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ORIGINAL ARTICLE

Primary dysmenorrhoea in adolescents and young women: A twin family study of maternal transmission, genetic influence and associations

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Aims: The extent to which maternal transmission of primary dysmenorrhoea is genetically determined in adolescents and young women has yet to be determined. We aimed to assess heritability and associations relevant to primary pain syndromes using a twin family study.

Methods: Participants were young menstruating female twins, and their oldest sisters and mothers, whose families were registered with Twins Research Australia and previously participated in a twin family study of primary paediatric pain disorders. Questionnaire packs were mailed, assessing current maximum and average menstrual pain intensity, current pain interference with activities and retrospective dysmenorrhea secondary symptoms.

Results: The sample comprised 206 twin individuals (57 monozygous (MZ) and 46 dizygous (DZ) pairs) aged 10–22 years, eldest siblings (n = 38) aged 13–28 years and mothers (n = 101) aged 32–61 years. The estimated regression coefficient of the relationship between mother–daughter and twin–sibling dyads indicated significant associations for the measures of dysmenorrhea and supported heritability. Adjusted for age, the within twin-pair correlation for MZ twins was generally more than twice that of DZ twins. Heritability estimates were maximal pain intensity 0.67 ($P = 3.8 \times 10^{-11}$), average pain intensity 0.63 ($P = 3.7 \times 10^{-10}$), pain interference 0.57 ($P = 1.8 \times 10^{-8}$) and retrospective symptoms 0.57 ($P = 1.8 \times 10^{-8}$). Twin individuals with a lifetime (three-month) history of iron deficiency and those with painless restless legs syndrome (RLS) were significantly more likely to have more intense pain associated with menstruation.

Conclusion: Primary dysmenorrhea in adolescents and young women was shown to be relatively strongly genetically influenced and associated especially with a history of iron deficiency and painless RLS which have potential therapeutic implications.

KEYWORDS

adolescents, associations, dysmenorrhoea, family, genetic

INTRODUCTION

Primary dysmenorrhea is defined as painful menstruation in the absence of pelvic pathology.[1] The International Association for the Study of Pain identifies dysmenorrhoea as an important recurring pain disorder with features of dysregulated somatosensory processing.[2] Paediatric primary dysmenorrhea shares characteristics with common recurrent and chronic pain disorders of childhood and adolescence without injury or definable disease.[3] Some characteristics include spontaneous onset; no clinically indicative biomarkers or pathology; disordered somatosensory processing in the central nervous system; multiple comorbidities or associations with additional disorders, including anxiety and depression; and multiple risk markers (with possible causal associations).[4]

Primary dysmenorrhoea typically presents within the first 6–12 months of menstruation, coinciding with the commencement of ovulatory cycles. In adolescents, primary dysmenorrhea can be as prevalent as 89%,[5] with about half of surveyed girls in that study reporting physical and social activity limitations, commonly including school absence.

Maternal transmission of paediatric pain has been extensively studied in recent years, with particular interest in psychosocial influences but relative neglect of genetic influences,[3,6] perhaps because the latter are not usually considered amenable to change. In primary dysmenorrhea in adolescents and young women, maternal, and to a lesser extent sister, associations have been reported in multiple studies in many countries but with limited further development of risk status.[7,8] The results of twin studies[9,10] and genetic/genomic studies[11,12] in women show definite evidence for genetic influence, barely mentioned in the studies of maternal transmission.[7,8,13] In the only twin study with adolescents,[8] in 1971, Kantero and Widholm limited the investigation to mother–daughter correlations and thus stated, 'The question as to whether the genetic constitution or whether an acquired behaviour plays the more important role in these correlations is still unclear'.

Our primary aim was to investigate the strength of genetic influence on dysmenorrhea in adolescents and young women (up to 22 years), applying twin family methodology.[14] Twin family studies are also a practical way to explore associations. In an earlier twin family study from the same database,[15] we showed extensive and often moderately strong associations between common primary paediatric pain disorders, persistent/chronic pain, restless legs syndrome (RLS), iron deficiency and anxious and/or depressed behaviours. These associations led to our current hypothesis that common aetiological mechanisms underpin primary pain disorders, including dysmenorrhea. Therefore, a secondary aim of this study was to seek evidence that primary dysmenorrhea has similar associations.

MATERIALS AND METHODS

Recruitment

Twin individuals registered with Twins Research Australia (TRA) who had completed other childhood pain disorders twin family case–control studies were recruited for the current study.[3,15] Female twin pairs were aged between 10 and 22 years. Mothers and non-twin eldest sisters of twin pairs were also invited to participate. Zygosity determination was described in Donnelly and colleagues.[15]

Participants

Of the 309 families meeting inclusion criteria and invited to participate, 114 (36.9%) families returned completed dysmenorrhoea questionnaires There were 345 individual respondents from the 114 families, consisting of 101 mothers, 206 twin individuals who had commenced menstruation (57 monozygous (MZ) pairs and 46 dizygous (DZ) pairs) and 38 non-twin eldest sisters who had commenced menstruation.

Procedure

Families meeting the inclusion criteria were mailed dysmenorrhoea questionnaire packs, as described by Donnelly and colleagues.[15] As part of this earlier study, these families previously completed measures pertaining to 10 chronic pain and other potentially associated conditions.[1,15,16] Separate questionnaires were included for each twin, mother and eldest female sibling, with separate versions of the survey for respondents aged below 18 years and for respondents aged 18 years and above. Younger respondents were assisted in their responses by their mothers as required.

Ethics

Ethics approval was granted by the Human Research Ethics Committee at the South-Eastern Sydney and Illawarra Area Health Service of New South Wales, Australia (approval number: 07/78).

Measures: dysmenorrhoea

Secondary dysmenorrhoea screening question

To screen for the presence of secondary dysmenorrhoea (an exclusion for primary dysmenorrhea), particularly endometriosis, all participants were asked whether their period had

always been painful (including pain before or at menarche) or whether onset of pain and associated symptoms began later in life; whether pelvic pain was experienced outside the menstrual periods (acyclic); and questions about medical attendance and treatment to control pain (ie, contraceptives or ibuprofen). While secondary dysmenorrhea is difficult to diagnose by questionnaire,[17,18] we expect that the profile of responses enabled the exclusion of some responders with secondary dysmenorrhoea, but we acknowledge the limitations of diagnosing secondary dysmenorrhoea, notably endometriosis, by questionnaire.[18]

Current menstrual period pain ratings

Participants were asked to rate their highest pain intensity during a current menstrual period. Daily ratings on a numeric rating scale from 0 (no pain) to 10 (worst pain you can think of) were completed for seven days accompanied by the binary question 'did menstrual period begin on this day?'

Retrospective Dysmenorrhoea Secondary Symptom Scale (RDSSS)

The Retrospective Symptom Scale[19] was modified (see Supportive Information) to assess the history of secondary symptoms associated with menstruation. Symptoms rated were period pain (including cramps), nausea, headache, backache, diarrhoea, sleeplessness, dizziness and irritability or nervousness. Individual symptom scores (ranging 0 = not noticeable to 4 = very severely bothersome = 4) were summed to produce a total symptom score indicating life prevalence (at least three months) severity of secondary menstrual symptoms. In the current study the derived questionnaire demonstrated good internal consistency (Cronbach's $\alpha = 0.81$).

Patient-Reported Outcomes Measurement Information System-Pain Interference (PROMIS-PI) Scale

The PROMIS-PI[20,21] was used to determine the level of interference dysmenorrhoea pain caused to daily activities. Depending on participant age, either the 'Pain Interference Scale – Short Form 8a' or the 'Paediatric Pain Interference Scale – Short Form 8a' version was completed.[22] Participants used a five-point-Likert scale (1 = not at all to 5 = very much) in response to the following: 'Please rate the extent to which the following statements were true for you over the past seven days of your menstrual cycle'. Responses to each item were summed to produce a total pain interference score, which was converted to a *t*-score using available norms.[23] The PROMIS-PI is validated in both paediatric and young-adult populations,[24,25] and reliability analyses indicated excellent internal consistency in this study (Cronbach's $\alpha = 0.95$).

Measures: primary pain disorder and associated conditions

The following pain disorders were assessed via questionnaires in earlier phases of this research: growing pains (GP), non-migraine headache, migraine, recurrent abdominal pain (RAP), persistent pain (including fibromyalgia) and RLS.[3,15,16] Respondents were classified as meeting criteria for iron deficiency if they endorsed both screening questions: 'have you ever had iron deficiency?' and 'did a doctor diagnose it?' The empirically derived anxious/depressed syndrome subscale of the Achenbach System was used to assess the presence of anxiety and depression within the previous six months.[15]

Statistical analyses

To assess whether data were matched for zygosity, we used regression analysis, linear regression for continuous data and logistic regression for binary data, with zygosity and age as covariates, where DZ twins were used as the reference category. For both regression methods the generalised estimating equations (GEEs) were used for estimation. Each mother–daughter transmission (association) was examined using simple linear regression, and the inverse variance-weighted average method[26] was used to combine all results to obtain the common estimated regression coefficient and its standard error. Heritability of each dysmenorrhea measure was computed using classic twin design.[27] Finally, regression analysis was used to assess the association between dysmenorrhoea measure (outcome) and pain disorder, iron deficiency and anxious depression (predictors), using GEE for twin data and least square for mother data. More detailed statistical methods are provided in the Results to Supporting Information.

All analyses, except classic twin design analysis, were performed using commercial software STATA, version 16.0 (http://www.stata.com).

Full details of statistical analyses are summarised in Supporting Information.

RESULTS

Sample descriptive statistics

Data for the dysmenorrhea measures were obtained from between 202 and 206 twin individuals (19 had not commenced menstruation), whereas data for pain disorders and iron deficiency were available for 226 twin individuals.

Twin individual ages ranged from 10 to 22 years (overall $M = 17.0$; SD (standard deviation) = 2.97; $M_{MZ} = 16.7$ years, SD = 3.15, $n = 129$; $M_{DZ} = 17.4$; SD = 2.70, $n = 97$; $P = 0.20$); siblings' ($n = 38$) from 13 to 28 years ($M = 20.7$; SD = 4.21); and mothers' ($n = 109$) from 32 to 61 years ($M = 49.0$; SD = 5.13).

TABLE 1 Summary statistics for responding twins for dysmenorrhoea and for pain disorders, iron deficiency and restless legs syndrome

	Total			MZ			DZ			
	N	Mean	SD	*N*	Mean	SD	*N*	Mean	SD	*P*
Dysmenorrhoea measures										
Pain intensity (≤10)[†,‡]	202	3.96	3.04	114	4.13	3.20	88	3.73	2.81	0.359
Average pain intensity (≤10)[†,‡]	203	2.79	2.24	115	2.90	2.36	88	2.65	2.09	0.428
Pain interference (≤78)[†,§]	203	43.5	23.4	113	43.3	24.3	90	43.8	22.4	0.940
RDSSS (≤32)[†]	206	6.75	6.15	114	7.02	6.26	92	6.41	6.04	0.464
Pain disorders, iron Deficiency and RLS[¶]	*N*	*n*	%	*N*	*n*	%	*N*	*n*	%	
Non-migraine headache	206	42	20.4	114	21	18.4	92	21	22.8	0.445
Migraine[†]	206	20	9.71	114	12	10.5	92	8	8.70	0.612
Recurrent abdominal pain	206	36	17.5	114	20	17.5	92	16	17.4	0.985
Persistent/chronic pain[†]	206	20	9.71	114	12	10.5	92	8	8.70	0.647
Iron deficiency[†]	206	15	7.28	114	9	7.89	92	6	6.25	0.711
GP specific	206	27	13.1	114	11	9.65	92	16	17.4	0.159
RLS painless	206	13	6.31	114	5	4.39	92	8	8.70	0.225
RLS painful	206	9	4.37	114	4	3.51	92	5	5.43	0.548
Anxious depression	173	15	8.67	101	9	8.91	72	6	8.33	0.872

Significance (*P*) compares the difference between MZ and DZ twins using generalised estimating equations.
DZ, dizygous; GP, growing pain; MZ, monozygous; RDSSS, Retrospective Dysmenorrhoea Secondary Symptom Scale.
[†] Adjusted for age; *N*, sample size; SD, standard deviation; *n*, number of cases for pain disorders, iron deficiency and restless legs syndrome (RLS); %, percentage of cases with that condition.
[‡] Denotes current menstrual period (during the study).
[§] PROMIS (Patient-Reported Outcomes Measurement Information System-Pain Interference) max scale score = 77 for adults/78 for adolescents.
[¶] All pain disorders, restless legs syndrome and history of iron deficiency frequencies and percentages are for lifetime prevalence.

Approximately 56% MZ twins completed the dysmenorrhoea questionnaires and 58% the questionnaires for pain disorders and associated conditions. As shown in Table 1, there were no differences between MZ and DZ twins for the dysmenorrhoea measures (pain and associated symptoms), pain disorders, anxious depression and iron deficiency (all $P > 0.15$).

Mother–daughter (twin–sibling) relationships for dysmenorrhea measures

The pooled estimate of relationships between daughters and mother is provided in Table 2, where all were significantly associated, except for average pain intensity ($P = 0.213$). The association between mother and daughter implies familial effects (Table S2).

Heritability estimates of dysmenorrhea

For genetic analyses of dysmenorrhoea measures, the maximum available data for MZ and DZ twins were 56 and 45 pairs, respectively. Adjusted for age, the within twin pair correlation for MZ twins was generally more than twice the correlation for DZ twins (Table 3), with heritability equal to, or higher than, 57%.

TABLE 2 Associations between mothers and daughters (twins and siblings combined) for dysmenorrhea measures

	Coefficient	SE	*P*	95% CI
Maximal pain intensity (≤10)	0.344	0.109	**0.002**	(0.13, 0.56)
Average pain intensity (≤10)	0.146	0.117	0.213	(−0.08, 0.38)
Pain interference (≤78)	0.264	0.082	**0.001**	(0.10, 0.42)
RDSSS (≤32)[†]	0.339	0.056	**<0.001**	(0.23, 0.45)

Significance (*P*) compares difference between mother and daughters (pooled).
[†] Retrospective Dysmenorrhea Secondary Symptom Scale (RDSSS). Coefficient: estimated regression coefficient. Sample sizes: twin 1 and mother pain intensity ($n = 48$) and RDSSS ($n = 89$); twin 2 and mother pain intensity ($n = 51$) and RDSSS ($n = 95$); eldest sibling and mother pain intensity ($n = 15$) and RDSSS ($n = 37$). CI, confidence interval; SE, standard error.

TABLE 3 Within twin pair correlation for MZ and DZ twins for dysmenorrhea measures and heritability estimate

	MZ			DZ			Heritability	
	N	ρ_{MZ}	95% CI	*N*	ρ_{DZ}	95% CI	$h^2 \pm SE$	*P*
Maximal pain intensity (≤10)†*	55	0.70	(0.53, 0.81)	42	0.22	(−0.09, 0.49)	0.67 ± 0.065	3.8×10^{-11}
Average pain intensity (≤10)†*	56	0.68	(0.50, 0.80)	42	0.17	(−0.14, 0.45)	0.63 ± 0.069	3.7×10^{-10}
Pain interference (≤78)*	55	0.63	(0.43, 0.76)	43	0.27	(−0.03, 0.53)	0.57 ± 0.075	1.8×10^{-8}
RDSSS (≤32)*	55	0.60	(0.40, 0.75)	45	0.21	(−0.09, 0.47)	0.57 ± 0.080	1.0×10^{-7}

PROMIS (Patient-Reported Outcomes Measurement Information System-Pain Interference) max scale score = 77 for adults, 78 for adolescents. Analyses were conducted adjusted for age*; *N* = number of twin pairs; ρ = within twin pair correlation; *P*-value (*P*) comparing correlations between MZ and DZ twins. CI, confidence interval; DZ, dizygous; MZ, monozygous; RDSSS: Retrospective Dysmenorrhea Secondary Symptom Scale; SE, standard error.
† Denotes current menstrual period (during the study).

Univariate and multivariate associations between dysmenorrhea and other disorders in twin individuals

In the univariate associations between each measure of menstrual pain and other pain disorders, anxious depression and iron deficiency for twin data, age was a significant confounder for all dysmenorrhoea measures (all $P < 0.01$), and thus in Table 4, the analyses adjusted for age are presented. The measures of current pain (pain intensity and average pain intensity) were positively associated with migraine, iron deficiency and painless RLS but negatively associated with non-migraine headache. However, in multivariable analysis, where age, pain disorders and iron deficiency with $P < 0.15$ were included in one model, current dysmenorrhea pain intensity was no longer associated with migraine ($P > 0.05$). Paediatric twin individuals with a lifetime (>three months) history of iron deficiency and painless RLS were more likely to have more intense pain associated with menstruation. Current pain interference and RDSSS were associated with painless RLS (all $P < 0.05$).

For mothers of twin associations, see Supporting Information.

DISCUSSION

Consistent with other publications,[8,13] and in line with our primary aim, this study demonstrated maternal transmission of primary dysmenorrhoea in adolescents and young women. This was the first twin family study to highlight substantial genetic influence on dysmenorrhea in adolescents and young women, this being demonstrated using two analytical methods applied to three current menstrual pain measures and a retrospective dysmenorrhea symptom scale. Of the three twin study publications in older women which have shown evidence of heritability of dysmenorrhea,[9,10,28] only the Silberg study[9] focussed on primary dysmenorrhea. Heritability estimates for primary dysmenorrhea in young females would be expected to be higher than dysmenorrhea in older adults who have diverse causal influences.

In applying the classical twin design to dysmenorrhea, we compared the phenotypic resemblance of MZ and DZ twins. Monozygotic twins scored similarly across all four measures,

TABLE 4 Univariate association between each dysmenorrhoea measure (outcome) and each pain disorder for twin data, restless legs syndrome and iron deficiency (predictors), adjusted for age

	Pain intensity (*N* = 202)	Average pain intensity (*N* = 203)	Pain interference (*N* = 203)	RDSSS (*N* = 206)
	$\beta \pm SE$	$\beta \pm SE$	$\beta \pm SE$	$\beta \pm SE$
Non-migraine headache	−1.19 ± 0.48*	−0.78 ± 0.36*	−4.20 ± 3.75	0.16 ± 0.99
Migraine	1.14 ± 0.52*	1.05 ± 0.46*	−1.93 ± 4.20	1.49 ± 1.60
Recurrent abdominal pain	0.34 ± 0.53	0.58 ± 0.41	2.72 ± 3.63	1.47 ± 1.22
Persistent/chronic pain	−0.09 ± 0.74	−0.08 ± 0.54	1.03 ± 4.52	−0.18 ± 1.17
Iron deficiency	1.60 ± 0.56**	1.26 ± 0.52*	−0.68 ± 5.10	1.43 ± 1.87
GP specific	0.06 ± 0.50	−0.23 ± 0.36	−1.79 ± 4.18	−1.02 ± 1.02
RLS painless	1.83 ± 0.71**	1.63 ± 0.65*	10.7 ± 4.59*	4.28 ± 1.81*
RLS painful	−0.66 ± 1.01	−0.09 ± 0.84	−2.52 ± 7.63	1.70 ± 2.52
Anxious depression	0.51 ± 0.58	0.69 ± 0.51	2.13 ± 3.53	1.15 ± 1.11

β, estimated regression coefficient; SE, standard error; *$P < 0.05$ and **$P < 0.01$. Sample size for anxious depression ranged from 170 for pain intensity to 173 for RDSSS. For pain intensity and average pain intensity, those predictors that were significant in the univariate association were considered in the multivariate analysis, and only migraine did not remain significant. GP, growing pain; RDSSS, Retrospective Dysmenorrhoea Secondary Symptom Scale; RLS, restless legs syndrome.

significantly more than DZ twins, consistent with significant genetic contribution to the variance in primary menstrual pain. The heritability of the phenotype (painful menstruation) was estimated from twice the difference between the MZ and DZ correlations and was found to be relatively high, of the order of 0.6 overall (Table 3), implying relatively modest contribution from shared and individual environmental influences. Environmental and lifestyle factors that are likely to occur in families may also include genetic factors, such as cigarette smoking.[29] Dysmenorrhea is associated with and probably shares genes with chronic pain.[30]

Dysmenorrhea is a complex multifactorial trait and would be expected to have multiple genetic and environmental causal influences, including multiple small gene effects. There is evidence for specific genes which may account for components or mechanisms of genetic risk on primary dysmenorrhea (see Supporting Information: Discussion for further details).

We hypothesised that primary dysmenorrhea, having several of the characteristics of a primary pain syndrome, would share associations with other paediatric primary pain conditions.[15] Consistent with this hypothesis, there were significant univariate associations between the two measures of current dysmenorrhea pain intensity and the following predictor variables: migraine, history of iron deficiency and painless RLS, but unexpectedly not with anxious depression. Painless RLS was also associated with current pain-related interference with activities and the RDSSS measure. In the multivariable analysis, the main associations retained were iron deficiency and painless RLS. More associations might have been retained if the sample size were larger.

Associations between dysmenorrhea and iron deficiency as well as RLS (the latter two conditions also being themselves associated) have not previously been reported. In previous studies using an identical sample,[15,16] it was demonstrated that iron deficiency may be a predictor for multiple pain disorders: migraine, non-migraine headaches, RAP and persistent and chronic pain. Furthermore, there is experimental evidence that induced iron deficiency in mice causally determined more intense pain.[31] There are potential therapeutic implications from associations between primary dysmenorrhoea and iron deficiency. Routine screening for iron deficiency is indicated, and supplementation not only is generally beneficial but might have a favourable effect on dysmenorrhoea. That remains to be tested. Screening for RLS could lead to pharmacotherapy to improve sleep, thereby reducing dysmenorrhoea intensity and impact.

Twin studies are valuable in achieving initial evidence for genetic influence; however, the current study has limitations which should be acknowledged. The cross-sectional design limited causal conclusions, and some recall bias was inevitable. Moreover, diagnoses were based on parent and self-report questionnaires, rather than face-to-face medical interviews, this being inevitable in an epidemiological survey. By questionnaire, we could not exclude an estimated low percentage of cases of secondary dysmenorrhoea. The prevalence of endometriosis has been estimated to be 6–10% in adults,[32–34] less in adolescents and young women. The true prevalence of endometriosis and the less frequent pelvic pathologies and their prevalence in dysmenorrhoea in young women are not known because definitive diagnosis usually requires pelvic examination and pelvic ultrasound imaging, sometimes magnetic resonance imaging, even laparoscopy,[17] and questionnaires applicable for community surveys have been inadequate.[4] Some endometriosis is asymptomatic. We expect that the profile of responses enabled the exclusion of some participants who had a high probability of secondary dysmenorrhea, particularly endometriosis.

Although there are limitations associated with the determination of iron deficiency history by self- and parent report, this method enabled lifetime prevalence assessment of iron deficiency, which could not practically be obtained by other methods.

The relatively small sample size, although clearly sufficient for the testing of heritability, limited the determination of those associations of interest which had large variability. Therefore, association analyses must be regarded with caution. The sample size determined that we could not control for potentially confounding variables such as socioeconomic factors, weight, activity and cigarette smoking.

In conclusion, primary dysmenorrhea in adolescents was confirmed as having characteristics typical of a primary pain disorder, including heritability and selected associations. There was a substantial contribution to maternal transmission from genetic influence. Guidance to mothers about their beliefs and the influence of their emotional factors on their daughters remains highly important, but remedial response is limited by the heritable factors. Screening for and treatment of associated iron deficiency and RLS might have therapeutic benefit.

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AUTHOR CONTRIBUTIONS

P.A. was involved in the interpretation of data, drafting the manuscript and supervision of students involved in the project at varying times throughout the study. M.B. was involved in the acquisition, analysis and interpretation of the data and also in drafting the manuscript. S.S., T.D., T.J. and J.E. were involved in the

interpretation of the data, drafting the manuscript and supervision of students over the course of the project. Y.C. was involved in the acquisition, preliminary analysis and interpretation of data as well as drafting the manuscript. G.D.C. was involved in the conception and design of the study as well as data acquisition and interpretation, was involved in drafting the manuscript and was the supervising senior academic for the study.

REFERENCES

1. Kho KA, Shields JK. Diagnosis and management of primary dysmenorrhea. *JAMA* 2020; **323**: 268–269.
2. Berkley KJ. Primary dysmenorrhea: an urgent mandate. *Pain* 2013; **1**: 8.
3. Champion D, Bui M, Bott A *et al*. Familial and genetic influences on the common pediatric primary pain disorders: a twin family study. *Children* 2021; **8**: 89.
4. Friedrichsdorf SJ, Giordano J, Desai Dakoji K *et al*. Chronic pain in children and adolescents: diagnosis and treatment of primary pain disorders in head, abdomen, muscles and joints. *Children* 2016; **3**: 42.
5. Söderman L, Edlund M, Marions L. Prevalence and impact of dysmenorrhea in Swedish adolescents. *Acta Obstet Gynecol Scand* 2019; **98**: 215–221.
6. Zadro JR, Nilsen TIL, Shirley D *et al*. Parental multisite chronic pain and the risk of adult offspring developing additional chronic pain sites: Family-linkage data from the Norwegian HUNT study. *J Pain* 2020; **21**: 968–978.
7. Fernández-Martínez E, Onieva-Zafra MD, Parra-Fernández ML. Lifestyle and prevalence of dysmenorrhea among Spanish female university students. *PLoS One* 2018; **13**: e0201894.
8. Kantero R-L, Widholm O. Correlations of menstrual traits between adolescent girls and their mothers. *Obstet Gynecol Surv* 1972; **27**: 631.
9. Silberg J, Martin N, Heath A. Genetic and environmental factors in primary dysmenorrhea and its relationship to anxiety, depression, and neuroticism. *Behav Genet* 1987; **17**: 363–383.
10. Treloar SA, Martin NG, Heath AC. Longitudinal genetic analysis of menstrual flow, pain, and limitation in a sample of Australian twins. *Behav Genet* 1998; **28**: 107–116.
11. Jones AV, Hockley JR, Hyde C *et al*. Genome-wide association analysis of pain severity in dysmenorrhea identifies association at chromosome 1p13. 2, near the nerve growth factor locus. *Pain* 2016; **157**: 2571.
12. Wei S-Y, Chao H-T, Tu C-H *et al*. The BDNF Val66Met polymorphism is associated with the functional connectivity dynamics of pain modulatory systems in primary dysmenorrhea. *Sci Rep* 2016; **6**: 1–11.
13. Azagew AW, Kassie DG, Walle TA. Prevalence of primary dysmenorrhea, its intensity, impact and associated factors among female students' at Gondar town preparatory school, Northwest Ethiopia. *BMC Women's Health* 2020; **20**: 1–7.
14. Hopper JL, Bishop DT, Easton DF. Population-based family studies in genetic epidemiology. *Lancet* 2005; **366**: 1397–1406.
15. Donnelly TJ, Bott A, Bui M *et al*. Common pediatric pain disorders and their clinical associations. *Clin J Pain* 2017; **33**: 1131–1140.
16. Champion D, Bui M, Aouad P *et al*. Contrasting painless and painful phenotypes of pediatric restless legs syndrome: a twin family study. *Sleep Med* 2020; **75**: 361–367.
17. Hewitt GD, Gerancher KR. ACOG committee opinion number 760: Dysmenorrhea and endometriosis in the adolescent. *Obstet Gynecol* 2018; **132**: E249–E258.
18. Surrey E, Carter CM, Soliman AM *et al*. Patient-completed or symptom-based screening tools for endometriosis: a scoping review. *Arch Gynecol Obstet* 2017; **296**: 153–165.
19. Cox DJ, Meyer RG. Behavioral treatment parameters with primary dysmenorrhea. *J Behav Med* 1978; **1**: 297–310.
20. Amtmann D, Cook KF, Jensen MP *et al*. Development of a PROMIS item bank to measure pain interference. *Pain* 2010; **150**: 173–182.
21. Varni JW, Stucky BD, Thissen D *et al*. PROMIS pediatric pain interference scale: an item response theory analysis of the pediatric pain item bank. *J Pain* 2010; **11**: 1109–1119.
22. Cook KF, Bamer AM, Amtmann D *et al*. Six patient-reported outcome measurement information system short form measures have negligible age-or diagnosis-related differential item functioning in individuals with disabilities. *Arch Phys Med Rehabil* 2012; **93**: 1289–1291.
23. Rothrock NE, Amtmann D, Cook KF. Development and validation of an interpretive guide for PROMIS scores. *J Patient Rep Outcomes* 2020; **4**: 1–7.
24. Askew RL, Cook KF, Revicki DA *et al*. Evidence from diverse clinical populations supported clinical validity of PROMIS pain interference and pain behavior. *J Clin Epidemiol* 2016; **73**: 103–111.
25. Howell CR, Gross HE, Reeve BB *et al*. Known-groups validity of the patient-reported outcomes measurement information system (PROMIS®) in adolescents and young adults with special healthcare needs. *Qual Life Res* 2016; **25**: 1815–1823.
26. Evangelou E, Ioannidis JP. Meta-analysis methods for genome-wide association studies and beyond. *Nat Rev Genet* 2013; **14**: 379–389.
27. Almasy L, Blangero J. Multipoint quantitative-trait linkage analysis in general pedigrees. *Am J Human Genet* 1998; **62**: 1198–1211.
28. Kendler K, Silberg J, Neale M *et al*. Genetic and environmental factors in the aetiology of menstrual, premenstrual and neurotic symptoms: a population-based twin study. *Psychol Med* 1992; **22**: 85–100.
29. Qin L-L, Hu Z, Kaminga AC *et al*. Association between cigarette smoking and the risk of dysmenorrhea: a meta-analysis of observational studies. *PLoS One* 2020; **15**: e0231201.
30. Li R, Li B, Kreher DA *et al*. Association between dysmenorrhea and chronic pain: a systematic review and meta-analysis of population-based studies. *Am J Obstet Gynecol* 2020; **223**: 350–371.
31. Dowling P, Klinker F, Amaya F *et al*. Iron-deficiency sensitizes mice to acute pain stimuli and formalin-induced nociception. *J Nutr* 2009; **139**: 2087–2092.
32. Missmer SA, Hankinson SE, Spiegelman D *et al*. Incidence of laparoscopically confirmed endometriosis by demographic, anthropometric, and lifestyle factors. *Am J Epidemiol* 2004; **160**: 784–796.
33. Singh S, Soliman AM, Rahal Y *et al*. Prevalence, symptomatic burden, and diagnosis of endometriosis in Canada: cross-sectional survey of 30 000 women. *J Obstet Gynaecol Can* 2020; **42**: 829–838.
34. Bernuit D, Ebert AD, Halis G *et al*. Female perspectives on endometriosis: findings from the uterine bleeding and pain women's research study. *J Endometr* 2011; **3**: 73–85.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1. Supporting Information: Univeriate associations; mother-daughter relationship; additional methods, results and discussion information, additional references.