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ORIGINAL RESEARCH ARTICLE

Heredity of pregnancy-related pelvic girdle pain in Sweden

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Abstract

Introduction: Pelvic girdle pain during and after pregnancy is a major public health problem with significant daily problems for affected women and their families. There is now accumulating evidence that pregnancy-related pelvic girdle pain originates from the sacroiliac joints and the pubic symphysis as well as their extra-articular ligaments. However, the heritability of the disease remains to be determined. We hypothesized that there is an increased familial risk of pregnancy-related pelvic girdle pain.

Material and methods: A population-based national database linkage registry study of approximately 9.3 million individuals within 4.2 million families in Sweden with a recruitment period from 1997 to 2018. The Swedish Multi-generation register was used to find female pairs of twins, full siblings, half-siblings and first cousins where both in the pairs had a completed pregnancy. The outcome measure was diagnosis of pregnancy-related pelvic girdle pain (International Classification of Diseases-10 O26.7 [1997–2018]) in the first pregnancy. Data was obtained from the Swedish Hospital Discharge Register, the Swedish Outpatient Care Register, the Swedish Medical Birth Register, the Primary Healthcare Register, and Medical Treatment Register. Cox regression analysis was used to calculate adjusted estimated effect of the exposure variable familial history of pregnancy-related pelvic girdle pain on the outcome variable pregnancy-related pelvic girdle pain at first birth.

Results: From the registers, 1 010 064 women pregnant with their first child within 795 654 families were collected. In total, 109 147 women were diagnosed with pregnancy-related pelvic girdle pain. The adjusted hazard ratio for a familial risk of pregnancy-related pelvic girdle pain was 2.09 (95% CI 1.85–2.37) among twins (monozygotic and dizygotic), 1.78 (95% CI 1.74–1.82) in full siblings, 1.16 (95% CI 1.06–1.28) in half-siblings from the mother, 1.09 (95% CI 1.024–1.16) in half-siblings from the father and 1.09 (95% CI 1.07–1.12) in first cousins.

Conclusions: This nationwide observational study showed a familial clustering of pregnancy-related pelvic girdle pain. The hazard ratio for the condition was associated with the degree of relatedness, suggesting that heredity factors contribute to

Abbreviations: 95%, CI 95% confidence interval; BMI, body mass index; DAG, directed acyclic graph.

the development of pregnancy-related pelvic girdle pain. There is no causal treatment available for pregnancy-related pelvic girdle pain and further studies are now encouraged to clarify the specific genetic factors that contribute to the disease and for future targeted interventions.

KEYWORDS
heredity, pelvic girdle pain, pregnancy

1 | INTRODUCTION

Pelvic girdle pain during and after pregnancy is a major public health problem with significant daily problems for affected women and their families. During pregnancy, the overall prevalence of disabling pelvic girdle pain is estimated to about 25%, of which 25% are in severe pain and 8% are severely disabled.[1] Furthermore, 5% of all mothers report chronic disabling pregnancy-related pelvic girdle pain that persist several years after delivery, even into old age.[2–5] The highest risk of developing such persistent pain after delivery increases with early onset of pregnancy-associated pain as well as with the inability to reduce weight to pre-pregnancy levels.[6]

There is now accumulating evidence that pregnancy-related pelvic girdle pain originates from the sacroiliac joints and the pubic symphysis as well as their extra-articular ligaments.[7–11] However, the heritability of the disease remains to be determined. Knowledge of familial risk could be of clinical use to provide information to women with a family history of the disease and for further studies aiming for the identification of specific and contributing genetic factors. Familial predisposition for any condition can be investigated using multi-generation registers. In Sweden, such a register was founded in 2000 and contains information about parents, siblings, grandparents and first cousins of a proband.

We hypothesized that there is an increased familial risk of pregnancy-related pelvic girdle pain. Therefore, we sought to use multi-generation registers to investigate the occurrence of pregnancy-related pelvic girdle pain among female twins, siblings, half-siblings and first cousins.

The aim of the study was to elucidate familial clustering of pregnancy-related pelvic girdle pain.

Key Message

This study strongly suggests that hereditary factors contributes to development of pregnancy-related pelvic girdle pain. Further studies are now encouraged to clarify specific genetic factors behind the disease.

2 | MATERIAL AND METHODS

The dataset used in this study was constructed by linking several national Swedish registers provided by the Swedish government-owned statistics bureau Statistics Sweden, and the National Board of Health and Welfare. This dataset included approximately 9.3 million individuals belonging to approximately 4.2 million families. The registers included were the Swedish Multi-generation register "Live Births Information System",[12] the National Census data, the Swedish Cause of Death Register (1964–2018), the Swedish Outpatient Register (2001–2018), the Swedish Hospital Register (1964–2018), the Medical Birth Register, and the Medical Treatment Register.[13–15]

The Swedish Multi-generation register contains information on family relationships for index persons born in Sweden from 1932 onwards and covers all persons who have been registered in Sweden since 1961.[12] The Swedish patient registers have a validity of about 85%–95% for most diseases.[13] The registers were linked using the national personal identification number that is assigned to every resident in Sweden for their lifetime. To preserve anonymity, a serial number replaced the personal identification number in the analyses. In addition, the serial numbers were used to check that all individuals were entered only once (for her first main or secondary diagnosis of pelvic girdle pain).

The study population in the present study included women born from 1932 and after, who were registered in the Swedish Medical Birth Register. The women were followed from the study start on January 1, 1997 and proceeded until diagnosis of pelvic girdle pain, death, emigration or end of study on December 31, 2018. The average follow-up time was 11.3 ± 6.7 years.

2.1 | Exposure

The exposure variable was a woman's family history of pregnancy-related pelvic girdle pain defined by the ICD-10 (International Classification of Diseases, 1997–2018) code O26.7 (according to *Handbook of diagnoses for women's health care*, based on ICD-10 the Swedish Society of Obstetrics and Gynecology; the code includes symphysiolysis, pelvic and back insufficiency).[16] In the cohort of women with at least one affected relative, the incidence rates over the study period were computed. In a family with two or more affected relatives, each affected relative was included in the cohort (as the relative of an affected woman).

Kinship was defined from the Swedish Multi-generation register and female full siblings were defined as having the same mother and father, female half siblings as having either the same mother or father, and first cousins by having one grandparent in common.

Kinship was used to find female twins where both sisters had a completed pregnancy, female full siblings where at least two sisters had a completed pregnancy, female half siblings where at least two half-sisters had a completed pregnancy, and first cousins where at least two first cousins had a completed pregnancy. Thus, women exposed were participants with a female relative with the diagnosis of O26.7. These women were compared with women not exposed, ie participants with a female relative without the diagnosis of O26.7. Women who were never pregnant during the study period and women without any relative who had completed a pregnancy were excluded from the analysis of familial female risks.

2.2 | Outcome

The outcome variable was the diagnosis of pelvic girdle pain in pregnancy, childbirth or the puerperium, defined by O26.7 in the first or last childbirth detected in any of the above registers. The definition of code O26.7 was as described in the exposure paragraph above. The first childbirth selects the nulliparous women and, as the degree of pelvic girdle pain is associated to the number of deliveries, the last childbirth was used in a sensitivity analysis.

2.3 | Covariates

The included covariates, their definitions and scaling were:

Age at child delivery was divided into three groups: <25 years, 25–34 years and ≥ 35 years.

Body mass index (BMI) at registration to antenatal care at first pregnancy (weight/height^2) was divided into five groups: <18.5, 18.5–24.9, 25–30.0, >30.0 and unknown.

Region of residence was divided into "large city" and "small city/countryside" from the original categories "large city", "southern Sweden" and "northern Sweden". "Large cities" were defined as one of the three largest cities in Sweden (Stockholm, Gothenburg and Malmö with >300 000 inhabitants). "Southern Sweden" and "northern Sweden" were divided into "small city/countryside".

Educational level was categorized as ≤9 years (partial or complete compulsory schooling), 10–12 years (partial or complete secondary schooling) and >12 years (some or completed college and/or university studies).

Birthweight of first child was categorized based on small for gestational age (SGA) and large for gestational age (LGA) (no/yes). SGA was defined as birthweight <2 standard deviations of the mean for gestational age (ie the 2.5th percentile) according to the Swedish reference curve for estimated fetal weight. LGA was defined accordingly, but >2 standard deviations of the mean for gestational age.

Preterm birth was defined as birth before 37 completed weeks of gestation categorized (no/yes).

Multiple birth was categorized as singleton vs multiple birth.

Smoking during pregnancy was categorized as no smoking, <9 cigarettes per day, ≥9 cigarettes per day, and unknown.

Immigration status was categorized based on the country of birth, born in Sweden or other countries.

Marital status was categorized into two groups: married and unmarried.

Comorbidities were identified according to ICD-10 codes for the following diagnoses: alcoholism (F10 and K70), hypermobility syndrome (M35.7), Ehlers-Danlos' and Marfan's syndromes (Q796 and Q874) and depression (F32).

2.4 | Statistical analyses

A cohort of individuals with at least one affected relative was defined and the incidence rates were computed in this cohort over the study period. In a family with two or more affected relatives, each affected individual was included in the cohort (as the relative of an affected individual).

Cox regression models were used to examine the temporal association and estimated effect of the exposure variable familial history of pregnancy-related pelvic girdle pain on the outcome variable pregnancy-related pelvic girdle pain at first birth. The results are presented as hazard ratios with a 95% confidence interval (95% CI) adjusted by the effect modifier age at first birth (crude) and by a minimal set of confounding factors (adjusted). The adjustments for confounders applies for both individuals in all pairs. The interrelationships between the variables that affect the exposure and outcome variables were sorted out in a directed acyclic graph (DAG) (Figure 1) using the software at Dagitty.net (version 3.0)[17] (see Appendix S1 for Digital Content for the full code for reproducing our DAG at Dagitty.net). The variables' mutual relation with each other, the exposure, and the outcome measure were considered and marked with a pointed arrow in the direction of affect as found correct from a clinical standpoint and the medical literature. In a second step, the software was used to derive a minimal sufficient set of covariates for appropriate adjustment to make the exposed and unexposed women comparable.[17] In addition, this avoids adjustment for mediators, which would introduce bias. The minimal set of confounders derived from the DAG were region of residence and immigration status.

A sensitivity analysis is presented on the temporal association and estimated effect of the exposure variable familial history of pregnancy-related pelvic girdle pain on the outcome variable pregnancy-related pelvic girdle pain at last childbirth. In addition, a logistic regression analysis was used.

Figure 3 presents family history score of probands by adjusted hazard ratio and 95% CI of pregnancy-related pelvic girdle pain of the first childbirth, endowed with an ordinal scale with not siblings (lowest genetic resemblance) registered as 0 (data not shown), first cousins as 1, half siblings as 2, siblings (not twins) as 3 and twins as 4.

Statistical significance was set at $P < 0.05$ and all tests were two-tailed. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc.).

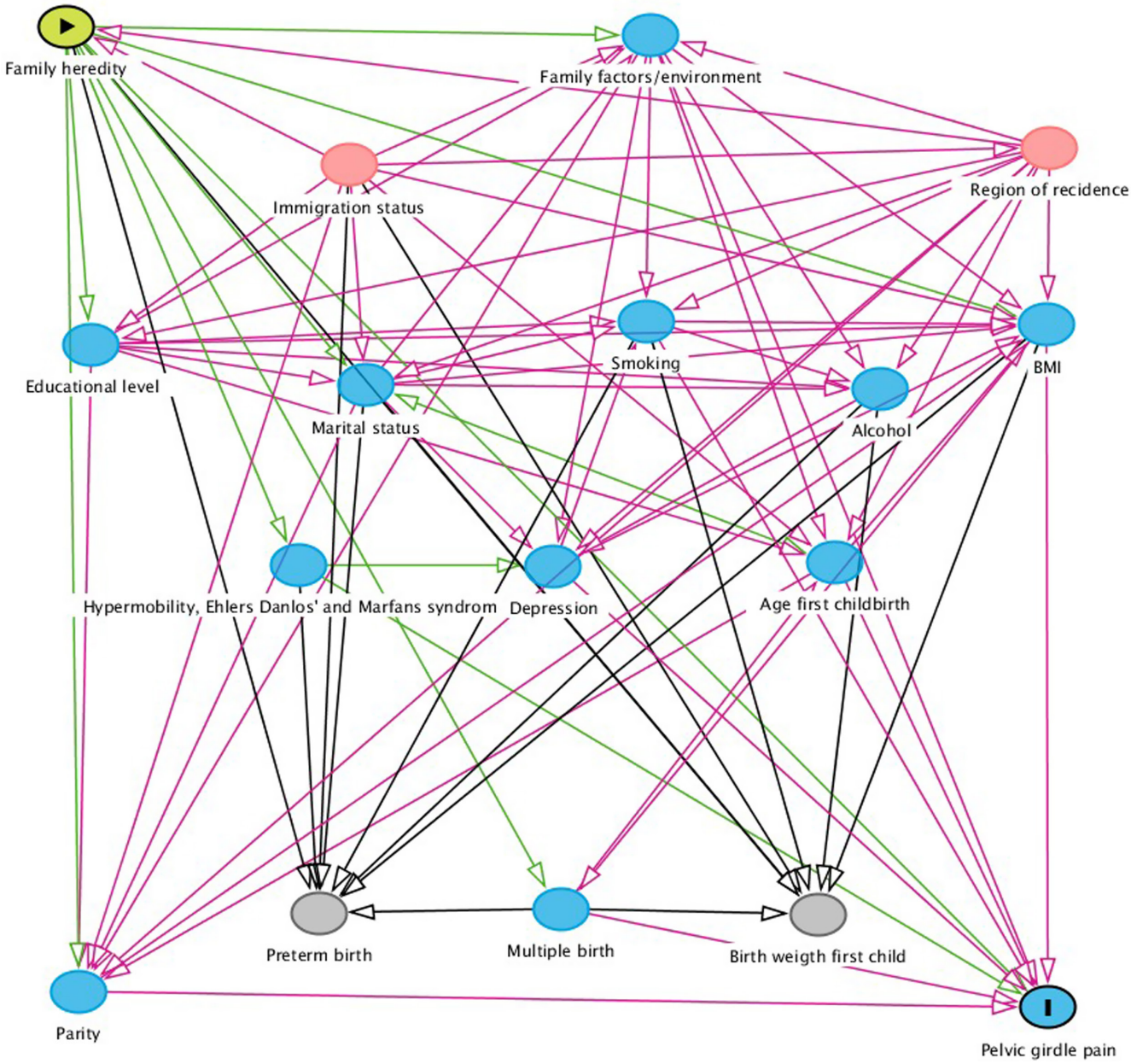

FIGURE 1 Directed acyclic graph. This model was constructed at www.dagitty.net (v3.0) to obtain a minimal sufficient adjustment set for the multiple regression model. Yellow circle for exposure, blue circle for outcome, pink circle for ancestor of exposure and outcome, pink arrow for biasing path, and green arrow for causal path. The full code is displayed in Appendix S1.

2.5 | Ethics statement

This study was approved by the Ethics Committee at Lund University, Lund, Sweden, on February 6, 2013 (Dnr 2012/795). Informed consent was waived by the ethics committee.

3 | RESULTS

We analyzed the familial risk of pregnancy-related pelvic girdle pain in relatives among 1 010 064 women pregnant with their first child within 795 654 families (Figure 2). In total, 109 147 women were diagnosed with pregnancy-related pelvic girdle pain, of which 20.35% were identified in the Swedish Hospital Register, 16.36% in the Swedish Outpatient Register, 61.18% in the Primary Health Care register and 2.12% in the Medical Birth Register.

Table 1 displays the characteristics of the total study population and the characteristics of the proportion of women with an event of diagnosis of pregnancy-related pelvic girdle pain. Women with a reported event had a larger proportion of relatives with a completed pregnancy and a history of the diagnosis of pregnancy-related pelvic girdle pain compared with women with a completed pregnancy without a reported event. Furthermore, a reasonably higher proportion of women with an event of pelvic girdle pain were immigrants, of

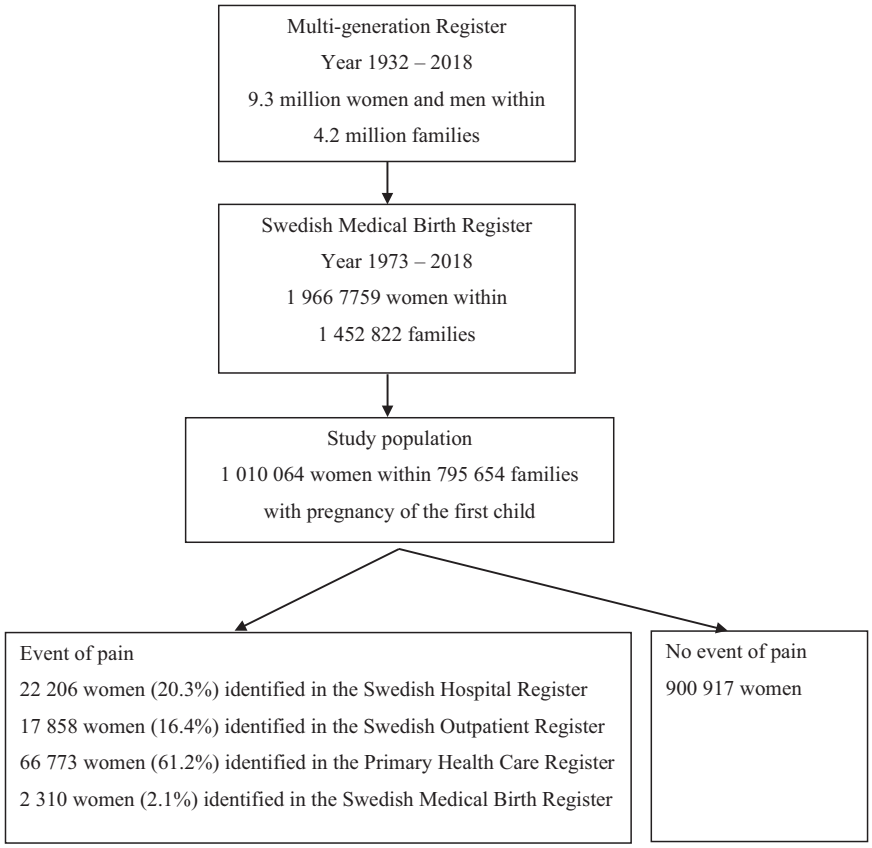

FIGURE 2 Flowchart of study population and diagnosis of events.

younger age, had a higher body mass index, a higher proportion of multiple births, and increased frequencies of hospitalization for hypermobility syndrome and depression compared with women without an event ($P < 0.001$).

Familial risk of an event of pregnancy-related pelvic girdle pain in the first pregnancy according to a diagnosis of pregnancy-related pelvic girdle pain among first-, second- and third-degree relatives of probands is summarized in Table 2 and Figure 3. The hazard ratio for a full sibling history, adjusted for age at first birth, was 2.20 (95% CI 2.15–2.25). The hazard ratio after additional adjustment for the minimal sufficient set of confounding factors was 1.78 (95% CI 1.73–1.82) for full siblings, 2.09 among twins, 1.16 in half-siblings from the mother, 1.09 in half-siblings from the father and 1.09 in affected first cousins. The results were almost identical in the logistic regression analysis (Table S1).

In a sensitivity analysis of the familial risk of events of pregnancy-related pelvic girdle pain among the women at their *last* childbirth, the hazard ratio for full siblings adjusted by the minimal set of confounding factors and number of parities was 1.98 (95% CI 1.94–2.02) (data not shown).

4 | DISCUSSION

This nationwide observational study showed a familial clustering of pregnancy-related pelvic girdle pain. The clustering was dependent on the degree of relatedness within families. These results strongly suggest that hereditary factors contribute to the development of pregnancy-related pelvic girdle pain.

To our knowledge, there are no previous studies of familial predisposition or heritability of pregnancy-related pelvic girdle pain. Shared genetic factors behind spinal pain has been suggested in a twin study of both sexes, more pronounced in women.[18] Suggested candidate genes for spinal pain and chronic low back pain may encode proteins involved in the extracellular matrix function, the central nervous system, skeletal muscle and other structural/anatomical features.[19,20] In addition, a study of adult female twins concluded that genetic factors may contribute to a lifelong history of low back pain through early structural disc degeneration and tendencies toward psychological distress.[21]

Based on our and previous data, we suggest that pregnancy-related pelvic girdle pain is a multifactorial condition resulting from a combination of environmental and genetic factors. A prior study has suggested that generalized joint hypermobility predisposes to pregnancy-associated pelvic pain.[22] In addition, pelvic girdle pain intensity was associated to an extracellular matrix degradation enzyme,[23] supporting the hypothesis that pelvic girdle pain is related to changes in the extracellular components in pelvic ligaments. Furthermore, isolated and generalized joint hypermobility may occur as a familial form[24] and could therefore be a predisposing condition for pregnancy-related pelvic girdle pain. Moreover, shared environmental factors may have contributed to our results, in line with the multifactorial etiology for the disease. However, it is unlikely that sisters share the same physical environment during

TABLE 1 Characteristics of 1 010 064 pregnant women within 795 654 families and of the 109 147 women with an event of pregnancy-related pelvic girdle pain (PGP) in their first pregnancy during 1997–2018 in Sweden.

	Total population		Event of pain		
Characteristic	***n***	**%**	***n***	**%**	***P*-value**
All	1 010 064	100.0	109 147	100.0	
Number of twins	1256	0.1	260	0.2	<0.001
Number of full sibship	45 635	4.5	8659	7.9	<0.001
Number of half sibship	16 017	1.6	1517	1.4	<0.001
Number of first cousins	59 069	5.8	7766	7.1	<0.001
Family history of PGP	56 456	5.6	10 652	9.8	<0.001
Age at delivery of first child					<0.001
<25	169 828	16.8	30 690	28.1	
25–34	673 525	66.7	68 775	63.0	
≥35	166 711	16.5	9682	8.9	
Body mass index					<0.001
Unknown	104 662	10.4	9314	8.5	
<18.5	21 007	2.1	2412	2.2	
18.5–24.9	572 388	56.7	56 688	51.9	
25.0–29.9	216 119	21.4	26 322	24.1	
≥30.0	95 888	9.5	14 411	13.2	
Region of residence					<0.001
Large cities	523 989	51.9	58 188	53.3	
Southern Sweden	335 755	33.2	35 847	32.8	
Northern Sweden	150 320	14.9	15 112	13.8	
Educational level					<0.001
≤9 years	57 608	5.7	8321	7.6	
10–12 years	127 122	12.6	11 772	10.8	
> 12 years	825 334	81.7	89 054	81.6	
Child born small for gestational age					<0.001
No	982 380	97.3	104 456	97.5	
Yes	27 684	2.7	2691	2.5	
Child born large for gestational age					<0.001
No	983 220	97.3	105 910	97.0	
Yes	26 844	2.7	3237	3.0	
Child born preterm birth	64 771	6.4	6675	6.1	<0.001
No	945 293	93.6	102 472	93.9	
Yes	64 771	6.4	6675	6.1	
Multiple birth					<0.001
Singleton	969 544	96.0	103 137	94.5	
Multiple birth	40 520	4.0	6010	5.5	
Smoking during pregnancy					<0.001
Unknown	45 754	4.5	4093	3.8	
Not smoking	870 258	86.2	93 051	85.2	
≤9 per day	67 898	6.7	9110	8.4	
≥10 per day	26 154	2.6	2893	2.6	
Marital status					0.009
Married	519 635	51.4	55 744	51.1	
Unmarried	490 429	48.6	53 403	48.9	

(Continues)

TABLE 1 (Continued)

Characteristic	Total population		Event of pain		P-value
	n	%	n	%	
Immigration status					<0.001
Born in Sweden	958 686	94.9	100 850	92.4	
Born in other countries	51 378	5.1	8297	7.6	
Hospitalization for alcoholism	27 660	2.7	4299	3.9	<0.001
Hospitalization for hypermobility syndrome	4331	0.4	944	0.9	<0.001
Hospitalization for depression	69 657	6.9	11 674	10.7	<0.001
Ehlers-Danlos' or Marfan's syndrome	163	0.0	43	0.0	<0.001

	Number of events	Crude model[b]		Adjusted model[c]	
		HR	95% CI	HR	95% CI
Twins (mono- and dizygotic)	260	2.54	2.25–2.87	2.09	1.85–2.37
Full siblings	8659	2.20	2.15–2.25	1.78	1.74–1.82
Singleton siblings	10 392	2.10	2.06–2.14	1.73	1.69–1.76
Maternal half-siblings	444	1.20	1.09–1.32	1.16	1.06–1.28
Paternal half-siblings	1073	1.13	1.06–1.20	1.09	1.02–1.16
First cousins	7766	1.12	1.10–1.15	1.09	1.07–1.12

[a]The interrelationships between variables affecting exposure and outcome were sorted out in a directed acyclic graph by the software at Dagitty.net (version 3.0).

[b]Adjusted for age at first birth.

[c]Adjusted for age at first birth, region of residence and immigration status.

TABLE 2 Cox regression models for examining association and effect estimation of the exposure variable (family history of pregnancy-related pelvic girdle pain) on the outcome variable pregnancy-related pelvic girdle pain in the first pregnancy according to first-, second- and third-degree relatives of probands. Adjustment was done for the effect modifier age at first birth and by a minimal sufficient set of confounding factors derived from a directed acyclic graph[a]. Hazard ratios (HR) and 95% confidence intervals (95% CI) are presented ($n = 1\,010\,064$).

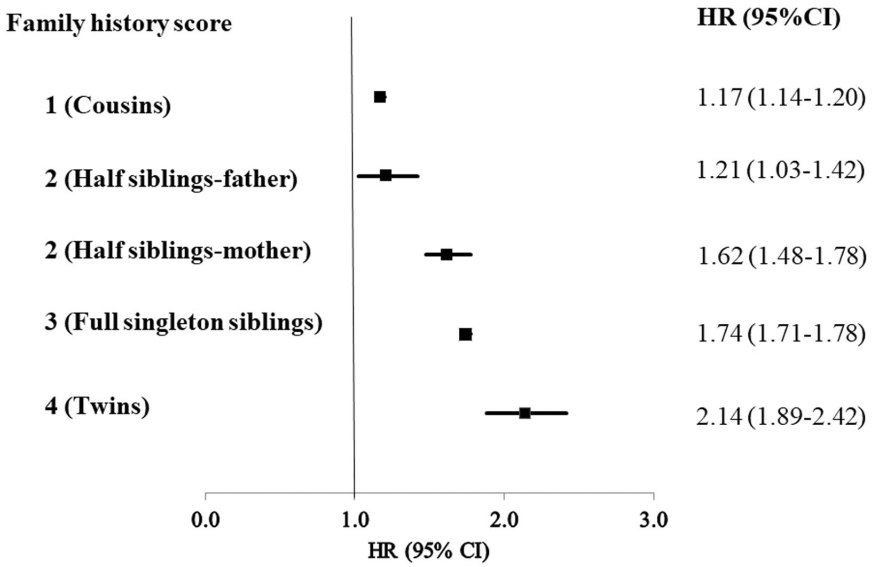

FIGURE 3 Adjusted hazard ratios (HR) and 95% confidence interval (95% CI) of pregnancy-related pelvic girdle pain, during the first pregnancy, according to family history score of probands.

their pregnancies and at the onset of pregnancy-related pelvic girdle pain, although sisters usually have a similar in utero and childhood environment. The increased risk among first cousins to affected women is more modest but it still supports a contribution of genetic factors that correlates to the lower proportion of genes shared by the descent. Moreover, in most cases, maternal half siblings share a household in early life (83%) and paternal half siblings in only a few cases (3%).[25] In addition, the highest risk was shown

among all twins with an unknown distribution of monozygotic and dizygotic twins. The increased risk, when compared with full siblings, could be explained by the proportion of monozygotic twins that are identical by descent. Altogether, our results suggest that genetic factors are important in the etiology of pregnancy-related pelvic girdle pain.

The magnitude of the familial clustering in the present study was about double the odds ratios in full siblings, compared with the reference population. For comparison, this is about the same magnitude as the twofold increased risk of gestational diabetes among pregnant women with parents affected by T2DM[26,27] but lower than the odds of familial aggregation of hyperemesis gravidarum.[28]

This study has limitations. The quality of the O26.7 coding is a main issue and the Swedish registers contain no information about actual diagnostic procedure. In addition, a registered code O26.7 implicates selection of more severe cases of pain.

One strength of the study was the use of the nationwide registers, minimizing selection and recall bias. Another important strength of our study is the high quality of the Swedish patient registers including the Swedish Multi-generation register[12,13] and that our dataset is almost 100% complete. A strength is also the elimination of self-report bias, a common problem in many case–control studies and in other studies on familial transmission of diseases relying on self-reports. In addition, during the whole study period, the ICD-10 and a national interpretation of the obstetric codes were available for the Swedish physicians in primary and secondary care for diagnosis coding. This favors a consistent coding between institutions rather than the opposite.

5 | CONCLUSION

This nationwide observational study showed familial clustering of pregnancy-related pelvic girdle pain. The clustering correlated with the degree of relatedness within families. These results strongly suggest that hereditary factors contribute to the development of pregnancy-related pelvic girdle pain. Further studies on independent cohorts are now encouraged to validate our findings and to identify specific genetic risk factors behind the disease.

AUTHOR CONTRIBUTIONS

P Kristiansson: Concept and design, statistical analysis and drafting the manuscript. B Zöller: Concept and design. P Kalliokoski: Concept and design and writing the draft. X Li: Concept and design, writing the draft, statistical analysis. All authors: Critical revision of the article for important intellectual content.

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SUPPORTING INFORMATION

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

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