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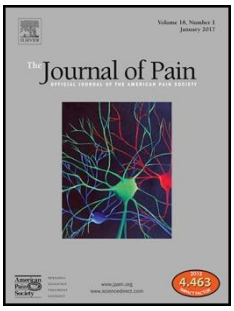

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The Long-term Footprint of Endometriosis: Population-based Cohort Analysis Reveals Increased Pain Symptoms and Decreased Pain Tolerance at Age 46

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Keywords: Endometriosis, Pain Threshold, Pain Tolerance, Pain Troublesomeness

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The authors declare no conflicts of interest.

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Highlights

- Endometriosis has been shown to increase pain sensitivity in fertile-aged women.
- The study shows decreasd pain threshold and maximal pain tolerance in women with endometriosis at age 46
- Women with endometriosis report increased pain sites and bothersome and intense pain at age 46
- Delay in diagnosis of endometriosis may lead to increased pain sensitization
- Endometriosis should be diagnosed and treated early on to ensure minimal comorbidity

Abstract

Previous studies have shown increased pain sensitivity in fertile-aged women with endometriosis in response to mechanical stimuli. As yet, population-based studies on the association of endometriosis with pain sensation and pain symptoms in late fertile age are lacking. The main objective of this population-based cohort study was to investigate whether a history of endometriosis is associated with altered pain sensation and musculoskeletal pain symptoms at age 46.

Our data is derived from the Northern Finland Birth Cohort 1966, which contains postal questionnaire data (72% response rate) as well as clinical data assessing pressure-pain threshold (PPT) and maximal pain tolerance (MaxPTo). The study population consisted of 284 women with endometriosis and 3390 controls.

Our results showed that at age 46 women with a history of endometriosis had a 5.3% lower PPT and 5.1% lower maxPTo compared with controls. The most significant contributors besides endometriosis were anxiety, depression and current smoking status. Women with endometriosis also reported an increased number of pain sites (0 pain sites, 9.6 vs. 17.9%; 5–8 pain sites, 24.8 vs. 19.1%, endometriosis vs. controls respectively, $p<0.001$), and their pain was more troublesome and intense. The results were adjusted for

BMI, smoking, depressive/anxiety symptoms, education and use of hormonal contraceptives.

This unique data revealed an altered pain sensation and a greater likelihood of reporting musculoskeletal pain at age 46 among women with a history of endometriosis. The results imply that endometriosis has a long-term footprint on affected women, thus underlying the need for psychological support and medical treatment beyond fertile age.

Perspective item

This is a population-based cohort study showing decreased pain threshold and maximal pain tolerance in women with endometriosis up till late fertile age of 46 years. The pain was also found to be more bothersome and intense compared with controls.

Introduction

Endometriosis is an estrogen-dependent, chronic gynecological disorder associated with pelvic pain and infertility, with a prevalence of 6–10% in the general population [6, 7, 13]. Affected women experience dysmenorrhea, deep dyspareunia, dyschezia and dysuria [13, 37] associated with low quality of life [8]. The disorder is under-diagnosed or there is a delay in diagnosis in many cases leading to chronic pelvic pain (CPP) [7, 28]. Diagnosis is made by laparoscopy or laparotomy, where endometrial lesions are found in extra-uterine locations, mainly the peritoneum and ovaries [6, 7, 13]. As endometriosis is not curable, its treatments and therapies are targeted at infertility and symptom relief [7, 11]. Endometriosis is also associated with other co-morbid conditions such as fibromyalgia and chronic fatigue syndrome [11, 28]. Moreover, it has a significant adverse impact on work productivity, social activity, family responsibilities, and daily life, resulting in a substantial economic burden on society [11, 30].

It is well accepted that endometriosis is associated with dysmenorrhea, but it is not known why some women undergo transition to a state of chronic pain, while others do not[1]. Depending on the study population, 30–70% of women with CPP have laparoscopic evidence of endometriosis [21, 34]. The pain symptoms, however, are poorly correlated to the severity of endometriosis, and the pathophysiology of endometriosis-associated pain remains somewhat elusive [9, 14, 23, 25, 36, 37]. Pain mechanisms in endometriosis are thought to be multifactorial; pain may be nociceptive, neuropathic or a combination of these, and emotional, cognitive and behavioral components are also present [3, 20, 23, 32]. Previous studies have shown increased pain sensitivity among women with endometriosis, with or without CPP, in response to mechanical stimuli compared with control [2]. Furthermore, pain-threshold studies have suggested hyperalgesia at extra-pelvic

sites, most likely due to peripheral and/or central sensitization mechanisms in affected women [5, 12, 16, 23, 24].

Endometriosis is anticipated to subside in menopause, as it is an estrogen-dependent disorder. However, in cases of peripheral and central sensitization, pain symptoms and hyperalgesia may persist beyond fertile age. As yet, no population-based data exist on pain symptoms among women with a history of endometriosis at late reproductive age. Thus, the aim of this study was to determine in a population-based cohort study setting whether women with a self-reported history of endometriosis experience altered pressure-pain sensitivity and adverse pain symptoms at age 46.

Materials and Methods

Study Population

The study population originated from the Northern Finland Birth Cohort 1966 (NFBC1966, http://www.oulu.fi/nfbc) which is a unique, large, prospective, longitudinal dataset comprising all expected births in 1966 in the Northern Finland area (live-born children n=12058, females n=5889). Originally the cohort was established to investigate the life-courses of various health-related conditions. Enrollment in this database began at the 24th gestational week, and, after birth, data-collection points were established at ages 1, 14, 31 and 46 years, this study utilizing the latest data-collection point, thus being a secondary, cross-sectional analysis of a prospective study cohort.

At 46 years of age, all participants who were alive and whose postal address in Finland was known received a questionnaire (5123 women). This was the first questionnaire in this longitudinal cohort study including questions on history of endometriosis and pain symptoms. The response rate was 72%. Furthermore, all women were also invited to undergo clinical examination including pressure-pain testing, and 2774

(55%) participated. All participants gave informed consent. The study followed the principles of the Declaration of Helsinki and the Ethics Committee of the Northern Ostrobothnia Hospital District approved the research. A flow chart of the study is shown in Figure 1.

Diagnosis of Endometriosis

The final analysis concerned all women self-reporting endometriosis, and those stating “no endometriosis” were considered as controls. Self-reported diagnosis was derived from the postal questionnaire item: “Have you ever been diagnosed with endometriosis by a physician?” resulting in an endometriosis population of 284 women (8% among women who answered the endometriosis question). There were 3390 women (92%) reporting no endometriosis and were considered as controls (Figure 1A).

Verification of diagnosis

Self-reported diagnosis of endometriosis has only recently been described in the literature [26]; hence the validity of the diagnosis was verified for the present study through the patient records available at the original study site at Oulu University Hospital (Supplemental Figure). Thirty-seven women (13%) did not give permission to enter their patient records. Of the 284 women with endometriosis we found patient records for 92 (32.4%). According to the patient records available, 71/92 women (77.2 %) were diagnosed as having endometriosis, of which 90.1% were established in laparoscopy/laparotomy. Fifteen women did not have a diagnosis of endometriosis and six were classified as unclear cases. It is possible that the diagnosis was established later in another hospital after moving from the area (groups “no endometriosis” and “unclear cases”). We also estimated the specificity of diagnoses from the national hospital discharge register including diagnosis established during hospital polyclinic visits or during hospitalization. In the endometriosis group 52% of the women also had a diagnosis in the national hospital

discharge register, compared with 1.5% among the women reporting not having endometriosis (Table 1). Thus, we concluded that a self-reported history of endometriosis is sufficiently a valid tool to identify endometriosis cases in this cohort.

Pressure-Pain Threshold (PPT) and Maximal Pain Tolerance (MaxPTo)

Pain measurements were carried out in 2470 controls and 234 women with endometriosis. A few of the four measurement-site readings were missing as a result of technical difficulties. Pressure-pain threshold and maxPTo readings were acquired using an algometer (Somedic AB, Hörby, Sweden) with a 10-mm contact head, which was applied perpendicularly to the skin. Briefly, the pressure was increased from 0 kPa at a constant rate of 50 kPa/s. Instructions to participants were, “A pressure will be applied at a gradual rate. Allow the pressure to increase until it reaches a point where it feels uncomfortable and then press the button down. As we continue increasing the pressure, release the button when you cannot tolerate the pressure any more”. The former pressure value was recorded as the PPT and the latter as MaxPTo. Pressure was terminated at the latest when the safety maximum of 1200 kPa was reached. The PPT and MaxPTo measurements were taken at four anatomical sites in the following order: 1) shoulder; the mid–point of the upper trapezius muscle (subject in a prone position), 2) the mid-point of the tibialis anterior muscle (supine position), 3) the dorsal aspect of the wrist joint line (supine position), and 4) the L5/S1 interspinous space (prone position). The test sites were identified and participants were positioned in a standardized manner. Each site was tested twice. Of the peripheral sites, primarily the right side was used. The exact anatomical point of pressure was shifted slightly between the tests in order to prevent sensitization of nociceptors at the contact site. The highest value of the two measurements was used in the analysis to avoid overestimating pain threshold or tolerance. In addition, mean PPT

and MaxPTo values at the four measured locations were calculated and used in the analyses.

Questionnaires on pain sites, pain intensity and pain troublesomeness

The numbers of musculoskeletal pain sites were assessed as follows: 0, 1, 2, 3, 4 or 5–8 sites. The pain sites were derived from the questionnaire, in which the prevalence of musculoskeletal pain during the previous 12-month period was investigated as follows: “Have you had any aches or pains in the following areas of your body?” 1) neck, 2) shoulders, 3) arms/elbows, 4) wrists/hands/fingers, 5) lower back, 6) hips, 7) knees, and 8) ankles/feet. The anatomical sites were illustrated in a drawing. If there had been pain, there was a following question on the frequency of pain: “How often have you had aches or pains during the last 12 months?” 1) not at all, 2) 1–7 days, 3) 8–30 days, 4) over 30 days, or 5) daily. If the person had experienced pain during the past 12 months, pain intensity and pain symptoms at work, during leisure time and sleep, at all musculoskeletal sites, were assessed by using a Numerical Rating Scale (NRS) off 0 (no pain / no disability) to 10 (extremely severe or disabling pain).

Confounders

Infertility

Infertility was inquired about at age 46: “Have you ever suffered from infertility (yes/no)?”

Parity

Parity was inquired about at age 46: “How many deliveries you have experienced?” We divided the women according to parity into three groups: no delivery, one delivery or more than one delivery.

Contraceptive use

Current or past hormonal contraception use was inquired about at age 46 “Have you ever used any hormonal contraception (yes/no)?” and “Are you currently using hormonal contraception (yes/no)?”

BMI

Height and weight were both self-reported and measured at 46 years. In the clinical examinations, participants’ weight (kg) was measured with a digital scale, which was calibrated regularly. Height (cm) was measured twice by using a standard calibrated stadiometer. BMI (kg/m^2) was calculated by using measured height (average of two measurements) and weight. Self-reported values were used if measured data was not available. There was no statistically significant difference between the self-reported and clinically measured BMI values.

Smoking

Smoking history and present smoking status were inquired about by way of two questions at the age of 46 years: 1) “Have you ever smoked (yes/no)?” and 2) “Are you currently smoking (yes/no)?” According to the answers we identified current and life-long nonsmokers.

Alcohol use

The subjects were also asked if they used alcohol, and if so, what kinds, how often and how much? Daily alcohol consumption was calculated according to the answers and classified three ways: 1) never, 2) light 3) moderate or heavy use (women >20g/day).

Education

Education was classified into three groups by the number of years of education: 9 years, 9–12 years and more than 12 years.

Anxiety and Depressive symptoms

Anxiety and depressive symptoms were assessed via the 25-item Hopkins Symptom Checklist (HSCL-25) at 46 years of age [22, 35]. HSCL-25 part I includes 10 items concerning anxiety symptoms and part II, 15 items concerning depression. The scale varies between 1 and 4: 1 = not troublesome to 4 = extremely troublesome. The commonly used cut-off point of 1.55 was used to pinpoint anxiety and depression symptoms [35].

Statistical analyses

A Tobit regression model [33] was used to evaluate independent associations between endometriosis and PPT/MaxPTo. The motivation behind this was the large amount of censoring seen at the maximum limit of 1200 kPa. The interpretation of regression coefficients depends on the probability of not being censored. The interpretation is a combination of 1) the change in outcome, given that it is not censored, weighted by the probability of not being censored; and 2) the change in the probability of not being censored, weighted by the expected outcome if uncensored. Models were adjusted for BMI, anxiety and depression symptoms, smoking and contraceptive use.

Chi-squared tests were used to analyze the associations between the distribution and numbers of pain sites, and ANOVA was used to investigate the effect of pain intensity and troublesomeness at work, during leisure time and sleep. The analyses were performed with R software version 3.2.2, using the AER package for Tobit regression[19].

Results

The prevalence of self-reported endometriosis was 8% and verification of the diagnosis was carried out by examining the hospital records (Supplemental Figure). Table 1 shows the characteristics of the study women and the controls. Of note is the fact that in the self-reported endometriosis group there was a relatively high percentage of women also having

a diagnosis of endometriosis according to the hospital discharge register. The women with self-reported endometriosis were more often nulliparous and suffering from infertility, compared with controls. Use of hormonal contraceptives at any time was more frequent in women with endometriosis. No statistically significant differences were observed between the groups in terms of BMI, smoking, alcohol use or education level (Table 1).

The distribution of pain perception in women according to different conditions/confounders at age 46 is shown in Figure 2. Self-reported endometriosis was associated with statistically significant decreases in both pressure-pain threshold ($p<0.05$, Fig. 2A) and maximal pain tolerance ($p<0.001$, Fig. 2B) and the decreases in these variables remained after adjusting for different confounders. Other contributing factors were depression, anxiety and smoking. Interestingly, BMI and contraceptive use at any time seemed to increase the pain thresholds (Fig 2).

In Tobit regression analysis, PPT measurement showed that the women with endometriosis had on average a 34.0 kPa lower (-5.3% [-1.1,-9.5]) pain threshold compared with controls ($p<0.05$). As for the measurement site, PPT measured at the wrist was significantly lower in women reporting endometriosis (-37.5 kPa, $p<0.05$, Table 2), whereas the results concerning other measurement sites (shoulder, lower back and leg) did not differ between the study groups. After adjusting for confounders, PPT remained 35.4 kPa lower in the endometriosis group ($p<0.01$). There were no statistically significant effects of BMI, anxiety, smoking or current or previous contraceptive use on pain threshold measured at the wrist.

Maximal pain tolerance was on average -48.2 kPa lower (-5.1% [-2.2, -8.1]) among women with endometriosis ($p<0.001$, Table 2) the change being significant at all measurement sites, even after adjusting for BMI, anxiety and depressive symptoms, smoking and contraceptive use (mean -51.2 kPa, $p<0.001$), wrist (-58.2kPa), shoulder (-

53.4 kPa), lower back (-58.0 kPa) and leg (-46.8 kPa).The most significant contributors besides endometriosis that lowered maximum pain tolerance were anxiety, depression and current smoking status (-29.7kPa, -28.5kPa, -34.2kPa, respectively) ($p<0.05$, Figure 2).

The women were also screened for number of musculoskeletal pain sites (0, 1, 2, 3, 4, 5–8 sites), pain troublesomeness and pain intensity (Fig. 3). Among women with endometriosis there were significantly fewer reporting no pain sites (9.6% vs. 17.9%, $p<0.001$, Fig. 3). Overall, the women with endometriosis also reported more pain sites compared with controls (1 site 17.4% vs. 16.2%, 2 sites 17.0% vs 18.5%, 3 sites 15.5% vs. 16.2%, 4 sites 15.6% vs. 12.2% and 5–8 sites 24,8% vs 19,1%, $p<0.001$, Fig. 3).

As for pain troublesomeness, endometriosis was associated with slightly more troublesome pain at work and during leisure time and sleep ($p=0.01$, $p=0.02$, $p=0.04$ respectively, Fig. 4A). After adjusting pain troublesomeness for smoking, BMI, depression, anxiety and contraceptive use it was still significant during work ($p=0.04$) whereas the significance was abolished for pain troublesomeness during leisure time and sleep ($p=0.05$, $p=0.06$, Fig. 4A). Adjusted overall pain intensity was also greater among women with endometriosis vs. controls ($p=0.03$, Fig. 4B).

Discussion

This is the first population-based study to show an altered musculoskeletal pain response and increased self-reported pain sensitivity, troublesomeness and intensity among women at late reproductive age with a history of endometriosis. The results indicate that endometriosis may have long-term consequences related to pain perception even at late reproductive years.

Our data show a lower pressure-pain threshold and lower maximal pain tolerance among 46-year-old women with a history of endometriosis compared with

controls in a population-based study setting. The data adds to the body of evidence in the literature showing altered pain sensitivity in endometriosis. However, previous studies have been hospital-related populations[1, 2, 4, 12]. In the present study, regression analysis suggested that endometriosis is associated independently with lower pain threshold and tolerance, whereas the strongest factors further decreasing the pain threshold and the maximal pain response were anxiety, depression and current smoking status. Given all this, it is worth noting that depression has been previously shown to be associated with altered pain perception [15] and interestingly, musculoskeletal pain responses are particularly increased among women with co-expressing endometriosis and anxiety or depression symptoms [31]. Interestingly, both past and current contraceptive use appeared to be associated with unchanged pain tolerance, supporting the clinical use of hormonal contraceptives also in women with pelvic pain. The role of estrogens in pain perception is, however, complex. Interestingly, low estrogen concentrations in late menstrual cycle or during menopause or increased estrogen-testosterone ratio in male to female transsexuals have been shown to associate with increased pain symptoms [38]. Whether menopause solves the endometriosis-related altered pain responses or make them worse remains to be evaluated in future studies as estrogen measurements or menopausal status were not available for the present study.

As for individual pain-measurement sites, the pain threshold measured at the wrist in women with endometriosis was significantly lower compared with that in the controls. A similar trend was also shown at other pain-measurement sites. To our knowledge, ours is the first population based study to show decreased MaxPTo at several measurement sites among women of late reproductive age with a history of endometriosis, compared with controls and the results are in line with several previous studies also showing altered pain responses in women with endometriosis. In a previous study in which

pressure-pain sensitivity was assessed in the thumbnail, the results showed significantly lower pain threshold among women with symptomatic endometriosis [2]. Visceral hypersensitivity testing also revealed lower pain thresholds among women with endometriosis in a rectal balloon dilation test [18] and lower pain thresholds and larger pain areas were reported in women with symptomatic endometriosis after an intramuscular saline injection into the hand [4]. In a more recent study concerning pressure-pain thresholds at 20 different body sites, with use of the visual analog scale, it was reported that there was a lower pain threshold in the greater trochanter and abdomen in fertile-aged women with endometriosis compared with controls [24]. A population-based study carried out by Slater et al., with similar musculoskeletal pain response testing as in the present study, showed decreased pain thresholds in women experiencing severe menstrual pain[29]. Given that about 70% of women with dysmenorrhea (CPP) present with endometriosis in laparoscopy, the data by Slater et al. are in line with the present results underlying altered pain perception in affected women. The mechanisms behind the lowered threshold are most likely multifactorial, involving peripheral and central mechanisms [23]. Whether the women with CPP are the ones who also have altered pain perception during late reproductive years remains to be investigated as the present data did not record dysmenorrhea or pelvic pain.

Women with endometriosis reported more pain sites, and graded pain to be more bothersome and intense compared with controls. This might be due to central and/or peripheral sensitization which has been shown to result from prolonged noxious pain stimulation sustaining central pain stimulation in these cases [17, 31]. Indeed, women with endometriosis have reported increased regional hyperalgesia and allodynia [31]. Moreover, the fact that pelvic pain correlates poorly with findings/severity of endometriosis further emphasizes the fact that central and/or peripheral sensitization is most likely involved in

356 the pain-regulatory system among affected women [3, 31]. All in all, delayed diagnosis and
357 prolonged pain sensations may bring about altered pain sensitization among women with
358 endometriosis.

359 There are several strengths but also some limitations in the present work.
360 This is the first population-based study carried out to investigate pain perception/sensitivity
361 related to a history of endometriosis in women of late reproductive age. Women with
362 endometriosis were identified from a unique, large population-based data set of
363 homogeneous ethnicity and age and with the possibility to adjust for several confounding
364 factors. The data included objective pain measurements as well as subjective
365 questionnaire data. Moreover, the data collection did not specifically target endometriosis
366 patients or patients only treated in hospitals. Hence, the questionnaires and clinical
367 measurements were carried out in the whole cohort, with minimal self-aware bias. The
368 study also has limitations, which include self-reported endometriosis diagnosis and lack of
369 data on clinical symptoms of endometriosis; thus it is possible that the control group also
370 included women with endometriosis, albeit with milder pain symptoms/sensitivity.
371 However, the control group in the present data set was fairly large and such cases would
372 have been diluted among the controls. Moreover, studies on endometriosis commonly
373 concern only laparoscopically verified cases, and thus women with endometriosis with
374 fewer pain symptoms are most likely underrepresented in these studies. The self-reported
375 diagnoses of endometriosis may also be considered as a limitation, although, the
376 diagnosis was validated from the patient records available and from the national hospital
377 discharge register. In a recent study by Saha et al, similar results were presented when
378 self-reported endometriosis diagnoses were verified from patient records [26]. This was
379 further supported by a recent study validating self-reported endometriosis diagnosis in a
380 Swedish national twin registry[27]. The authors concluded that self-reported diagnosis

seems to be moderately accurate, and when additional information is also available the accuracy is even better. It must be noted, however, that even though laparoscopy is the gold standard in endometriosis diagnosis, in some milder cases the operation is not justified and thus the diagnosis remains clinical. Although our measurements showed statistically significant 5% decreases in pain threshold and maximal pain tolerance in women with endometriosis, the clinical significance remains uncertain, although these women also self-reported more pain symptoms. Furthermore, the associations between endometriosis-related pain symptoms and other comorbid pain syndromes, menopause or estradiol levels were not investigated due to lack of available data, thus these aspects remain to be evaluated in future studies.

To conclude, this is the first population-based study showing a decreased pain threshold and a decreased maximal pain response among women of late fertile age with a history of endometriosis. The fact that the women also reported a higher number of pain sites, with a greater prevalence of troublesome and intense pain at age 46 underlines the fact that endometriosis may have a long-term footprint as regards pain perception in these women. Given all this, women with endometriosis symptoms should be screened and diagnosed as early as possible by a multidisciplinary team in order to ensure minimal comorbidity, adequate pain relief and psychological support. Further studies are warranted to address the diagnostic difficulties and different endometriosis phenotypes and also to elucidate the pain mechanisms and best treatment options for these women.

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504

505 **Figure 1.** Flowchart showing the study population ($n_{endometriosis}$ = 284, $n_{controls}$ = 3390)
506 derived from Northern Finland Birth Cohort 1966.

507

508 **Figure 2. Pain perception in women according to different conditions/confounders**
509 **at**
510 **age 46.** The horizontal reference line reflects the whole study population. Self-reported
511 endometriosis appeared to result in decreases in both pressure pain threshold (PPT)
512 ($p<0.05$, A), and maximum pressure pain tolerance (MaxPTo) ($p<0.001$, B) compared with
513 the effect of BMI and contraceptive use at any time.

514

515 **Figure 3. The numbers of reported pain sites in women with endometriosis (black)**
516 **and in controls (gray) at age 46.** Percentages of women experiencing 0, 1, 2, 3, 4 or 5–8
517 pain sites per year. Fewer women with endometriosis (black bars) reported having no pain
518 sites compared with controls (gray bars) ($p<0.001$). The numbers of pain sites were
519 increased in women with endometriosis compared with controls ($p<0.001$).

520

521 **Figure 4. Pain troublesomeness (A) and intensity (B) in women with endometriosis**
522 **and in controls at age 46.** A) The mean pain troublesomeness score was increased in
523 women with endometriosis (black bars) compared with controls (gray bars) at work. A
524 similar trend was seen during leisure and sleep. B) The women with endometriosis
525 reported having more intense pain compared with controls. Mean numerical rating (MNR)
526 is the mean of pain scoring from 0 to 5.

527

Suppelemental Figure. Validation of 284 self-reported endometriosis diagnosis was carried out by going through patient records available (92 cases) at the original study site.

Table 1. Patient characteristics in women with self-reported endometriosis and controls at age 46 according to questionnaire data.

	Endometriosis (n=284)* **%**	**Controls (n=3390)*** **%**	**p-value**
Endometriosis diagnosis in the national hospital discharge registry	52.0	1.5	
Suffering from infertility	33.8	14.1	**<0.001**
No delivery	13.9	9.8	
One delivery	24.2	16.2	**<0.001**
More than one delivery	61.9	73.9	
Use of hormonal contraceptives			
Ever	93.3	89.2	**0.033**
Current	20.2	27.1	**0.028**
BMI (kg/m2)			
<18.5	0.8	0.9	
18.5 - 24.999	48.5	45.4	0.676
25 - 29.999	32.8	32.8	
≥30	17.8	20.9	
Smoking			
Ever	51.4	52.3	0.804
Current	33.6	32.6	
Alcohol use			
Never	6.0	6.2	
Light (less than monthly)	11.7	11.7	0.603
Moderate/heavy (at least once in a month)	76.3	77.7	
Education			
Basic	1.8	2.3	
Secondary	50.7	57.1	0.072
Tertiary	47.5	40.6	

* n varies in some of the variables due to missing questionnaire data

Table 2. Tobit regression analysis of pressure pain threshold (PPT) and maximal pain tolerance (MaxPTo) in women with endometriosis compared with controls

		Location of pressure pain measurement			
	Average	**Wrist**	**Shoulder**	**Lower back**	**Leg**
	kPa (95% CI)	**kPa (95% CI)**	**kPa (95% CI)**	**kPa (95% CI)**	**kPa (95% CI)**
Observations (total)	n=2609	n=2730	n=2747	n=2635	n=2738
#Constant PPT (crude)	642.6 (634.2, 650.9)	648.8 (639.6, 657.9)	585.8 (575.8, 595.8)	710.2 (699.1, 721.3)	641.1 (630.7, 651.5)
Endometriosis PPT (crude)	**-34.0* (-60.8, -7.3)**	**-37.5* (-67.3, -7.7)**	-27.8 (-58.9, 3.2)	-26.9 (-63.0, 9.1)	-29.9 (-63.5, 3.7)
^Difference [%]	**-5.3% (-1.1,-9.5)**	**-5.8% (-1.2, -10.4)**	-4.8% (0.5, -10.1)	-3.8% (1.3, -8.9)	-4.7% (0.6, -9.9)
Constant PPT (adjusted)**	645.7 (620.9, 670.6)	648.6 (620.8, 676.4)	602.1 (572.3, 631.9)	690.8 (657.4, 724.1)	649.1 (617.3, 680.8)
Endometriosis PPT (adjusted)**	**-35.4* (-62.2, -8.6)**	**-36.4* (-66.3, -6.6)**	-25.7 (-56.5, 5.0)	-33.8 (-69.5, 2.0)	-31.3 (-65.0, 2.3)
^Difference [%]	**-5.5% (-1.3, -9.6)**	**-5.6% (-1.0, -10.2)**	-4.3% (0.8, -9.4)	-4.9% (0.3, -10.1)	-4.8% (0.4, -10.0)
Constant MaxPTo (crude)	939.9 (932.0, 947.9)	932.2 (922.5, 941.8)	957.8 (946.2, 969.4)	1031.3 (1018.9, 1043.8)	941.4 (989.1, 1069.1)
Endometriosis MaxPTo (crude)	**-48.2* (-76.1, -20.4)**	**-58.1* (-90.6, -25.6)**	**-55.4* (-93.1, -17.7)**	**-50.6* (-91.0, -10.2)**	**-43.7* (-81.0, -6.3)**
^Difference [%]	**-5.1% (-2.2, -8.1)**	**-6.2% (-2.7, -9.7)**	**-5.8% (-1.8, -9.7)**	**-4.9% (-1.0, -8.8)**	**-4.6% (-0.7, -8.6)**
Constant MaxPTo (adjusted)**	952.7 (928.2, 977.3)	930.8 (901.7, 960.0)	997.5 (962.2, 1032.7)	1029.1 (989.1, 1069.1)	953.2 (917.4, 989.0)
Endometriosis MaxPTo (adjusted)**	**-50.1* (-78.0, -22.2)**	**-58.2* (-90.8, -25.6)**	**-53.4* (-90.7, -16.2)**	**-58.0* (-97.8, -18.1)**	**-46.8* (-84.2, -9.5)**
^Difference [%]	**-5.3% (-2.3, -8.2)**	**-6.3% (-2.8, -9.8)**	**-5.4% (-1.6, -9.1)**	**-5.6% (-1.8, -9.5)**	**-4.9% (-1.0, -8.8)**

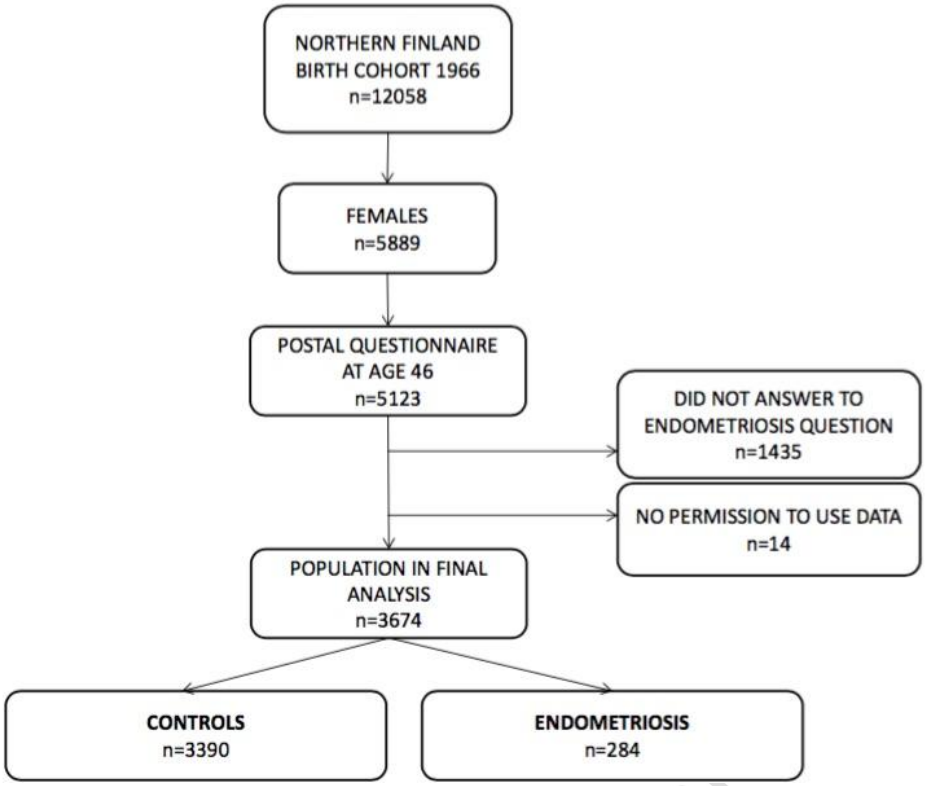
*p<0.05

**Adjusted for BMI, anxiety and depressive symptoms, smoking and use of hormonal contraceptives

#Constant, a built estimate reference value for subjects with BMI at the mean level of the population, no significant anxiety or depressive symptoms, never smoker and no use of hormonal contraceptives

^Difference compared with controls

Figure 1



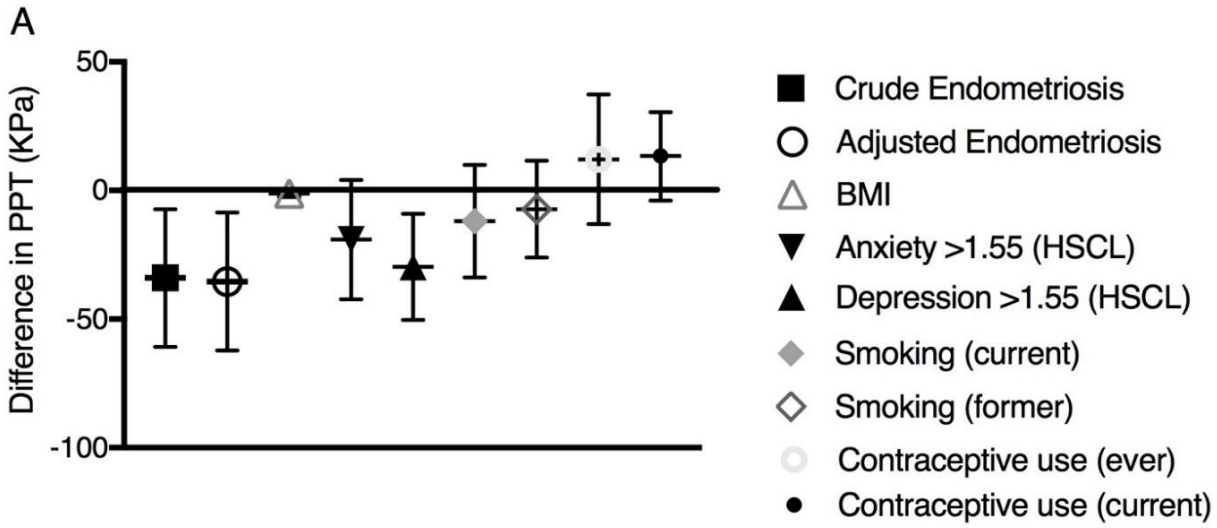
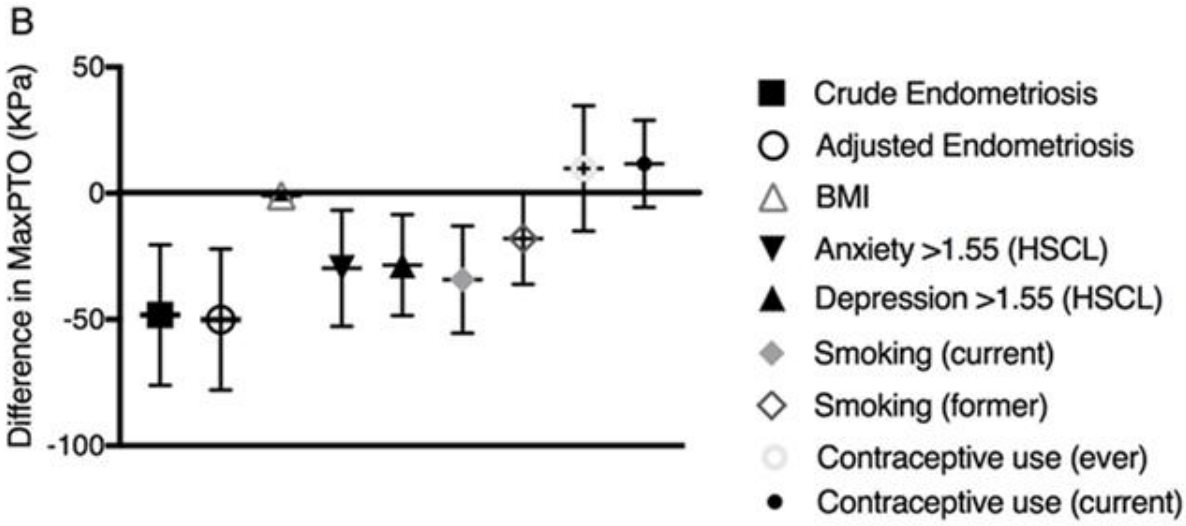


Figure 2A



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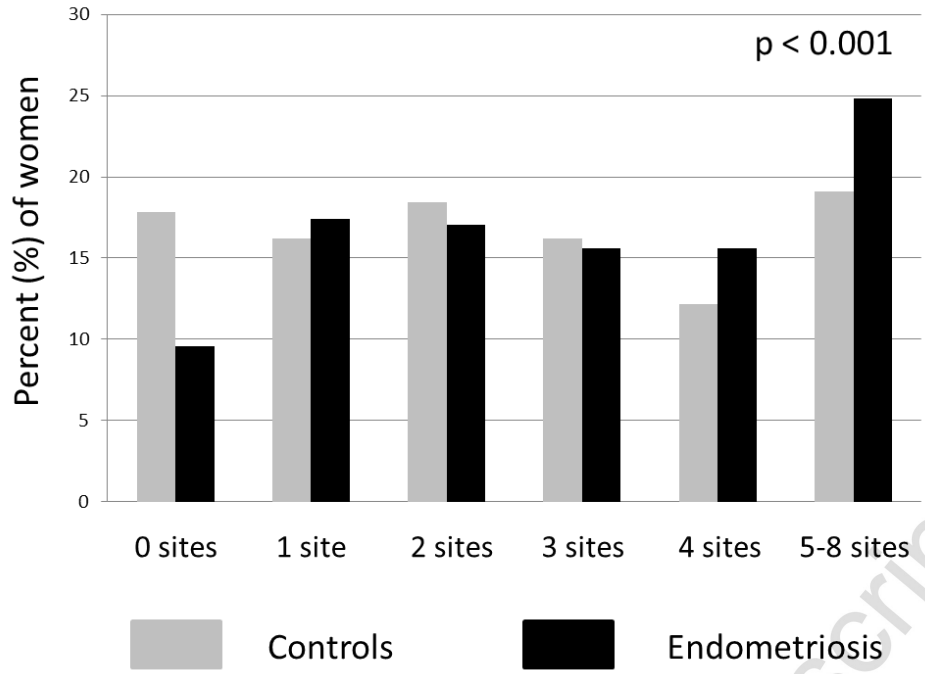

Figure 3

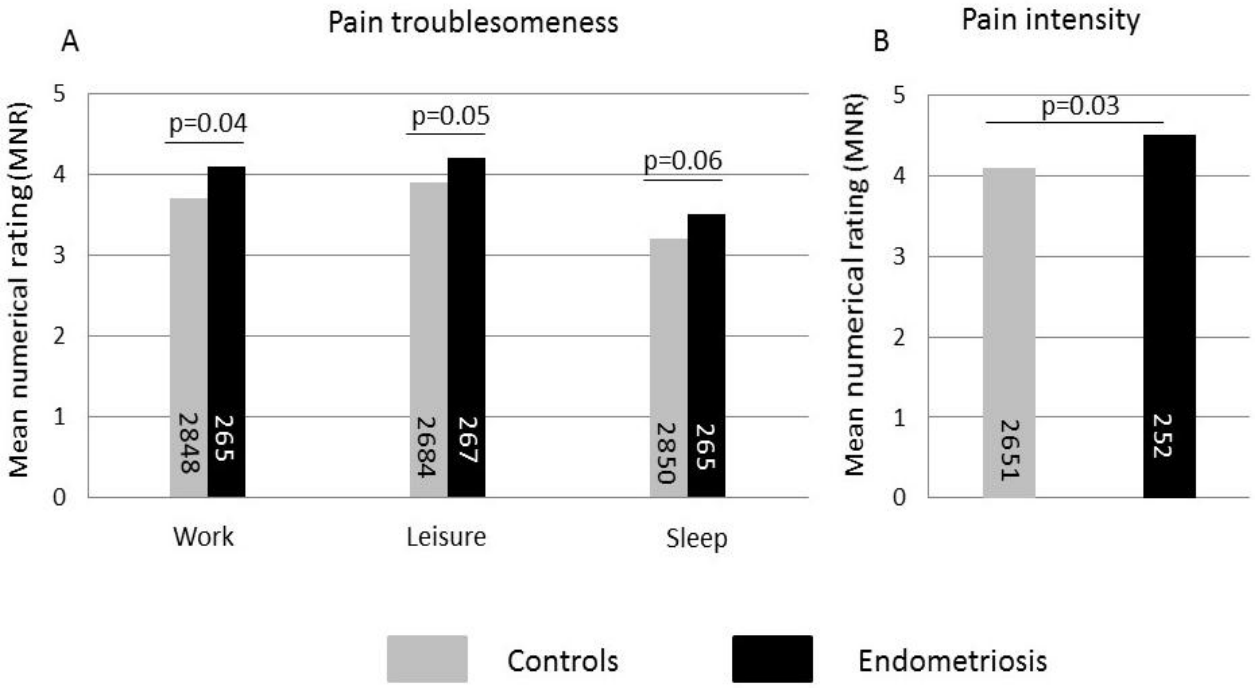

Figure 4