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Pointers to earlier diagnosis of endometriosis:

a nested case-control study using primary care electronic health records

Abstract

Background

Endometriosis is a condition with relatively non-specific symptoms, and in some cases a long time elapses from first-symptom presentation to diagnosis.

Aim

To develop and test new composite pointers to a diagnosis of endometriosis in primary care electronic records.

Design and setting

This is a nested case-control study of 366 cases using the Practice Team Information database of anonymised primary care electronic health records from Scotland. Data were analysed from 366 cases of endometriosis between 1994 and 2010, and two sets of age and GP practice matched controls: (a) 1453 randomly selected females and (b) 610 females whose records contained codes indicating consultation for gynaecological symptoms.

Method

Composite pointers comprised patterns of symptoms, prescribing, or investigations, in combination or over time. Conditional logistic regression was used to examine the presence of both new and established pointers during the 3 years before diagnosis of endometriosis and to identify time of appearance.

Results

A number of composite pointers that were strongly predictive of endometriosis were observed. These included pain and menstrual symptoms occurring within the same year (odds ratio [OR] 6.5, 95% confidence interval [CI] = 3.9 to 10.6), and lower gastrointestinal symptoms occurring within 90 days of gynaecological pain (OR 6.1, 95% CI = 3.6 to 10.6). Although the association of infertility with endometriosis was only detectable in the year before diagnosis, several pain-related features were associated with endometriosis several years earlier.

Conclusion

Useful composite pointers to a diagnosis of endometriosis in GP records were identified. Some of these were present several years before the diagnosis and may be valuable targets for diagnostic support systems.

Keywords

diagnosis; electronic health records; endometriosis; primary care.

INTRODUCTION

Endometriosis is a common gynaecological condition in which there is often a long time between first primary care consultation and diagnosis.¹⁻⁴ A longer time to diagnosis is associated with prolonged symptoms, particularly pain and^{5,6} subfertility, along with patient frustration and demoralisation.⁷ Endometriosis can be difficult to diagnose clinically; its symptoms are both common⁸ and non-specific, so are often considered by GPs as part of the normal menstrual experience,⁹ or attributed to other conditions.⁵ The use of very detailed questions about symptoms can increase diagnostic accuracy.¹⁰ However, current biomarkers¹¹ and imaging¹² have limited benefit, and there is substantial variation in guideline recommendations for diagnosis and management of this condition.¹³

Most research on the clinical features of endometriosis in primary care has focused on features present at a single point in time, typically the time of diagnosis.^{5,14} However, with endometriosis, the symptoms at any single point in time have only limited predictive value² and the problem of delays in diagnosis requires an understanding of when symptoms first appear. Although data in electronic records contain many single items, experienced practitioners typically recognise composite patterns that involve combinations of items. For example,

repeated episodes of dysmenorrhoea, except when taking hormonal contraception,¹⁵ are recognised by experienced clinicians as having diagnostic value in endometriosis. Although such knowledge-derived features¹⁶ are not immediately present in electronic records, they can be constructed.¹⁷ However, the authors are not aware of studies that have attempted to do this using primary care data or for endometriosis.

This study aimed to: (a) construct enriched datasets from electronic health records, which contained conventional and composite features potentially predictive of endometriosis; (b) examine the association of these features with a subsequent diagnosis of endometriosis in a nested case-control study; and (c) examine the relationship of these features to diagnosis at different time periods before the date of diagnosis.

METHOD

Data source

Data from the Practice Team Information (PTI) database, a subset of the Primary Care Clinical Informatics Unit Research database held by the University of Aberdeen, were obtained. It includes anonymised data from primary care electronic health records of approximately 224 000 patients registered with a primary care physician, and is broadly representative of the Scottish population

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How this fits in

Endometriosis is a relatively common condition but the time from first presentation to diagnosis is often longer than ideal as symptoms are non-specific. This study used anonymised GP record data to construct new pointers to diagnosis, which identified patterns of symptoms in time. Distinct episodes of gynaecological pain and combinations of gynaecological pain on one occasion with menstrual symptoms or lower gastrointestinal symptoms on another appear to be useful pointers to endometriosis. Patterns such as these make sense to clinicians and could be integrated into electronic diagnostic support systems.

with regards to age, sex, deprivation, and urban/rural ratio mix. It includes data collected annually between 2004 and 2010. Practices in the PTI project were expected to record every clinical encounter using Read Codes for clinical diagnoses and/or main reasons for consultation. All GP prescriptions were automatically recorded. Investigations and therapeutic procedures were coded differently over time — increasing towards the end of the database period.

Box 1. Categories of data grouped by data type

Data type	Data description	Included data categories
Specific features	Classical features of endometriosis (pelvic pain, dysmenorrhoea, dyspareunia and infertility) ^{2,5,9,14}	Pain (pelvic pain, dyspareunia, dysmenorrhoea) Menstrual (flow) Infertility Ovarian (for example, cysts)
Non-specific symptoms	Abdominal pain and gastrointestinal symptoms, fatigue, urinary symptoms; additional diagnoses, including irritable bowel syndrome ⁵	Menstrual (timing) Genital/other gynaecological Urinary Lower GI Upper GI Fatigue
Diagnostic tests and procedures	Primary care tests, referred investigations such as diagnostic ultrasound, and specialist procedures such as laparoscopy	Full blood count Genital swabs Laparoscopy Abdominal or pelvic ultrasound Thyroid function
Treatments	Hormonal treatment for endometriosis (for example, gonadotropin-releasing hormone agonists) Prescriptions for contraception Analgesic drugs Antidepressant drugs	Hormonal treatment Contraception NSAID Codeine or other opioids Tricyclic SSRI and related antidepressants

Lower GI = pain, bloating, irritable bowel syndrome. NSAID = non-steroidal anti-inflammatory drugs. SSRI = selective serotonin reuptake inhibitor. Upper GI = dyspepsia, reflux, nausea.

Populations

This study was a nested case-control study. Cases were females with a diagnosis of endometriosis, who were born after 1 January 1974 and were, therefore, ≤36 years on 1 January 2010. This enabled us to capture teenage menstrual symptoms for the majority of females and avoid the possibility that an apparent new diagnosis in an older female was actually a historical diagnosis being recorded for the first time due to the creation of computerised record summaries.

Population controls were randomly selected for each case and individually matched by age and GP practice, with up to four controls per case (subject to availability). A second control group comprised females with codes for gynaecological symptoms (pain, menstrual symptoms, or infertility) but with no recorded diagnosis of endometriosis. These controls were also randomly selected for each case and individually matched by age and GP practice, with up to four symptomatic controls per case. The index date for cases was defined as the date of diagnosis of endometriosis and for controls as the date of diagnosis of endometriosis in the matched case. All cases and controls were required to have been registered with their GP practice for at least 1 year before the index date.

Data extraction and preparation

Box 1 lists the key data extracted and the categories into which related items were grouped. Most items were allocated to a single time point. However, for contraception prescriptions, which commonly lasted for 6 months or longer, details were used about each prescription to estimate the onset and offset of contraception using methods previously employed to ascertain the continuity of prescribing.¹⁸

The data was enriched by introducing composite features that were based on the clinical experience of the investigators and on interviews with 10 experts (six gynaecologists, two specialists in reproductive health, and two representatives of a lay support organisation). Interviews sought to identify tacit patterns in symptoms, which clinicians thought may be predictive of a diagnosis, were audio recorded, transcribed, and analysed thematically. Composite features were specified according to one of five relationships: proximity, following, separated, during, and exclusive. These are summarised in Box 2.

The presence of each feature (single and composite) was ascertained in the record of each individual at any time, and during a

Box 2. Types of composite features used in constructing predictors

Relationship	Specification	Example
Proximity	An occurrence of one feature within a given number of days of the other but with no specification of which should come first	Pain and fatigue within 90 days of each other
Following	An occurrence of one feature within a given number of days of the other with specification of which should come first	Pain occurring within 90 days of estimated cessation of contraception
Separated	Two consecutive recordings of a single feature occurring at least a given number of days apart (this permits differentiation of separate episodes from repeated consultation during the same episode)	Two consecutive episodes of pain separated by at least 180 days
During	An occurrence of a symptom or other feature after the onset, and before the expected offset, of a contraception prescription	Pain during estimated duration of prescription for contraception
Exclusive	A feature only occurring in the absence of another	Pain but only outside of estimated periods of prescribed contraception

series of overlapping 3-year time windows set at different intervals from the index date (for diagnosis or matching). The windows were defined using intervals between the end of the window and the index date of 0, 3, 6, 12, 18, 24, and 36 months. The appearance of statistical associations between available information in the record and diagnosis over time were examined by comparing the same measure in different windows. The purpose of this was to differentiate between features that were present long before diagnosis (and may thus indicate missed diagnostic opportunities) and those that appeared only shortly before diagnosis (and may thus have triggered referral).

Analysis of association of features and patterns with diagnosis

Conditional logistic regression was carried out to examine the association between each feature (conventional or composite) and the diagnosis of endometriosis. Each feature was reported as either present or absent within the time period. Rather than use counts of how often a feature occurred, the 'separated' composite variables were used to indicate multiple episodes. Conditional logistic regression was conducted for all features for which at least 10 individuals (cases or controls) had the feature present and reported as the odds ratio (OR), with 95% confidence intervals (CIs). All analyses were conducted in R 3.3.2 (version 2016).

The analysis was conducted separately with population and symptomatic control groups. For the population comparison all cases and their matched controls were

included. For the symptomatic comparison, only cases that had recorded symptoms and their matched controls were included. For the time window analysis, the data were limited to females who had been registered with their practice for at least 1 year before the beginning of the gap. The odds ratios for each feature at each of the six different time gaps were plotted in order to visualise the appearance of predictive features over time.

RESULTS

Patient characteristics

Data from 366 cases and 1453 matched population controls were obtained. Of these, 243 cases had gynaecological symptoms (pain, menstrual symptoms, and infertility) and were matched to a further 610 controls with comparable symptoms. The median age at diagnosis was 25 years, interquartile range 22–28 years, and age at diagnosis was <20 years in 47 (12.8%) cases.

Data quality

In total, 191 cases (52.2%) were registered with the same GP practice for at least 5 years before diagnosis and, therefore, had continuous records in the PTI database; 114 (31.2%) were registered for at least 8 years before diagnosis. Similar proportions were seen for population controls (746 [51.3%] and 469 [32.3%] respectively), but more of the symptomatic controls had been registered for these time periods (414/610, 67.9% and 273/610, 44.8%). A recorded code for laparoscopy was found in only 47 (12.8%) cases despite this being the commonest diagnostic procedure for endometriosis. This is likely to represent a preference for recording the diagnosis rather than the procedure by which it was made, although instances of a clinical diagnosis being entered without any confirmatory tests cannot be excluded. Likewise, there were few coded surgical procedures, for example, 13 cases (3.5%) had a recorded operation for tubal or ovarian problems excluding diagnostic laparoscopy. These procedures were excluded from the analysis, focusing instead on clinical features, investigations, and medical treatments.

Occurrence of diagnostic features

There were 145 cases (39.6%) that had a code recorded for gynaecological pain (dysmenorrhoea, pelvic pain) during the 3 years prior to diagnosis and 39 (10.7%) had a code for infertility. And 198 cases (54.1%) had neither of these during the 3 years prior to diagnosis.

The numbers and proportions of females with at least one instance of each feature,

Table 1. Numbers, proportions, and odds ratios (95% CI) for features in cases of endometriosis compared with population controls

Specific features	Occurrence of features in 3 years before index date ^a						Occurrence of features at any time before index date ^a					
	Cases (N= 366)		Controls (N= 1453)				Cases (N= 366)		Controls (N= 1453)			
	n	%	n	%	OR	95% CI	n	%	n	%	OR	95% CI
Subfertility	39	10.7	24	1.7	7.7	[4.4 to 13.3]	41	11.2	31	2.1	5.9	[3.6 to 9.7]
Menstrual — bleeding	121	33.1	179	12.3	3.8	[2.8 to 5.0]	151	41.3	267	18.4	3.3	[2.6 to 4.3]
Menstrual — timing	39	10.7	80	5.5	2.1	[1.4 to 3.2]	45	12.3	117	8.1	1.6	[1.1 to 2.3]
Ovarian	24	6.6	7	0.5	13.7	[5.9 to 31.8]	25	6.8	11	0.8	9.8	[4.7 to 20.4]
Pain	145	39.6	79	5.4	14.9	[10.1 to 21.9]	169	46.2	146	10.1	9.9	[7.1 to 13.6]
Non-specific symptoms												
Fatigue	56	15.3	121	8.3	2.0	[1.4 to 2.8]	79	21.6	178	12.3	2.0	[1.5 to 2.7]
Gynaecological	51	13.9	47	3.2	5.0	[3.3 to 7.7]	77	21.0	97	6.7	4.0	[2.8 to 5.6]
Lower GI	104	28.4	144	9.9	3.7	[2.8 to 5.0]	126	34.4	213	14.7	3.3	[2.5 to 4.3]
Upper GI	27	7.4	62	4.3	1.8	[1.1 to 3.0]	50	13.7	107	7.4	2.1	[1.4 to 3.0]
Urinary	25	6.8	49	3.4	2.1	[1.3 to 3.5]	42	11.5	80	5.5	2.3	[1.5 to 3.5]
Tests and procedures												
Full blood count	40	10.9	102	7.0	2.0	[1.2 to 3.2]	50	13.7	112	7.7	2.6	[1.6 to 4.2]
Genital swabs	64	17.5	77	5.3	4.5	[3.0 to 6.7]	73	20.0	111	7.6	3.5	[2.5 to 5.0]
Laparoscopy	42	11.5	13	0.9	14.6	[7.5 to 28.4]	47	12.8	15	1.0	13.9	[7.5 to 25.7]
Thyroid function	53	14.5	112	7.7	2.4	[1.6 to 3.5]	67	18.3	132	9.1	2.8	[1.9 to 4.1]
Ultrasound	14	3.8	5	0.3	12.3	[4.0 to 37.8]	14	3.8	11	0.8	5.0	[2.2 to 11.4]
Treatments												
Contraception	201	54.9	716	49.3	1.3	[1.0 to 1.6]	234	63.9	800	55.1	1.5	[1.2 to 2.0]
NSAID	171	46.7	276	19.0	4.8	[3.6 to 6.4]	191	52.2	393	27.1	3.8	[2.9 to 5.1]
Analgesic	136	37.2	254	17.5	3.0	[2.3 to 4.0]	156	42.6	343	23.6	2.7	[2.1 to 3.5]
SSRI	65	17.8	188	12.9	1.5	[1.1 to 2.0]	85	23.2	229	15.8	1.7	[1.2 to 2.2]
Tricyclic	29	7.9	60	4.1	2.2	[1.3 to 3.6]	42	11.5	82	5.6	2.4	[1.6 to 3.6]

^aIndex date: date of diagnosis for cases, date of diagnosis of matched case for controls. CI = confidence interval. Gynaecological = vulvo-vaginal symptoms, pelvic inflammation. Lower GI = pain, bloating, irritable bowel syndrome. NSAID = non-steroidal anti-inflammatory drug. OR = odds ratio. Ovarian = coded diagnosis of ovarian cysts and related conditions. SSRI = selective serotonin reuptake inhibitor and related antidepressants. Upper GI = dyspepsia, reflux, nausea.

either in the 3 years prior to the index date or at any time, are shown in Table 1 (all cases [N=366] and population controls) and Table 2 (symptomatic cases [N=261] and controls). Table 1 and Table 2 also show the odds ratios (OR), with 95% CIs for the two comparisons: all cases versus population controls and symptomatic cases (gynaecological pain, menstrual symptoms, or infertility) versus matched symptomatic controls.

As expected, pain was more common in cases in both comparisons: OR 14.9, 95% CI = 10.1 to 21.9 versus population controls and OR 5.6, 95% CI = 3.9 to 8.1 versus symptomatic controls over 3 years' data. Menstrual bleeding and timing symptoms were coded more commonly than in population controls, OR 3.8, 95% CI = 2.8 to 5.0 and 2.1, 95% CI = 1.4 to 3.2, but not in comparison with symptomatic

controls, OR 1.0, 95% CI = 0.7 to 1.4 and 1.2, 95% CI = 0.7 to 1.9. Non-specific clinical features such as fatigue, vulvo-vaginal problems, and lower gastrointestinal symptoms were all more common in cases than population controls.

Although simple tests such as full blood count were more common in cases than population controls, there was no significant difference in the symptomatic comparison. Genitourinary swab tests (presumably ordered because of the possibility that symptoms were due to pelvic inflammation) were more common in cases than controls in both comparisons.

Occurrence of prescribed treatments

In both the population and the symptomatic group comparisons, both analgesics (OR 3.0, 95% CI = 2.3 to 4.0 and OR 2.7, 95% CI = 1.9 to 3.9, in 3 years before index date

Table 2. Numbers, proportions, and odds ratios (95% CI) for features in cases of endometriosis compared with symptomatic controls

Specific features	Occurrence of features in 3 years before index date ^a						Occurrence of features at any time before index date ^a					
	Cases (N= 261)		Controls (N= 610)				Cases (N= 261)		Controls (N= 610)			
	N	%	N	%	OR	95% CI	N	%	N	%	OR	95% CI
Subfertility	39	16.1	52	8.5	2.4	(1.4 to 3.9)	41	16.9	64	10.5	1.9	(1.2 to 3.1)
Menstrual — bleeding	121	49.8	304	49.8	1.0	(0.7 to 1.4)	151	62.1	443	72.6	0.7	(0.5 to 0.9)
Menstrual — timing	30	12.4	64	10.5	1.2	(0.7 to 1.9)	34	14.0	111	18.2	0.7	(0.5 to 1.1)
Ovarian	14	5.8	3	0.5	12.2	(3.5 to 42.7)	15	6.2	6	1.0	7.0	(2.7 to 18.1)
Pain	145	59.7	148	24.3	5.6	(3.9 to 8.1)	169	69.6	241	39.5	4.0	(2.8 to 5.6)
Non-specific symptoms												
Fatigue	45	18.5	84	13.8	1.4	(0.9 to 2.1)	66	27.2	138	22.6	1.3	(0.9 to 1.9)
Gynaecological	41	16.9	34	5.6	4.2	(2.4 to 7.4)	64	26.3	68	11.2	3.6	(2.3 to 5.6)
Lower GI	79	32.5	109	17.9	2.3	(1.6 to 3.2)	95	39.1	180	29.5	1.7	(1.2 to 2.3)
Upper GI	24	9.9	51	8.4	1.3	(0.8 to 2.3)	44	18.1	87	14.3	1.5	(1.0 to 2.3)
Urinary	20	8.2	29	4.8	1.8	(1.0 to 3.4)	36	14.8	64	10.5	1.5	(1.0 to 2.4)
Tests and procedures												
Full blood count	34	14.0	82	13.4	1.2	(0.7 to 2.2)	42	17.3	97	15.9	1.4	(0.8 to 2.4)
Genital swabs	43	17.7	71	11.6	2.2	(1.3 to 3.5)	50	20.6	90	14.8	1.9	(1.2 to 3.0)
Laparoscopy	31	12.8	4	0.7	20.0	(7.0 to 57.1)	35	14.4	13	2.1	7.2	(3.7 to 14.1)
Thyroid function	43	17.7	86	14.1	1.5	(0.9 to 2.4)	53	21.8	103	16.9	1.7	(1.1 to 2.7)
Ultrasound	11	4.5	6	1.0	5.2	(1.6 to 17.0)	11	4.5	7	1.2	4.3	(1.4 to 13.0)
Treatments												
Contraception	151	62.1	373	61.2	1.1	(0.8 to 1.5)	178	73.3	421	69.0	1.3	(0.9 to 1.9)
NSAID	133	54.7	185	30.3	3.0	(2.1 to 4.2)	150	61.7	264	43.3	2.6	(1.8 to 3.7)
Analgesic	100	41.2	142	23.3	2.7	(1.9 to 3.9)	116	47.7	203	33.3	2.3	(1.6 to 3.4)
SSRI	43	17.7	115	18.9	1.0	(0.7 to 1.5)	57	23.5	148	24.3	1.1	(0.8 to 1.6)
Tricyclic	20	8.2	37	6.1	1.5	(0.8 to 2.7)	29	11.9	58	9.5	1.3	(0.8 to 2.1)

^aIndex date: date of diagnosis for cases, date of diagnosis of matched case for controls. CI = confidence interval. Gynaecological = vulvo-vaginal symptoms, pelvic inflammation. Lower GI = pain, bloating, irritable bowel syndrome. NSAID = non-steroidal anti-inflammatory drug. OR = odds ratio. Ovarian = coded diagnosis of ovarian cysts and related conditions. SSRI = selective serotonin reuptake inhibitor and related antidepressants. Upper GI = dyspepsia, reflux, nausea.

comparison) and NSAIDs (OR 4.8, 95% CI = 3.6 to 6.4 and OR 3.0, 95% CI = 2.1 to 4.2, in 3 years before index date comparison) were more commonly prescribed to cases than controls. When comparing cases and symptomatic controls, there was no association with antidepressant drugs (either tricyclic or SSRI and related).

Composite features

Table 3 shows the number and proportion of patients with at least one instance of each of the composite features over the 3 years before date of diagnosis/matching. Several composite features had high ORs when cases were compared with symptomatic controls: pain and menstrual symptoms within the same year (pain proximity menstrual [360]), OR 6.5, 95% CI = 3.9 to 10.6 and lower gastrointestinal symptoms occurring within 90 days of gynaecological

pain (OR 6.1, 95% CI = 3.6 to 10.6). Episodes of gynaecological pain separated by at least 180 days were approximately eight times as likely in cases than symptomatic controls (OR 8.5, 95% CI = 4.3 to 16.9). Although pain or analgesic use on stopping contraception was suggested by some of the experts, these composite features occurred in less than 10% of cases, and with only moderate ORs of approximately 3.

Occurrence of diagnostic features over the time prior to diagnosis

Figure 1 shows plots of eight diagnostic features, describing the ORs for 3-year time windows with different intervals between the end of the 3-year window and the diagnosis/matching date. Each plot compares cases with matched population controls and symptomatic cases with their matched symptomatic controls. In all plots, 95% CIs

Table 3. Numbers, proportions, and odds ratios (95% CI) for composite features in the 3 years before diagnosis/matching^a

Composite feature	Comparison with population controls						Comparison with symptomatic controls					
	Cases (N= 366)		Controls (N= 1453)				Cases (N= 261)		Controls (N= 610)			
	n	%	n	%	OR	95% CI	n	%	n	%	OR	95% CI
Pain during contraception	40	10.9	24	1.7	7.4	[4.3 to 12.7]	40	16.5	38	6.2	3.0	[1.9 to 5.0]
Pain follow contraception (180)	17	4.6	8	0.6	8.5	[3.7 to 19.7]	17	7.0	17	2.8	3.1	[1.5 to 6.4]
Pain exclusive contraception	105	28.7	55	3.8	14.2	[9.1 to 22.0]	105	43.2	110	18.0	4.3	[2.9 to 6.2]
Menstrual during contraception	38	10.4	65	4.5	2.6	[1.7 to 4.1]	38	15.6	87	14.3	1.1	[0.7 to 1.8]
Menstrual follow contraception (180)	14	3.8	8	0.6	7.0	[2.9 to 16.7]	14	5.8	17	2.8	2.0	[1.0 to 4.2]
Analgesic during contraception	51	13.9	90	6.2	2.5	[1.7 to 3.7]	39	16.1	59	9.7	2.0	[1.3 to 3.1]
Analgesic follow contraception (180)	27	7.4	26	1.8	4.5	[2.5 to 7.8]	21	8.6	21	3.4	2.8	[1.5 to 5.3]
Analgesic exclusive contraception	116	31.7	68	4.7	12.0	[8.1 to 17.8]	116	47.7	132	21.6	3.9	[2.7 to 5.6]
NSAID during contraception	56	15.3	92	6.3	2.9	[2.0 to 4.2]	48	19.8	68	11.2	2.0	[1.3 to 3.0]
NSAID follow contraception (90)	27	7.4	28	1.9	4.0	[2.3 to 6.8]	21	8.6	19	3.1	3.0	[1.6 to 5.8]
Pain proximity menstrual (360)	61	16.7	23	1.6	15.1	[8.5 to 26.6]	61	25.1	34	5.6	6.5	[3.9 to 10.6]
Analgesic proximity menstrual (90)	29	7.9	19	1.3	6.3	[3.5 to 11.4]	29	11.9	30	4.9	2.6	[1.5 to 4.6]
Analgesic proximity pain (90)	45	12.3	15	1.0	15.5	[8.0 to 30.1]	45	18.5	20	3.3	7.1	[4.0 to 12.5]
NSAID proximity pain (90)	63	17.2	28	1.9	10.9	[6.7 to 17.7]	63	25.9	40	6.6	6.0	[3.7 to 9.7]
Lower GI proximity pain (90)	48	13.1	12	0.8	15.9	[8.4 to 29.9]	48	19.8	24	3.9	6.1	[3.6 to 10.6]
Lower GI proximity menstrual (90)	35	9.6	23	1.6	6.3	[3.7 to 10.7]	35	14.4	39	6.4	2.6	[1.6 to 4.1]
Pain separated by >180 days	36	9.8	14	1.0	12.5	[6.3 to 24.6]	36	14.8	14	2.3	8.5	[4.3 to 16.9]

^aComposite feature names follow the format X relationship Y [N] where relationship is defined as follows:

X during Y; only used where Y= contraception. X= feature and occurs at least once after the onset date and before the expected offset date of at least one contraceptive prescription.

X follow Y [N]; N= number of days. Y= discrete time point event. X= feature and occurs between 1 and N days after Y. Where Y= contraception, N days relate to the expected offset date. X proximity Y [N]; used where X and Y= discrete time point events and N is a number of days. X occurs between N days before and N days after Y. X exclusive Y; currently only used where Y= contraception: X= feature. X and Y are present but criteria for X during Y are never met. A single prescription of contraception occurring on the same day as a code for dysmenorrhoea would meet X exclusive Y criteria as X during Y requires X after the onset of contraception. X separated by >(N) days; two consecutive occurrences of X separated by more than N days.

CI= confidence interval. GI= gastrointestinal. NSAID= non-steroidal anti-inflammatory drug. OR= odds ratio.

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Ethical approval

The study involved analysis of anonymised data. Access to the data was approved by the Research Applications and Data Management Team at the University of Aberdeen.

Provenance

Freely submitted; externally peer reviewed.

Competing interests

The authors have declared no competing interests.

are indicated. These show differing patterns.

The plot for fertility problems (infertility) shows that until 1.5 years before diagnosis there was no association with a diagnosis of endometriosis, but from there the OR increased until about 0.5 years before diagnosis, at which point it stayed elevated. This is interpreted as indicating that the time delay from the occurrence of infertility to diagnosis is relatively short, presumably as infertility leads to referral including diagnostic laparoscopy.

The plot for gynaecological pain shows that the OR was significantly elevated several years prior to diagnosis and that this increased in the year prior to diagnosis (at least in the population comparison). The two plots for non-specific symptoms (fatigue and lower gastrointestinal symptoms) show patterns of longstanding modest elevation.

The bottom row of plots in Figure 1 shows two composite features: lower GI symptoms within 90 days of gynaecological pain and

episodes of gynaecological pain >180 days apart. Although CIs for these composites were wider there was a suggestion of a trend over time in the lower GI plus pain combination.

DISCUSSION

Summary

This study has two important new findings. First, the predictive value of several composite features for a subsequent diagnosis of endometriosis in routine records was evaluated. Second, for the first time, different time trends in the appearance of recorded clinical features of endometriosis were demonstrated.

Strengths and limitations

The choice of features as pointers used principles of feature selection based on expert input,¹⁹ and methods of data consolidation and aggregation that have been developed for use with clinical data sources

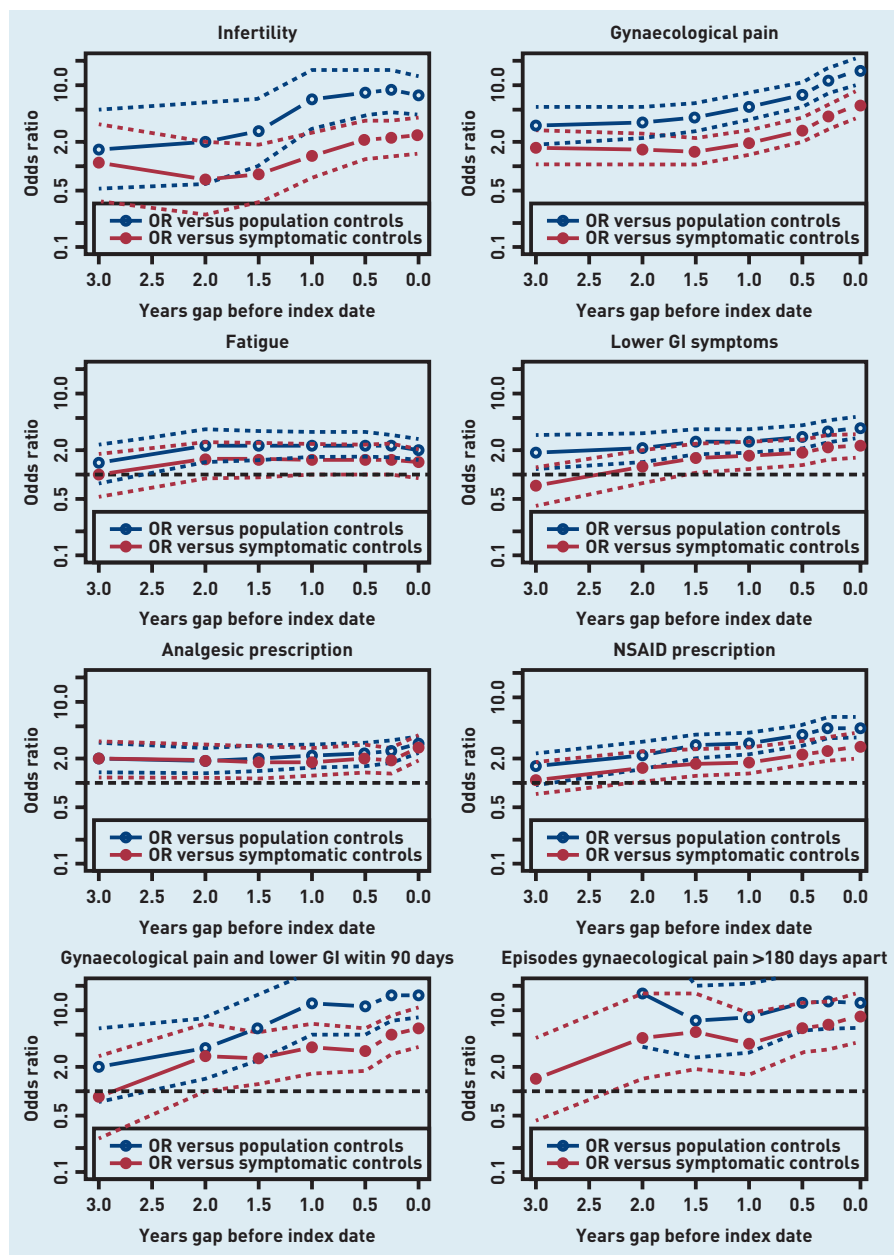


Figure 1. Plots of OR for individual features over 3 years, by gap between the end of the 3-year window and the date of diagnosis/matching. Dotted lines indicate 95% CI for ORs. CI = confidence interval. OR = odds ratio.

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The data were more sparse than anticipated, with only around half of cases having cardinal clinical features of endometriosis recorded prior to diagnosis. This probably reflects the limited use of symptom codes by GPs, even in this database where a reason for consultation was meant to be given for each attendance. The rates of coding of procedures such as laparoscopy was surprisingly low; the authors suspect this is because GP practices had coded the findings of the laparoscopy rather than the procedure itself. Finally, as the duration of the database was shorter than a female's reproductive period, a decision was made to exclude some females aged >35 years and diagnosed with endometriosis in order to maintain a focus on females for whom electronic health records were more likely to have data about earlier menstrual and related symptoms.

Comparison with existing literature

The authors are not aware of other studies that have looked for combinations of features in time as predictors of diagnoses in GP records. Although combinations of symptoms are commonly used in cancer prediction tools, these are usually simply recorded as present or absent,²² whereas in this study temporal relationships were specified in order to increase the specificity of pointers. Other studies of endometriosis have only reported single items.⁵

Implications for research and practice

The composite predictors of a diagnosis of endometriosis variables reflect the patterns that clinicians observe, and, for the first time, they have been tested using data in routine GP records over time. These combinations — including pain and menstrual symptoms in the same year; pain and lower GI symptoms in the same 90 days; and episodes of pain separated by at least 6 months — are likely to be clinically useful, as pointers to a diagnosis in their own right. However, the fact that they can be derived from existing data means that they have potential to be included in diagnostic support software within GP records.²³ This study did not have sufficient cases to split the data into derivation and test sets, but future studies can use these composite features to test their predictive value in larger and better linked datasets. Additionally, machine learning techniques have a potential value in feature reduction and model selection.^{24,25} Ultimately, the aim must be to apply these observations within predictive models for earlier referral and diagnosis of endometriosis.

other than GP records.^{17,20} This sequence of steps is broadly comparable with other recent approaches to the summarisation of clinical data.^{20,21} An established anonymised GP record set was used that contained both diagnostic and symptom codes using the Read Code format, which means that the method is transferable to other research datasets and potentially to clinical use.

There were limitations relating to the data, as the data were from standalone primary care records with no linkage to secondary care records, meaning that the reliability of GPs' diagnoses of endometriosis could not be assessed. However, in the authors' experience, GP practices tend not to code such diagnoses without specialist opinion.

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