pain experiences in the first decade of life can be seen as sensitizing—at biological and psychosocial levels—for multisite pain in adolescence, in which case these associations suggest a cumulative effect of repeated episodes on the adolescent's outcome. Both explanations are consistent with empirical data from trajectory studies in paediatric ages (Coenen et al., 2017; Dunn et al., 2011; Isensee et al., 2018).

The timing of previous pain was more relevant in girls, among whom worse experiences at age 7 predicted adolescent multisite pain, even when absent at age 10. In a life-course framework, it is plausible that earlier pain experiences lead to worse outcomes, either because they happen during sensitive periods, when the effect of noxious experiences can be amplified, for example, prepubertal years, or because they imply longer exposure to sensitizing experiences. Earlier pain experiences may also reflect higher background susceptibility regardless of whether they remain stable through age 10. Some research supports that a younger age at chronic pain onset leads to worse clinical and psychosocial prognosis, as seen for childhood migraine (Hernandez-Latorre & Roig, 2000) and adult nonmalignant pain (Owiredua et al., 2020), but this was not apparent in other settings (Gauntlett-Gilbert & Eccleston, 2007). More robust evidence is available for the neonatal period when invasive medical procedures and related stress are well-documented to interfere with somatosensory and emotional components of pain response later in life (Walker, 2019). Moreover, these procedures evoke sex-specific changes to somatosensory function that may determine different pain sensitivity between sexes in the long term (Walker et al., 2018), which could provide a basis for our observation of a greater relevance of earlier pain in girls.

The predictors used in the present study were proxy-reported by parents. When considering only pain reported at the moment of evaluation at age 7 using a shorter questionnaire, parent reports had low sensitivity but high specificity, with 95% or more of children who reported they had pain being correctly identified as having pain by their parents (Gorito et al., 2021). This suggests that the strategy adopted in the present paper is more likely to under-than to overestimate child experiences. Conceptually, parental report is an interpretation of the child's experience, which in turn reflects the child's innate susceptibility to an adverse pain trajectory as well as his/her history of exposure to nociceptive stimuli, including organic disease, which are commonly shared between parents and children. In addition, the parents' own pain experiences affect the child's learned pain behaviour as well as parental appraisal of the child's suffering (Stone & Wilson, 2016). All of those mechanisms are likely involved in the intergenerational transmission of chronic pain, which is also clear in our data through the association between family history and adolescent multisite pain. This has also been documented in other population-based cohorts, such as the HUNT study, where parental chronic pain was associated with chronic multisite pain among adolescents aged 13–18 years (Hoftun et al., 2013).

Our study aimed to refine the prediction of the adolescent's future pain experience on the basis of previous parental reports, regardless of the specific constellation of mechanisms involved. Still, several methodological issues and limitations need discussion. Our population-based design provided a realistic spectrum of pain experiences but resulted in limited sample sizes in the highest severity profiles. Therefore, our predictive accuracy estimates for different profiles have acceptable precision within each sex but are likely underpowered for direct comparisons between sexes. Additionally, since participants were selected regardless of pain history, our findings may not directly translate to clinical subpopulations with specific pain severity profiles and active care-seeking behaviour. Moreover, we collected data from adolescents at a single moment in time and we do not have information on the reproducibility or long-term outcomes of multisite pain in the cohort. In addition, we did not capture pain experiences that occurred before age 7 or in-between follow-up waves, which might be relevant to refine pain trajectories. Also, we analysed pain experiences reported by parents without formally assessing sex/gender interactions in parental perceptions of pain and suffering. There are conflicting findings on whether mothers and fathers report girls' and boys' pain experiences differently (Earp et al., 2019; Moon et al., 2008; Rosenbloom et al., 2011). In this

cohort, we ran the same analysis using only mother reported profiles and the estimates remained similar (data not shown). Additionally, our results were obtained from a single cohort and we cannot be sure that they are applicable to external populations, even though the associations found are generally consistent with findings from different settings, as mentioned above. Finally, the present study includes only cohort participants who were retained through all three follow-up waves examined and whose parent-respondent lived with the child. Nevertheless, pain features at ages 7 and 10 were similar between adolescents who were evaluated or not at age 13, and our sensitivity analyses comparing participants included and excluded at ages 7 and 10 suggested little impact of attrition and missing data on the course of pain (Lucas et al., 2021). Our study provides prospective evidence from a large cohort of children of the same chronologic age who were recruited at birth, and regularly reassessed, independently of their health status, with regard to multiple pain features.

In this study, we found important sex heterogeneity in the nature of the most useful pain features in childhood to predict adolescents' multisite pain. Recurrent, multisite pain with psychosocial triggers was most useful to rule in multisite pain in adolescent girls, whereas recurrent medium- to high-frequency pain leading to restrictions was more specific in adolescent boys. Accumulation of adverse pain experiences seemed to be important in both sexes, whereas earlier pain reports were better predictors in adolescent girls. These findings provide important clues for the early stratification of children at higher risk of developing chronic pain.

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CONFLICTS OF INTEREST

The authors have no relevant financial relationships or other conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS

RL defined the study hypothesis and drafted the paper. MB, VG and MT revised the manuscript text and remaining materials. MT designed and conducted the statistical analysis, and supervised the conceptual model and the overall intellectual content of the manuscript. MB and VG contributed to the clinical and epidemiological interpretation of results. All authors discussed the results and commented on the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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5) DISCUSSION

5.1) Main findings and overall discussion

Through the serial assessment of our prospective pediatric birth cohort, we found in our 7-year evaluation that parental reports were highly specific in excluding overall pain, high-intensity pain, and multiple pain. Also, the accuracy of parent reports to predict pain complaints in their children was limited, especially concerning high-intensity pain and multiple pain. The low prevalence of complaints reported in this sample, according to children's reports, largely accounts for the low positive predictive values and high negative predictive values, above 90%. Although several studies have shown that, at age 7, children can interpret an appropriate pain scale (242-245), self-reports by children have often been underused (167-170). Recent research has compared children's and parents' perspectives on children's pain complaints. These studies reported an overall poor agreement between parent and child ratings and found that children reported pain more often (and of greater intensity) than their parents, corroborating our results (168, 179, 180, 181).

In the 10-year evaluation wave, approximately one-quarter of participants reported intense pain. A similar proportion reported chronic pain, and roughly one-quarter mentioned multisite pain. Most common pain triggers were sports activities, anxiety or new challenges, and food habits, which are consistent with the literature (104). We emphasize that perceived triggers must be framed within the biopsychosocial model of pain, as they are determining factors in the process of internalization and possibly even in the suffering and behavior associated with pain. Psychological factors, such as the situational and emotional elements present when we experience pain, can profoundly affect the strength of these perceptions (246).

In this sense, several studies have been conducted within the same cohort. Children who reported psychosocial triggers or contexts at age 7 were likely to have similar attributions at age 10, and those triggers/contexts were very frequent in cases of the highest severity of pain. Causal attributions can be particularly relevant for identifying early maladaptive pain. Attributional styles that feature psychological causes seem to influence clinical presentation as well as somatization and psychologization of distress in adults (247). Causal attributions in children also appear to play an important role in the entire pain

experience (248-250), and their relevance for prognosis is illustrated by a lower likelihood of recurrence in children with traumatic pain etiology compared to those with non-traumatic pain (251). A brief classification of the number of pain sites and causal attributions, which are not typically collected outside specialized pediatric pain clinics, may be useful in broader contexts to distinguish particularly adverse experiences in the absence of organic disease (252).

In the 10-year evaluation, we also found some differences in pain complaints according to sex, with females presenting more frequent, intense, and painful complaints. Sex differences in pain experiences become apparent even at pediatric ages, with females generally showing a higher frequency of pain, being more likely to transition to chronic pain, and more frequently reporting multiple pain sites (166, 253). Multiple mechanisms underlying these sex differences are plausible, either alone or in combination, including biological factors—namely genetic, hormonal, and neurophysiological differences—and psychosocial factors—including coping strategies, catastrophizing, self-efficacy, gender roles, and sociocultural beliefs (254).

More than a quarter of our children experiencing pain at age 10 were affected in at least one daily activity, with a greater impact observed in children with longer-lasting, more frequent, more intense, or multisite pain. Previous studies have shown a variable impact of pain on daily activities, including school absenteeism and impaired physical activity reported by adolescents (20). Roth-Isigkeit and colleagues concluded that only the intensity of pain was predictive of the degree of restrictions in daily activities attributable to pain (104), while in our study we found that pain that was more frequent, longer-lasting, of higher intensity, multisite, or managed with medication increased the odds of the pain impacting children's daily activities. These differences can be attributed to variations in populations and age groups, as well as sociocultural differences and pain behaviors that have evolved over the last few decades. Our results are also consistent with the recent concept of HICP. Specifically, participants with HICP reported higher levels of physical and psychological repercussions and school absenteeism, which may negatively influence their physical, psychological, and social development (99).

Our findings differ from common conceptions suggesting a higher burden of pain on females in terms of its effects on children's lives and care-seeking profiles. Our results challenge stereotypical sex-based interpretations and highlight the need for further investigation in this area because pain is a subjective and personal experience that must be approached independently of sex. Suffering pain and one's behavior are individual

experiences, reinforcing the necessity for the development and application of validated impact scales/tools to better understand these possible differences. Moreover, independent of sex at birth, gender can affect how an individual contextualizes and copes with pain and may also influence susceptibility to developing chronic pain. Human neuroimaging has revealed sex and gender differences in the neural circuitry associated with pain (256).

Around 17% of Generation XXI children with pain sought health care services. A higher frequency, longer duration of pain, and the use of medication for pain were associated with the utilization of these services. As expected, the vast majority of pediatric pains are managed without resorting to health care, which may reflect a rational use but can simultaneously indicate an under-evaluation of complaints and a diagnostic delay that can be crucial in the sensitization process, contributing to amplified, chronic, and varied pain in both sexes.

Approximately three-quarters of children observed in a health care setting received a medical diagnosis for their pain, primarily related to musculoskeletal disorders (34.4%), gastroenterological conditions (13.5%), and psychological disorders (12%). Concerning these main diagnoses, we can speculate that they may be early manifestations of the same pathological spectrum and part of a FPS starting in childhood. The worldwide prevalence of all FPS is estimated at 15–20%. The exact diagnosis typically derives from the organ system displaying the predominant symptoms, such as musculoskeletal pain in GCPS and visceral or IBS. Evidence is growing that FPS represents the phenotypic output of a complex interplay between genetic susceptibility, gene-environment interactions, and environmental triggers, mostly precipitated by high psychological distress (52).

We particularly highlight the significant percentage of musculoskeletal conditions. More than one third of children were diagnosed with musculoskeletal conditions, which is consistent with studies from other countries. The economic burden of musculoskeletal pain in children and adolescents is a global concern (257). The notable prevalence of musculoskeletal complaints may be partly justified because childhood and adolescence are periods of growth and development of the musculoskeletal system, marked by changes in structural properties, biomechanics, and motor control before the system stabilizes in adulthood (258).

A prospective study on musculoskeletal symptoms with formal rheumatologic evaluation over a 3-year interval showed persistence of musculoskeletal pain during the teenage years; 54.3% of the subjects, mostly pre-pubertal, were still symptomatic after 3 years of

follow-up (259). Corroborating this, the Generation XXI adolescents at age 13 who had current musculoskeletal pain and a history of musculoskeletal pain at ages 7 and/or 10 showed decreased pressure pain tolerance. There were no differences in quantitative sensory test (QST) responses when pain was defined by duration reported at age 13. Thus, in this generally healthy population, there is some evidence of a sensitizing role of long-term musculoskeletal pain on sensory responses to pressure stimuli at age 13. However, participants with musculoskeletal pain assessed in more than one cohort showed some evidence of hyperalgesia. This may suggest that long-standing recurrent pain since childhood (at 7 and/or 10 years) has a measurable impact on adolescent pain sensitivity (260). In the same line of reasoning, the 10-year evaluation showed an association between the number of adverse childhood experiences and bodily pain, suggesting that the embodiment of adverse childhood experiences begins in childhood, contributing to chronicity and maladaptive pain (261).

Further exploring early childhood as a sensitive period for the future development of life-course pain, we found that children whose parents reported atopic dermatitis-like symptoms at 6 months and 15 months had a higher risk of reporting any pain and multisite pain, respectively, at 10 years of age. In addition to the increased risk of pain associated with atopic dermatitis in early life, food allergy-like symptoms and wheezing episodes at 15 months were also associated with future pain reported by parents, although those results were less robust. Atopic dermatitis can negatively affect sensorimotor and cognitive development, behavior, pain responses, pharmacological requirements, and the long-term health status of children (262). Multisite pain is one of the most recognized indicators of adverse pain experiences in pediatric ages (253), and associations with atopic-like symptoms were slightly more robust with multisite and intense pain than with chronic pain. Impaired skin barriers, neurogenic inflammation mediators, and peripheral and central sensitization of pain processing pathways may possibly explain nociplastic pain mechanisms in atopic dermatitis (263).

Skin pain is increasingly recognized as a significant symptom in atopic dermatitis due to its association with patient discomfort, disease burden, and reduced quality of life (264, 265). Although the nature of skin pain in atopic dermatitis has not been systematically studied and is therefore not well understood, patients report soreness, discomfort, and tenderness that may reflect peripheral and central pain sensitization (49, 263). It is believed that nociceptive pain events in the first years of life can partly trigger amplified pain syndromes (266). Pain and atopic dermatitis share common inflammatory pathways.

IL-1β has been implicated in painful and inflammatory processes, particularly in promoting hyperalgesia (50). Elevated inflammatory cytokines such as IL-1β, IL-6, and TNF-α in fibromyalgia suggest an inflammatory component in the induction of widespread pain (48). Additionally, serum levels of IL-8, TNF-α, and IL-6 may serve as important markers of disease severity and for monitoring children with atopic disorders (49). The lifelong interaction between pain and immunity highlights the importance of early interventions and managing pain and inflammation from infancy through adulthood to avoid possible long-term consequences of the sensitization process.

In our 13-year evaluation, 39% of girls and 27% of boys aged 13 self-reported multisite pain in the 3 months prior to the interview. Adolescent girls had a higher risk of multisite pain when adverse experiences were reported from age 7, namely multisite and recurrent pain, and an even higher risk if psychosocial triggers were also present. In contrast, for boys, the presence of recurrent pain of medium to high frequency which restricted activity, or multisite recurrent pain with passive coping at ages 7 and 10, was the most predictive of future multisite pain.

What's more, multiple mechanisms underlying sex differences are plausible, either alone or in combination, as previously discussed; however, the timing when those disparities become established is crucial. The timing of previous pain was more relevant in females, among whom worse experiences at age 7 predicted adolescent multisite pain, even when absent at age 10.

In a life-course framework, it is plausible that earlier pain experiences lead to worse outcomes, either because they occur during sensitive periods when the effects of harmful experiences can be amplified (for example, during prepubertal years), or because they imply longer exposure to sensitizing experiences. Earlier pain experiences may also reflect higher background susceptibility, regardless of whether they remain stable through age 10.

In general, the presence of two reports of previous pain (ages 7 and 10) was more strongly associated with future multisite pain than a single report across different features. At the age of 10, another study in our cohort also observed that recurrent pain increased with the age of participants and had specific locations, with each pain site being predictive of its own recurrence in both boys and girls.

Although the ability to predict pain in the same location was mainly observed at age 10, the study also identified two pain sites at age 7 that were predictive of the same pain

location at age 13 — specifically, recurrent musculoskeletal pain in boys and recurrent headaches in girls (166).

Repeated pain reports may reflect a single longstanding pain condition detected as early as age 7, which is subsequently captured again at ages 10 and 13. In this case, strong associations are expected, given that they reflect the same underlying phenotype at different points in time.

Alternatively, pain experiences in the first decade of life can be seen as sensitizing factors for multisite pain in adolescence, suggesting a cumulative effect of repeated episodes on the adolescent's outcomes. Both explanations are consistent with empirical data from trajectory studies in pediatric populations (267-269).

The timing of previous pain was more relevant in girls, among whom worse experiences at age 7 predicted adolescent multisite pain, even when absent at age 10. This reinforces the idea that earlier pain experiences lead to worse outcomes, either because they occur during sensitive periods when the effects of noxious experiences can be amplified (for example, during prepubertal years) or because they imply longer exposure to sensitizing experiences. Earlier pain experiences may also reflect higher background susceptibility, regardless of whether they remain stable through age 10 (166).

Some research supports the notion that chronic pain onset at a younger age leads to worse clinical and psychosocial prognosis (270, 271). Overall, there is a wealth of evidence that symptoms of depression, anxiety, and emotional distress strongly contribute (more strongly than pain intensity, in many studies) to key long-term outcomes of persistent pain, such as physical disability (272-274) and health care costs (275, 276).

All these pain experiences that occurred in these children during the first decade of life shaped their pain experiences and likely contributed to the results obtained during the first assessment in adolescence. Another study in the Generation XXI at age 13 concluded that adverse experiences in the first decade of life may contribute to a higher risk of developing pain conditions throughout life.

Moreover, social adversity is a key modifiable risk factor—it is a source of stress that affects children's well-being, bodily processes, and the production of health inequalities (277, 278). In the same population, the presence of bullying profiles at age 10 predicted pain at age 13. When compared to adolescents “not involved,” participants classified as “victim only” or “both victim and aggressor” at age 10 had a higher risk of pain related to: psychosocial triggers, pain that led to skipping leisure activities, multisite pain, pain

of higher intensity, and pain of longer duration. Bullying victimization was associated with reported pain and experimental pressure pain responses.

In addition, bullying in childhood may manifest as physical pain into adolescence and have a long-term influence on the risk of chronic musculoskeletal pain, interfering with responses to painful stimuli (279).

A Generation XXI study concluded that 13-year-olds who were dissatisfied with their body image had lower tolerance to pressure pain (QST test). This again reinforces the importance of integrating biological and psychosocial contexts, highlighting the significance of body image and pain in the interpretation of complaints during the first decades of life (280).

Understanding pain requires not only an understanding of the nociceptive system but also recognition and control of the many environmental and psychological factors that modify human pain perceptions and shape this experience, with long-term effects in children's lives.

5.2) Methodological considerations

In the present work, we analyzed data from a cohort of children followed prospectively since birth and evaluated at 7, 10, and 13 years of age. Knowing that only women giving birth in public maternity hospitals were invited to participate, selection bias at the time of recruitment is possible. Although it was estimated that, at the time of recruitment, births occurring in public hospitals corresponded to 91.6% of the total number of deliveries in the entire catchment population, an overrepresentation of women from lower socioeconomic backgrounds is likely. In the Porto region, following national practices, Level III public maternity units with differentiated pre-and perinatal support are the preferred referral centers for high-risk pregnancy cases, consequently leading to a higher risk of obstetric complications. Therefore, an overrepresentation of women with complicated pregnancies is also expected. Additionally, due to logistical limitations at each maternity unit, including the availability of human resources, we were only able to invite 70% of all eligible women to participate in the cohort, and we did not collect information on the characteristics of the remaining women (281). The mothers integrated into the cohort were slightly younger but similar in marital status compared to women from the catchment region who gave birth in 2005 and 2006 (282). The cohort's prevalence of cesarean sections was slightly higher than the prevalence estimated for

Portugal in 2004. Babies in the cohort had similar sex distributions to those born in Portugal over the same period regarding delivery features. However, a higher proportion of multiple fetuses was found among cohort participants compared to national estimates. Furthermore, the cohort also showed a higher proportion of preterm and low birth weight newborns, in comparison to deliveries in Portugal between 2005 and 2006.

These differences can be attributed to the highly contrasting perinatal support provided by all the Level III maternity units enrolled in this overrepresentation of complicated pregnancies context.

Despite this, it is challenging to speculate whether these differences may have biased our effect estimates. Since the selection of public maternity hospitals was not related to the objectives of this thesis, we expect that these selection criteria have not significantly biased our associations. Additionally, the perinatal and sociodemographic characteristics we analyzed were not associated with pain.

An additional selection strategy that needs to be discussed as a potential source of selection bias relates to the subset of participants included in our analyses. We used data from subsamples of children randomly selected at 6 and 15 months for partial evaluations. These participants corresponded to about 18% and 12% of the entire cohort, respectively. We compared the sociodemographic and clinical characteristics at the baseline of participants that met the inclusion criteria with those of all other participants in the Generation XXI. Non-eligible participants had similar sex distributions, maternal education levels, household income, type of delivery, and birth weight proportions.

However, non-eligible participants were more frequently premature (9.1%) and admitted to the NICU (8.9%). Thus, we believe these subsamples are representative of the characteristics of the cohort, and we expect minimal selection bias, considering the design and objectives of the study (paper III).

In cohort studies, the potential for participation bias should be considered, possibly due to non-participation at the baseline or attrition throughout follow-up. In the Generation XXI study, 91.4% of the invited mothers accepted participation. Mothers who refused to participate are likely to be systematically different from those who accepted. We did not collect information on eligible individuals who declined to participate, so we cannot estimate the extent of such differences. However, we believe the high participation rate at baseline may lessen the impact of this potential limitation (132).

Additionally, previous evidence regarding the effects of non-participation in a cohort study of pregnant women showed small effects on the relative risk estimates concerning perinatal outcomes (283).

With respect to losses to follow-up, our analyses utilized data collected at the 7-, 10-, and 13-year evaluations, during which 80%, 74%, and 54% of the entire cohort, respectively, participated in the in-person evaluations. Previous research on a longitudinal study of mothers of 18-month-old children has demonstrated that even when the characteristics of those who stay differ from those who drop out of a study, estimates of associations tend to remain robust against such differences and are only minimally affected by attrition rates (284).

Comparisons of baseline characteristics between Generation XXI participants with pain assessment questionnaires at the 7-, 10-, and 13-year evaluations (along with those with pain assessments at ages 7 and 10 but no assessment at age 13) revealed that the latter group was born to younger mothers, with lower educational attainment, and slightly higher parity, and were more likely to have had a low birth weight or to have been born prematurely. These findings were consistent with baseline comparisons between those with assessments of pain experience at ages 7 or 10, and those without such assessments (252). Considering the objectives of our study, we believe this potential participation bias has a minor effect on our results.

Specifically in paper IV, none of these baseline characteristics were associated with multisite pain at age 13 (our response variable). Except for maternal education, there were no clear associations between baseline characteristics and pain features at ages 7 or 10 (252).

In our sensitivity analysis, we found no relevant differences in the dose-response relationship between feature severity at ages 7 and 10 and multisite pain at age 13 when estimates were stratified by maternal educational level.

Finally, a comparison of pain features at ages 7 and 10 between children included in the final analytic sample and those excluded, reveals only a slightly higher prevalence of recurrent pain of medium to high frequency or intensity, or with activity restrictions, among those excluded compared to those included. This finding leaves our results regarding multisite pain at age 13 (our response variable) unchanged, and, with the exception of maternal education, there were no clear associations between baseline characteristics and pain features at ages 7 or 10 (252).

Moreover, specifically in paper III, we conducted our study by selecting subsamples of children with early-life atopic events from a population cohort, and our results may also be influenced by non-participation bias and/or attrition. However, the analysis between eligible and non-eligible participants showed similar sex distribution, maternal education, household income, type of delivery, and birth weight proportions. Only prematurity and admissions to the NICU were higher among non-eligible participants. Therefore, we believe that non-participation had a minor impact on our results.

Overall, although differential losses to follow-up are a major concern for the ability to generalize findings from birth cohorts, these studies remain the most valuable approach to assess relations between risk or protective factors and later health outcomes (285). Cohort studies are particularly useful for understanding the temporal sequence between exposure and outcome, estimating effects over a comparatively long term, and studying growth trajectories during infancy without being affected by cohort or period effects (286).

We believe that differential misclassification may be a key concern regarding our results, particularly in medical diagnoses and symptoms (paper II, III).

Paper II is partly based on reports of diagnoses without consulting medical records or clinical validation of these diagnoses. Parental insensitivity to identify children with pain may translate to limitations in recognizing signs that could be interpreted by clinicians as red flags associated with a high burden of pain.

Paper III is based on reports without doctors' information or clinical validation of the diagnosis of atopy and lacks clinical attribution for pain reports. For example, pain at age 10 could be directly related to a worsening of an atopic disease and not the result of cumulative sensitization.

Also, we measured atopic-like symptoms in the first 15 months of life, as reported by parents, rather than the prevalence of established or diagnosed atopic diseases, which would likely be lower if validated through clinical records.

It should also be noted that parents who report medical diagnoses or symptoms may be more likely to report pain experiences due to increased health consciousness or vulnerability to physical symptoms. This could create an association between certain conditions and pain due to surveillance bias.

However, some research has indicated that there is no relevant difference between data sourced from self-reports and from recorded information regarding certain issues, such as depression, anxiety, and sickness absence (287-289).

On the other hand, musculoskeletal problems are often accurately self-reported while being underrepresented in clinical records (287). This suggests that our population-based approach may have some degree of misclassification or surveillance bias concerning the presence of some—not all—conditions.

Furthermore, considering pain as a subjective experience and knowing that children can report their pain, we acknowledge a potential misclassification of pain complaints when parents answer on behalf of their children, particularly in paper II.

However, in papers I, III, and IV, we also included children's reports, and in paper IV, we relied solely on adolescents' reports. Therefore, we believe this misclassification had a minor impact on our results.

5.3) Implications for clinical practice and health policies

Pain, recognized as the fifth vital sign, should be routinely assessed in Health Care Units to allow for opportunistic screening of complaints, whether in hospital care, primary health settings, or school health measures in the community.

Through validated and easy-to-apply tools, tracking the presence of pain is the first step to consider, both in patients with chronic conditions (e.g. atopic dermatitis) and in the healthy population. Routine medical appointments should be utilized to screen for pain. It is essential to acknowledge and address the pain process before it becomes maladaptive—chronic, amplified, and multiple.

As previously discussed, methods for assessing pain are available and must be utilized, even in younger patients and those with intellectual, communication, or motor limitations. Pain must be made visible by conducting a valid and developmentally appropriate pain assessment for each child.

Pain assessment in children is an inferential process in which all available information about the child must be considered as a subjective and individual experience. In adolescents, we should prioritize pain impact tools and particularly emphasize perceived triggers and the psychosocial context. In Portugal, in line with clinical guidelines for pain management, we need to develop and validate tools that assess pain based on its impact, especially in older children and adolescents.

This study also reinforces the necessity for a multidisciplinary approach to pain assessment. The presence of chronic, multiple, and high-impact pain in the first decade of life should serve as a red flag for pain in adolescence. Furthermore, pain is often the

first indication of a dysfunctional life context that requires investigation and prompt treatment.

Creating informed protocols for pain prevention and treatment, encompassing pharmacological, psychological, and physical methods, would represent a potential advantage. These protocols should facilitate the rapid evaluation of relevant manifestations by health care professionals. We must not forget that pain is frequently a symptom of a serious illness, and alongside the potential for relief or treatment, accurate assessments performed by competent health care professionals can improve prognosis and prevent the progression of maladaptive pain.

Health care policies should promote equity in pain screening and access to health services to address pediatric suffering due to pain, along with education about pain for children, adolescents, parents, educators, and health care providers. Prevention and health promotion actions will always serve as the foundation of a multidimensional approach.

5.4) Future research

Many questions need further investigation to better understand the causes and consequences of persistent pain, improve prevention practices, and minimize long-term impacts. By elucidating the interplay between established and exploratory determinants of pediatric pain, researchers can advance our understanding of pain mechanisms and develop targeted interventions to improve pain management and outcomes in children with painful conditions. In the same vein, it is important to clarify sex and gender differences, particularly their impact on daily activities, long-term consequences, and pain expression. The new concept of HICP should be better defined in the next few years to facilitate the improvement of tools for measuring its repercussions in pediatric populations. Thus, QST may be helpful in providing some standardization to pain measurement and allowing for the comparison of experiences from pediatric age through to adulthood.

From a clinical perspective, therapeutic targets can be addressed promptly, and clinical phenotypes of functional disease will be better characterized. Considering FPS as a means to clarify the chronicity process, nociplastic pain, and the pathways that lead to amplified and widespread pain can be the first step toward targeting possible therapeutic approaches. Ongoing research into the developmental aspects of pain processing and modulation continues to provide insights into new therapeutic targets. Understanding the

mechanisms underlying pain plasticity and modulation may lead to the development of novel treatments that can more effectively manage pain in pediatric populations (290).

Studying the interactions between pain and immunity opens up possibilities for novel pain management strategies. Targeting immune pathways to modulate pain responses is an emerging area of research. Anti-inflammatory treatments, including nonsteroidal anti-inflammatory drugs, corticosteroids, and biologics that target specific cytokines, have demonstrated efficacy in managing pain by reducing inflammation (291-293).

Furthermore, interventions aimed at modulating glial cell activity and reducing neuroinflammation represent a promising area of investigation (294-296).

Specifically in atopic dermatitis, the current evidence and advances for the potential treatment of atopic dermatitis have been studied by targeting specific IL (e.g. IL1, IL33), common in both inflammatory pathways, in atopic dermatitis. Pharmacological treatment targeting these specific IL (e.g., canakinumab) may be a potential treatment for atopic dermatitis, especially those associated with pain (297).

Addressing individual differences in immune responses to pain can inform personalized approaches to pain management by considering genetic, developmental, and environmental factors that influence both pain and immune function. Advances in genetic research are paving the way for personalized pain management strategies that take individual genetic profiles into account.

In the near future, we aim to further pursue this line of investigation and clarify potential exploratory determinants of pediatric pain. By emphasizing the concept of HICP, we strive to identify children and adolescents at high risk of developing FPS in late adolescence and early adulthood, while considering potential differences related to sex and gender. Through the utilization of QST, we seek to compare experiences from childhood through adulthood. From a clinical perspective, we hope to compare QST responses among healthy children, those with nonspecific chronic pain, and a subset of children with a chronic rheumatological condition—specifically, JIA. Although there is currently limited evidence regarding QST differences in pediatric patients with JIA compared to healthy populations, we believe that children with JIA in this study may exhibit measurable abnormalities in sensory processing when compared to their healthy peers. These changes in sensory profiles could be indicative of a pattern of central sensitization, underscoring the need to enhance JIA management through a multidisciplinary treatment approach to minimize the sensitization process and improve the quality of life for individuals living with this chronic condition.

The Generation XXI study offers excellent opportunities to continue clarifying the roots and trajectories of pediatric pain, combining both epidemiological and clinical perspectives.

6) CONCLUSION

In our population-based study, we conclude that parents are useful in excluding major complaints but limited in identifying children's pain at 7 years of age. Recognizing pain as a subjective and emotional experience, where the child's report is the gold standard, we emphasize the importance of assessing the child's experience and collecting its specific attributes to avoid underestimating pediatric pain through a validated and appropriate instrument for each child's developmental stage.

At age 10, we concluded that pain has a significant impact on children's lives, but only a subset of children with pain is evaluated in health care services. Despite the higher prevalence of pain among girls, we highlight the similar impact on both sexes. As expected, the vast majority of pediatric pains are managed without resorting to health care. The main diagnoses of pain at 10 years of age (musculoskeletal, gastroenterological, and psychological) raise the possibility that they constitute the first manifestations of a spectrum of chronic FPS. Tracking their trajectories may be useful to estimate the risk of chronicity and amplification of pain, particularly musculoskeletal pain, which has a high burden worldwide.

Pain in the first decade could be shaped by early determinants. Atopic dermatitis symptoms in the first 15 months of life seem to be linked to an increased likelihood of experiencing pain at age 10, suggesting that exploring the potential for sensitization is a worthwhile area of investigation to avoid potential long-term consequences of the sensitization process.

Predicting multisite pain in adolescents by tracking previous pain features during the first decade of life can be a useful contribution to the risk stratification of chronic, multiple pain. Our findings, supported by the biopsychosocial model of pain, suggest that individual profiles including multisite pain and pain with psychosocial triggers are helpful in ruling out future multisite pain in girls. In contrast, for boys, the profile that included repeated reports of pain of medium to high frequency that led to restricted activity seemed more relevant in predicting future multisite pain. Early recognition of disability and a multidisciplinary approach may improve prognosis, reduce overall costs, and possibly minimize the long-term consequences of the maladaptive pain process.

6.1) Reflections on pediatric pain management: bridging research and clinical practice

As a final reflection, this research has broadened my perspective as a Pediatrician. In clinical practice, we are often limited to addressing serious and chronic pathologies within a hospital setting, especially given the scarcity of Pediatricians in Primary Health Care in Portugal. The Generation XXI project has allowed us to expand our knowledge and strengthen the "Outpatient/Community Pediatrician" initiative, which aims to screen and promote health in apparently healthy children. This step is always essential, but in this specific context, it proves particularly useful for preventing chronic pain complaints that may later be observed in a hospital environment. These complaints often already form part of prevalent syndromes seen in general pediatric and pediatric rheumatology consultations, for example.

This study reinforces the necessity and the capacity that Pediatricians must possess to assess the child holistically. It is fundamental to look beyond their immediate complaints and consider their psychosocial environment, especially when the symptoms do not fit into an identifiable organic disease. Clinicians must increasingly be able to treat not only diagnoses and diseases, but also symptoms and complaints, in order to improve the quality of life and prognosis for our patients.

Moreover, from a pediatric perspective, a correct, multidisciplinary, and early assessment can have a significant impact on the child's entire life. Besides taking a thorough medical history with valuable input from parents and conducting a comprehensive physical examination, I emphasize the importance of always listening to the child's complaints — both in understanding their pain and in characterizing their psychosocial context.

Through this study of healthier children than those I am accustomed to seeing in my clinical practice, I conclude that primary care offers a golden opportunity—through educational promotion activities, community screenings, and Public Health policies—to address early intervention and modify many risk factors for chronic pain. Doing so before these issues develop into maladaptive pain processes in a hospital setting can positively impact both the lives of children and their future health care. It is also crucial for diagnosing and prognosing patients with pathologies, particularly rheumatic conditions. Early identification of children with organic diseases can significantly improve their treatment response and their prognosis.

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8) SUPPLEMENTARY MATERIAL

A – Portuguese Clinical Guidance for Pediatric Pain Approach

ORIENTAÇÃO
DA DIRECÇÃO-GERAL DA SAÚDE

Francisco Henrique Moura George

Direcção-Geral da Saúde
www.dgs.pt
Ministério da Saúde

NÚMERO: 014/2010
DATA: 14/12/2010

ASSUNTO:	Orientações técnicas sobre a avaliação da dor nas crianças
PALAVRAS-CHAVE:	Dor na criança; avaliação; escalas de avaliação
PARA:	Todos os profissionais de saúde que tratam crianças.
CONTACTOS:	Direcção de Serviços de Prevenção e Controlo da Doença; Coordenador da Comissão Nacional de Controlo da Dor: helenam@dgs.pt; jmromao2@gmail.com

Nos termos da alínea c) do n.º 2 do artigo 2.º do Decreto Regulamentar n.º 66/2007, de 29 de Maio, na redacção dada pelo Decreto Regulamentar n.º 21/2008, de 2 de Dezembro, esta Direcção-Geral recomenda o cumprimento das orientações técnicas abaixo descritas referentes à avaliação da dor nas crianças dos 0 aos 18 anos.

I – AVALIAÇÃO DA DOR NAS CRIANÇAS

As crianças diferem na forma como respondem a eventos dolorosos. Aos factores de variabilidade individual somam-se os factores relacionados com o contexto da dor, pelo que a avaliação deve ser sempre multifacetada.

1. Orientações gerais:

Considera-se como norma de boa prática na avaliação da dor:

a) Acreditar sempre na criança que refere dor;
b) Privilegiar a auto-avaliação a partir dos 3 anos, sempre que possível;
c) Dar tempo à criança para expressar a sua dor;
d) Ter sempre presente o comportamento habitual da criança ou de uma criança sem dor da mesma idade;
e) Dialogar com a criança (a partir dos 3 anos) / pais / cuidador principal, observar a criança e utilizar um instrumento de avaliação da dor;
f) Realizar a história de dor na admissão da criança ao hospital e na primeira consulta;
g) Manter o mesmo instrumento em todas as avaliações da mesma criança, excepto se a situação clínica justificar a mudança;
h) Utilizar de forma rigorosa as instruções metodológicas específicas de cada instrumento;
i) Em situação de dor intensa dar prioridade ao tratamento em detrimento da sua avaliação.

2. Orientações específicas:

2.1. História da dor:

Consiste na colheita de informação que permita orientar a avaliação e o controlo da dor utilizando todas as fontes de informação documentais disponíveis, aliada à observação e entrevista dos pais /cuidador principal e da criança a partir dos 3 anos. Esta colheita deve ser realizada logo que possível considerando os seguintes parâmetros:

a) Características da dor (localização, intensidade, qualidade, duração, frequência e sintomas associados);
b) Factores de alívio e de agravamento;
c) Uso e efeito de medidas farmacológicas e não farmacológicas;
d) Formas de comunicar /expressar a dor;
e) Experiências anteriores traumatizantes e medos;
f) Habilidades e estratégias para enfrentar a dor e outros problemas de saúde;
g) Comportamento da criança e ambiente familiar;
h) Efeitos da dor na vida diária;
i) Impacto emocional e socioeconómico.

2.2. Avaliação da intensidade da dor:

Consiste em quantificar a sensação dolorosa através de instrumentos válidos, seguros e clinicamente sensíveis, tendo em atenção o tipo de dor, situação clínica e idade da criança. Apesar de existirem instrumentos para as várias idades pediátricas e situações clínicas, não existe uma solução universalmente aceite.

Esta avaliação deve ser feita de forma regular e sistemática a todas as crianças, desde o primeiro contacto: no caso da criança internada, a avaliação deve ser feita, pelo menos, uma vez em cada turno de trabalho (8 horas).

O registo deve ser complementado no processo clínico com informação qualitativa de outros aspectos considerados úteis para interpretar a dor na criança, uma vez que a maioria destas escalas avalia a intensidade da dor.

De acordo com a idade, e por ordem de prioridade, recomenda-se a utilização dos seguintes instrumentos[1]:

Recém-nascidos

a) EDIN (Échelle de Douleur et d'Inconfort du Nouveau-Né). De referência para Unidades de Cuidados Intensivos Neonatais;
b) NIPS (Neonatal Infant Pain Scale). Mais apropriada para prematuros e recém-nascidos de termo;
c) PIPP (Premature Infant Pain Profile). Útil para a avaliação da dor em procedimentos;
d) N-PASS (Neonatal Pain, Agitation & Sedation Scale). Útil para recém-nascidos em ventilação assistida.

Menores de 4 anos ou crianças sem capacidade para verbalizar

FLACC (Face, Legs, Activity, Cry, Consolability).

Entre 4 e 6 anos

a) FPS-R (Faces Pain Scale – Revised). Válida a partir dos 4 anos;
b) Escala de faces de Wong-Baker. Válida a partir dos 3 anos.

[1] Escalas de avaliação da dor em anexo

A partir de 6 anos

a) EVA (Escala Visual Analógica);
b) EN (Escala Numérica);
c) FPS-R (Faces Pain Scale – Revised);
d) Escala de faces de Wong-Baker.

Criança com multideficiência

FLACC-R (Face, Legs, Activity, Cry, Consolability – Revised)

Outros instrumentos de avaliação podem ser utilizados para situações muito particulares, desde que válidos, fiáveis, sensíveis, específicos e com utilidade clínica.
Todos os serviços prestadores de cuidados de saúde devem elaborar, para cada instrumento de avaliação que utilizam, um algoritmo de tratamento em função da intensidade da dor. Considera-se como critério de boa qualidade de cuidados no controlo da dor que a intensidade da dor se mantenha inferior a 3/10 (dor ligeira).

II – FUNDAMENTAÇÃO

A preocupação com a dor das crianças resulta do reconhecimento que as crianças têm dor, guardam memória da dor e que a dor não tratada tem consequências a longo prazo. A avaliação da dor nas crianças reveste-se de particularidades que obrigam a considerá-la separadamente de outros grupos etários.

A investigação na área da Neurobiologia demonstra que as vias nervosas ascendentes necessárias à experiência de dor estão presentes na vida fetal a partir das 20 semanas de gestação e totalmente desenvolvidas por volta das 28 semanas de gestação. Em contrapartida, as vias de controlo descendente são ainda imaturas, daí resultando, nos recém-nascidos pretermo, uma hipersensibilidade aos estímulos dolorosos.

As experiências precoces e repetidas de dor no período neonatal parecem exercer influência sobre as experiências posteriores de dor, quer no que respeita à sensibilidade dolorosa, quer no que respeita à forma de lidar com o stress.

Apesar de ser possível avaliar e tratar a dor das crianças, existe um hiato entre o conhecimento existente e o que é efectivamente posto em prática. Um estudo publicado em 2008, realizado no Hospital for Sick Children de Toronto, sobre a prevalência da dor nas crianças hospitalizadas, mostra que, nas 24 horas precedentes ao inquérito, apenas 27% das crianças tinham registo da avaliação da dor, apesar de 64% das crianças entrevistadas relatarem ter tido dor moderada ou intensa.

O Programa Nacional de Controlo da Dor (PNCDor), aprovado por Despacho da Ministra da Saúde de 8 de Maio de 2008, prevê, nas suas estratégias de intervenção, a criação e divulgação junto dos profissionais de saúde de orientações técnicas e a implementação de programas eficientes de

avaliação e tratamento, com o objectivo da melhoria efectiva da qualidade de vida dos doentes com dor.

A Circular Normativa nº 09/DGCG, de 14 de Junho de 2003, equipara a dor a 5º sinal vital e considera como norma de boa prática a avaliação e o registo regular da intensidade da dor em todos os serviços prestadores de cuidados de saúde.

Assim, a emanação da presente Orientação teve em consideração que:

1. A dor é uma experiência pessoal, multidimensional, desagradável, com grande variabilidade na sua percepção e expressão, sem indicadores específicos e que acompanha, de forma transversal, a generalidade das situações que requerem cuidados de saúde.
2. A avaliação da dor permite identificar e reconhecer a criança com dor, objectivar um fenómeno por natureza subjectivo, uniformizar a linguagem dentro da equipa de saúde facilitando a tomada de decisões homogéneas, adaptar de forma personalizada o seu controlo e avaliar a eficácia das intervenções e sua correcção em tempo útil.
3. A gestão adequada da dor nos serviços de saúde é, actualmente, considerada pelas entidades acreditadoras, a nível internacional, como padrão de qualidade, e passa pela necessidade de implementação de programas de melhoria contínua da avaliação da dor nas crianças.
4. O controlo da dor, cujo sucesso depende da sua avaliação e reavaliação sistemáticas, é um dever dos profissionais de saúde e um direito das crianças consignado, entre outros, na Carta da Criança Hospitalizada.

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ANEXO
ESCALAS DE AVALIAÇÃO DA DOR

ECHELLE DE DOULEUR ET D'INCONFORT DU NOUVEAU NÉ (EDIN)

IDENTIFICAÇÃO				DATA												
				HORA												
	0	**1**	**2**	**3**												
ROSTO	Rosto calmo	Caretas passageiras: sobrancelhas franzidas / lábios contraídos / queixo franzido / queixo trémulo.	Caretas frequentes, marcadas ou prolongadas	Crispação permanente ou face prostrada, petrificada ou face acinzentada												
CORPO	Corpo calmo	Agitação transitória, geralmente calmo	Agitação frequente, mas acalma-se	Agitação permanente: crispação das extremidades e rigidez dos membros ou motricidade muito pobre e limitada, com corpo imóvel												
SONO	Adormece facilmente, sono prolongado, calmo	Adormece dificilmente	Acorda espontânea e frequentemente, sono agitado	Não adormece												
INTERACÇÃO	Atento	Apreensão passageira no momento do contacto	Contacto difícil, grito à menor estimulação	Recusa o contacto, nenhuma relação possível. Grito ou gemido sem a menor estimulação												
RECONFORTO	Sem necessidade de reconforto	Acalma-se rapidamente com carícias, com a voz ou chupeta	Acalma-se dificilmente	Inconsolável. Sucção desesperada												
PONTUAÇÃO TOTAL																

Debillon T, Sgaggero B, Zupan V, Tres F, Magny JF, Bouguin MA. Séméiologie de la douleur chez le prématuré. Arch Pediatr 1994; 1:1085-92.
Batalha L, Santos LA, Guimarães H. Avaliação de dor e desconforto no recém-nascido. Acta Pediatr Port 2003; 34 (3): 159-13..

NIPS
(Neonatal Infant Pain Scale)

	DESCRIÇÃO
Expressão facial	
0 –Relaxada	Face serena, expressão neutra
1 - Careta	Músculos faciais tensos, sobrancelhas, queixo e maxilares enrugados (expressão facial negativa – nariz, boca e sobrancelha).
Choro	
0 – Ausente	Sereno, não chora.
1 – Choramingo	Choraminguo brando, intermitente.
2 – Choro vigoroso	Gritos altos, agudos, contínuos, que vão aumentando de intensidade. (NOTA: O Choro silencioso pode ser detectado se o RN estiver entubado e é evidenciado por um movimento óbvio facial e local.
Respiração	
0 - Relaxada	Padrão normal para o RN.
1 – Mudança na respiração	Inspiração irregular, mais rápida do que o normal, sufocante, que impede a respiração.
Braços	
0 – Relaxados/Controlados	Ausência de rigidez muscular, movimentos ocasionais e esporádicos dos braços
1 – Flexionados/Estendidos	Braços tensos, esticados e/ou extensão/flexão rígida e/ou rápida.
Pernas	
0 – Relaxadas/controladas	Ausência de rigidez muscular, movimentos ocasionais e esporádicos das pernas.
1 – Flexionadas/Estendidas	Pernas tensas, esticadas e/ou extensão/flexão rígida e/ou rápida.
Estado de vigília	
0 – Dorme/calmo	Calmo, tranquilo, a dormir ou acordado e estável.
1 - Agitado	Alerta, inquieto e agitado

Lawrence J, Alcock D, Mcgrath P, Kay J, Macmurray SB, Dulberg C. The development of a tool to assess neonatal pain. Neonatal Network 1993; 12: 59-66.
Batalha L, Santos LA, Guimarães H. Avaliação da dor no período neonatal. Acta Pediat Port 2005; 36(4): 201-7.

PREMATURE INFANT PAIN PROFILE (PIPP)

PROCESSO	INDICADORES	0	1	2	3
	Idade gestacional (semanas)	≥ 36	32 -35 e 6 dias	28 – 31 e 6 dias	< 28
Observar RN 15 segundos e anotar FC e saturação de oxigénio basal	**Estado de alerta**	Activo /acordado Olhos aberto Movimentos faciais	Quieto / acordado Olhos abertos Sem mímica facial	Activo /dorme Olhos fechados Movimentos faciais	Quieto / dorme Olhos fechados Sem mímica facial
Observar RN 30 segundos	**FC máxima**	↑0 – 4 bpm	↑5 – 14 bpm	↑ 15 – 24 bpm	↑ ≥ 25 bpm
	SO_2 mínimo	↓ 0 – 2,4 %	↓ 2,5 –4,9 %	↓5,0 – 7,4 %	↓ ≥ 7,5 %
	Testa franzida	Ausente (0 a 9% do tempo)	Mínimo (10-39% do tempo)	Moderado (49-69% do tempo)	Máximo (≥ 70% do tempo)
	Olhos espremidos	Ausente (0 a 9% do tempo)	Mínimo (10-39% do tempo)	Moderado (49-69% do tempo)	Máximo (≥ 70% do tempo)
	Sulco naso-labial	Ausente (0 a 9% do tempo)	Mínimo (10-39% do tempo)	Moderado (49-69% do tempo)	Máximo (≥ 70% do tempo)

Stevens B, Johnston CC, Petryshen P, Taddio A. Premature infant pain profile: development and initial validation. Clin J Pain 1996; 12: 13-22.
Batalha L, Santos LA, Guimarães H. Avaliação da dor no período neonatal. Acta Pediat Port 2005; 36(4): 201-7.

FACE, LEGS, ACTIVITY, CRY, CONSOLABILITY (FLACC)

IDENTIFICAÇÃO			DATA											
			HORA											
	0	1	2											
FACE	Nenhuma expressão particular ou sorriso.	Caretas ou sobrancelhas franzidas de vez em quando, introversão, desinteresse.	Tremor frequente do queixo, mandíbulas cerradas											
PERNAS	Posição normal ou relaxadas	Inquietas, agitadas, tensas	Aos pontapés ou esticadas											
ACTIVIDADE	Deitado calmamente, posição normal, mexe-se facilmente	Contorcendo-se, virando-se para trás e para a frente, tenso	Curvado, rígido ou com movimentos bruscos											
CHORO	Ausência de choro (acordado ou adormecido).	Gemidos ou choramingos; queixas ocasionais.	Choro persistente, gritos ou soluços; queixas frequentes.											
CONSOLABILIDADE	Satisfeito, relaxado	Tranquilizado por toques, abraços ou conversas ocasionais; pode ser distraído	Difícil de consolar ou confortar											
			Pontuação total											

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Merkel SI, Yopel-Lewis T, Shayevitz J, Malvi S. The FLACC: A behavioral scale for scoring postoperative pain in young children. Pediatr Nurs.1997; 23(3): 293-7.
Batalha LMC, Reis GMR, Costa LPS, Carvalho MDR, Miguens APM. Adaptação cultural e validação da reprodutibilidade da versão Portuguesa da escala de dor Face, Legs, Activity, Cry, Consolability (FLACC) em crianças. Referência 2009:10:7-14.

ESCALA DE FACES Revista



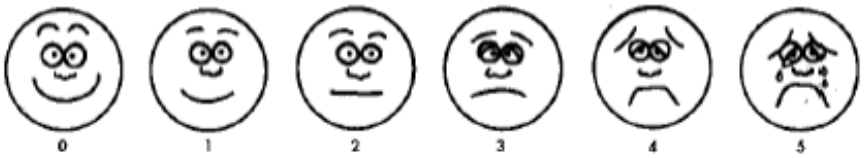
0 2 4 6 8 10

Nas instruções que se seguem, diga "magoar" ou "doer", de acordo com o que lhe parece correcto para determinada criança.

"Estas caras mostram o quanto algo pode magoar. Esta cara [aponte para a face mais à esquerda] não mostra dor. As caras mostram cada vez mais dor [aponte para cada uma das faces da esquerda para a direita] até chegar a esta [aponte para a face mais à direita] – que mostra muita dor. Aponta para a cara que mostra o quanto te dói [neste momento]."

Hicks et al., 2001; Bieri et al., 1990: http://painsourcebook.ca/pdfs/pps92.pdf

ESCALA DE FACES WONG-BAKER



0 1 2 3 4 5

Instruções:

Explique às crianças que cada face representa uma pessoa que está feliz porque não tem dor, ou triste por ter um pouco ou muita dor.

Face O está muito feliz porque não tem nenhuma dor.

Face 1 tem apenas um pouco de dor.

Face 2 tem um pouco mais de dor.

Face 3 tem ainda mais dor.

Face 4 tem muita dor.

Face 5 tem uma dor máxima, apesar de que nem sempre provocar o choro.

Peça à criança que escolha a face que melhor descreve como ela se sente.

FACE, LEGS, ACTIVITY, CRY, CONSOLABILITY Revised (FLACC-R)

Face 0 = Nenhuma expressão em especial ou sorriso 1 = Caretas ou sobrancelhas franzidas de vez em quando, introversão ou desinteresse; aparenta estar triste ou preocupada 2 = Caretas ou sobrancelhas franzidas frequentemente; tremor frequente/constante do queixo, maxilares cerrados; face parece ansiosa; expressão de medo ou pânico Comportamento individualizado:
Pernas 0 = Posição normal ou relaxadas; tonificação normal & movimentação dos membros inferiores e superiores 1 = Inquietas, agitadas, tensas; tremores ocasionais 2 = Pontapeando ou com as pernas esticadas; aumento significativo da espasticidade, tremores constantes ou movimentos bruscos Comportamento individualizado:
Actividade 0 = Quieta, na posição normal, move-se facilmente; respiração regular, rítmica 1 = Contorcendo-se, movendo-se para trás e para a frente, movimentos tensos ou cuidadosos; ligeiramente agitada (ex. cabeça para trás e para a frente, agressão); respiração pouco profunda, estabilizada; suspiros intermitentes. 2 = Curvada, rígida ou fazendo movimentos bruscos; agitação grave; bater com a cabeça; a tremer (sem arrepios); suster a respiração, arfar ou respirar fundo, grave contracção muscular Comportamento individualizado:
Choro 0 = Sem choro/ verbalização 1 = Gemido ou choramingo, queixa ocasional; explosão verbal ou "grunhidos" ocasionais 2 = Choro continuado, gritos ou soluços, queixas frequentes; explosões repetidas, "grunhidos" constantes Comportamento individualizado:
Consolabilidade 0 = Satisfeita e relaxada 1 = Tranquilizada por toques, abraços ou conversas ocasionais. Pode ser distraída. 2 = Difícil de consolar ou confortar afastando o prestador de cuidados, resistindo aos cuidados ou às medidas de conforto Comportamento individualizado:

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Malviya S,Yopel-lewis T, Burke C; Merkel S, Tait A. The revised FLACC observational pain tool: improved reliability and validity for pain assessment in children with cognitive impairment. Pediatric Anesthesia 2006;16(3):258-265.

B – Pain questionnaires applied in Generation XXI evaluation waves

- Children 7 years

ID

QUESTIONÁRIO DE SINTOMAS

CRIANÇA

Inquiridor

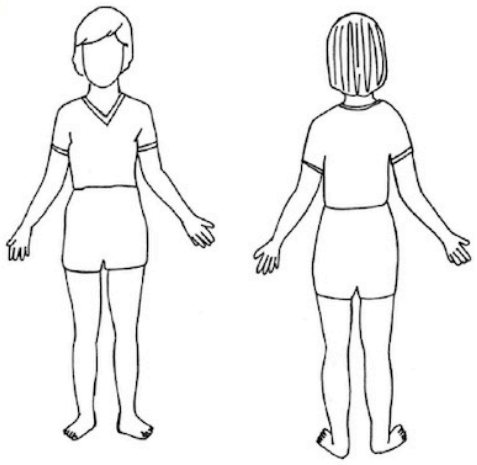
Data de realização – – (dd-mm-aaaa)

1. Neste momento, sentes dor em alguma região do teu corpo?

O Não (**FIM DO QUESTIONÁRIO**)

O Sim (passar à pergunta 2)

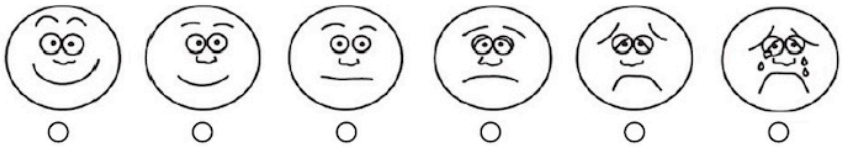
2. Se sim, indique com uma cruz (X) a(s) região(ões) onde a criança sente dor neste momento na figura que se segue.



O Cabeça	O Pescoço
O Maxilar esquerdo	O Maxilar direito
O Parte de cima das costas	O Fundo das costas
O Ombro esquerdo	O Ombro direito
O Antebraço esquerdo	O Antebraço direito
O Braço esquerdo	O Braço direito
O Peito	O Abdómen
O Anca esquerda	O Anca direita
O Coxa esquerda	O Coxa direita
O Perna esquerda	O Perna direita
O Pé esquerdo	O Pé direito
O Outra. Qual?	

3. Na sua opinião, qual das dores acima assinaladas incomoda mais a criança?

4. Na sua opinião, qual a intensidade dessa dor? (Selecionar a face que melhor descreve essa intensidade)



37712

- Parents 7 years

ID ☐☐☐☐☐☐☐☐ ☐☐

QUESTIONÁRIO DE SINTOMAS

PAIS

Inquiridor ☐☐

Data de realização ☐☐ - ☐☐ - ☐☐☐☐ (dd-mm-aaaa)

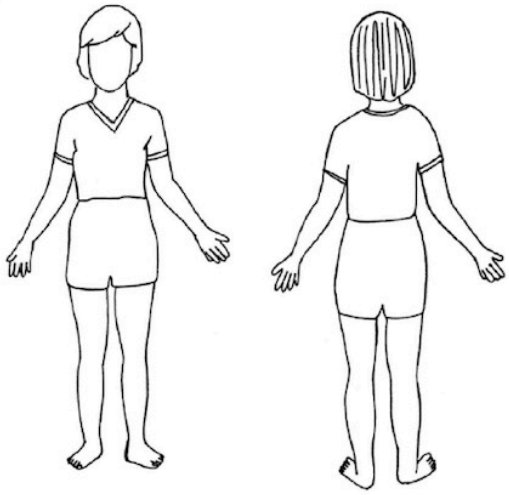
Respondido por: O Pai O Mãe O Outro. Quem? ☐

1. Neste momento, a criança sente dor em alguma região do corpo?

O Não (**FIM DO QUESTIONÁRIO**)

O Sim (passar à pergunta 2)

2. Se sim, indique com uma cruz (X) a(s) região(ões) onde a criança sente dor neste momento na figura que se segue.

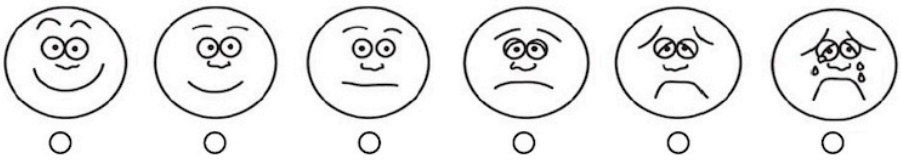


O Cabeça	O Pescoço
O Maxilar esquerdo	O Maxilar direito
O Parte de cima das costas	O Fundo das costas
O Ombro esquerdo	O Ombro direito
O Antebraço esquerdo	O Antebraço direito
O Braço esquerdo	O Braço direito
O Peito	O Abdómen
O Anca esquerda	O Anca direita
O Coxa esquerda	O Coxa direita
O Perna esquerda	O Perna direita
O Pé esquerdo	O Pé direito
O Outra. Qual? ☐	

3. Na sua opinião, qual das dores acima assinaladas incomoda mais a criança?

☐

4. Na sua opinião, qual a intensidade dessa dor? (Selecionar a face que melhor descreve essa intensidade)



O O O O O O

12365

DOR

68. O/A *[nome da criança]* queixou-se de dor nos últimos 3 meses?

O Não, não teve nenhuma dor *(Fim do Questionário, assinalar hora de fim p24)*

O Sim, teve dor *(Passar para a pergunta 69)*

O Não sabe *(Fim do questionário, assinalar hora de fim pág. 24)*

69. O/A *[nome da criança]* queixou-se de quais das seguintes dores nos últimos 3 meses?

	Não	Sim	Não sabe	
1. Dor de cabeça	O	O	O	
2. Dor de costas	O	O	O	
3. Dor de ouvidos	O	O	O	
4. Dor abdominal (barriga)	O	O	O	
5. Dor pélvica (fundo da barriga)	O	O	O	
6. Dor nos braços	O	O	O	
7. Dor nas pernas	O	O	O	
8. Dor torácica (peito)	O	O	O	
9. Dor de garganta	O	O	O	
10. Dor de dentes	O	O	O	
11. Outras dores	O	O	O	Quais?

70. Na sua opinião, qual destas foi a principal dor do/a *[nome da criança]* nos últimos 3 meses?

☐☐ (registar apenas uma opção)

71. A dor principal ocorreu mais de uma vez nos últimos 3 meses?

O Não *(Fim do questionário, assinalar hora de fim pág. 24)* O Sim

O Não sabe *(Fim do questionário, assinalar hora de fim pág. 24)*

72. *[Se sim]*, quando começou essa dor *[principal]*?

O <1mês O 1-3 meses O 4-6 meses O 7-12 meses O >12 meses O Não sabe

73. Nos últimos 3 meses, com que frequência é que o/a *[nome da criança]* sentiu essa dor *[principal]*?

O Menos de 1 vez por mês

O 1 vez por mês

O 2 a 3 vezes por mês

O 1 vez por semana

O Mais de uma vez por semana

O Todos os dias

O Não sabe

GERAÇÃO 21

74. De um modo geral, qual foi a intensidade dessa dor *[principal]* <u>nos últimos 3 meses</u>? *(a mãe/pai deve indicar a face que melhor descreve essa intensidade e na linha qual o ponto que a reflete)*

Cara ☐☐



☐☐☐

Dor quase impercetível (mínima) — Dor mais forte que pode imaginar (máxima)

75. Devido a esta dor *[principal]*:

	Nunca	Às vezes	Frequentemente	Sempre	Não sabe
75.1. O/A *[nome da criança]* tomou medicamentos	○	○	○	○	○
75.2. O/A *[nome da criança]* foi ao médico	○	○	○	○	○
75.3. O/A *[nome da criança]* faltou às aulas	○	○	○	○	○
75.4. O/A *[nome da criança]* não pôde encontrar-se com os amigos	○	○	○	○	○
75.5. O/A *[nome da criança]* teve falta de apetite/não conseguiu comer	○	○	○	○	○
75.6. O/A *[nome da criança]* teve problemas em dormir	○	○	○	○	○
75.7. O/A *[nome da criança]* não pôde fazer as atividades de tempos livres	○	○	○	○	○
75.8. Alguém teve de ficar em casa a tomar conta do/a *[nome da criança]*	○	○	○	○	○
75.9. O/A *[nome da criança]* precisou de se deitar/descansar	○	○	○	○	○
75.10. O/A *[nome da criança]* foi afetada de outro modo	○	○	○	○	○

Como? ☐

76. Na sua opinião, o que pensa ter provocado essa dor *[principal]*?

○ **Não** ○ **Sim** ○ **Não sabe** 76.1. Mudanças de tempo

○ **Não** ○ **Sim** ○ **Não sabe** 76.2. Dormir pouco

○ **Não** ○ **Sim** ○ **Não sabe** 76.3. Ruído

○ **Não** ○ **Sim** ○ **Não sabe** 76.4. Situações novas

○ **Não** ○ **Sim** ○ **Não sabe** 76.5. Irritação/conflitos/zanga

○ **Não** ○ **Sim** ○ **Não sabe** 76.6. Resfriado/Constipação

○ **Não** ○ **Sim** ○ **Não sabe** 76.7. Problema familiar

○ **Não** ○ **Sim** ○ **Não sabe** 76.8. Esforço físico/desporto

GERAÇÃO 21

O **Não** O **Sim** O **Não sabe** 76.9. Problema escolar

O **Não** O **Sim** O **Não sabe** 76.10. Ver televisão

O **Não** O **Sim** O **Não sabe** 76.11. Usar o computador

O **Não** O **Sim** O **Não sabe** 76.12. Agitação/Nervosismo

O **Não** O **Sim** O **Não sabe** 76.13. Solidão

O **Não** O **Sim** O **Não sabe** 76.14. Trabalhos escolares

O **Não** O **Sim** O **Não sabe** 76.15. Alimentação/consumo de doces

O **Não** O **Sim** O **Não sabe** 76.16. Tristeza

O **Não** O **Sim** O **Não sabe** 76.17. Nada definido

O **Não** O **Sim** O **Não sabe** 76.18. Outro. O quê? ☐

77. Em que situação surgiu essa dor principal pela primeira vez (*assinalar apenas 1 opção*)?
Pergunta aberta, deve ser imediatamente assinalado na opção correspondente ou em "Depois de outro evento/situação".

O Após lesão/acidente/ferimento
O Após uma intervenção cirúrgica/operação
O Após a morte de um familiar
O Após uma mudança de casa
O Durante uma doença
O Após uma atividade desportiva /esforço físico
O Após uma mudança de escola
O Após separação/divórcio dos pais
O Não sei
O Sem motivo aparente
O Depois de outro evento/situação
Qual? ☐

78. Existe uma razão conhecida e/ou diagnóstico médico para essa dor *[principal]*?

O Não sabe O Não O Sim. Qual? ☐

79. Alguém na família do/a *[nome da criança]* sofre de dor persistente ou que se repete frequentemente?

O Não sabe O Não O Sim. Quem? ☐

OBSERVAÇÕES

☐

Hora de fim ☐☐:☐☐

GERAÇÃO 21

- **Children 10 years**

ID

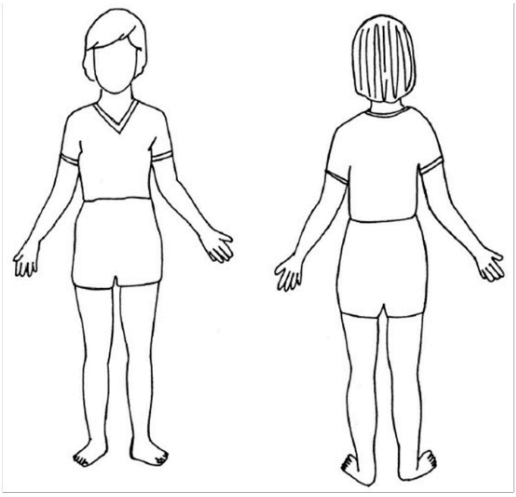
QUESTIONÁRIO DE SINTOMAS
CRIANÇA

Inquiridor ☐☐☐ **Data de realização** ☐☐ - ☐☐ - ☐☐☐☐ (dd-mm-aaaa)

1. Na última semana, sentiste dor em alguma região do teu corpo?

O Não (**FIM DO QUESTIONÁRIO**) O Sim (passar à pergunta 2) O Não sabe (**FIM DO QUESTIONÁRIO**)

2. [Se sim], indica na figura as regiões do teu corpo onde sentiste dor na última semana (registar na tabela as regiões reportadas com dor).

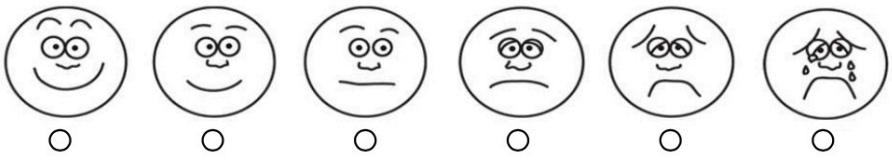


1. Cabeça	O Não	O Sim
2. Pescoço	O Não	O Sim
3. Costas (cima e meio)	O Não	O Sim
4. Costas (fundo, região lombar)	O Não	O Sim
5. Ombro esquerdo	O Não	O Sim
6. Ombro direito	O Não	O Sim
7. Membro superior esquerdo (antebraço, braço)	O Não	O Sim
8. Membro superior direito (antebraço, braço)	O Não	O Sim
9. Mão esquerda (punho, pulso, mãos, dedos das mãos)	O Não	O Sim
10. Mão direita (punho, pulso, mãos, dedos das mãos)	O Não	O Sim
11. Peito (peito, tórax, costelas)	O Não	O Sim
12. Abdómen (abdómen, barriga, zona pélvica)	O Não	O Sim
13. Anca esquerda	O Não	O Sim
14. Anca direita	O Não	O Sim
15. Membro inferior esquerdo (coxa, perna, joelho, canela)	O Não	O Sim
16. Membro inferior direito (coxa, perna, joelho, canela)	O Não	O Sim
17. Pé esquerdo (pé, calcanhar, tornozelo, dedos pés, unhas dedos pés)	O Não	O Sim
18. Pé direito (pé, calcanhar, tornozelo, dedos pés, unhas dedos pés)	O Não	O Sim
19. Dor em outra região (boca, dentes, cara, garganta, gengivas, língua, nariz, olhos, ouvidos, orelhas, orgãos genitais, queixo, virilha, bexiga, ânus,dor generalizada na pele)	O Não	O Sim

3. Qual das dores que referiste te incomodou mais na última semana (registar o número da região assinalada)**?**

☐☐ (de 1 a 19)

4. Qual a cara que melhor representa a intensidade com que sentiste essa dor?



O O O O O O

61790

- **Parents 10 years**

16.1. *[Se sim]*,

Local*	Nº Fraturas	Idade da fratura (anos)	Traumatismo**
|___|___|	|___|___|	|___|___| anos	|___|
|___|___|	|___|___|	|___|___| anos	|___|
|___|___|	|___|___|	|___|___| anos	|___|

***Codificação do local:**

1.Anca	6. Coluna dorsal	11. Joelho	16. Tornozelo	21. Esterno
2.Antebraço	7. Coluna lombar	12. Mão	17. Outra	22. Sacro
3.Bacia	8. Costelas	13. Pé	18. Coxa	23. Sacro
4.Braço	9. Dedo da mão	14. Perna	19. Clavícula	88. Não sabe
5.Coluna cervical	10. Dedo do pé	15. Punho	20. Crânio	

****Codificação Traumatismo**

1. Ligeiro - Cair ao chão de uma altura inferior a 0.5 metros; Cair numa superfície resiliente (borracha ou areia) de 0.5 a 3 metros; Cair da cama ou berço; Ao brincar incluindo brigas com os colegas.

2.Moderado - Lesões desportivas, como jogar à bola, judo, karaté, ginástica ou outro; Cair em superfície dura, como betão, de uma altura entre 0.5 a 3 metros; Cair de um beliche (cama de cima); Deixar cair o bebé/criança do colo de um adulto; Cair abaixo das escadas; Cair de uma bicicleta ou cavalo; Cair de um baloiço ou escorrega (ou outro similar); Ser atingido por uma bicicleta; Queda a andar de skate ou patins

3. Grave - Cair de uma altura superior a 3 metros; Acidentes de viação; Ser atingido por um objecto pesado

17. O/A *[nome da criança]* teve, alguma vez, diagnóstico médico de:

Não	Sim	Não sabe	Patologias
O	O	O	Asma
O	O	O	Epilepsia
O	O	O	Diabetes mellitus. Se sim, O Tipo I O Tipo II O Outro. Qual? _____
O	O	O	Hipertensão arterial
O	O	O	Doença cardíaca. Se sim, qual? _____
O	O	O	Doença renal. Se sim, qual? _____

DOR

18. *O/A [nome da criança]* queixou-se de dor <u>nos últimos 3 meses</u>?

O Não, não teve nenhuma dor *(p30)*

O Sim, teve dor *(p19)*

O Não sabe *(p30)*

19. *O/A [nome da criança]* queixou-se de quais das seguintes dores <u>nos últimos 3 meses</u>?

	Não	Sim	Não sabe
1. Dor de cabeça	O	O	O
2. Dor de costas	O	O	O
3. Dor de ouvidos	O	O	O
4. Dor abdominal (barriga)	O	O	O
5. Dor pélvica (fundo da barriga)	O	O	O

GERAÇÃO XXI

6. Dor nos braços	O	O	O
7.Dor nas pernas	O	O	O
8. Dor torácica (peito)	O	O	O
9. Dor de garganta	O	O	O
10. Dor de dentes	O	O	O
11. Outras dores. Quais?_____	O	O	O

20. Na sua opinião, qual destas foi a principal dor o/a *[nome da criança]* nos últimos 3 meses?

|__|__| (registar apenas uma opção)

21. A dor principal ocorreu mais de uma vez nos últimos 3 meses?

O Não *(p30)* O Sim O Não sabe *(p30)*

22. *[se sim,]* quando começou essa dor *[principal]*?

O <1mês O 1-3 meses O 4-6 meses O 7-12 meses O >12 meses O Não sabe

23. Nos últimos 3 meses, com que frequência é que o/a *[nome da criança]* sentiu essa dor *[principal]*?

O Menos de 1 vez por mês
O 1 vez por mês
O 2 a 3 vezes por mês
O 1 vez por semana
O Mais de uma vez por semana
O Todos os dias
O Não sabe

24. De um modo geral, qual foi a intensidade dessa dor *[principal]* nos últimos 3 meses? *(a mãe/pai deve indicar a face que melhor descreve essa intensidade e na linha qual o ponto que a reflete)*

Cara: |___|



|__|__|__|

Dor quase impercetível (mínima) — Dor mais forte que pode imaginar (máxima)

25. Devido a esta dor *[principal]*:

	Nunca	**Às vezes**	**Frequentemente**	**Sempre**	**Não sabe**
25.1. O/A *[nome da criança]* tomou medicamentos	O	O	O	O	O
25.2. O/A *[nome da criança]* foi ao médico	O	O	O	O	O
25.3. O/A *[nome da criança]* faltou às aulas	O	O	O	O	O

GERAÇÃO XXI

ID |__|__|__|

Não	Sim	Não sabe	
O	O	O	26.18. Outro. O quê?_____

27. Em que situação surgiu essa dor principal pela primeira vez *(assinalar apenas 1 opção)*?

Pergunta aberta, deve ser imediatamente assinalado na opção correspondente ou em "Depois de outro evento/situação".

- O Após lesão/acidente/ferimento
- O Após uma intervenção cirúrgica/operação
- O Após a morte de um familiar
- O Após uma mudança de casa
- O Durante uma doença
- O Após uma atividade desportiva /esforço físico
- O Após uma mudança de escola
- O Após separação/divórcio dos pais
- O Não sei
- O Sem motivo aparente
- O Depois de outro evento/situação. Qual? _____

28. Existe uma razão conhecida e/ou diagnóstico médico para essa dor *[principal]*?

O Não sabe O Não O Sim. Qual? _____

29. Alguém na família *do/a [nome da criança]* sofre de dor persistente ou que se repete frequentemente?

O Não sabe O Não O Sim. Quem? _____

As perguntas seguintes devem ser respondidas apenas pela mãe do/a [nome da criança], diretamente no computador.

As perguntas seguintes referem-se a eventuais situações de conflito e stresse que podem ter sido experienciadas por si durante a sua infância e/ou durante a vida adulta.

30. Durante a sua infância, algum adulto próximo de si, a agrediu fisicamente?

O Não O Sim O Não responde

31. Na sua vida adulta, alguém importante para si, alguma vez a agrediu fisicamente?

O Não O Sim O Não responde

32. Durante a gravidez deste seu filho, alguma vez foi fisicamente agredida?

O Não O Sim O Não responde

OBSERVAÇÕES

Hora de fim |___|___|: |___|___|

10

GERAÇÃO XXI

- **Adolescents 13 years**

- ○ Lojas de conveniência/estações de serviço
- ○ Papelarias/tabacarias
- ○ Bares, cafés e discotecas
- ○ A amigos com mais de 18 anos
- ○ A amigos com menos de 18 anos
- ○ Pais/ Responsáveis por ti
- ○ A irmãos com mais de 18 anos
- ○ A irmãos com menos de 18 anos
- ○ Outros familiares com mais de 18 anos
- ○ Outros familiares com menos de 18 anos

30. Dos teus familiares, assinala quem fuma ou fumou.

(assinala a resposta para cada alínea sem preencher os retângulos sombreados. Se a pessoa já faleceu responde o que fazia antes de falecer)

	Nunca fumou	Fumou, mas deixou de fumar	Fuma	Não sei	Não tenho
Pai	○	○	○	○	
Mãe	○	○	○	○	
Irmãos mais novos	○	○	○	○	○
Irmãos mais velhos	○	○	○	○	○
Avó (a mãe do pai ou da mãe)	○	○	○	○	
Avô (o pai do pai ou da mãe)	○	○	○	○	

31. Alguma das pessoas que vive na tua casa fuma (não te incluindo a ti)? ○ Não ○ Sim

31.1. Se sim, quantas pessoas? |___|___|

32. Algum dos teus amigos fuma? ○ Não ○ Sim

33. Se um dos teus amigos te oferecer um cigarro, tu fumas?

○ Com certeza que não ○ Provavelmente não ○ Talvez fume ○ Claro que fumo

DOR

34. Tiveste alguma dor <u>nos últimos 3 meses</u>?

○ Não tive dor nenhuma *(p44)*

○ Sim, tive dor

35. Quais das seguintes dores tiveste <u>nos últimos 3 meses (podes escolher mais de uma opção)</u>?

Dor de cabeça	○
Dor de costas	○
Dor de ouvidos	○
Dor de barriga (abdominal)	○

Geração 21

Dor no fundo da barriga (pélvica)	O
Dor nos braços	O
Dor nas pernas	O
Dor no peito (torácica)	O
Dor de garganta	O
Dor de dentes	O
Outras dores. Quais?_____	O

36. Qual foi a dor que te incomodou mais nos últimos 3 meses?

Dor de cabeça	O
Dor de costas	O
Dor de ouvidos	O
Dor de barriga (abdominal)	O
Dor no fundo da barriga (pélvica)	O
Dor nos braços	O
Dor nas pernas	O
Dor no peito (torácica)	O
Dor de garganta	O
Dor de dentes	O
Outras dores.	O

As seguintes questões são sobre a dor que te incomodou mais nos últimos 3 meses e que assinalaste acima.

37. Tiveste essa dor mais de uma vez nos últimos 3 meses?

O Não *(p44)* O Sim

38. *[Se sim,]* quando começou essa dor?

O Há menos de 3 meses O Há mais de 3 meses e menos de 1 ano O Há 1 ano ou mais

39. N<u>os últimos 3 meses</u>, com que frequência tiveste essa dor?

O Menos de 1 vez por mês
O 1 vez por mês
O 2 a 3 vezes por mês
O 1 vez por semana
O Mais de uma vez por semana
O Todos os dias

40. De um modo geral, numa escala de 0 a 100, qual foi a intensidade dessa dor nos últimos 3 meses? *Sendo 0=dor mínima (quase nenhuma) e 100=dor máxima (a mais forte que consegues imaginar)*

|__|__|__|

41. Na tua opinião, o que causou essa dor (podes escolher mais de uma opção)?

Doença. Qual? _____	O
Queda	O

Geração 21

Briga/luta ○
Mudança de tempo (calor, frio) ○
Dormir pouco ○
Barulho, ruído ○
Resfriado/Constipação ○
Esforço físico/desporto ○
Ver televisão ○
Usar o computador ○
Alimentação/consumo de doces ○
Situações novas ou desconhecidas ○
Irritação/conflitos/zanga ○
Problema familiar ○
Problema na escola ○
Agitação/Nervosismo ○
Solidão ○
Trabalhos da escola ○
Tristeza ○
Não sei dizer/Nada definido ○
Outro. O quê? _____ ○

42. Devido a essa dor, faltaste às aulas? ○ Não ○ Sim

43. Devido a essa dor, deixaste de fazer alguma das tuas atividades dos tempos livres? ○ Não ○ Sim

ACIDENTES

Muitas pessoas lesionam-se ou magoam-se no decorrer de diversas atividades (ex.: a praticar desporto, no dia-a-dia, em lutas com outras pessoas) e em diferentes locais (ex.: em casa, na rua ou na escola). As lesões podem ser queimaduras, cortes, fraturas ou afogamento. As lesões não incluem doenças como a varicela ou a gripe.
As seguintes questões são sobre lesões que possas ter sofrido nos últimos 12 meses.

44. Nos últimos 12 meses, magoaste-te/ lesionaste-te e tiveste de ser visto ou tratado por um médico ou enfermeiro?

○ Não ○ Sim

45.1. Quantas vezes te magoaste/ lesionaste e tiveste de ser visto ou tratado por um médico ou enfermeiro?

- ○ 1 vez
- ○ 2 vezes
- ○ 3 vezes
- ○ 4 vezes ou mais

44.1.1. Em alguma dessas situações em que te magoaste/ lesionaste tiveste de ser operado?

Geração 21