Comorbidity Co-occurrence in Women with Endometriosis: A Retrospective Matched Cohort Study

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Background

Endometriosis (endo') is a gynecological, chronic, multi-systemic, inflammatory and estrogen-dependent disease that affects 10% of women[1–3], with an average delay in diagnosis of about 12 years.[4–6] The disease is characterized by cells, similar to those of the inner uterine lining (endometrium), that grow outside the uterus, predominantly in the pelvic area. These cells respond to hormonal signals, in particular to estrogen, causing inflammation in the surrounding tissue and developing scar tissue and adhesions that attach pelvic tissues and organs to each other. Because endo' is a multisystem disease, patients may suffer from many and varied symptoms such as severe pain during menstruation and ovulation, chronic pelvic pain, severe lower back pain, pain during intercourse, digestive problems, rectal bleeding, nausea, vomiting, frequent and painful urination, chronic fatigue, migraines, mood swings, and infertility.[2,7–10]

Recent studies have shed light on the potential association between endo' and a range of comorbidities.[7,11–16] These comorbidities encompass autoimmune diseases[16–19], cardiovascular diseases[20], various allergies[16,21,22], fibromyalgia and chronic fatigue syndrome[7], migraines[8], as well as fertility problems.[23,24] Given the intricate and multifaceted nature of endo', it is imperative to thoroughly investigate the increased risk of comorbidities in women affected by this condition, particularly those mentioned above. Here, we explore the co-occurrence of various comorbidities in women with endo', compared to a matched non-endometriosis cohort. Elucidating these associations may enhance our understanding of the disease and help develop targeted interventions to improve the overall health and well-being of women with endo'.

Methods

Study design. A retrospective, matched cohort study using routinely collected healthcare data, standardized to the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM).

Data sources. IQVIA Medical Research Data (IMRD) contains longitudinal non-identified patient electronic healthcare records (EHR) collected from UK General Practitioner (GP) clinical systems: IMRD-THIN (version: 2022-09, 17M individuals) incorporates data from a Cegedim database; and IMRD-EMIS (version: 2022-12, 5.4M individuals). The use of IMRD for research has been approved by the NHS Health Research Authority (NHS Research Ethics Committee ref 18/LO/0441) for medical and public health research; this study received SRC approval ref 23SRC021.

Study population. The endo' cohort includes females, aged 14-50 years, diagnosed with endo' or adenomyosis. Individuals in the endo' cohort were matched 1:1 to counterparts not diagnosed with endo', by birth year and sex. The index date of each matched pair is the calendar date of the first endo' diagnosis. Eligible pairs were selected to have at least 1 year of prior observation on that date. Comorbidity cohorts rely on corresponding diagnoses, and include females, aged 14-50 years.

Statistical analysis. For each comorbidity, we compare its prevalence in the endo' and non-endo' cohorts,

measure the discrepancy using Standardized Mean Differences (SMD; with values >0.1 considered meaningful) and assign it with an adjusted P-value[25] (with values <0.05 considered significant).

Results

The endometriosis cohorts consisted of 26,630 and 11,781 individuals in the IMRD-THIN and IMRD-EMIS databases, respectively, of which 26,605 and 11,772, respectively, have been matched to a non-endo' counterparts. Table 1 provides an overview of the characteristics of the endometriosis and non-endometriosis cohorts in the IMRD-THIN and IMRD-EMIS databases. In both databases, the median age is 35, with longer baseline and follow-up periods in IMRD-EMIS.

Table 1. Characteristics of the endo' and non-endo' cohorts in the IMRD-THIN and IMRD-EMIS databases.

	IMRD-THIN			IMRD-EMIS		
	Endo	Non-endo	P-value[†]	Endo	Non-endo	P-value[†]
N	26,605		–	11,772		–
Age [years][*]	35 (29, 41)		–	35 (29, 41)		–
Baseline period [years][*]	4.6 [2.4, 8.5]	5.1 [2.7, 8.9]	<0.001	6.6 [2.9, 14.3]	7.7 [3.6, 15.4]	<0.001
Follow-up period [years][*]	5.0 [2.1, 9.9]	5.0 [2.0, 9.7]	0.018	6.0 [2.4, 12.9]	5.6 [2.2, 12.1]	<0.001

[*]Median (IQR); [†]Wilcoxon rank sum test

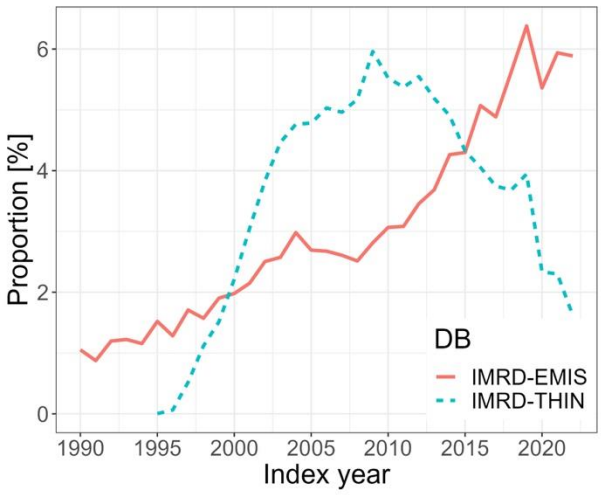

Figure 1. Index year histogram

Figure 1 shows the distribution of index years in IMRD-THIN and IMRD-EMIS. The disparity in these distributions is likely attributed to differences in the annual number of covered individuals in each database.

Our comprehensive results are summarized in Table 2, showcasing the consistency of findings across the IMRD-THIN and IMRD-EMIS databases for all comorbidities examined. Among the 14 tested comorbidities, migraines and headaches were most prevalent in endometriosis patients (44% and 42% in the IMRD-THIN and IMRD-EMIS databases, respectively; migraines alone were also associated with a significant risk), followed by chronic fatigue syndrome, fatigue, or asthenia (39% and 35%), autonomic nervous system disorders (22% and 24%), and allergies or mast cell activation syndrome (19% and 20%).

Conclusion

This retrospective cohort study provides evidence of a potential heightened risk of comorbidities in women with endometriosis. Several mechanisms may explain these increased risks: (1) misdiagnosis of endometriosis-like symptoms, e.g., gastrointestinal and abdominal pain as inflammatory bowel disease; (2) enhanced health surveillance, identifying conditions not otherwise detected; (3) shared or related physiological mechanism, for example, the inflammatory response elicited by endometriosis or a higher sensitivity to hormones fluctuation can contribute to the development or exacerbation of comorbidities. Teasing out the correct mechanism for each comorbidity requires more careful examination, e.g., of timelines, and will be a focus of our future work.

Table 2. Comorbidity co-occurrence in endo' patients, compared to age-matched non-endo' women.

	IMRD-THIN					IMRD-EMIS				
Comorbidity	N	Endo	Non-endo	Adj. P-value*	SMD†	N	Endo	Non-endo	Adj. P-value*	SMD†
Allergy Mast Cell	467,609	4,997 (19%)	3,867 (15%)	<0.001	0.11	149,748	2,367 (20%)	1,693 (14%)	<0.001	0.2
Anemia	184,795	3,083 (12%)	2,237 (8.4%)	<0.001	0.11	79,635	1,868 (16%)	1,141 (9.7%)	<0.001	0.2
Appendicitis	5,778	154 (0.6%)	45 (0.2%)	<0.001	0.067	3,029	119 (1.0%)	38 (0.3%)	<0.001	0.085
Autonomic Nervous System Disorders	341,288	5,921 (22%)	4,263 (16%)	<0.001	0.2	113,271	2,860 (24%)	1,806 (15%)	<0.001	0.2
Fatigue, Asthenia	606,663	10,360 (39%)	7,171 (27%)	<0.001	0.3	173,988	4,118 (35%)	2,591 (22%)	<0.001	0.3
Female Infertility	119,378	4,061 (15%)	1,477 (5.6%)	<0.001	0.3	49,176	1,912 (16%)	698 (5.9%)	<0.001	0.3
Fibromyalgia	28,706	783 (2.9%)	370 (1.4%)	<0.001	0.11	10,809	458 (3.9%)	189 (1.6%)	<0.001	0.14
Inflammatory Bowel Disease	64,579	1,320 (5.0%)	802 (3.0%)	<0.001	0.1	31,001	829 (7.0%)	451 (3.8%)	<0.001	0.14
Migraine	221,119	4,027 (15%)	2,452 (9.2%)	<0.001	0.2	80,456	2,097 (18%)	1,202 (10%)	<0.001	0.2
Migraine + Headache	741,920	11,821 (44%)	8,274 (31%)	<0.001	0.3	218,199	4,930 (42%)	3,104 (26%)	<0.001	0.3
Osteoporosis (no age limit)	225,611	464 (1.7%)	326 (1.2%)	<0.001	0.043	70,705	310 (2.6%)	218 (1.9%)	<0.001	0.053
Pelvic Inflammatory Disease	205,747	4,514 (17%)	2,479 (9.3%)	<0.001	0.2	133,340	3,389 (29%)	1,988 (17%)	<0.001	0.3
Thyroid Disorder	123,601	1,860 (7.0%)	1,427 (5.4%)	<0.001	0.068	51,009	993 (8.4%)	663 (5.6%)	<0.001	0.11
Uterine Fibroids	53,236	2,007 (7.5%)	627 (2.4%)	<0.001	0.2	26,541	1,365 (12%)	408 (3.5%)	<0.001	0.3

*Wilcoxon rank sum test, P-value adjusted for multiple comparisons; †SMD: Standardized Mean Differences

Moreover, we will examine additional conditions such as diabetes[26,27], thyroid disorders[28], cardiovascular diseases[20], and osteoporosis[29–31]; as well as autoimmune diseases[16–19], including systemic lupus erythematosus, Sjogren's syndrome, rheumatoid arthritis, and multiple sclerosis. We also plan to apply a data-driven analysis and compare the prevalence of all occurring condition groups in the endo` versus non-endo` – or other disease – cohorts.

In addition to investigating whether endometriosis patients face a higher risk of developing these conditions, we will also test whether patients with autoimmune diseases are more susceptible to endometriosis. We also plan to explore the interplay between various conditions, e.g., to determine if suffering from multiple diseases increases the likelihood of experiencing infertility. Finally, we aim to extend the scope of analysis by incorporating additional data sources and geographies.

This effort seeks to deepen our understanding of the intricate associations between endometriosis and various comorbidities. These insights may contribute to the development of comprehensive clinical management strategies and proactive interventions, ultimately leading to improved care for patients affected by endometriosis and its associated comorbidities.

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