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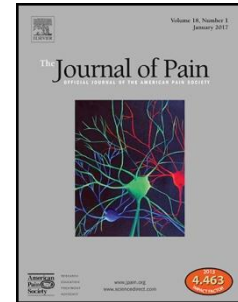
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1 **The Long-term Footprint of Endometriosis: Population-based Cohort**
2 **Analysis Reveals Increased Pain Symptoms and Decreased Pain**
3 **Tolerance at Age 46**

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32

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44 Highlights

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

54

55 Abstract

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

62 Our data is derived from the Northern Finland Birth Cohort 1966, which contains postal
63 questionnaire data (72% response rate) as well as clinical data assessing pressure-pain
64 threshold (PPT) and maximal pain tolerance (MaxPTo). The study population consisted of
65 284 women with endometriosis and 3390 controls.

66 Our results showed that at age 46 women with a history of endometriosis had a 5.3%
67 lower PPT and 5.1% lower maxPTo compared with controls. The most significant
68 contributors besides endometriosis were anxiety, depression and current smoking status.

69 Women with endometriosis also reported an increased number of pain sites (0 pain sites,
70 9.6 vs. 17.9%; 5–8 pain sites, 24.8 vs. 19.1%, endometriosis vs. controls respectively,
71 $p < 0.001$), and their pain was more troublesome and intense. The results were adjusted for

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

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

78

79

80 **Perspective item**

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

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84 Introduction

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

97 It is well accepted that endometriosis is associated with dysmenorrhea, but it
98 is not known why some women undergo transition to a state of chronic pain, while others
99 do not¹. Depending on the study population, 30–70% of women with CPP have
100 laparoscopic evidence of endometriosis ^{21, 34}. The pain symptoms, however, are poorly
101 correlated to the severity of endometriosis, and the pathophysiology of endometriosis-
102 associated pain remains somewhat elusive ^{9, 14, 23, 25, 36, 37}. Pain mechanisms in
103 endometriosis are thought to be multifactorial; pain may be nociceptive, neuropathic or a
104 combination of these, and emotional, cognitive and behavioral components are also
105 present ^{3, 20, 23, 32}. Previous studies have shown increased pain sensitivity among women
106 with endometriosis, with or without CPP, in response to mechanical stimuli compared with
107 control ². Furthermore, pain-threshold studies have suggested hyperalgesia at extra-pelvic

108 sites, most likely due to peripheral and/or central sensitization mechanisms in affected
109 women^{5, 12, 16, 23, 24}.

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

117

118 **Materials and Methods**

119 Study Population

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

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

133 (55%) participated. All participants gave informed consent. The study followed the
134 principles of the Declaration of Helsinki and the Ethics Committee of the Northern
135 Ostrobothnia Hospital District approved the research. A flow chart of the study is shown in
136 Figure 1.

137 Diagnosis of Endometriosis

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

144 Verification of diagnosis

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

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

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

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

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

184 Questionnaires on pain sites, pain intensity and pain troublesomeness

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

197 Confounders

198 *Infertility*

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

200 *Parity*

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

204

205

206 *Contraceptive use*

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

210 *BMI*

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

218 *Smoking*

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

223 *Alcohol use*

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

227 *Education*

228 Education was classified into three groups by the number of years of education: 9 years,
229 9–12 years and more than 12 years.

230

231 *Anxiety and Depressive symptoms*

232 Anxiety and depressive symptoms were assessed via the 25-item Hopkins Symptom
233 Checklist (HSCL-25) at 46 years of age^{22, 35}. HSCL-25 part I includes 10 items concerning
234 anxiety symptoms and part II, 15 items concerning depression. The scale varies between
235 1 and 4: 1 = not troublesome to 4 = extremely troublesome. The commonly used cut-off
236 point of 1.55 was used to pinpoint anxiety and depression symptoms³⁵.

237 Statistical analyses

238 A Tobit regression model³³ was used to evaluate independent associations between
239 endometriosis and PPT/MaxPTo. The motivation behind this was the large amount of
240 censoring seen at the maximum limit of 1200 kPa. The interpretation of regression
241 coefficients depends on the probability of not being censored. The interpretation is a
242 combination of 1) the change in outcome, given that it is not censored, weighted by the
243 probability of not being censored; and 2) the change in the probability of not being
244 censored, weighted by the expected outcome if uncensored. Models were adjusted for
245 BMI, anxiety and depression symptoms, smoking and contraceptive use.

246 Chi-squared tests were used to analyze the associations between the distribution and
247 numbers of pain sites, and ANOVA was used to investigate the effect of pain intensity and
248 troublesomeness at work, during leisure time and sleep. The analyses were performed
249 with R software version 3.2.2, using the AER package for Tobit regression¹⁹.

250

251 **Results**

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

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

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

268 In Tobit regression analysis, PPT measurement showed that the women with
269 endometriosis had on average a 34.0 kPa lower (-5.3% [-1.1,-9.5]) pain threshold
270 compared with controls ($p < 0.05$). As for the measurement site, PPT measured at the wrist
271 was significantly lower in women reporting endometriosis (-37.5 kPa, $p < 0.05$, Table 2),
272 whereas the results concerning other measurement sites (shoulder, lower back and leg)
273 did not differ between the study groups. After adjusting for confounders, PPT remained
274 35.4 kPa lower in the endometriosis group ($p < 0.01$). There were no statistically significant
275 effects of BMI, anxiety, smoking or current or previous contraceptive use on pain threshold
276 measured at the wrist.

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

281 53.4 kPa), lower back (-58.0 kPa) and leg (-46.8 kPa). The most significant contributors
282 besides endometriosis that lowered maximum pain tolerance were anxiety, depression and
283 current smoking status (-29.7kPa, -28.5kPa, -34.2kPa, respectively) ($p < 0.05$, Figure 2).

284 The women were also screened for number of musculoskeletal pain sites (0,
285 1, 2, 3, 4, 5–8 sites), pain troublesomeness and pain intensity (Fig. 3). Among women with
286 endometriosis there were significantly fewer reporting no pain sites (9.6% vs. 17.9%,
287 $p < 0.001$, Fig. 3). Overall, the women with endometriosis also reported more pain sites
288 compared with controls (1 site 17.4% vs. 16.2%, 2 sites 17.0% vs 18.5%, 3 sites 15.5% vs.
289 16.2%, 4 sites 15.6% vs. 12.2% and 5–8 sites 24,8% vs 19,1%, $p < 0.001$, Fig. 3).

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

297

298 Discussion

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

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

306 controls in a population-based study setting. The data adds to the body of evidence in the
307 literature showing altered pain sensitivity in endometriosis. However, previous studies
308 have been hospital-related populations^{1, 2, 4, 12}. In the present study, regression analysis
309 suggested that endometriosis is associated independently with lower pain threshold and
310 tolerance, whereas the strongest factors further decreasing the pain threshold and the
311 maximal pain response were anxiety, depression and current smoking status. Given all
312 this, it is worth noting that depression has been previously shown to be associated with
313 altered pain perception¹⁵ and interestingly, musculoskeletal pain responses are
314 particularly increased among women with co-expressing endometriosis and anxiety or
315 depression symptoms³¹. Interestingly, both past and current contraceptive use appeared
316 to be associated with unchanged pain tolerance, supporting the clinical use of hormonal
317 contraceptives also in women with pelvic pain. The role of estrogens in pain perception is,
318 however, complex. Interestingly, low estrogen concentrations in late menstrual cycle or
319 during menopause or increased estrogen-testosterone ratio in male to female transsexuals
320 have been shown to associate with increased pain symptoms³⁸. Whether menopause
321 solves the endometriosis-related altered pain responses or make them worse remains to
322 be evaluated in future studies as estrogen measurements or menopausal status were not
323 available for the present study.

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

331 pressure-pain sensitivity was assessed in the thumbnail, the results showed significantly
332 lower pain threshold among women with symptomatic endometriosis ². Visceral
333 hypersensitivity testing also revealed lower pain thresholds among women with
334 endometriosis in a rectal balloon dilation test ¹⁸ and lower pain thresholds and larger pain
335 areas were reported in women with symptomatic endometriosis after an intramuscular
336 saline injection into the hand ⁴. In a more recent study concerning pressure-pain
337 thresholds at 20 different body sites, with use of the visual analog scale, it was reported
338 that there was a lower pain threshold in the greater trochanter and abdomen in fertile-aged
339 women with endometriosis compared with controls ²⁴. A population-based study carried
340 out by Slater et al., with similar musculoskeletal pain response testing as in the present
341 study, showed decreased pain thresholds in women experiencing severe menstrual pain²⁹.
342 Given that about 70% of women with dysmenorrhea (CPP) present with endometriosis in
343 laparoscopy, the data by Slater et al. are in line with the present results underlying altered
344 pain perception in affected women. The mechanisms behind the lowered threshold are
345 most likely multifactorial, involving peripheral and central mechanisms ²³. Whether the
346 women with CPP are the ones who also have altered pain perception during late
347 reproductive years remains to be investigated as the present data did not record
348 dysmenorrhea or pelvic pain.

349 Women with endometriosis reported more pain sites, and graded pain to be
350 more bothersome and intense compared with controls. This might be due to central and/or
351 peripheral sensitization which has been shown to result from prolonged noxious pain
352 stimulation sustaining central pain stimulation in these cases ^{17, 31}. Indeed, women with
353 endometriosis have reported increased regional hyperalgesia and allodynia ³¹. Moreover,
354 the fact that pelvic pain correlates poorly with findings/severity of endometriosis further
355 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 registry²⁷. The authors concluded that self-reported diagnosis

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

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

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504

505 **Figure 1.** Flowchart showing the study population ($n_{\text{endometriosis}} = 284$, $n_{\text{controls}} = 3390$)
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

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

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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/m ²)			
<18.5	0.8	0.9	
18.5 - 24.999	48.5	45.4	
25 - 29.999	32.8	32.8	0.676
≥30	17.8	20.9	
Smoking			
Ever	51.4	52.3	
Current	33.6	32.6	0.804
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

1 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)

2

*p<0.05

3

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

4

#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

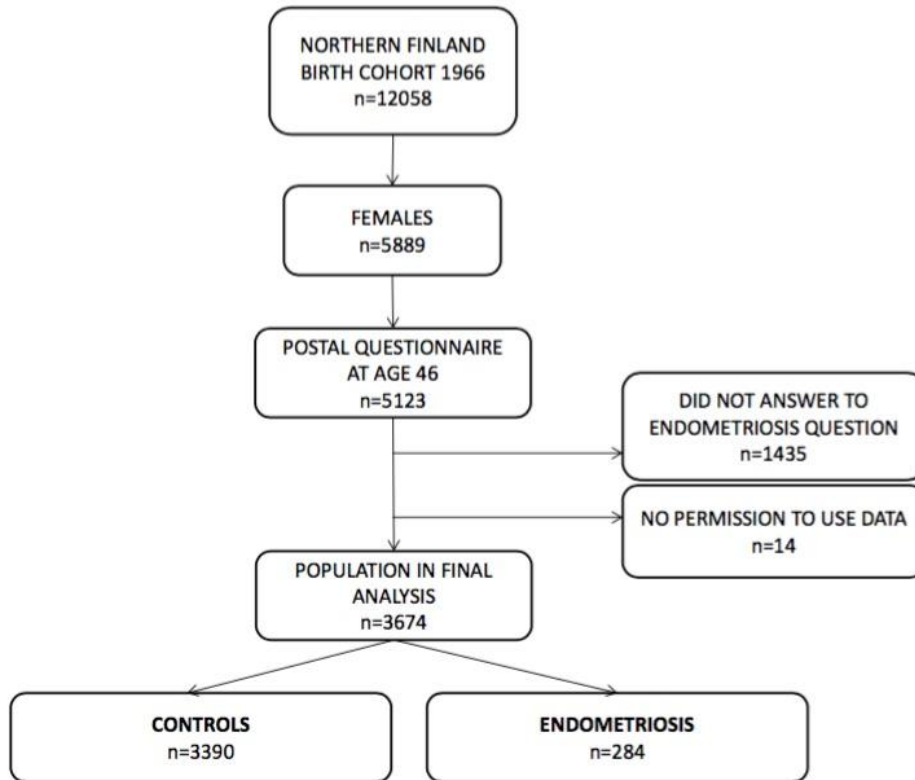
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^Difference compared with controls

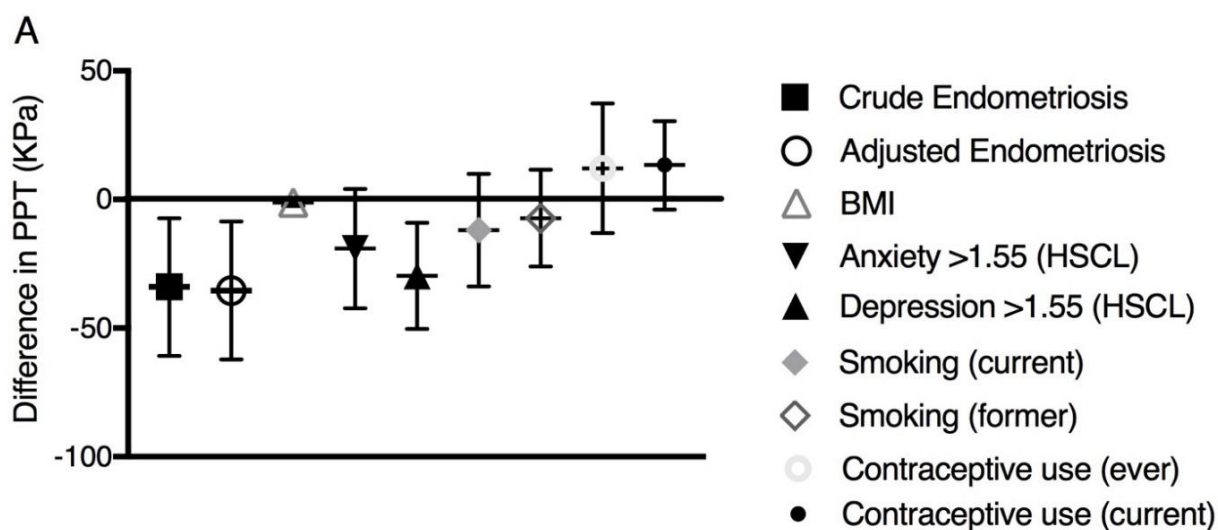
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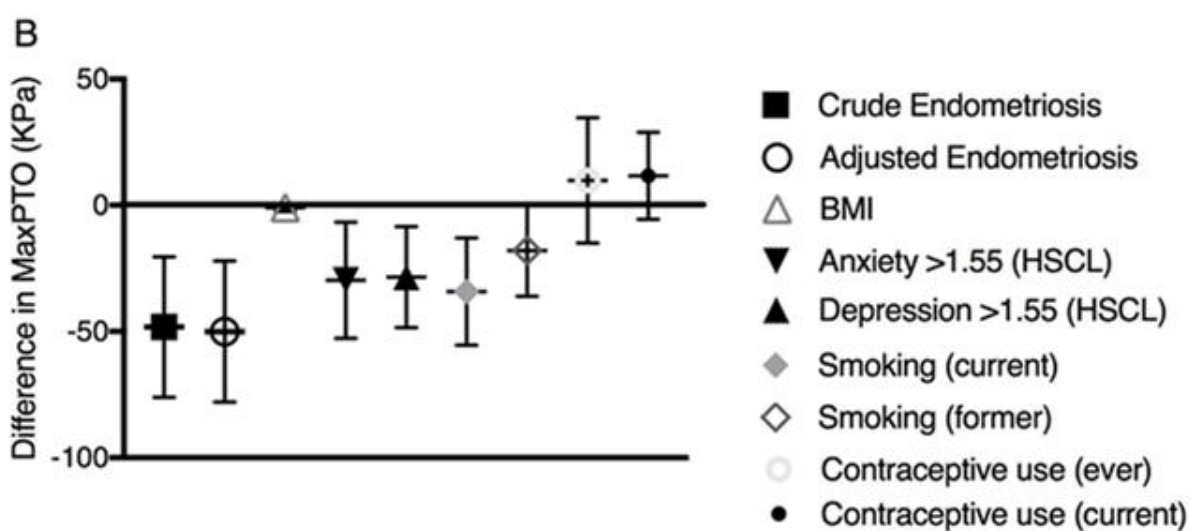
9 **Figure 1**

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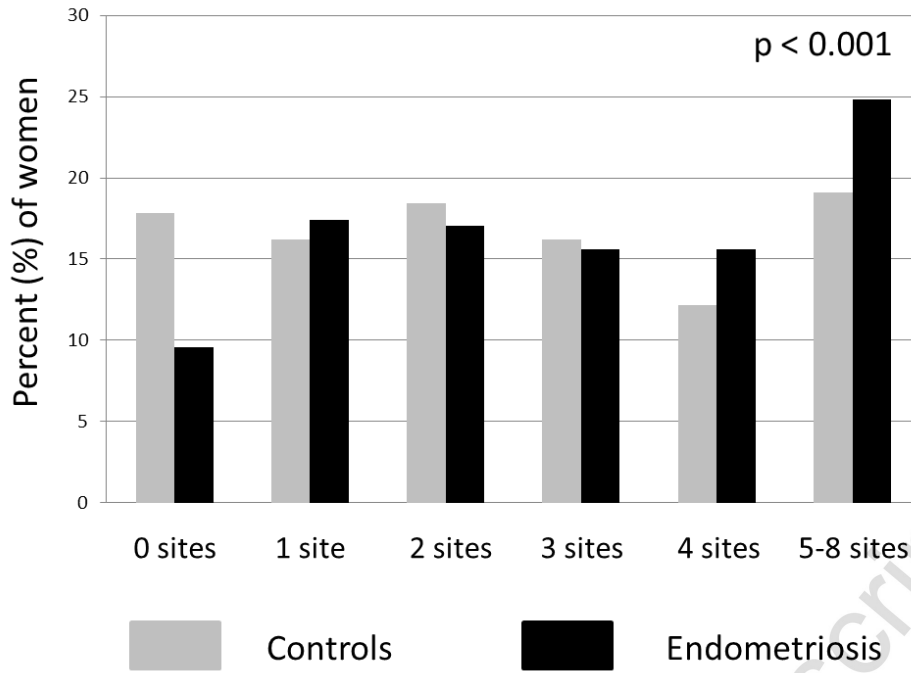
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Figure 2A



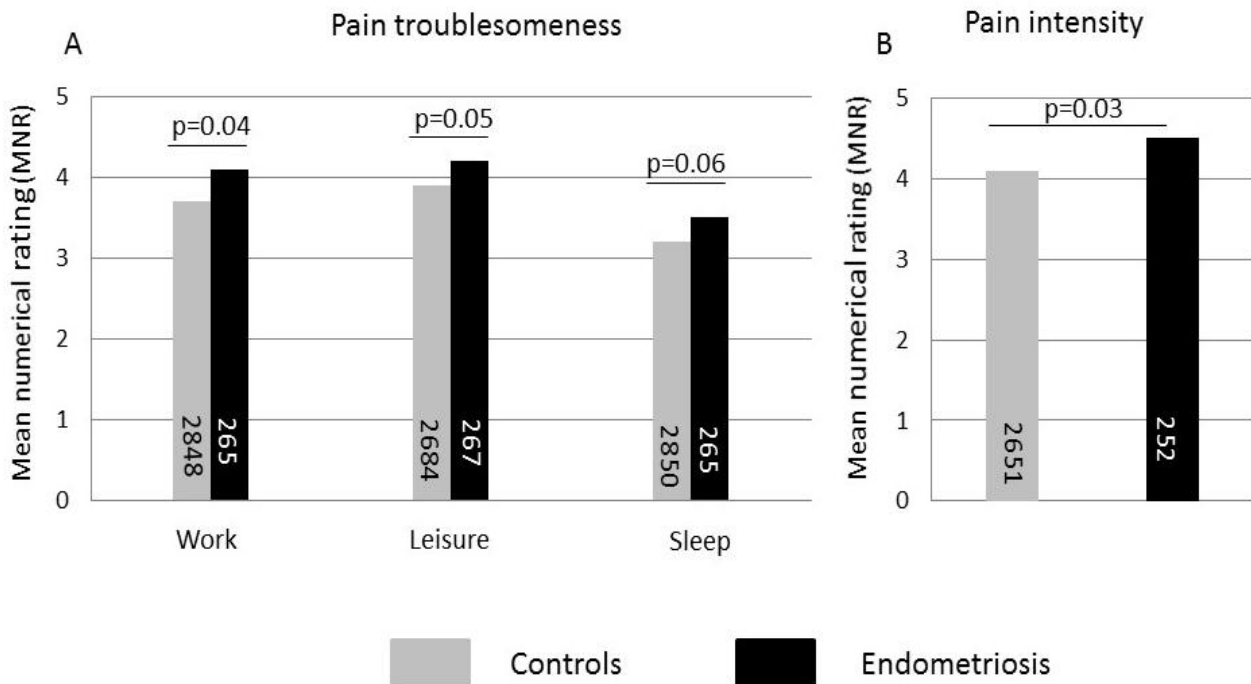
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Figure 2B



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Figure 3



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Figure 4