Title: Pointers to earlier diagnosis of endometriosis: nested case-control study using electronic health records.

Running Title: Pointers to endometriosis in electronic health records

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Abstract

Background

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

Aim

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

Design & Setting

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

Methods

Composite pointers comprised patterns of symptoms, prescribing or investigations, in combination or over time. We used conditional logistic regression to examine the presence of both new and established pointers during the three years before diagnosis of endometriosis and identify when they appeared.

Results

Several composite pointers were strongly predictive of endometriosis: including pain and menstrual symptoms occurring within the same year (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). While 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.

Conclusions

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

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Keywords

Endometriosis, Diagnosis, Primary Care, Electronic Health Records,

How this fits in

Endometriosis is a relatively common condition but the time from first presentation to diagnosis is often longer than ideal because symptoms are non-specific. We used anonymised GP record data to construct new pointers to the 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.

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(5, 6), subfertility, and with patient frustration and demoralisation(7). Endometriosis can be difficult to diagnose clinically; its symptoms are both common(8) and non-specific, so are often considered by general practitioners (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 biomarkers(11) and imaging (12) 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 value (2) and the problem of delays in diagnosis requires an understanding of when symptoms first appear. While data in electronic records contains many single items, experienced practitioners typically recognise composite patterns which involve combinations of items. For example repeated episodes of dysmenorrhoea except when taking hormonal contraception(15), is recognised by experienced clinicians as having diagnostic value in endometriosis. While such knowledge-derived features (16) are not immediately present in electronic records, they can be constructed(17) but we are not aware of studies which have attempted to do this using primary care data or for endometriosis.

We 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; (c) examine the relationship of these features to diagnosis at different time periods before the date of diagnosis.

Methods

Data source

We obtained 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. 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 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.

Populations

We conducted a nested case-control study. Cases were women with a diagnosis of endometriosis, who were born after 1/1/1974 and therefore aged 36 or less on 1/1/2010 . This enabled us to (a) capture teenage menstrual symptoms for the majority of women (b) avoid the possibility that an apparent new diagnosis in an older woman 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 women 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. We defined the index date for cases as the date of diagnosis of endometriosis and for controls as the date of diagnosis of

endometriosis in the matched case. We required that all cases and controls had been registered with their GP practice for at least one year before the index date.

Data extraction and preparation

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

We enriched the data by introducing composite features. We based these on clinical experience of the investigators and on interviews with ten experts (6 gynaecologists, 2 specialists in reproductive health and 2 representatives of a lay support organisation). Interviews sought to identify tacit patterns in symptoms which clinicians thought may be predictive of a diagnosis and were audio recorded, transcribed and analysed thematically. We specified composite features according to one of five relationships: proximity, following, separated, during and exclusive. These are summarised in Table 2.

For each feature (single and composite) we ascertained its presence in the record of each individual at any time in the record, and during a series of overlapping three-year time windows set at different intervals from the index date (for diagnosis or matching). We defined the windows using intervals between the end of the window and the index date of 0, 3, 6, 12, 18, 24 and 36 months. We then examined the appearance of statistical associations between available information in the record and diagnosis over time by comparing the same measure in different windows. The purpose of this was to differentiate between features which were present long before diagnosis (and might thus indicate missed diagnostic opportunities) and those which appeared only shortly before diagnosis (and may thus have triggered referral).

Analysis of association of features and patterns with diagnosis

We carried out conditional logistic regression 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, we used the "separated" composite variables 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, CI). All analyses were conducted in R 3.3 (19).

We conducted the analysis separately with population and symptomatic control groups. For the population comparison we included all cases and their matched controls. For the symptomatic comparison we included only cases which had recorded symptoms and their matched controls. For the time window analysis, we limited the data to women who had been registered with their practice for at least one year before the beginning of the gap. We plotted the odds ratios for each feature at each of the six different time gaps in order to visualise the appearance of predictive features over time.

Results

Patient characteristics

We obtained data from 366 cases and 1453 matched population controls. 243 cases had gynaecological symptoms (pain, menstrual symptoms and infertility) and were matched to a further 610 controls with comparable symptoms. Median age at diagnosis was 25 years, interquartile range (22 to 28). Age at diagnosis was younger than 20 years in 48 (12.8%) cases.

Data quality

201 cases (53.5%) were registered with the same GP practice (and therefore had continuous records in the PTI database) for at least five years before diagnosis

and 121 (32.2%) for at least 8 years before diagnosis. Similar proportions were seen for population controls (51.8% and 32.6% respectively) but more of the symptomatic controls had been registered for these time periods (65.3% and 43.0%). We found a recorded code for laparoscopy 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 we cannot exclude instances of a clinical diagnosis being entered without any confirmatory test. Likewise, there were few coded surgical procedures e.g. 13 cases (3.5%) had a recorded operation for tubal or ovarian problems excluding diagnostic laparoscopy. We excluded these procedures from the analysis, instead we focused on clinical features, investigations and medical treatments.

Occurrence of diagnostic features

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

The numbers and proportions of women with at least one instance of each feature, either in the 3 years prior to the index date or at any time are shown in table 3 (all cases and population controls) and table 4 (symptomatic cases and controls). Tables 3 & 4 also show the ORs (with 95% CIs) for the two comparisons: all cases vs. population controls and symptomatic cases (gynaecological pain, menstrual symptoms, or infertility) vs. matched symptomatic controls.

As expected, pain was more common in cases in both comparisons: OR=14.9 (95% CI 10.1 to 21.9) vs. population controls and OR=5.6 (95% CI 3.9 to 8.1) vs. symptomatic controls over 3 years' data. Menstrual bleeding and timing symptoms were coded more commonly than in population controls, OR 3.8 (2.8 to 5.0) and 2.1 (1.4 to 3.2), but not in comparison with symptomatic controls, OR 1.0 (0.7 to 1.4) and 1.2 (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. While simple tests such as full blood count were more common in cases than population controls, there was no difference in the symptomatic comparison. Genito-urinary 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) and NSAIDS (OR 4.8, 95% CI 3.6 to 6.4 and OR 3.0, 95% CI 2.1 to 4.2) 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 5 shows the number and proportion of patients with at least one instance of each of the composite features over the three 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 (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 was approximately eight times as likely in cases than symptomatic controls (OR 8.5, 95%CI 4.3 to 16.9). While 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 odds ratios of approximately 3.

Occurrence of diagnostic features over the time prior to diagnosis.

Figure 1 shows plots of eight diagnostic features, showing the ORs for three-year time windows with different intervals between the end of the three-year window and the diagnosis / matching date. Each plot compares cases with matched

population controls (in blue) and symptomatic cases with their matched symptomatic controls (in red). In all plots, 95% confidence intervals are indicated by dotted lines. These show differing patterns.

The plot for fertility problems (infertility) shows that until 18 months before diagnosis there is no association with a diagnosis of endometriosis, but from there the OR increases until about 6 months before diagnosis at which point it stays elevated. We interpret this 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 a significantly elevated odds ratio is present several years prior to diagnosis and that this increases in the year prior to diagnosis (at least in the population comparison). The two plots for non-specific symptoms (fatigue and lower gastro-intestinal symptoms) show patterns of long-standing modest elevation.

The bottom row of plots in figure 1 shows two composite features: lower GI symptoms within 90 days of gynaecological pain and analgesic prescription after cessation of contraception. While confidence intervals for these composites are wider there is a suggestion of a trend over time in the lower GI plus pain combination.

Discussion

Summary

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

Strengths and Limitations

Our choice of features as pointers used principles of feature selection based on expert input (20) and methods of data consolidation and aggregation which have been developed for use with clinical data sources other than GP records (17, 21). This sequence of steps is broadly comparable with other recent approaches to the summarisation of clinical data (21, 22). We used an established anonymised GP record set which contained both diagnostic and symptom codes using the Read code format which means that the method is transferrable to other research datasets and potentially into clinical use.

There were limitations relating to the data. As the data was from stand-alone primary care records with no linkage to secondary care records we could not assess the reliability of GPs' diagnosis of endometriosis, however in our experience GP practices tend not to code such diagnoses without specialist opinion. 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: we 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 women's reproductive period, we chose to exclude some older women diagnosed with endometriosis in order to maintain a focus on women for whom we were more likely to have data about earlier menstrual and related symptoms.

Comparison with existing literature

We are not aware of other studies which have looked for combinations of features in time as predictors of diagnoses in GP records. While combinations of symptoms are commonly used in cancer prediction tools, these are usually simply recorded as present or absent(23) whereas in this study we specified temporal relationships. We did this 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 we have tested them 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, but 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(24). In this study, we 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 (25, 26) have potential value in feature reduction and model selection. Ultimately the aim must be to apply these observations within predictive models for earlier referral and diagnosis of endometriosis.

Conclusion

We have developed and tested composite pointers to a diagnosis of endometriosis in GP records. Some of these were present several years before the diagnosis and may be valuable targets for systems to support earlier diagnosis.

Contribution to Authorship

CB, LI, LS and SB conceived the study which was designed by CB, LI, DS, SB, LS and DA. Interviews were conducted and primarily analysed by SB and DS. Data processing and analysis was designed by CB, LI and DA and conducted by CB and DA. All authors contributed to the manuscript. CB acts as guarantor,

Ethics

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.

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Competing interests

The authors declare no competing interests

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Table 1 Data Extracted and categories which individual codes were mapped to.

Feature type	Description	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 (e.g. cysts)
Non-specific symptoms	Abdominal pain and gastro-intestinal symptoms, fatigue, urinary symptoms; additional diagnoses, including irritable bowel syndrome(5);	Menstrual (timing) Genital / other gynae 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 (e.g. gonadotrophin releasing hormone agonists). Prescriptions for contraception Analgesics Antidepressant drugs	Hormonal treatment Contraception NSAIDs Codeine or other opioids Tricyclic SSRI and related

Table 2 Types of composite feature used in constructing predictors

Relationship	Specification	Example
Proximity	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	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 item occurred 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	Occurrence of a symptom or other feature after the onset of and before the expected offset of a contraception prescription	Pain during estimated duration of prescription for contraception
Exclusive	Feature only occurring in the absence of another.	Pain but only outside of estimated periods of prescribed contraception

Table 3: Numbers, proportions and odds ratios (95% CI) for features in cases of endometriosis compared with population controls

	Occurrence of features in 3 years before index date						Occurrence of features at any time before index date					
	Cases (N=366)		Controls (N=1489)				Cases (N=366)		Controls (N=1489)			
Specific features	N	%	N	%	OR	95% CI	N	%	N	%	OR	95% CI
Subfertility	39	10.7	24	1.7	7.7	(4.4 , 13.3)	41	11.2	31	2.1	5.9	(3.6 , 9.7)
Menstrual - bleeding	121	33.1	179	12.3	3.8	(2.8 , 5.0)	151	41.3	267	18.4	3.3	(2.6 , 4.3)
Menstrual -timing	39	10.7	80	5.5	2.1	(1.4 , 3.2)	45	12.3	117	8.1	1.6	(1.1 , 2.3)
Ovarian	24	6.6	7	0.5	13.7	(5.9 , 31.8)	25	6.8	11	0.8	9.8	(4.7 , 20.4)
Pain	145	39.6	79	5.4	14.9	(10.1 , 21.9)	169	46.2	146	10.1	9.9	(7.1 , 13.6)
Non-specific symptoms												
Fatigue	56	15.3	121	8.3	2.0	(1.4 , 2.8)	79	21.6	178	12.3	2.0	(1.5 , 2.7)
Gynaecological	51	13.9	47	3.2	5.0	(3.3 , 7.7)	77	21.0	97	6.7	4.0	(2.8 , 5.6)
Lower.GI	104	28.4	144	9.9	3.7	(2.8 , 5.0)	126	34.4	213	14.7	3.3	(2.5 , 4.3)
Upper.GI	27	7.4	62	4.3	1.8	(1.1 , 3.0)	50	13.7	107	7.4	2.1	(1.4 , 3.0)
Urinary	25	6.8	49	3.4	2.1	(1.3 , 3.5)	42	11.5	80	5.5	2.3	(1.5 , 3.5)
Tests& procedures												
Full Blood count	40	10.9	102	7.0	2.0	(1.2 , 3.2)	50	13.7	112	7.7	2.6	(1.6 , 4.2)
Genital swabs	64	17.5	77	5.3	4.5	(3.0 , 6.7)	73	20.0	111	7.6	3.5	(2.5 , 5.0)
Laparoscopy	42	11.5	13	0.9	14.6	(7.5 , 28.4)	47	12.8	15	1.0	13.9	(7.5 , 25.7)
Thyroid function	53	14.5	112	7.7	2.4	(1.6 , 3.5)	67	18.3	132	9.1	2.8	(1.9 , 4.1)
Ultrasound	14	3.8	5	0.3	12.3	(4.0 , 37.8)	14	3.8	11	0.8	5.0	(2.2 , 11.4)
Treatments												
Contraception	201	54.9	716	49.3	1.3	(1.0 , 1.6)	234	63.9	800	55.1	1.5	(1.2 , 2.0)
NSAID	171	46.7	276	19.0	4.8	(3.6 , 6.4)	191	52.2	393	27.1	3.8	(2.9 , 5.1)
Analgesic	136	37.2	254	17.5	3.0	(2.3 , 4.0)	156	42.6	343	23.6	2.7	(2.1 , 3.5)
SSRI	65	17.8	188	12.9	1.5	(1.1 , 2.0)	85	23.2	229	15.8	1.7	(1.2 , 2.2)
Tricyclic	29	7.9	60	4.1	2.2	(1.3 , 3.6)	42	11.5	82	5.6	2.4	(1.6 , 3.6)

Features: **Ovarian** :coded diagnosis of ovarian cysts etc.; **Gynaecological**: vulvovaginal symptoms, pelvic inflammation; **Lower GI**: pain, bloating, irritable bowel syndrome, **Upper.GI:** dyspepsia, reflux, nausea; **SSRI**: Selective Serotonin Reuptake Inhibitor & related antidepressants**; NSAID**: Non-steroidal Anti-inflammatory Drugs
Index date: date of diagnosis for cases, date of diagnosis of matched case for controls

Table 4 Numbers, proportions and odds ratios (95% CI) for features in cases of endometriosis compared with- symptomatic controls

	Occurrence of features in 3 years before index date						Occurrence of features at any time before index date					
	Cases (N=261		Controls (N=884)				Cases (N=261		Controls (N=884)			
Specific features	N	%	N	%	OR	95% CI	N	%	N	%	OR	95% CI
Subfertility	39	16.1	52	8.5	2.4	(1.4 , 3.9)	41	16.9	64	10.5	1.9	(1.2 , 3.1)
Menstrual - bleeding	121	49.8	304	49.8	1.0	(0.7 , 1.4)	151	62.1	443	72.6	0.7	(0.5 , 0.9)
Menstrual -timing	30	12.4	64	10.5	1.2	(0.7 , 1.9)	34	14.0	111	18.2	0.7	(0.5 , 1.1)
Ovarian	14	5.8	3	0.5	12.2	(3.5 , 42.7)	15	6.2	6	1.0	7.0	(2.7 , 18.1)
Pain	145	59.7	148	24.3	5.6	(3.9 , 8.1)	169	69.6	241	39.5	4.0	(2.8 , 5.6)
Non-specific symptoms												
Fatigue	45	18.5	84	13.8	1.4	(0.9 , 2.1)	66	27.2	138	22.6	1.3	(0.9 , 1.9)
Gynaecological	41	16.9	34	5.6	4.2	(2.4 , 7.4)	64	26.3	68	11.2	3.6	(2.3 , 5.6)
Lower.GI	79	32.5	109	17.9	2.3	(1.6 , 3.2)	95	39.1	180	29.5	1.7	(1.2 , 2.3)
Upper.GI	24	9.9	51	8.4	1.3	(0.8 , 2.3)	44	18.1	87	14.3	1.5	(1.0 , 2.3)
Urinary	20	8.2	29	4.8	1.8	(1.0 , 3.4)	36	14.8	64	10.5	1.5	(1.0 , 2.4)
Tests & procedures												
Full Blood count	34	14.0	82	13.4	1.2	(0.7 , 2.2)	42	17.3	97	15.9	1.4	(0.8 , 2.4)
Genital swabs	43	17.7	71	11.6	2.2	(1.3 , 3.5)	50	20.6	90	14.8	1.9	(1.2 , 3.0)
Laparoscopy	31	12.8	4	0.7	20.0	(7.0 , 57.1)	35	14.4	13	2.1	7.2	(3.7 , 14.1)
Thyroid function	43	17.7	86	14.1	1.5	(0.9 , 2.4)	53	21.8	103	16.9	1.7	(1.1 , 2.7)
Ultrasound	11	4.5	6	1.0	5.2	(1.6 , 17.0)	11	4.5	7	1.2	4.3	(1.4 , 13.0)
Treatments												
Contraception	151	62.1	373	61.2	1.1	(0.8 , 1.5)	178	73.3	421	69.0	1.3	(0.9 , 1.9)
NSAID	133	54.7	185	30.3	3.0	(2.1 , 4.2)	150	61.7	264	43.3	2.6	(1.8 , 3.7)
Analgesic	100	41.2	142	23.3	2.7	(1.9 , 3.9)	116	47.7	203	33.3	2.3	(1.6 , 3.4)
SSRI	43	17.7	115	18.9	1.0	(0.7 , 1.5)	57	23.5	148	24.3	1.1	(0.8 , 1.6)
Tricyclic	20	8.2	37	6.1	1.5	(0.8 , 2.7)	29	11.9	58	9.5	1.3	(0.8 , 2.1)

Features: **Ovarian** :coded diagnosis of ovarian cysts etc.; **Gynaecological**: vulvovaginal symptoms, pelvic inflammation; **Lower GI**: pain, bloating, irritable bowel syndrome, **Upper.GI:** dyspepsia, reflux, nausea; **SSRI**: Selective Serotonin Reuptake Inhibitor & related antidepressants**; NSAID**: Non-steroidal Anti-inflammatory Drugs
Index date: date of diagnosis for cases, date of diagnosis of matched case for controls

Table 5 Numbers, proportions and odds ratios (95% CI) for composite features in the three years before diagnosis / matching

	Comparison with population controls						Comparison with symptomatic controls					
	Cases (N=366)		Controls (N=1489)				Cases (N=261)		Controls (N=884)			
	N	%	N	%	OR	95%CI	N	%	N	%	OR	95%CI
Pain during contraception	40	10.9	24	1.7	7.4	(4.3 , 12.7)	40	16.5	38	6.2	3.0	(1.9 , 5.0)
Pain following contra'n (180)	17	4.6	8	0.6	8.5	(3.7 , 19.7)	17	7.0	17	2.8	3.1	(1.5 , 6.4)
Pain exclusive contraception	105	28.7	55	3.8	14.2	(9.1 , 22.0)	105	43.2	110	18.0	4.3	(2.9 , 6.2)
Menstrual during contraception	38	10.4	65	4.5	2.6	(1.7 , 4.1)	38	15.6	87	14.3	1.1	(0.7 , 1.8)
Menstrual follow contra'n (180)	14	3.8	8	0.6	7.0	(2.9 , 16.7)	14	5.8	17	2.8	2.0	(1.0 , 4.2)
Analgesic during contra'n	51	13.9	90	6.2	2.5	(1.7 , 3.7)	39	16.1	59	9.7	2.0	(1.3 , 3.1)
Analgesic follow contra'n (180)	27	7.4	26	1.8	4.5	(2.5 , 7.8)	21	8.6	21	3.4	2.8	(1.5 , 5.3)
Analgesic exclusive contra'n	116	31.7	68	4.7	12.0	(8.1 , 17.8)	116	47.7	132	21.6	3.9	(2.7 , 5.6)
NSAID during contra'n	56	15.3	92	6.3	2.9	(2.0 , 4.2)	48	19.8	68	11.2	2.0	(1.3 , 3.0)
NSAID follow contra'n (90)	27	7.4	28	1.9	4.0	(2.3 , 6.8)	21	8.6	19	3.1	3.0	(1.6 , 5.8)
Pain proximity menstrual (360)	61	16.7	23	1.6	15.1	(8.5 , 26.6)	61	25.1	34	5.6	6.5	(3.9 , 10.6)
Analgesic proximity menst'l (90)	29	7.9	19	1.3	6.3	(3.5 , 11.4)	29	11.9	30	4.9	2.6	(1.5 , 4.6)
Analgesic proximity pain (90)	45	12.3	15	1.0	15.5	(8.0 , 30.1)	45	18.5	20	3.3	7.1	(4.0 , 12.5)
NSAID proximity pain (90)	63	17.2	28	1.9	10.9	(6.7 , 17.7)	63	25.9	40	6.6	6.0	(3.7 , 9.7)
Lower GI proximity pain (90)	48	13.1	12	0.8	15.9	(8.4 , 29.9)	48	19.8	24	3.9	6.1	(3.6 , 10.6)
Lower GI proximity menst'l (90)	35	9.6	23	1.6	6.3	(3.7 , 10.7)	35	14.4	39	6.4	2.6	(1.6 , 4.1)
Pain separated by >180 days	36	9.8	14	1.0	12.5	(6.3 , 24.6)	36	14.8	14	2.3	8.5	(4.3 , 16.9)

Feature names follow the format X *relationship* Y where relationship is defined as follows

X during Y – only used where Y = contraception: X 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 is a number of days; where Y is a discrete time point event. X occurs between 1 and N days after Y**.** Where Y = contraception, N days relates to the expected offset date

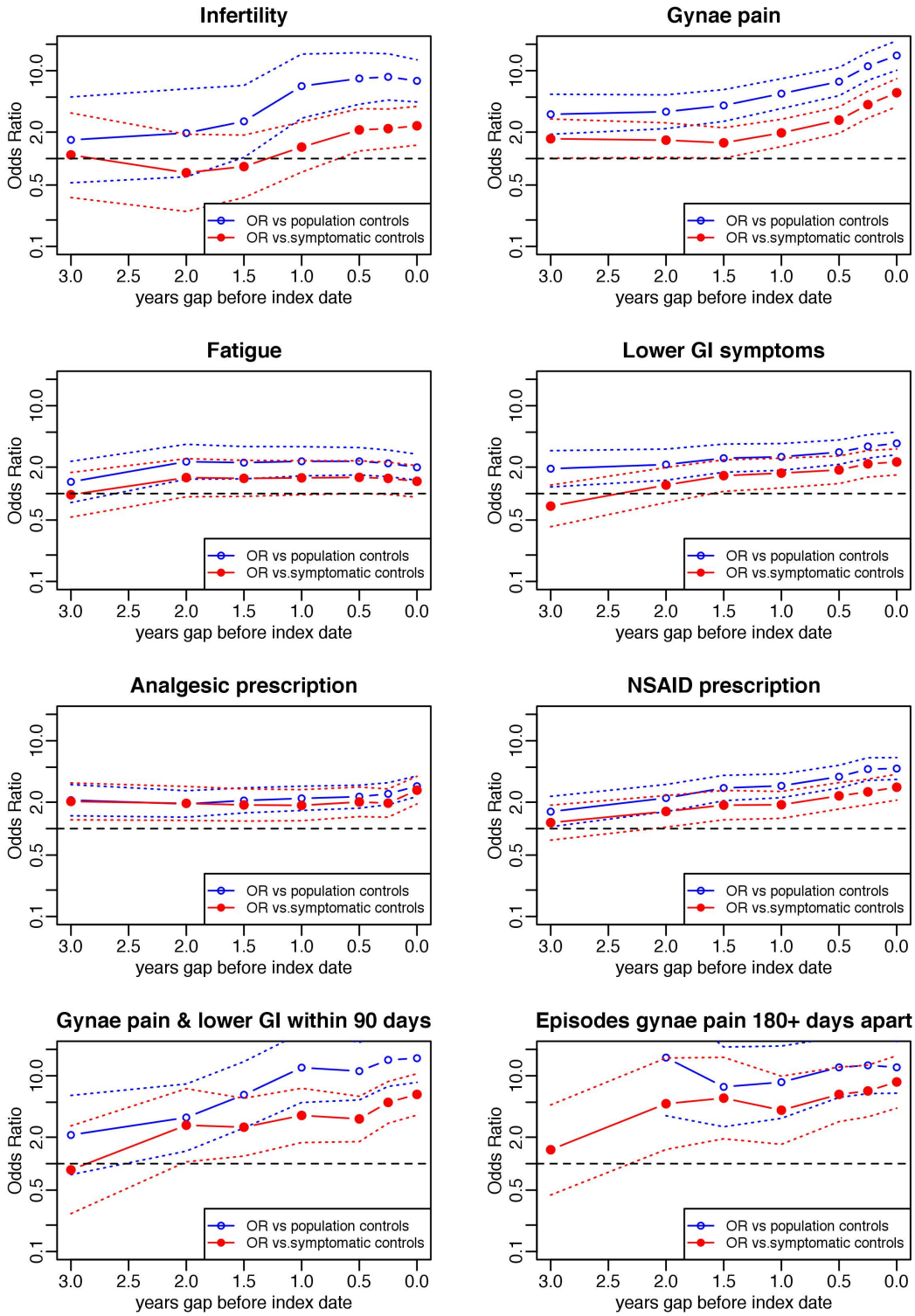
X proximity Y (N) – used where X and Y are both discrete time point events and N is a number of days. X occurs between N days before and N days after Y

X exclusive Y – currently only used where Y = contraception: X 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

For individual feature explanations, see footnotes to tables 1 & 2

Figure 1 Plots of odds ratio for individual features over three years, by gap between the end of the three year window and the date of diagnosis / matching



Dotted lines indicate 95% confidence intervals for odds ratios