Increased overall morbidity in women with endometriosis: a population-based follow-up study until age 50

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Objective: To investigate whether there is an association between endometriosis and nongynecological diseases in the general female population by age 50?
Design: A prospective cohort study.
Setting: Study participants with and without endometriosis were identified from a general population-based birth cohort. The analyzed data, linking to the national hospital discharge registers, spanned up to the age of 50 years.
Patient(s): Endometriosis case identification was based on national register data and self-reported diagnoses, producing a study population of 349 women with endometriosis and 3,499 women without endometriosis.
Main Outcome Measure(s): *International Classification of Diseases* diagnosis codes from 1968 to 2016 were accumulated from the Finnish national Care Register for Health Care, whereas self-reported symptoms and continuous medication usage data were collected from the questionnaires distributed at age 46. The associations between endometriosis and comorbidities were assessed using logistic regression models that included several covariates. The odds ratios and 95% confidence intervals (CIs) were modeled. Endometriosis subtype and temporal analyses were also performed.
Result(s): Women with endometriosis were on average twice as likely to have hospital-based nongynecological diagnoses as women without endometriosis (adjusted odds ratio [aOR] 2.32; 95% CI, 1.07–5.02). In more detail, endometriosis was associated with allergies, infectious diseases, pain-causing diseases, and respiratory diseases. Moreover, the affected women presented with nonspecific symptoms and signs (aOR 3.56; 95% CI, 2.73–4.64), especially abdominal and pelvic pain (aOR 4.33; 95% CI, 3.13–4.76) more often compared with nonendometriosis controls. The temporal analysis revealed that diagnoses accumulated at a significantly younger age among women with endometriosis than in nonendometriosis counterparts.
Conclusion(s): Women with endometriosis have a high risk for several chronic diseases compared with women without endometriosis, underlying the need for awareness and targeted resources for these women in the health care system. Moreover, endometriosis should be considered in the presence of nonspecific symptoms and abdominal pain, as they may conceal the disease and cause considerable delay in diagnosis and treatment. (Fertil Steril® 2023;119:89–98. ©2022 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: Endometriosis, comorbidity, immunological diseases, pain-causing disease, diagnostic delay

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Endometriosis is a chronic estrogen-dependent disorder affecting 6%–10% of women in the reproductive age. It may cause dysmenorrhea, chronic abdominal/pelvic pain, and infertility (1, 2). The etiology of endometriosis is multifactorial, including genetic, environmental, and lifestyle components (3, 4). Abnormalities in steroidogenesis, immune response, angiogenesis, inflammation, and apoptosis have been identified as possible predisposing factors in the

pathogenesis of endometriosis, and they may act as pathogenic features to endometriosis-related comorbidities as well (1).

The symptoms of endometriosis can be nonspecific and overlap with gastrointestinal and pelvic pain-causing diseases, resulting in misdiagnoses and diagnostic delays. Normalization of endometriosis-related symptoms, especially the ones related to menstrual cycles, is another main cause of diagnostic delay (5). Although the onset of the symptoms may occur soon after menarche, several studies have reported a diagnostic delay of 7–9 years, which results in impaired quality of life for the affected women (5–7). Moreover, women with endometriosis have several health service contacts before the endometriosis diagnosis is established, and patients with longer diagnostic delays accumulate more comorbid diagnoses, causing heavy social and economic burden (8–10). Endometriosis is associated with an increased risk of nongynecological comorbidities, such as autoimmune diseases, bowel diseases, migraine, mental, and cardiovascular diseases (11–16). However, only few studies have systematically assessed endometriosis-related overall comorbidity in a population-based setting (17–20). Moreover, previous studies have limitations in considering confounding factors, temporality of comorbidities, and the associations between morbidity and peritoneal, ovarian, and deep endometriosis separately.

The aim of this study was to investigate the prevalence of nongynecological diagnoses and comorbidities in women with endometriosis by exploring the *International Classification of Diseases* (ICD) diagnoses in a prospective population-based data set.

MATERIALS AND METHODS

Study Population

The study was based on the *Northern Finland Birth Cohort 1966* (NFBC1966), which is a population-based cohort consisting of 96.3% of all expected births during 1966 in Northern Finland area (12,055 mothers, 12,058 live-born children, of which 5,889 were girls). The cohort has been originally designed to assess long term health and workability. The data collection points for the cohort have been birth and ages 1, 14, 31, and 46 years. This study used the NFBC1966 data collected at the age of 46 years through postal questionnaires and/or clinical examinations. The ethics committee of *Northern Ostrobothnia hospital* district approved the study (EETTMK:94/2011). All participants of the NFBC provided informed consent for the use of their data as well as linkages to national registers. The NFBC1966 study was conducted in accordance with the Helsinki Declaration.

Identification of Women with Endometriosis

Women with endometriosis were identified using 2 different data sources as previously described (21, 22):

- Endometriosis diagnoses were retrieved from the *Finnish national Care Register for Health Care* (CRHC), in which endometriosis cases were identified based on the ICD 8, 9, and 10 codes (ICD-8/9: 617.1–617.9; ICD-10: N80.1–N80.9). The register data linkage was available for all women in the NFBC data set.
- Given that not all endometriosis diagnoses are hospital-based and, to reduce the effect of possible selection bias, endometriosis case identification was extended to self-reported data.

At age 46, the NFBC1966 women were asked, "Have you ever been diagnosed with endometriosis by a physician?" The self-reported endometriosis diagnosis has been validated previously (23). Seventy-two percent of the participants answered the questionnaire. The total endometriosis population consisted of 349 women (ICD-based n = 224 and/or self-reported n = 284). In cases where both diagnostic methods were available (n = 152) women were counted only once for the analysis. For the secondary analysis, the ICD code based endometriosis group (n = 224) was divided into the following endometriosis subtypes according to ICD-10 code: 59 (26%) peritoneal endometriosis (N80.2 and N80.3), 107 (48%) ovarian endometriosis (N80.1), 35 (16%) deep endometriosis (N80.4, N80.5, and N80.8), and other endometrioses (N80.9, N80.6) 23 (10%). Women who did not have an ICD code for endometriosis and did not self-report endometriosis were considered women without endometriosis (n = 3,499). A flow chart of the study population is shown in Supplemental Figure 1 (available online).

Comorbidity Assessment Using National Hospital Discharge Register ICD Code Data

The Finnish National CRCH systematically collects data from all patient encounters within the Finnish health care system hospitals. The register includes diagnoses according to the *World Health Organization* (WHO) ICD codes including dates for each inpatient hospital visit accordingly. In the Finnish health care system, ICD codes are used primarily for clinical purposes and health surveillance and secondarily for municipal billing. The ICD codes are set by the clinicians when discharging the patients and thus are considered accurate and reliable. These national registers are widely used in academic research, auditing and guiding national health care policies (24). The NFBC1966 population was linked to the CRHC using the personal identification code given to each Finnish citizen at birth or immigration. Data were available and collected for the period from 1968 to 2016. The lifetime accumulation of any nongynecological ICD codes were analyzed to assess the overall morbidity in women with endometriosis. Diagnosis codes related to neoplasms of female genital organs (C51-C58, D25-D27, and D39), genitourinary system diseases (N00–N99) and pregnancy, childbirth, and the puerperium (O00–O94), were excluded from the analysis as obstetric and gynecologic morbidity as well as were outside our research scope. The ICD codes were divided into main categories and subcategories according to the WHO classification (www.who.int/classifications/icd/ICD10Volume2_en_2010.pdf).

The endometriosis subcategories in CRHC are confirmed and captured by the clinician performing the gynecological surgery. Here, ICD-10 main categories were analyzed, and certain subcategories of ICD codes were reported in more

TABLE 1

Characteristics of the study population at age 46 years.

	No endometriosis n = 3,499 (%/SD)	Endometriosis n = 349 (%/SD)	*P* value
Contraception use (ever)	2,958 (89.2%)	299 (93.2%)	.023
Parity			
0	303 (9.7%)	42 (13.8%)	
1–2	1,696 (54.5%)	174 (57.0%)	.017
≥3	1,111 (35.7%)	89 (29.2%)	
BMI	26.5 (5.3)	26.0 (5.1)	.113
Smoking			
Nonsmoker	1,886 (53.9%)	203 (58.2%)	
Former/occasional	807 (23.1%)	69 (19.8%)	.419
Smoker	635 (18.1%)	62 (17.8%)	
Alcohol consumption			
Absteiner	383 (11.4%)	46 (13.5%)	
Low-risk drinker	2,707 (80.7%)	274 (80.6%)	.250
At risk drinker	264 (7.9%)	20 (5.9%)	
Physical activity			
Low	746 (22.2%)	65 (19.2%)	
Moderate	1,376 (41.0%)	150 (44.2%)	.351
High	1,232 (36.7%)	124 (36.6%)	
Marital status			
Single	784 (22.4%)	70 (20.1%)	.314
In a relationship	2,715 (77.6%)	279 (79.9%)	
Education			
Basic	210 (6.2%)	15 (4.4%)	
Secondary	2,148 (63.8%)	208 (61.4%)	.152
Tertiary	1,010 (30.0%)	116 (34.2%)	

Note: Data reported as mean (SD) or numbers (percentages). Significance tests for continuous variables were performed by using the independent samples *t* test or the Mann-Whitney *U* test, as appropriate.
Two-sided *P* value < .05 was considered significant.
Differences in numbers vary in different analyses as a result of some missing data.
P values are for women with endometriosis compared with control women. BMI = body mass index

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detail based on the results of the analysis and the existing literature. The ICD-8 and ICD-9 codes were converted to ICD-10 codes and included in the analyses as such.

Self-reported Allergic, Infectious, and Autoimmune Symptoms and Regular Medication Usage

In the Finnish health care system, allergies and autoimmune symptoms are mainly diagnosed and treated in outpatient clinics and are therefore not obtainable from the CRCH. Thus, self-reported lifetime allergic, infectious, and autoimmune symptoms, susceptibility to infections, and continuous medication use data were collected from the 46-year questionnaires (https://www.oulu.fi/nfbc/1966datacollections). The medication data included self-reported continuous medication usage, and the data were organized according to the *WHO Anatomical Therapeutic Chemical Classification* system.

Covariates

Several possible confounding variables were considered for the associations between endometriosis and morbidity according to the literature: parity and lifetime contraceptive use, body mass index (BMI), smoking, alcohol consumption, physical activity, socioeconomic status, and relationship status. More detailed description of covariates can be found in our earlier studies (21, 22) and the summary list is shown in Table 1. In short, parity was based on questionnaires and classified as 0, 1–2, and ≥3. The respondents were asked if they had ever used hormonal contraceptives. Weight and height were measured during 46-year follow-up visit, and BMI was calculated according to these measurements (kg/m^2). The respondents were categorized as nonsmokers, former or occasional smokers, and active smokers. In terms of alcohol consumption, the respondents were classified as abstainers, low-risk drinkers (≤20 g/day), and high risk drinkers (>20 g/day). Physical activity was calculated as the metabolic equivalent of task (MET) scores in hours per week, considering the frequency and duration of leisure activities (3 METs = light and 5 METs = brisk physical activity). Educational status was categorized into basic (basic or vocational school), secondary, and tertiary (polytechnic or university degree). Relationship status was classified as "in a relationship" in the case of self-reported marriage or cohabitation.

Statistical Analyses

Characteristics of categorical variables were presented as frequencies and percentages and continuous variables were presented as means ± standard deviation (SD). Differences in categorical variables between the study and reference groups were analyzed using Pearson's χ^2 -test. Differences in continuous variable were analyzed using two-tailed independent samples *t* test. A *P* value of < .05 was considered statistically significant. The association between endometriosis and

nongynecological diagnoses (risk for having diagnosis in any main category or individual ICD-10 codes, gynecologic diseases [C51-C58, D25-D27, D39] and obstetrics [group O] codes excluded), self-reported symptoms, and continuous medication use among women with and without endometriosis were analyzed using a binary logistic regression model. Previously mentioned confounding factors were included in multivariable analysis models. The results are reported as odds ratios (ORs) with 95% confidence intervals (CIs). Benjamini-Hochberg correction for multiple comparisons was performed to minimize the risk of type I error. Finally, Kaplan-Meier survival analysis (Mantel-Cox test) was used to estimate the ICD code accumulation in women with and without endometriosis until 2016, when the cohort participants turned 50. These analyses were performed using IBM SPSS Statistics version 24 for Windows and graphs were created using GraphPad Prism version 7.03.

RESULTS

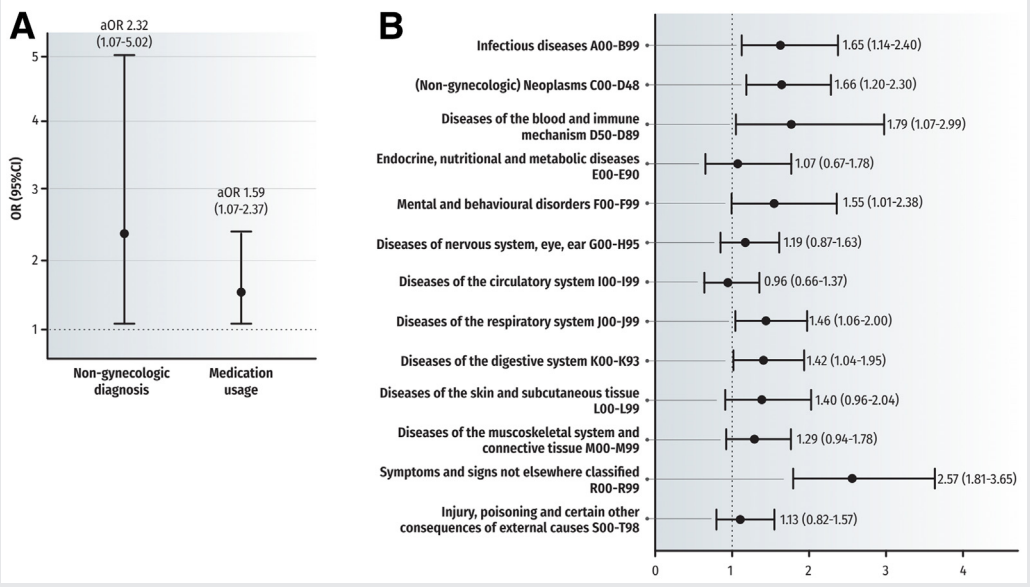
The characteristics of the study population are shown in Table 1. The average age of endometriosis diagnosis was 31.6 (SD 7.3) years. As expected, women with endometriosis had used contraceptives more often and had lower parity than women without endometriosis. There were no differences in BMI, socioeconomic status, relationship status, or lifestyle factors between the 2 groups at age 46 (Table 1).

ICD Diagnoses Registered in the CRCH

Women with endometriosis were twice as likely to have diagnoses for nongynecological ICD10 diseases compared with women without the disease (adjusted OR [aOR] 2.32; 95% CI, 1.07–5.02) (Fig. 1A). There was also high rate of ICD10 codes diagnoses in several main categories among women with endometriosis compared with nonendometriosis group (Fig. 1B).

In ICD codes subcategory analysis, the multivariable model showed that endometriosis was significantly associated with the following diagnoses (in order from the strongest to the weakest association): more than twofold odds of "nonspecific symptoms, signs, and clinical findings (R00–R99)" (aOR 2.57; 95% CI, 1.81–3.65), especially "abdominal and pelvic pain (R10)" (aOR 4.33; 95% CI, 3.13–6.00); pain-related diagnoses, such as "migraine (G43)" (aOR 2.11; 95% CI, 1.34–3.33) and "dorsopathies (M40–M54)" (aOR 1.56; 95% CI, 1.16–2.10); nearly twofold odds of "mood disorders (F30–F39)" (aOR 1.86; 95% CI, 1.20–2.88),"infectious diseases (A00–B99)" (aOR 1.65; 95% CI, 1.14–2.40); and "respiratory diseases (J00–J99)" (aOR 1.46; 95% CI, 1.06–2.00) and "diseases of the digestive system (K00–K93)" (aOR 1.42; 95% CI, 1.04–1.95) (Fig. 1B) (Supplemental Table 1, available online). Interestingly, there were almost identical findings between the 2 study groups, register-based endometriosis and self-reported endometriosis. The only discrepancy between the groups was the association between endometriosis and digestive system diseases (K00–K93) that was significant in medically confirmed cases but not in the self-reported subgroup (aOR 1.63; 95% CI, 1.10–2.41; aOR 1.29; 95% CI, 0.91–1.82). Temporal analyses showed that endometriosis diagnoses started to accumulate after the age of 25 years (data available only for the register-based cases). (Fig. 2A). There were no differences between women with and without endometriosis in terms of age of nongynecological ICD code accumulation (Fig. 2B). However, the diagnoses related to

FIGURE 1



(**A**) Association between endometriosis and overall morbidity and use of medication. (**B**) Association between endometriosis and different ICD codes from the Care Register for Health Care. *P* values corrected with Benjamini-Hochberg.

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"symptoms, signs, and abnormal clinical and laboratory findings (R00–R99)," and especially "abdominal and pelvic pain (R10)," occurred earlier in women with than without endometriosis (Fig. 2C and D).

Stratified Analysis of Subtypes of Endometriosis

The prevalence of any nongynecological diagnoses or within the main ICD10 categories did not reach statistical significance between the different endometriosis subtypes, partly owing to the limited sample size (Supplemental Table 2).

Self-reported Symptoms and Medication Usage

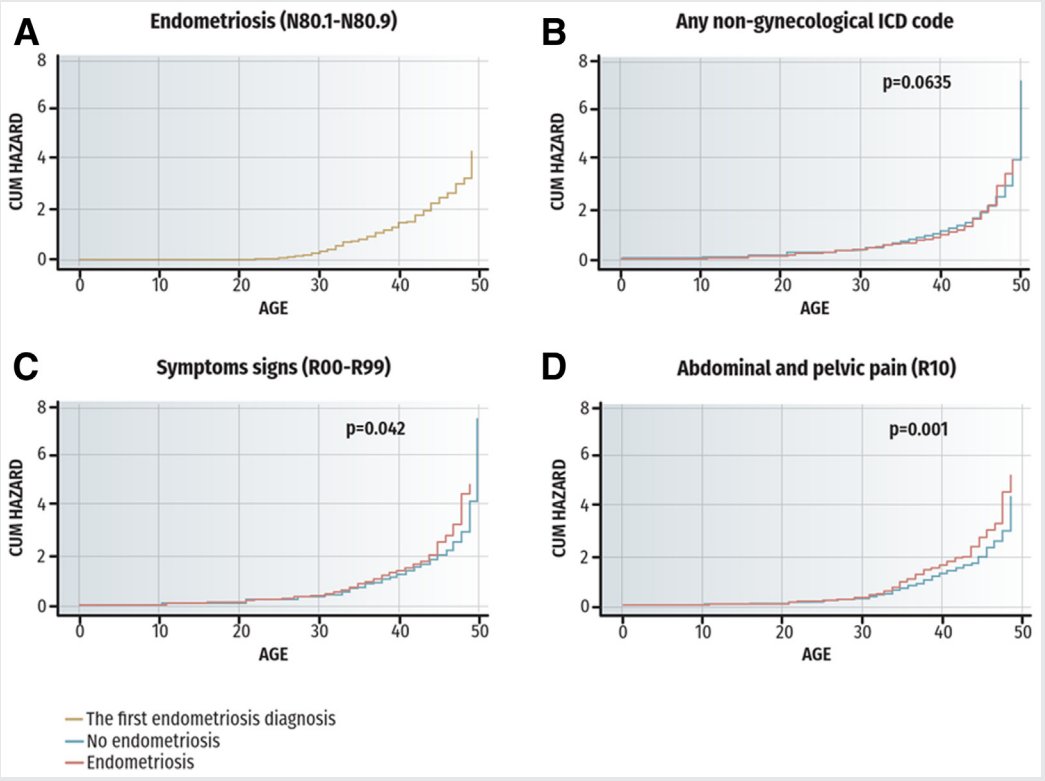
In terms of self-reported symptoms, there were associations between endometriosis and self-reported asthma (aOR 1.51; 95% CI, 1.1–2.15), atopic and allergic eczema (aOR 1.39; 95% CI, 1.07–1.81), symptoms of eye allergies (aOR 1.54, 95% CI 1.61–2.04), and emphysema/chronic bronchitis (aOR 1.72, 95% CI 1.01–2.95). Women with endometriosis reported being "more susceptible to infections than other people," and there were significant associations between endometriosis and self-reported "recurrent respiratory infections" (aOR 1.36; 95% CI, 1.04–1.77), "repeated pneumonia" (aOR 1.55; 95% CI, 1.05–2.31), and "hospitalization because of recurrent infections" (aOR 1.75; 95% CI, 1.14–2.67). A symptom related to autoimmune diseases (dry mouth) was also more prevalent in women with endometriosis (Table 2).

Regarding medications, women with endometriosis reported continuous medication use more frequently than the women without endometriosis (aOR 2.37; 95% CI, 1.03–5.44) (Fig. 1A). In the *Anatomical Therapeutic Chemical Classification* subcategory analysis, only the medications labeled "genitourinary systems and sex hormones" in the H-group were associated with having endometriosis (aOR 1.83; 95% CI, 1.08–3.11) (Supplemental Table 3).

DISCUSSION

This population-based study shows the independent association of endometriosis with several diseases and symptoms by the end of fertile age. Affected women presented more often with migraine, musculoskeletal diseases, mood disorders, immune and respiratory diseases, pain and unspecific symptoms and signs as well as abnormal clinical and laboratory findings compared with those without endometriosis. Despite the increased comorbidity rate, high medication usage in endometriosis group at the age of 46 was mainly attributed to the high use of hormonal preparation. The stratification analysis, although with limited number of cases, did not show different accumulation profile for comorbidities in different

FIGURE 2



Mantel-Cox estimate for the lifetime accumulation of (**A**) endometriosis diagnosis, (**B**) any diagnosis, (**C**) R00-R99 diagnosis, and (**D**) R10 diagnosis in the Care Register for Health Care register among women with or without endometriosis until year 2016. *Blue:* women without endometriosis, *red:* women with endometriosis.

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TABLE 2

Self-reported allergic, infection and autoimmune symptoms at age 46. Univariate and multivariate binary logistic regression analysis model.

	No Endometriosis	Endometriosis	*P* value[a]	Unadjusted odds ratio (95% confidence interval)	Adjusted odds ratio (95% confidence interval)
	n = 3,499 (%)	n = 349 (%)			
Questions concerning asthma and allergy					
Asthma	501 (15.4%)	62 (19.2%)	.14	1.31 (0.97–1.75)	**1.51 (1.10–2.15)**[c]
Emphysema, chronic bronchitis	154 (4.7%)	24 (7.3%)	.10	**1.58 (1.01–2.47)**[c]	**1.72 (1.01–2.95)**[c]
Atopic, infantile or allergic eczema	**1,344 (41.1%)**[c]	**163 (50.2%)**[c]	**.02**	**1.44 (1.15–1.81)**[c]	**1.39 (1.07–1.81)**[c]
Allergic eye symptoms	**982 (30.0%)**[c]	**122 (37.3%)**[c]	**.03**	**1.39 (1.10–1.76)**[c]	**1.54 (1.61–2.04)**[c]
Questions concerning infection symptoms					
Pneumonia at least twice	310 (9.2%)	43 (12.6%)	.10[b]	1.39 (0.99–1.96)	**1.55 (1.05–2.31)**[c]
Recurrent respiratory infections	**1,396 (42.8%)**[c]	**164 (50.3%)**[c]	**.04**[b]	**1.36 (1.08–1.70)**[c]	**1.36 (1.04–1.77)**[c]
Hospitalization because of recurrent infections	**368 (11.0%)**[c]	**58 (17.1%)**[c]	**.03**	**1.68 (1.24–2.27)**[c]	**1.75 (1.14–2.67)**[c]
More susceptible to infections than other people	166(4.9%)	27 (7.9%)	.09	**1.66 (1.09–2.53)**[c]	**1.92 (1.06–3.48)**[c]
Questions concerning autoimmune symptoms					
Dry eyes	**1,253 (37.3%)**[c]	**150 (44.2%)**[c]	**.05**	**1.33 (1.06–1.67)**[c]	1.27 (0.93–1.74)
Dry mouth	**440 (13.1%)**[c]	**66 (19.4%)**[c]	**.01**[b]	**1.59 (1.20–2.12)**[c]	**2.11 (1.43–3.12)**[c]
Solar dermatitis	967 (28.8%)	117 (34.5%)	.09	**1.30 (1.03–1.65)**[c]	1.34 (0.96–1.86)
Thrombocytopenia	**81 (2.4%)**[c]	**18 (5.4%)**[c]	**.03**	**2.28 (1.35–3.86)**[c]	**2.53 (1.33–4.83)**[c]
Joint pain	1,228 (36.5%)	147 (43.4%)	**.06**	**1.33 (1.06–1.70)**[c]	1.29 (0.93–1.78)

Note: Data reported as numbers (percentages), Two-sided *P*< .05 was considered significant.
Differences in numbers vary in different analyses because of some missing data.
In multivariate analysis: lifetime contraceptive use, parity, body mass index, alcohol, smoking, educational status, marital status, and physical activity.
[a] *P* values corrected with Benjamini-Hochberg.
[b] Significant in the Care Register for Health Care.
[c] Significant *P* values marked with bold.

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endometriosis subtypes (peritoneal, ovarian, or deep endometriosis).

Only a few previous studies, and even fewer prospective population-based studies, have investigated the association between endometriosis and overall morbidity (17–20). These studies have found that women with endometriosis have a high risk of ovarian and breast cancer, cutaneous melanoma, thyroid cancer, asthma, autoimmune, gastrointestinal, chronic liver and cardiovascular diseases, diabetes mellitus, rheumatoid arthritis, and pelvic inflammatory disease (17, 18, 20). Therefore, our data support previous findings on the associations between endometriosis and several nongynecological diseases and overall morbidity. Conversely, and unlike earlier studies, we found no associations among endometriosis and endocrine, metabolic and cardiovascular diseases or cancers. However, the fact that the follow-up was limited at the age of 50 years may have resulted in an underestimation of such associations, especially concerning diseases that occur at an older age.

Women with endometriosis suffer from chronic pelvic pain and prolonged noxious pain stimulation, which may lead to central and/or peripheral sensitization (25). Previous studies, including ours, have reported increased regional hyperalgesia and allodynia, altered musculoskeletal pain response, and increased pain sensitivity in affected women (23, 25). Considering the mechanisms underlying chronic pain, an association between endometriosis and other pain-causing diseases can be expected. A good example is the coexistence of endometriosis and migraine, one case-control study showing a prevalence of 38.3% of migraine in endometriosis compared with 15.1% in nonendometriosis cases (14). In line with this, our data showed a twofold risk for migraine in women with endometriosis. As for the mechanistic approach, a recent study found significant genetic concordance across endometriosis and migraine in a genome wide association analysis (26). Both diseases displayed genetic enrichment for biologic pathways, involving inflammatory, mitogen-activated protein kinase and cell cycle -related PI3K-Akt-mTOR signaling. However, Mendelian randomization did not show causality between these 2 conditions, implying that the conditions share genetically-controlled biologic mechanisms rather than true causality (27).

To our knowledge, there are no previous reports on the association between endometriosis and musculoskeletal diseases that was evident in our hospital-based ICD code data. This is not surprising, considering that endometriosis-related pain symptoms can be multifaceted (28). However, it is surprising that the prevalence of fibromyalgia did not differ between women with and without endometriosis in our data set, which again might be because fibromyalgia is usually diagnosed and treated in outpatient centers. Mental distress may also lower the pain threshold and induce altered pain responses. Indeed, women with endometriosis have been shown to be at a high risk of depression, anxiety, stress-related disorders, alcohol/drug dependence, and attention-deficit/hyperactivity disorder than the general population (15). Part

of the psychological distress may be due to chronic pain and difficulties in achieving pregnancy (28, 29). Our data showed almost two-fold odds for mood disorders in women with endometriosis, although we found no association between endometriosis and hospital-based diagnosis of depression or anxiety, again most likely due to the fact that most of these diagnoses are set in outpatient centers and thus, not included in our hospital register data.

Regarding autoimmune diseases, 2 population-based studies, a Danish register study and the Nurses Health Study II, reported a higher risk of several autoimmune diseases, such as systemic lupus erythematosus, Sjögren syndrome, rheumatoid arthritis, and multiple sclerosis, in women with endometriosis (11, 30). Our data showed an association between endometriosis and diseases of the immune system as well. These associations suggest impaired immune surveillance in women with endometriosis. Given that endometriosis is an estrogen-dependent disease, this comorbidity may be suggestive of steroid hormone response alterations, especially as estrogens have been shown to act as immune stimulants (31, 32). Indeed, an experimental study showed that steroid hormones promote specific immunologic events in some of the autoimmune diseases (31). Immune system-related factors may also contribute to the susceptibility toward infections (31). In accordance with this, we found endometriosis associating with diagnoses related to respiratory diseases. Furthermore, allergic manifestations, asthma, and atopic diseases were more prevalent in women with endometriosis (33–35). The pathogeneses of these conditions bear certain similarities. Almost all types of immune cells are dysregulated in the peritoneal fluid of affected women, with increased levels of peritoneal neutrophils and macrophages, reduced cytotoxic function of natural killer cells, and aberrant numbers of T and B lymphocytes (36). Additionally, a shared genetic mechanism underlying allergies and endometriosis has been suggested (37).

A recent meta-analysis showed >twofold risk of irritable bowel syndrome in endometriosis (13), although the association is difficult to ascertain, given the shared gastrointestinal symptomatology between these 2 conditions. In line with this, we found a significant association between endometriosis and digestive syndromes. Furthermore, women with endometriosis had more diagnoses of "symptoms, signs, and abnormal clinical and laboratory findings not classified elsewhere" (R00–R99), especially ICD codes related to "abdominal and pelvic-related symptoms" (R10), which had >fourfold likelihood in women with endometriosis. In Kaplan-Meier analysis, the accumulation of R00–R99 codes occurred significantly earlier in women with than without endometriosis. This may be attributed to the known diagnostic delay. Although patients may seek medical attention for their symptoms, endometriosis may remain undetected, covered by R-diagnosis. Hospital-based endometriosis diagnoses started to accumulate after the age of 25 years, and the mean age of diagnosis was almost 32 years.

There are some strengths in our study. Compared with earlier studies, our study represents a population-based birth cohort with a long term follow-up of 50 years with no ethnic variation. We used a two-source data strategy to detect endometriosis cases at the population level—medically confirmed and self-reported cases—which offered a high specificity of cases. Data from national registers include medically confirmed diagnoses and covers whole population, reducing the misclassification and drop-out bias that may occur when using self-reported data only. On the other hand, self-reported data may reflect milder cases and symptoms that are diagnosed and treated in outpatient centers. Second, we were able to consider the wide range of covariates measured with established survey instruments. Furthermore, we performed stratified analyses of the subtypes of endometriosis (peritoneal, ovarian, and deep infiltrating endometriosis). However, it should be noted that the statistical differences were lacking, at least partly owing to the limited sample size. Moreover, recently emerging data also indicate that the ICD-10 coding for endometriosis subtypes and locations may be limited and fail to categorize endometriosis accurately (38). Lastly, we were able to show the temporal accumulation of diagnoses using Kaplan-Meier analyses.

This study also has certain limitations. Even if participation rate in this follow-up study was quite high (72%), there might be minor bias because of those not reached or participated. However, this bias only applies to self-reported cases because the register-based linkage is available for all regardless of the participation status for the study visit. Given that the cohort consists of a relatively homogeneous Finnish population with mainly Caucasian ethnic background, the findings may not be generalizable globally. However, many of the findings are in accordance with the previous literature, suggesting the results may be applicable in other populations as well, although warranting verification (17–20). The self-reported diagnoses of endometriosis may be considered a limitation. However, self-reported endometriosis diagnosis has been verified through the patient records in our previous study showing almost 80% cases having hospital diagnosed endometriosis and thus enables a wider detection of cases and offers a reliable method with high specificity (22). Previous studies have also concluded that self-reported diagnoses can be considered moderately accurate, and that accuracy improves when additional information is available (39, 40). It must be noted that although laparoscopy is the reference standard for endometriosis diagnosis, the operation is not justified in some cases, which may lead to selection bias in surgically based, clinically rooted case-control studies. Our data set included women up to the age of 50 years, which limits the possibility of identifying the associations between endometriosis and those diseases that develop at an older age. Additionally, for some rare health events the size of the cohort may be limited. Furthermore, individuals receiving hospital care might be more susceptible to additional investigations and diagnoses. In terms of medication usage, more frequent use of hormonal drugs in treatment for endometriosis may cause a bias during high medication usage among women with endometriosis still at the age of 46 years.

CONCLUSION

Our findings suggest that women with endometriosis are at a high risk of several chronic diseases warranting deeper

understanding of these associations by future mechanistic studies. Early diagnosis of endometriosis without a long diagnostic delay is crucial for improving women's health and reducing the social, economic, and personal burden of endometriosis and related disorders. Lastly, affected women should be given more attention and targeted resources in health care systems to achieve more efficient and targeted care in multidisciplinary settings.

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Mayor morbilidad general en mujeres con endometriosis: un estudio poblacional de seguimiento hasta los 50 años.

Objetivo: Investigar si existe asociación entre la endometriosis y enfermedades no ginecológicas en la población general femenina a los 50 años.

Diseño: Estudio prospectivo de cohorte.

Ámbito: Las participantes del estudio con y sin endometriosis se identificaron a partir de una cohorte de población general, la Cohorte de Nacimientos del Norte de Finlandia de 1966 (NFBC1966). Los datos analizados, vinculados a los registros nacionales de altas hospitalarias, abarcaron hasta la edad de 50 años.

Paciente(s): La identificación de casos de endometriosis se basó en datos de registros nacionales y diagnósticos autoinformados, lo que produjo una población de estudio de 349 mujeres con endometriosis y 3499 mujeres sin endometriosis.

Principal(es) medida(s) de resultado: Los códigos de diagnóstico de la Clasificación Internacional de Enfermedades de 1968 a 2016 se recopilaron del Registro nacional finlandés de atención médica, mientras que los síntomas autoinformados y los datos de uso continuo de medicamentos se recopilaron de los cuestionarios distribuidos a los 46 años en el NFBC. Las asociaciones entre la endometriosis y las comorbilidades se evaluaron mediante modelos de regresión logística que incluyeron varias covariables. Se modelaron las razones de probabilidad y los intervalos de confianza (IC) del 95%. También se realizaron análisis temporales y de subtipos de endometriosis.

Resultado(s): Las mujeres con endometriosis tenían en promedio el doble de probabilidades de tener diagnósticos no ginecológicos en el hospital que las mujeres sin endometriosis (odds ratio ajustado [aORa] 2,32; IC del 95%, 1,07-5,02). Más detalladamente, la endometriosis se asoció con alergias, 92 enfermedades infecciosas, enfermedades causantes de dolor y enfermedades respiratorias. Además, las mujeres afectadas presentaron síntomas y signos inespecíficos (aOR 3,56; IC 95%, 2,73-4,64), especialmente dolor abdominal y pélvico (aOR 4,33; IC 95%, 3,13-4,76) con mayor frecuencia en comparación con los controles sin endometriosis. El análisis temporal reveló que los diagnósticos se acumularon a una edad significativamente más temprana entre las mujeres con endometriosis que entre las contrapartes sin endometriosis.

Conclusión(es): Las mujeres con endometriosis tienen un alto riesgo de varias enfermedades crónicas en comparación con las mujeres sin endometriosis, lo que subraya la necesidad de concienciación y recursos específicos para estas mujeres en el sistema de atención médica. Además, se debe considerar la endometriosis ante la presencia de síntomas inespecíficos y dolor abdominal, ya que pueden ocultar la enfermedad y provocar un retraso considerable en el diagnóstico y tratamiento.