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Full length article

Characteristics of endometriosis: A case-cohort study showing elevated IgG titers against the TSH receptor (TRAb) and mental comorbidity

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ABSTRACT

Objectives: Endometriosis has been associated with a wide range of factors. The disease share immunological features with autoimmune diseases, and the prevalence of both hypo- and hyperthyroidism has been reported to be increased. However, the associations have to be confirmed and the mechanisms explored. The aim of this observational study was to investigate socioeconomic factors, lifestyle habits, and somatic and mental comorbidities in endometriosis compared to the general population.

Study design: In all, 172 women with endometriosis completed a study questionnaire and were interviewed regarding socioeconomic factors, lifestyle habits, psychological well-being, and medical history. Bowel symptoms were measured by the Visual Analogue Scale for Irritable Bowel Syndrome (VAS-IBS). Serum was analyzed for IgG levels of TSH receptor antibodies (TRAb) and anti-thyroid peroxidase (TPO) antibodies. Women from the general population served as controls. Differences were calculated by logistic regression, adjusted for confounders.

Results: Alcohol intake, leisure time physical activity, body mass index and asthma were inversely, whereas IBS was positively associated with endometriosis. Hypothyroidism and anti-TPO antibodies did not associate, but elevated TRAb antibody titers were associated with endometriosis (odds ratio (OR): 539.26; 95% confidence interval (CI): 114.29–2544.32 for highest versus lowest tertile; p for trend < 0.001). Impaired psychological well-being (p for trend = 0.003) and current intake of antidepressant medication (OR: 3.54; 95% CI: 1.22–10.28; p = 0.020) associated with endometriosis, and impaired psychological well-being correlated with all gastrointestinal symptoms measured (all p < 0.001).

Conclusions: Lifestyle habits and asthma are inversely associated, and IBS and impaired psychological well-being are positively associated with endometriosis. TRAb titers are associated with endometriosis, supporting a link between endometriosis, autoimmunity and thyroid pathophysiology, although overt thyroid diseases do not associate.

Introduction

Endometriosis is one of the most common gynecological diseases, affecting approximately 6–10% of all women [1]. Early menarche, heavy menstrual cycles, high socioeconomic status, high alcohol consumption and low body mass index (BMI) are associated with the disease, whereas regular physical activity has shown inverse association [2,3].

Several autoimmune diseases, e.g. hypothyroidism [4,5] and Graves' disease [6], are over-represented in women with endometriosis compared to controls, though not confirmed by other studies [4–7]. Shared immunological features of endometriosis and autoimmune diseases include increased levels of cytokines and decreased apoptosis [5].

The prevalence of psychiatric disorders and gastrointestinal (GI) symptoms, mirroring those of irritable bowel syndrome (IBS), are increased in endometriosis [8–11]. Abdominal and pelvic pain symptoms in endometriosis are not associated with the extent of the disease, and psychological factors have been suggested to affect pain perception [12]. Since anxiety and pain intensity are positively correlated in endometriosis [13], visceral hypersensitivity has been suggested as a mechanism behind painful symptoms [14]. It remains to determine whether psychiatric comorbidity is a consequence of the abdominal and pelvic symptoms, or a consequence of other unknown factors such as inflammatory activity.

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The aim of the present observational study was to investigate socioeconomic factors, lifestyle habits, and somatic and mental comorbidities in endometriosis compared to the general population.

Materials and methods

This study was approved by the Ethics Review Board of Lund University, Dnr 2012/564, 2016/56 and 2012/594. All subjects gave their written, informed consent before inclusion.

Patients

Women with endometriosis were recruited at the Department of Gynecology, Skåne University Hospital, Malmö, Sweden, between March 2013 and March 2017. Patients were identified using the International Statistical Classification of Diseases and Related Health Problems, ICD-10, N 80. The inclusion criterion was a definite diagnosis of endometriosis confirmed by laparotomy or laparoscopy. Exclusion criteria were living too far from the geographical area of the hospital, an uncertain endometriosis diagnosis, multiple and severe somatic or psychiatric comorbidity, inflammatory bowel disease, or current pregnancy.

Controls

The Malmö Offspring Study (MOS) consists of offspring to subjects participating in the Malmö Diet and Cancer cardiovascular cohort (MDCS; n = 6103) [15]. Recruitment of participants is currently ongoing. A randomly selected cohort from MOS has previously been used to study basal characteristics and GI symptoms in the population, where the study is more closely described [16]. From this cohort, women < 60 years were selected to serve as controls in the present study.

Study design

Subjects were contacted via mail and telephone. A clinical data survey and *the Visual Analogue Scale for Irritable Bowel Syndrome* (VAS-IBS) were completed. At a clinical appointment, the patients were interviewed and blood samples were drawn and kept frozen at −20 °C. A review of the patients' medical records was conducted to document medical conditions. Blood samples from patients and controls were analyzed simultaneously at the Department of Laboratory Medicine.

Questionnaires

The clinical data survey addressed socioeconomic factors, lifestyle habits, medical history, and current pharmacological treatment. VAS-IBS is a validated test for measuring the GI symptoms abdominal pain, diarrhea, constipation, bloating and flatulence, vomiting and nausea, psychological well-being, and intestinal symptom's influence on daily life on a scale from 0 to 100 mm, where 0 represents a complete lack of symptoms, and 100 represents very severe symptoms. The values are inverted from the original format [17].

Autoantibodies

Analysis of IgG antibodies directed at the TSH receptor (TRAb) and thyroid peroxidase (anti-TPO) were conducted in serum according to clinical routines, using a competitive Electro Chemi Luminescence Immunoassay (ECLI) detection technique based on Ruthenium derivative [18,19]. Detection limit for TRAb IgG was 0.3 IE/L. Titers > 1.7 IE/L were considered positive, and titers between 1.2–1.7 IE/L were considered grey-zone values, according to the laboratory protocol. TRAb titers above cut-off value has a specificity of 99% and sensitivity of 97% for Graves' disease [20]. For anti-TPO IgG antibodies, detection limit was 5.0 kIE/L. Titers > 34 kIE/L were considered positive. Titers of anti-TPO antibodies above cut-off value are present in 95% of patients with autoimmune thyroiditis [21], but are also frequently present in euthyroid subjects with a prevalence of 12–26% [22].

Data categorization

The continuous variables were not normally distributed and therefore categorized into quartiles, based on the values of the control group. A majority of the controls had levels of TRAb IgG antibodies at or below detection limit, and the values were therefore divided into three groups based on detection limit and the median value of TRAb IgG titers. BMI was divided into normal-weight (BMI <25 kg/m [3]), over-weight (25–29.9 kg/m [3]) and obesity (≥ 30 kg/m [3]), according to the WHO classification [23]. Educational level was divided into primary school, secondary school and university/college. Occupation was divided into working/student or sick leave/unemployed. Marital status was divided into single/living alone and married/cohabitation. The MOS questionnaire also included the alternatives widowed and divorced. Women who stated any of these alternatives were added to missing values/other, since it was unclear whether they currently lived alone or cohabitated. Smoking habits were divided into never smoked, former smokers, or current smokers. The amount of alcohol intake was categorized into never/less than one standard glass/week, 1–4 standard glass/week or > 4 standard glass/week. Physical activity during leisure time was estimated ranging from sedentary leisure time, moderate exercise, regular exercise and regular training. Data on comorbidities were obtained from the questionnaires, and in the case of endometriosis, also from medical records.

Statistical analyses

Data was analyzed using the software SPSS, version 23.0 for Windows. Values are presented as median (interquartile range (IQR)) or number and percentage. Factors intended to study (independent variables) for influence on endometriosis, namely education, occupation, marital status, smoking habits, alcohol consumption, leisure time physical activity, and BMI were chosen because they by experience may influence health. Unconditional logistic regression was used to calculate odd ratios (OR) with 95% confidence intervals (CI). The reference was set to the lowest category of each variable. Analyses of socioeconomic factors and lifestyle habits were then performed adjusted for age and all variables. Analyses of comorbidity, psychological well-being, and antidepressant medication were adjusted for age, alcohol consumption, leisure time physical activity and BMI, since these basal parameters differed between endometriosis and controls. Analyses of antibodies were adjusted for age and BMI. The adjusted analyses were performed as complete case-analysis. Comparisons between groups were performed by Mann-Whitney *U* test and correlations by Spearman's test. $P < 0.05$ was considered statistically significant.

Results

Study population

In total, 32 women with endometriosis were excluded due to severe somatic or psychiatric comorbidity, most commonly malignant tumors and substance abuse of alcohol or narcotics. A

total of 573 women fulfilling inclusion criteria were identified. Of those, 307 declined to participate, 72 had moved from the region, 18 had an uncertain diagnosis and 4 denied the diagnosis. Altogether, a total of 172 women with surgically confirmed endometriosis were included in the study. Isolated ovarian endometriosis was the most common localization of endometriosis (Supplementary Table 1). The GI symptoms did not differ between these patients and the others (data not shown).

In all, 57 women (33.1%) had undergone in vitro *fertilization* (IVF). As a consequence of this, or due to severe symptoms, 15 women (8.7%) were currently using GnRH analogs and 95 women (55.2%) had current or previous use of GnRH analogs. Patients with current use of GnRH analogs experienced worse abdominal pain ((74.0 (35.0–90.3) vs. 40.0 (5.0–70.0); p = 0.006) compared to the remaining patients. 30 women (17.4%) were currently using opioids, and they experienced more severe GI symptoms compared to the remaining patients (Supplementary Table 2).

From MOS, 158 female controls under the age of 60 years were identified [16]. Since there were no questionnaires and blood samples for some controls, finally 117 women served as controls for socioeconomic factors, lifestyle habits, psychological well-being, GI symptoms and comorbidity, and 114 women served as controls for chemical analyses.

Subject characteristics

Basal characteristics for patients and controls are presented in Table 1. There was a tendency towards younger age in endometriosis compared to controls; 38 [32–43] years vs. 42 (28–52) years (p = 0.083). Alcohol consumption, leisure time physical activity and BMI were inversely associated with endometriosis. Educational level, occupation, marital status and smoking habits were similar in women with endometriosis and controls (Table 2).

Comorbidity and psychological well-being

Women with endometriosis also had received the diagnoses IBS (n = 32), hypothyroidism (n = 19), allergies (n = 18), migraine (n = 12), hypertension (n = 9), asthma (n = 7), fibromyalgia (n = 6), rheumatoid arthritis (n = 3), psoriasis (n = 3), celiac disease (n = 2), and Graveś disease (n = 2). Controls suffered from hypertension (n = 15), IBS (n = 14), asthma (n = 11), hypothyroidism (n = 6) and rheumatoid arthritis (n = 1). There were no questions in the data survey regarding allergies, fibromyalgia, Graveś disease, migraine, psoriasis, or psychiatric diseases, why these disease categories could not be determined in controls. Asthma was inversely associated with endometriosis. There was a tendency for an association between hypothyroidism and endometriosis in crude analysis, but not after adjusted calculations. Neither hypertension nor rheumatoid arthritis associated with endometriosis (Table 3).

IBS, diagnosed by a physician, was associated with endometriosis, and 87.8% of the patients had experienced GI symptoms in the past 2 weeks, compared to 11.1% of controls (Table 3). When evaluating the questionnaire, as many as 73 (42.4%) endometriosis patients suffered from IBS-like symptoms. Bloating and flatulence were rated as the most impairing GI symptom in endometriosis followed by abdominal pain (Table 4).

Of the women with endometriosis, totally 49 patients (28.5%) had been diagnosed with either depression or/and anxiety disorder in the past 5 years (37 depression, 15 anxiety disorder). Current use of antidepressant medication and impaired psychological well-being was associated with endometriosis (p for trend = 0.003) (Table 3). Women who had been diagnosed with depression and/or anxiety disorder (n = 49) experienced worse abdominal pain (59.5 (25.5–80.0) vs. 35.0 (5.0–65.0); p = 0.011), constipation (50.0 (2.0–77.0) vs. 20.0 (0.0–62.5); p = 0.045) and psychological well-being (59.0 (20.8–80.0) vs. 26.0 (5.0–50.0); p < 0.001) compared to endometriosis patients without these conditions. Impaired psychological well-being correlated positively with all GI symptoms in endometriosis (all p < 0.001), but inversely with age (r=−0.21, p = 0.005) (Table 4).

Table 1
Socioeconomic factors and lifestyle habits in endometriosis and controls.

	Endometriosis N = 172 N (%)	Controls N = 117 N (%)
Age (years)		
<28	19 (11.0)	27 (23.1)
28–41.9	99 (57.6)	31 (26.5)
42–51.4	54 (31.4)	30 (25.6)
≥51.5	0 (0.0)	29 (24.8)
Education		
Primary school	5 (2.9)	4 (3.4)
Secondary school	31 (18.0)	52 (44.4)
University or college degree	135 (78.5)	60 (51.3)
Missing	1 (0.6)	1 (0.9)
Occupation		
Working/student	152 (88.4)	102 (87.2)
Sick leave/unemployed	19 (11.0)	8 (6.8)
Missing	1 (0.6)	7 (6.0)
Marital status		
Single/living alone	51 (29.7)	23 (19.7)
Married/cohabitation	113 (65.7)	79 (67.5)
Missing/other	8 (4.7)	15 (12.8)
Smoking habits		
Never smoked	109 (63.4)	70 (59.8)
Former smoker	36 (20.9)	25 (21.4)
Current smoker	26 (15.1)	17 (14.5)
Missing	1 (0.6)	5 (4.3)
Alcohol consumption		
No consumption/< 1 sd/week	108 (62.8)	22 (18.8)
1–4 sd/week	52 (30.2)	65 (55.6)
5–14 sd/week	12 (7.0)	24 (20.5)
Missing	0 (0.0)	6 (5.1)
Physical activity		
Sedentary leisure time	56 (32.6)	11 (9.4)
Moderate exercise	30 (17.4)	40 (34.2)
Regular exercise	29 (16.9)	32 (27.4)
Regular intensive exercise	56 (32.6)	29 (24.8)
Missing	1 (0.6)	5 (4.3)
BMI (kg/m [2])		
<25	99 (57.6)	65 (55.6)
25–29.9	52 (30.2)	28 (23.9)
≥30	16 (9.3)	24 (20.5)
Missing	5 (2.9)	0 (0.0)

Basal characteristics of patients and controls. BMI = body mass index, sd = standard glass of alcohol. Values are presented as number and percentages (%).

Thyroid antibodies in endometriosis

Since hypothyroidism was common in endometriosis (11.0%), autoantibodies against thyroid tissue were analyzed. Only 7.9% of controls expressed TRAb IgG titers above the detection limit of 0.3 IE/L, compared to 93.0% of endometriosis patients (Fig. 1).

Elevated titers of TRAb IgG (p for trend < 0.001) and IgG levels of TRAb in grey-zone values were associated with endometriosis, whereas IgG levels of TRAb above the cut-off value were not (Table 5). TRAb IgG titers did not correlate with age, BMI or GI symptoms (data not shown). Anti-TPO IgG antibodies did not associate with endometriosis (Table 5).

Table 2
Associations of socioeconomic factors and lifestyle habits in endometriosis.

	Endometriosis N = 172 %	Controls N = 117 %	Crude OR, 95% CI	P-value	Adj. OR, 95% CI	P-value
Education						
Primary school	2.9	3.4	1.00 (reference)		1.00 (reference)	
Secondary school	18.0	44.4	0.48 (0.12–1.91)	0.296	0.75 (0.10–5.57)	0.781
University or college degree	78.5	51.3	1.80 (0.47–6.94)	0.393	2.17 (0.32–14.90)	0.430
Missing	0.6	0.9				
Occupation						
Working/student	88.4	87.2	1.00 (reference)		1.00 (reference)	
Sickleave/ unemployed	11.0	6.8	1.59 (0.67–3.78)	0.290	1.04 (0.28–3.85)	0.948
Missing	0.6	6.0				
Marital status						
Single/living alone	29.7	18.8	1.00 (reference)		1.00 (reference)	
Married/cohabitation	65.7	67.5	0.65 (0.37–1.14)	0.132	0.66 (0.30–1.47)	0.311
Missing	4.7	12.8				
Smoking habits						
Never smoked	63.4	59.8	1.00 (reference)		1.00 (reference)	
Former smoker	20.9	21.4	0.98 (0.50–1.94)	0.959	0.83 (0.29–2.37)	0.732
Current smoker	15.1	14.5	0.93 (0.51–1.67)	0.796	1.43 (0.60–3.40)	0.420
Missing	0.6	4.3				
Alcohol consumption						
No consumption/<1 sd/week	62.8	18.8	1.00 (reference)		1.00 (reference)	
1–4 sd/week	30.2	55.6	0.16 (0.09–0.30)	<**0.001**	0.13 (0.06–0.30)	<**0.001**
5–14 sd/week	7.0	20.5	0.10 (0.04–0.23)	<**0.001**	0.09 (0.03–0.28)	<**0.001**
Missing	0.0	5.1				
Physical activity						
Sedentary leisure time	32.6	9.4	1.00 (reference)		1.00 (reference)	
Moderate exercise	17.4	34.2	0.15 (0.07–0.33)	<**0.001**	0.22 (0.07–0.64)	**0.006**
Regular exercise	16.9	27.4	0.18 (0.08–0.40)	<**0.001**	0.25 (0.08–0.78)	**0.016**
Regular intensive exercise	32.6	24.8	0.38 (0.17–0.83)	**0.016**	0.46 (0.16–1.33)	0.152
Missing	0.6	4.3				
BMI, kg/m [2]						
<25	57.6	55.6	1.00 (reference)		1.00 (reference)	
25–29.9	30.2	23.9	1.22 (0.70–2.13)	0.484	0.61 (0.26–1.40)	0.242
≥30	9.3	20.5	0.44 (0.22–0.89)	**0.022**	0.32 (0.11–0.95)	**0.039**
Missing	2.9	0.0				

Adj = adjusted, BMI = body mass index, CI = confidence, OR = odds ratio, sd = standard glass of alcohol. Values are presented as percentages (%). ORs and 95% CI were calculated using a binary logistic regression model, adjusted for age, education, occupation,marital status, smoking and alcohol habits, leisure time physical activity and BMI. $P < 0.05$ was considered statistically significant.

Comments

Alcohol consumption, leisure time physical activity, and BMI were inversely associated with endometriosis, whereas IBS, impaired psychological well-being, and current use of antidepressant medication associated positively. Worse psychological well-being correlated with aggravated GI symptoms. Elevated IgG titers of TRAb were associated with endometriosis, which supports a link between endometriosis, autoimmunity and thyroid function.

Autoimmune diseases including hypothyroidism and Grave's disease have been found in slightly increased prevalence in endometriosis in some studies [4–6,24], although not confirmed by others [4–7]. Endometriosis share immunological features with autoimmune diseases including increased levels of cytokines, impaired apoptosis and increased autoantibody formation [5]. Hypothyroidism is associated with female infertility [25]. The infertility in endometriosis is supposed to depend on altered pelvic anatomy [1], but molecular mechanisms may be involved in this entity as well.

Elevated IgG titers of TRAb were associated with endometriosis. mRNA and proteins of TSH receptor and thyroid hormone receptors are expressed in human endometrial stromal- and Ishikawa cells [26,27]. Furthermore, the endometrium is a site of extra-thyroidal hormone production, where endometrial Ishikawa cells secrete thyroid hormones in response to TSH [26]. The extra-uterine endometrial implants in endometriosis may hypothetically also express TSH receptors, inducing TRAb IgG formation [28]. This is, to our knowledge, the first study to report increased TRAb titers in endometriosis, why the mechanisms and importance have to be further evaluated.

A longitudinal study comprising over 10.000 women with endometriosis reported an increased risk of developing depression and anxiety disorders in this condition compared to the general population [29]. Furthermore, a systematic review concluded that 56% of endometriosis patients met criteria for a psychiatric disorder [8]. This is in line with our results where almost one-third of the patients had sought medical treatment for depression and/or anxiety disorders in the past five years. There are several hypothetical explanations to this. First, there is aberrant immunological responses in endometriosis with elevated cytokines, e.g. IL-6 and TNF-alpha, which may weaken the blood-brain barrier and affect certain brain areas [30]. Second, gonadotropin-releasing hormone (GnRH) analogs are regularly used to treat endometriosis, and depressive symptoms have been shown to develop during this treatment [31].

Table 3
Somatic and psychological comorbidity in endometriosis.

	Endometriosis N = 172 N (%)	Controls N = 117 N (%)	Crude OR, 95% CI	P-value	Adj. OR, 95 % CI	P-value
Asthma						
No asthma	165 (96.0)	106 (90.6)	1 (reference)		1 (reference)	
Asthma	7 (4.0)	11 (9.4)	0.41 (0.15–1.09)	0.073	0.23 (0.06–0.94)	**0.040**
Hypertension						
No hypertension	163 (94.8)	102 (87.2)	1 (reference)		1 (reference)	
Hypertension	9 (5.2)	15 (12.8)	0.38 (0.16–0.89)	**0.026**	0.61 (0.17–2.22)	0.455
Hypothyroidism						
No hypothyroidism	153 (89.0)	111 (94.9)	1.00 (reference)		1 (reference)	
Hypothyroidism	19 (11.0)	6 (5.1)	2.30 (0.89–5.94)	0.086	2.31 (0.66–8.06)	0.189
Rheumatoid arthritis						
No rheumatoid arthritis	169 (98.3)	116 (99.0)	1.00 (reference)		1.00 (reference)	
Rheumatoid arthritis	3 (1.7)	1 (1.0)	2.06 (0.21–0.04)	0.534	1.09 (0.09–2.78)	0.948
IBS						
No IBS	140 (81.4)	103 (97.7)	1.00 (reference)		1.00 (reference)	
IBS	32 (18.6)	14 (12.3)	1.63 (0.83–3.22)	0.157	2.58 (1.01–6.63)	**0.049**
GI symptoms last 2 weeks						
No symptoms	18 (10.5)	100 (85.5)	1.00 (reference)		1.00 (reference)	
Symptoms	151 (87.8)	13 (11.1)	64.53 (30.28–137.54)	<**0.001**	91.75 (30.14–279.33)	<**0.001**
Missing	3 (1.7)	4 (3.4)				
Psychological well-being (mm)						
<5	37 (21.5)	21 (17.9)	1.00 (reference		1.00 (reference)	
5–14	14 (8.1)	32 (27.4)	0.25 (0.11–0.57)	**0.001**	0.23 (0.08–0.67)	**0.007**
15–25	25 (14.5)	27 (23.1)	0.53 (0.25–1.13)	0.099	0.68 (0.25–1.88)	0.459
>25	93 (54.1)	26 (22.2)	2.03 (1.02–4.05)	**0.044**	2.54 (0.98–6.55)	0.054
Missing	3 (1.7)	11 (9.4)				
Antidepressant medication						
No current medication	139 (80.8)	111 (94.9)	1.00 (reference)		1.00 (reference)	
Current medication	33 (19.2)	6 (5.1)	4.39 (1.78–0.86)	**0.001**	3.54 (1.22–0.28)	**0.020**

Adj = adjusted, CI = confidence interval, GI = gastrointestinal, OR = odds ratio. Psychological well-being was measured on the Visual Analogue Scale for Irritable Bowel Syndrome scale, where 0 mm represent a complete lack of symptoms and 100 mm represents very severe symptoms. Values are presented as number and percentages (%). ORs and 95% CI were calculated using a binary logistic regression model, adjusted for age, BMI, alcohol habits and physical activity. $P < 0.05$ was considered statistically significant.

Impaired psychological well-being correlated with aggravated GI symptoms. Visceral hypersensitivity is common in endometriosis [14], and may be connected to abnormal central pain processing [32,33]. It is well described how cognitive, emotional and psychosocial factors interfere with pain modulation, and reinforces and perpetuates chronic pain [34]. It is, however, still unclear whether psychiatric comorbidity is triggered by painful symptoms, or if depression and anxiety are factors that worsen

Table 4
Correlations between age, gastrointestinal symptoms and psychological well-being in endometriosis.

	Endometriosis N = 172	Correlation between psychological well-being and GI symptoms
Age (years)	38.0 (32.0–43.0)	R = −0.21, **p = 0.005**
Abdominal pain (mm)	40.0 (10.0–72.0)	R = 0.60, **p < 0.001**
Diarrhea (mm)	15.0 (0.0–55.0)	R = 0.319, **p < 0.001**
Constipation (mm)	28.0 (0.0–69.5)	R = 0.46, **p < 0.001**
Bloating and flatulence (mm)	55.0 (17.5–80.0)	R = 0.48, **p < 0.001**
Vomiting and nausea (mm)	9.0 (0.0–45.0)	R = 0.49, **p < 0.001**
GI symptom's influence on daily life (mm)	40.0 (8.5–75.0)	R = 0.61, **p < 0.001**
Psychological well-being (mm)	30.0 (8.0–63.5)	–
Missing value (n, %)	3 (1.7)	3 (1.7)

Gastrointestinal symptoms were measured on the Visual Analogue Scale for Irritable Bowel Syndrome scale, where 0 mm represent a complete lack of symptoms and 100 mm represents very severe symptoms. Values are presented as median (interquartile range) and number and percentages (%). Correlations were calculated by the Spearman's Rho test. $P < 0.05$ was considered statistically significant.

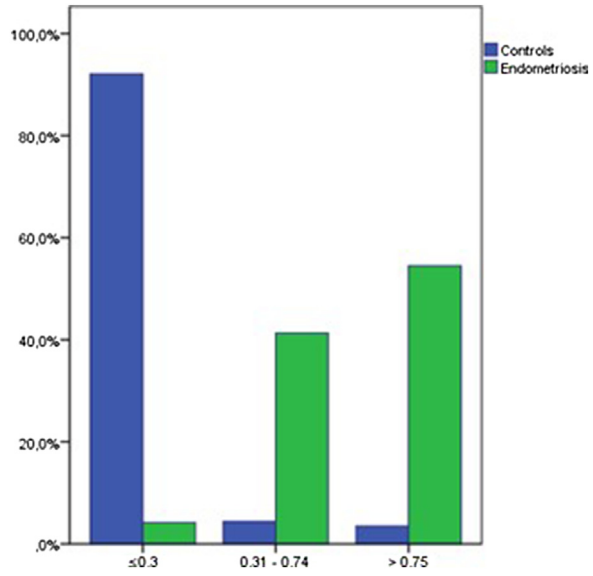

Fig. 1. IgG titers of TSH receptor antibodies (TRAb) titers (IE/L) in endometriosis and controls. Values are presented as percentages.

Table 5
Thyroid antibodies in endometriosis.

	Endometriosis N = 172 %	Controls N = 114 %	Crude OR, 95% CI	P-value	Adj. OR, 95% CI	P-value
Age (years)						
<25.1	7.0	28.1	1.00 (reference)		–	–
25.1–31.0	15.1	23.7	2.57 (1.09–6.04)	**0.031**	–	–
31.1–42.2	48.8	23.7	8.30 (3.76–18.33)	<**0.001**	–	–
>42.2	29.1	24.6	4.76 (2.12–10.69)	<**0.001**	–	–
BMI (kg/m [2])						
<25	57.6	56.1	1.00 (reference)		–	–
25–29.9	29.7	24.6	1.18 (0.67–2.06)	0.566	–	–
>30	9.3	19.3	0.47 (0.23–0.96)	**0.039**	–	–
Missing	2.9	0.0				
TRAb IgG						
Negative	86.6	97.4	1.00 (reference)		1.00 (reference)	
Grey-zone	8.7	0.9	11.17 (1.45–85.86)	**0.020**	10.41 (1.29–83.83)	**0.028**
Positive	1.7	1.8	1.12 (0.18–6.80)	0.904	1.32 (0.18–9.44)	0.784
Missing	2.9	0				
TRAb IgG (IE/L)						
≤0.30	4.1	92.1	1.00 (reference)		1.00 (reference)	
0.31–0.74	40.1	4.4	207.00 (63.15–678.49)	<**0.001**	305.23 (70.49–1321.66)	<**0.001**
>0.74	52.9	3.5	341.25 (96.78–1203.21)	<**0.001**	539.26 (114.29–2544.32)	<**0.001**
Anti-TPO IgG						
Negative	81.4	89.5	1.00 (reference)		1.00 (reference)	
Positive	15.7	10.5	1.64 (0.79–3.39)	0.182	1.61 (0.74–3.52)	0.227
Missing	2.9	0				
Anti-TPO IgG (kIE/L)						
<12.5	32.6	24.6	1.00 (reference)		1.00 (reference)	
12.5–14.6	15.1	25.4	0.45 (0.22–0.90)	**0.024**	0.58 (0.27–1.23)	0.155
14.7–18.1	21.5	25.4	0.64 (0.33–1.24)	0.185	0.72 (0.35–1.49)	0.371
>18.1	27.9	24.6	0.86 (0.45–1.64)	0.642	0.90 (0.45–1.80)	0.767

TRAb = TSH receptor antibodies, Anti-TPO = anti-thyroid peroxidase, adj = adjusted, OR = odds ratio. Cut off levels of anti-TPO antibodies was set to > 34 kIE/L and cut off levels of TRAb was set to > 1.7 IE/L. All values are given as percentages (%). ORs were calculated by a binary logistic regression model, adjusted for age and BMI. $P < 0.05$ was considered statistically significant.

symptoms from endometriosis, or both. The medication to treat endometriosis may affect GI symptoms. However, only a minority of patients were treated with opioids and GnRH analogs, why medication can not explain all differences, and also patients without opioids had more aggravated symptoms compared to controls [35].

Alcohol intake has been found to increase the risk of estrogen-dependent diseases [36], hypothetically through elevated levels of bio-available estrogens and pro-inflammatory cytokines [37,38]. A meta-analysis concluded that alcohol intake was associated with increased risk of endometriosis, although no dose-risk relationship could be determined, which may reflect a reversed causation [2]. In the present study, patients reported a very low alcohol consumption compared to the general population, with inverse association to endometriosis.

Leisure time physical activity and BMI were also inversely associated with endometriosis, in line with previous findings, although inconsistent results exist [3]. Physical activity may decrease estrogen levels, but may also protect from inflammatory responses and oxidative processes, thereby reducing the risk to develop endometriosis [39]. However, painful symptoms in endometriosis may prevent patients from exercising, explaining the inverse association observed. Nevertheless, low levels of physical activity could contribute to aggravated GI symptoms [40,41]. The inverse association between BMI and endometriosis may depend on several factors. Diagnosing endometriosis by ultrasound and/or laparoscopy may be more difficult in overweight women. The lower alcohol consumption may render lower BMI, and GI symptoms may lead to reduced appetite and food intake. A prospective study has shown a persistent inverse relationship between body size in childhood and risk of endometriosis [42]. Hypothetically, different age of menarche and hormonal levels depending on varying BMI could be the etiological factors behind this phenomenon. Although endometriosis cause severe disability in young women, their ability to manage education, occupation and family formation seems not to be prevented by the disease.

The strength of the present observational study in comparison to other studies is the adjustment for basal characteristics in the association calculations between endometriosis and comorbidity, but also the choice of controls from the same geographical area [43]. The limitations include the relative small cohort size and that we miss data on endometriosis and some diseases in controls.

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Conflicts of interests

The authors have no conflicts to declare.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ejogrb.2018.09.034.

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