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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

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

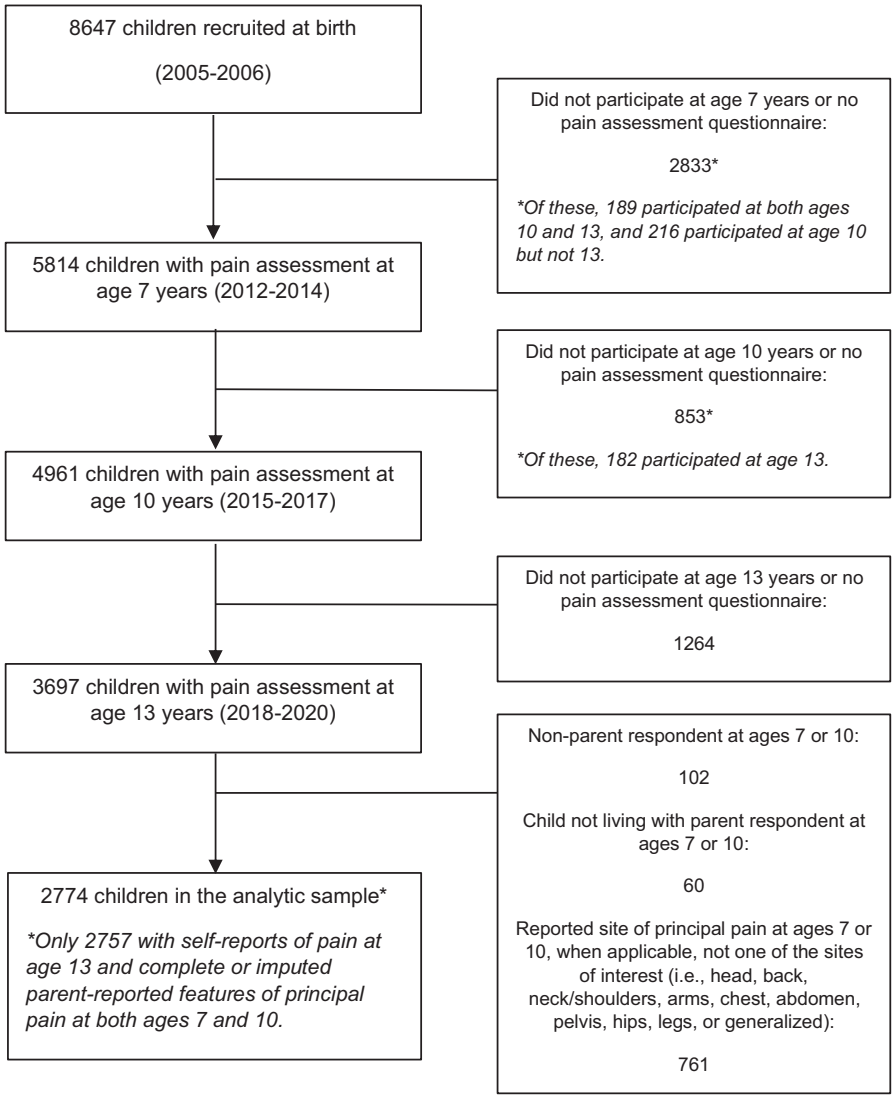

FIGURE 1 Selection of analytic sample for the Generation XXI cohort

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.

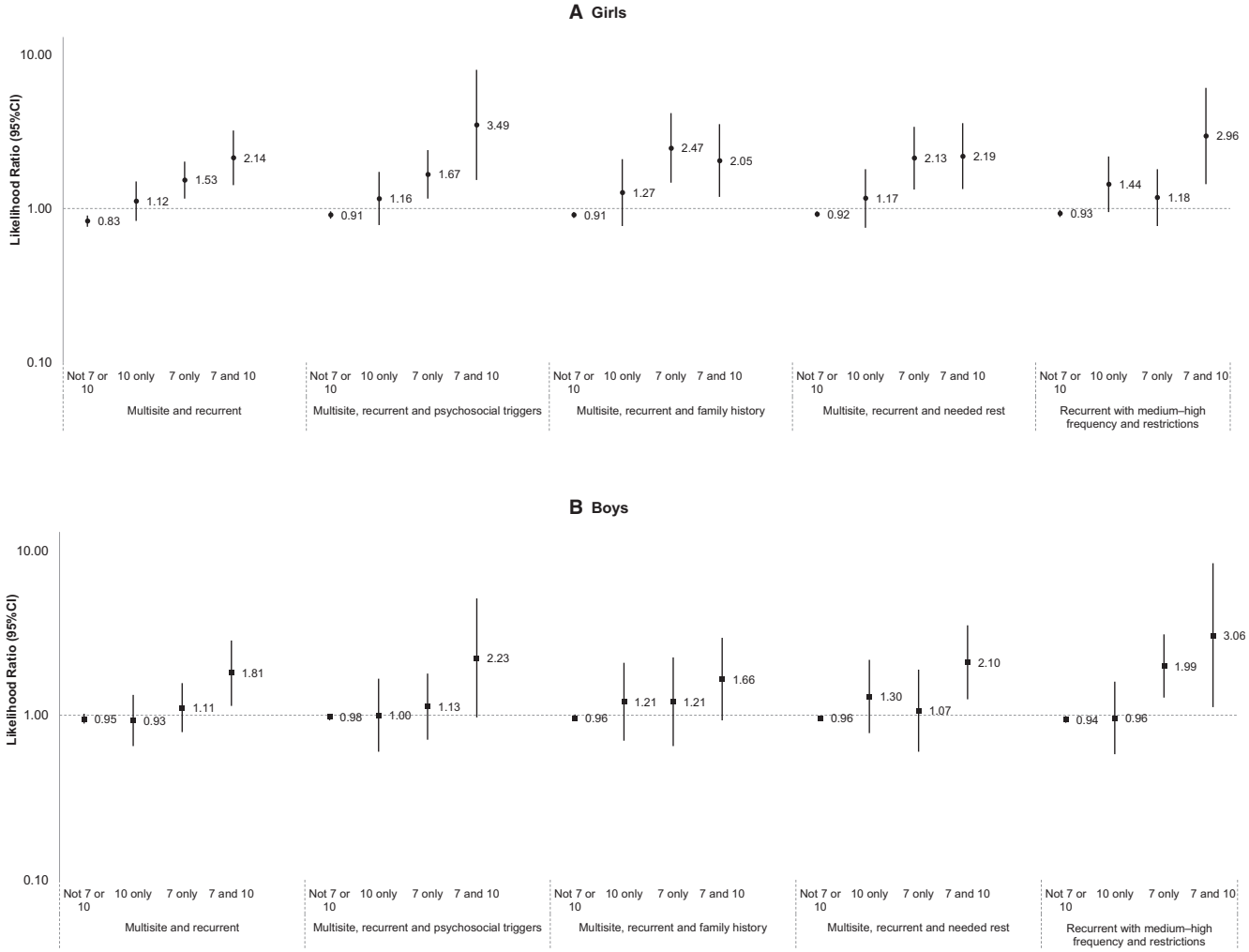

FIGURE 2 Likelihood ratios and 95% confidence intervals of different childhood pain profiles (parent-reported pain at ages 7 and 10) to predict self-reported multisite pain at age 13 in girls (panel a, circles) and boys (panel b, squares). Legend: Not 7 or 10: combination of features absent at both 7-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

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